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**Series:** History of epidemiology

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# Origins and early development of the case-control study: part 1, Early evolution

**Summary**

This paper traces the origins and early development of the case-control study, focusing on its evolution in the 19th and early 20th century. As with other forms of clinical investigation, the case-control study emerged from practices that originally belonged to the realm of patient care. This form of disease investigation can be viewed as the knitting together of medical concepts (caseness, disease etiology, and a focus on the individual) – and medical procedures (anamnesis, grouping of cases into series; and comparisons of the diseased and the healthy) – that are of ancient origin, but which were seldom brought together until the 20th century. The analytic form of the case-control study can be found in 19th century medical literature, but did not appear to be viewed as a special or distinct methodology. A number of clinical investigations, and several sociological studies, in the first half of this century can be described as case-control studies, the most fully developed of which was Janet Lane-Claypon's 1926 study of breast cancer.

"Judging from the manner in which the subject is usually handled, the study of the etiology of diseases is generally undertaken with great levity, even by men of high acquirement. Some slight general knowledge, supported by a little more or a little less common sense, is quite sufficient to fit its possessor for the discovery of the causes of disease, in other words, to qualify him for the most complicated problem within the whole range of pathology."

PCA Louis (Louis 1844: 487)

A computerised MEDLINE search did not find the term "case-control" in the title of a biomedical paper until 1967, and did not find it in the titles of more than two papers in a year until 1973. By 1980, 91 titles included the term, but in the year 2000 1795 papers had "case-control" in the title or abstract. This enormous increase is only partly a reflection of preferences in terminology, such as a shift from the term "retrospective study" to "case-control study", and of the general increase in medical publications over the last four decades. The case-control study is now firmly ensconced in epidemiology, and, because of its widespread use and the value of its results, it now rivals in importance the more straightforward cohort approach to unravelling disease etiology.

From where did this investigative tool come? The modern form of the case-control study is most easily recognised in Janet Lane-Claypon's study of breast cancer in 1926, and crystallised in the years following World War II. 1950, a year that saw the publication of four case-control studies of smoking and lung cancer, was a watershed in the acceptance of this approach to assessing disease etiology. Part 1 of this paper is a brief investigation into its earlier history.

Each of the component practices of the case-control design, as well as each of its underlying concepts, had been used or discussed in some earlier medical setting. The embryonic development of this unique study design resulted from the knitting together of these elements for a specific purpose, namely, the uncovering of factors predisposing to disease operating at the level of the individual. Setting this as the objective for study implied a causal paradigm which was emerging but not yet fully articulated, that is, the notion that multiple causal agents may act to increase the risk of disease, particularly chronic disease. The search for risk factors would supplant the search for necessary and sufficient causes as the guiding principle of epidemiologic research.

If the period traced in part 1 of our paper might be considered as the embryology of this synthetic conception, then the period after its birth in 1950 might be seen as the

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development of the infant into a full-fledged being. Advances in methodology since then have been particularly important in the modern era of the case-control study, but these latter advances did not require quite the same conceptual shifts as did the earlier developments.

## Components of the case-control study

In our view, the case-control study is distinguished by six essential elements, each of which evolved separately in medical history. These elements include three inter-related underlying concepts:

1. The idea of the case: that is, that disease entities are specific, and are likely to have one or more specific causes.
2. An interest in disease etiology and prevention.
3. A focus on individual, as opposed to group, etiologies.

These elements of the case-control study also include three practices:

4. Anamnesis, or history taking from patients, which permits the collapse of time past without enduring its slow passage until outcomes under study evolve.
5. Grouping individual cases together into series.
6. Making comparisons of the differences between groups, in order to elicit **average** risk at the level of the individual.

### *Caseness*

The case series presupposes that there is some organising principle that unites the individuals so assembled. This principle in turn depends upon the view that diseases are specific and distinguishable entities. The 17th century physician Thomas Sydenham, dubbed the English Hippocrates, was perhaps the first forceful advocate of the concept of diseases as entities distinguishable by their symptoms and signs, course and prognosis (Sydenham 1848). This view may seem self-evident, but as late as the 19th century it was not so to many physicians (Merton 1957). Different diseases were frequently viewed as the varying responses of individuals to differing environmental circumstances. Thomas Southwood Smith, perhaps the leading British physician-sanitarian of the first half of the 19th century argued that: "This mode of viewing fever as one great and extensive malady never differing in nature, but in every two cases differing in intensity, and giving rise by these differences in intensity to various forms of disease, thus affords a principle of arrangement, which, while it is at one simple and comprehensive, is at the same time in the highest degree practical." (Southwood Smith 1830). In fact, this unitary concept of febrile diseases was a very powerful stimulus to sanitary reform, as it implied that all such illnesses might be prevented by environmental improvement.

Critical to the concept of caseness was the development of morbid pathology. From the time of the publication of Morgagni's classic "*De sedibus…*" or "Seat of disease" (Morgagni 1761), in which the Italian physician and anatomist showed the clear relationship between local pathology and disease symptomatology, medicine began its slow but steady march towards acceptance of the distinctiveness of the several diseases. The fuller development of scientific pathology by physicians of the early 19th century – including Louis in France, Henle in Germany, Von Rokitansky in Austria and among others – gave force to the concept of unique biomedical entities with clinical manifestations linked to specific pathological findings. Louis' American student William Wood Gerhard demonstrated the concept when he first clearly separated typhoid fever from typhus fever. In making the distinction, Gerhard relied principally on the difference in intestinal pathology between the "typhus" fever he treated in Philadelphia and the "typhoid" fever he had seen with Louis in Paris (Gerhard 1837).

### *Disease etiology*

The conceptual basis of the case-control study is an interest in the etiology of disease, as contrasted to its prognosis or treatment. This interest is of course very ancient in medicine, but the extent of interest in etiology has varied from time to time in medical history among the ancient Greeks, the god Aesculapius presided over treatment, and another, Hygiea, over prevention. Hygiea was Aesculapius' daughter, and, paralleling the situation for daughters in ancient Greece, interest in etiology has historically been eclipsed by interest in treatment.

Interest in etiology tends to become dominant during serious epidemics, when prognosis is poor and the limitations of medical treatment are most evident. At such times, often stimulated by public alarm and political pressure, medicine has focused more intensely on etiology and prevention, and the sometimes furious investigative efforts that have surrounded epidemics in the past two centuries have often yielded major leaps in understanding. The modes of transmission of cholera (Snow 1855), yellow fever (Reed et al. 1900) and plague (Advisory Committee 1906) were each worked out under the pressure of epidemic disease. This perhaps explains the name of our discipline, which, in spite of its focus on the etiology of diseases of all kinds, including those that are rarely viewed as epidemic, continues to be epidemiology.

### *Etiology at the individual level*

Not always emphasised in text-book descriptions of case-control studies is the focus of this design on causes of disease

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that operate at the level of the individual. Case-control studies have not generally contributed to an understanding of broad ecological risk factors such as air or water pollution, because the usual methods for choosing controls are unlikely to produce populations with differences in exposure. Optimum controls, in most definitions, are drawn from the same source population (or study base) as the cases. To obtain such controls, typical source populations are in the neighbourhood in which the case resides, or in the hospital in which the case is ascertained, the choice depending on the object of the study and the extent of ascertainment bias entering into the case diagnosis. The need to ensure the same study base for controls and cases constraints the variety of source populations that can be used to obtain controls. This constraint often eliminates any possibility of finding differences in ecological risk factors between cases and controls, because these will differ *across* rather than *within* such populations.

At least until the mid-19th century, most etiologic comparisons made in medicine were ecologic. Hippocrates contrasted the salubrity of different geographic regions, seasons of the year, and ethnic groups, but provided little description of individual behaviours as risks for disease (Hippocrates 1734). The concept of various occupations predisposing to particular diseases, as developed by Ramazzini (1700) and by Thackrah (1832), also viewed disease risk as a function of group membership. Comparisons of the mortality rates of counties, cities and neighbourhoods are staples of the literature of 19th century sanitarians such as Chadwick (1842), Shattuck (1850) and Farr (1852). Much rarer are comparisons of disease risk according to characteristics which, unlike water supply or weather conditions, need to be measured at the level of the individual. Nineteenth century sanitarians concerned themselves almost exclusively with broad ecological contributors to disease such as sewerage, water supply, climate and weather patterns, and poverty and crowding. The case-control study represents a very different etiologic focus.

*Anamnesis*

Anamnesis elicits by interview a retrospective account of events in a patient's life that the questioner, usually the physician, hypothesises may be of importance in understanding the disease process. Although the main purpose of interviewing patients in clinical practice is to establish the acute symptoms of the illness and their chronological order, the practice of asking patients about behaviours and conditions antecedent to the illness, such as places of residence, usual diet and patterns of physical activity, goes back to the Hippocratic writings of the 4th century B.C.

Epidemiology, learning from survey methods developed in the social sciences, has in recent years refined its anamnestic techniques. Although the case-control study is not in principle wedded to the interview as its only means of obtaining exposure data, to this day the bulk of case-control studies elicit most etiologic information by personal interview. This is not accidental, but rather a function of the kind of exposures that the case-control study is typically after, namely, personal exposures of long or varying duration and remote origin, rarely available from any other source than the subjects themselves. When sources other than the patient are available, as, for example, in birth and other vital statistics registers and in military or other occupational records, they are often amenable to the construction of exposure cohorts, which makes the retrospective cohort design more attractive.

In the chronic diseases that are commonly investigated in case-control studies, physical examination or laboratory testing are limited as sources of exposure to characteristics that are stable over many years, such as HLA-type, antibody status, genes, or genetic polymorphisms. Occasionally, anamnesis can be confirmed by physical examination, as in the self-report of circumcision, which has been assessed as a risk factor for cancer both by history and, with greater precision, by examination. (Schrek & Lenowitz 1947; Dunn & Buell 1959). With the availability of banks of stored data, including especially tissue specimens, more opportunities will arise for other kinds of exposure ascertainment in nested case-control studies, including assessment of serum markers representing exposures earlier in the subject's life.

*Making comparisons*

The second and most essential case-control practice is the comparison of like with like in order to discern differences of interest or importance. In philosophical terms, this is exemplified in John Stuart Mill's second canon – *"the method of difference,"* – which states:

„In an instance in which the phenomenon under investigation occurs, and an instance in which it does not occur, have every circumstance in common save one, that one occurring only in the former; the circumstance in which alone the two instances differ, is the effect, or cause, or a necessary part of the cause, of the phenomenon." (Mill 1856).

In a case-control study, the instance in which the phenomenon under investigation occurs is the case-state, and the instance in which the phenomenon does not occur is the control-state. The circumstance "occurring only in the former" is the hypothesised exposure. This kind of comparison is not a new element in medicine; one can find many early

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attempts to elucidate Mill's method of difference to make assertions about causes of disease. But the case-control study differs from most of these historical comparisons in that the direction of the comparison runs backwards in time from caseness to etiology, rather than forward from etiology to caseness (the former being more intuitively understandable).

An elaboration of this logic was required for the development of the case-control study. In practice, the design is not used to establish a one-to-one relation between caseness and exposure. Rather, the question is whether the exposure occurs more frequently in cases than controls (Greenwood 1935), and the presence of this association implies that the converse will also be true, namely, that the disease occurs more often in the exposed than the unexposed. The repositing of the question in this way is essential to the causal paradigm underlying the design, which holds that many exposures can be causes of a single disease, and that each of these exposures can increase the probability of disease in an individual. It was in part for this reason that figures such as Major Greenwood and Bradford Hill (the first and second chairs of Epidemiology and Statistics at the London School of Hygiene and Tropical Medicine), who were statisticians as well as epidemiologists, played a prominent role in the early evolution of the case control study (1925–50), as did later their statistician counterpart in the United States, Jerome Cornfield (1951).

*Case series*

It may seen intuitively obvious that before any useful comparisons along the lines discussed above could be made, a group of cases would need to be brought together. But the case series is largely a 19th century development. The assembly and description of cases – groups of patients with similar characteristics – was first used to study issues of practical interest to physicians – clinical presentation and prognosis. Studies gradually extended into diagnosis, pathological findings, and treatment. Etiology was less commonly of interest.

Although clinicians had occasionally assembled groups of patients and described them before the 19th century, the earliest, most systematic and most celebrated proponent of such work was the Parisian physician PCA Louis (1788–1875). A physician of great personal influence, many of whose students became leading medical figures in Britain, Germany, and the United States, Louis promulgated a belief in what he called the "numerical method", a technique whose principal tool was the tabulation of aggregated data about patients with similar pathologic and clinical findings. The disease he studied most comprehensively was tuberculosis, then usually called phthisis. Louis' interest in case series was principally designed for understanding pathology and for elaborating clinical and diagnostic observations; prognosis and treatment were his second interest; etiology, though not completely absent, took a distant third place.

## 19th century case-contol approaches

The 19th century provides a few interesting examples of studies that contained some or most of the essential elements of the case-control study. Below we describe three.

*Louis on heredity in tuberculosis*

The quote that inaugurates this chapter is taken from Louis' treatise on tuberculosis, a book of 566 pages in its English translation, which contains just one 32-page chapter entitled "Etiology" (Louis 1844, Chapter 5: 477–508). In that chapter, Louis prefigured the case-control approach by considering the hereditary predisposition to phthisis. After first acknowledging the difficulty of obtaining good information from patients about the causes of death of their parents, he notes that in a series of phthisical patients assembled by sBriquet, 36 of 101 had "phthisical parents". He then reasons thus:

"But..if the mortality produced by phthisis at the Necker hospital during the space of three years averaged 11/37ths, or somewhat less than one third of the whole mortality; this would signify that 11/37ths of the population of Paris die phthisical, and that, consequently, whenever we proceed to the investigation of the hereditary influence in respect of any disease, we must find tuberculous parents eleven times out of thirty seven. So that if the same ratio existed in the instance of the parents of tuberculous subjects, hereditary influence would be shown not to exist all." (Louis 1844: 484)

Here we have perhaps the first reference to the absence of a higher rate of exposure in the diseased ("the same ratio") supporting a null hypothesis about disease etiology. Louis' insight was to recognize the insufficiency of Briquet's case series standing alone as supporting hereditary or other causes of the disease. For his theoretical comparison, therefore, he resorted to a series of deaths in a Paris hospital. Less justifiably, Louis viewed this series as a reasonable approximation of Parisian mortality overall.

Louis also developed the idea of comparison in his work on treatment. Famously, in his demonstration (widely criticised at the time) that bloodletting for acute lobar pneumonia was not especially helpful, he compared patients admitted to hospital, and hence bled, at successively longer intervals after onset. Fatalities were highest among those bled earliest (Louis

1835). Although Louis was a pioneer in promoting the concept of fair and accurate comparison of treatments, he did not systematise the reasoning expressed in the quote above, and did not add control series to his many notable case series.

*Whitehead on cholera and the Broad Street pump*

John Snow, in his famous investigation of the Broad Street pump outbreak, did not systematically assess pump water exposure in individuals without cholera (Snow 1855). But a local minister, the Reverend Henry Whitehead, did just that (Whitehead 1855). Initially skeptical of Snow's findings, Whitehead inquired in detail (returning up to five times to the same person) as to pump water consumption among residents of Broad Street between August 30th and the removal of its handle on September 8th. He began by asking the families of cholera deaths about the habits of the decedents, and found that 45 had "decidedly" drunk from the pump, while 13 had not. Extending his inquiry to cholera survivors, he found 35 "certainly" drank pump water, while 7 did not. He then reasoned that to perform "a proper inquiry into this subject …. I must likewise examine, upon this matter, as many as possible of those who, being resident in Broad Street at the beginning of September, did not suffer at all either from Cholera or Diarrhoea." [*He thus*] **Thereupon, he** interviewed 336 non-cholera cases, and found that 279 had not used the pump, while 57 had. Whitehead concluded that "among those attacked, the ratio of pump water drinkers to non-drinkers of the same water is 80 to 20, whilst among those who escaped the corresponding ratio is but 57 to 279". This gives an odds ratio of 19.6 for pump water use and cholera ($p < .001$).

This study, designed to investigate a specific exposure ascertained through interview, and using a control series of individuals, chosen from the same source population but free of the condition of interest, is, to our knowledge, the first case-control study in the medical literature. A case has been made (Lilienfeld & Lilienfeld 1979) that William August Guy's investigation of occupation in relation to pulmonary consumption (Guy 1843) was the first case-control study. Guy, however, while making very interesting remarks about the problems of selection bias in occupational health research, compared the proportion of deaths due to consumption in the different occupations. His outcome of interest, the relative odds of dying from consumption as compared to dying from other causes in the different occupations, though of considerable interest, was not an exposure-disease odds ratio.

*Baker on breast cancer*

Another pioneering use of analyses close to the modern case-control method was read to the Royal Medical and Chirurgical Society in 1862 by James Paget (of Paget's disease) but authored by W.M. Baker, entitled "Statistics of cancer" (Baker 1862). The data source was notes on 500 cases of cancer described by Paget between 1843 and 1861. Most of the paper is a listing of typical case-series statistics, such as the age distribution and duration of survival of cases of cancer, but in two instances, the author provides a case-control type of comparison. The comparisons are of marital status and of prior pregnancy in women with breast cancer and in women with other cancers (Table 1).

**Table 1** Baker's case-control comparisons of marriage and fertility in breast cancer patients (1862)

**Social conditions, &c.**
Incidence of marriage &c. – The condition of the female patient, whether single, married or widow, was noted in 260 cases of cancer of the breast, the proportion being –

| | |
|---|---|
| Single | 23.0 % |
| Married | 72.4 % |
| Widow | 4.6 % |

The percentage of each in fifty-four cases of cancer on other organs was

| | |
|---|---|
| Single | 20.4 % |
| Married | 68.5 % |
| Widow | 11.0 % |

**Pregnancy**
Of 163 married women suffering from cancer of the breast, 126 were fruitful, 37 barren. Of 25 cases of cancer in other organs, 22 were fruitful, 3 barren.

Baker's study appears to be one of the first case-control approaches to the study of a chronic disease, and the numbers in the table in relation to reproductive risk factors parallel current thinking, with an odds ratio for breast cancer of 1.2 for the single state, and 3.0 for marital nulliparity. But Baker was conservative, stating that "the number is too small to allow of a very fair comparison being made between them and the cancers of the breast in this respect."

## Early 20th century case-control studies

A handful of studies published in the first half of the 20th century have been identified as early case-control studies by a variety of authors. These early studies appear to have lit few fires among epidemiologists and other students of disease etiology at the time, but they do clearly fall in the line of development. Not by accident, many of these studies concerned the etiology of cancer. During this period, many epidemiologists were aware of a shifting health profile in developed countries, and particularly of the increased frequency of cancer. There was some debate as to whether epidemiology should be extended from infectious to other etiologies. The position that it should be, was most fully articulated by the influential Major Greenwood, who argued that cancer was, like infectious diseases, a "crowd-sickness", and therefore within the purview of the epidemiologist (Greenwood 1935).

*Mayo clinic study of lip cancer*

AC Broders of the Mayo Clinic described 537 cases (526 male) of squamous-cell epithelioma of the lip, and investigated tobacco use, including the method of use (chewing, smoking, snuff-taking or any combination of same), and among smokers, the distribution of pipe, cigar, and cigarette use. In 500 "men without epithelioma of the lip" similar smoking data were tabulated. This study, sometimes cited as an early case-control study, makes no mention of the source of the controls, nor of the method of interview, and the mean age of cases and controls differed by more than 20 years. Though seemingly not much more advanced than the work of Whitehead in 1854 or Baker in 1862, the study did suggest a role for pipe-smoking in lip cancer (78.5% in cases vs. 38.0% in controls) (Broders 1920).

*Pellagra investigations in South Carolina*

Appearing almost simultaneously with the above paper, the work of Goldberger and his colleagues in South Carolina mill villages, comparing the diets in households with cases of pellagra and those without such cases, represented a signal advance in method (Goldberger et al. 1920). The investigators first identified all active cases of pellagra in their seven study villages, in a house-to-house survey. Their method was distinguished by the use of strict clinical criteria to define a case, and by the attention paid to specifying the date of onset. Though not entirely aware of the significance of using incident versus prevalent cases, the team considered the potential differences between new, recurrent, and remitted cases, and in fact the study included mainly new and recurrent cases that were of very recent onset.

The investigators chose a two-week period in late spring (when pellagra incidence rose to its seasonal peak) to ascertain family diets, by recording purchases at company stores, and by interviewing study families. Using formulas for food consumption based on age and gender, they estimated the probable relative intake of foodstuffs within households. The authors tried to take account of what they termed "disturbing or confusing factors", for instance, by restricting both case and control households to those with the lowest incomes. The study showed a clear deficiency of fresh meat and milk products in pellagrous households. Goldberger and his colleagues appear to have designed the first case-control study in which a confounding factor (income) was taken into account.

The next case-control study to appear in the medical literature was a comprehensive study of the etiology of breast cancer by Janet Lane-Claypon. Since this study can reasonably be viewed as the first "modern" case-control study, we will initiate part 2 of this paper with her investigation.

## Conclusions

A constellation of developments in medicine had to be in place before the case-control study could be conceptualised and actualised. These include the definition of unique disease entities (cases), the assembling of case series, an interest in etiology at the individual level, and the practice of interviewing patients about past events. Most crucial has been the practice, refined over many years, of comparing cases of disease to cases of non-disease so that factors that might account for the difference might be ascertained. These desiderata were very rarely met in the 19th century, and only occasionally before 1950. As it emerged in the beginning of the 20th century, in the work of Goldberger and his colleagues, the case-control study was but one part of a broader plan of attack to reduce the burden of disease, which also included experimental studies at the individual level, and investigating causes and interventions at a broader societal level. We will see in part 2 that over the course of the twentieth century the precision and logic of the design was greatly enhanced, but its use was less clearly integrated with other public health actions.

**Zusammenfassung**

**Ursprünge und frühe Entwicklung der Fall-Kontroll-Studie: Teil 1, Frühe Evolution**

Dieser Artikel verfolgt die Ursprünge und frühe Entwicklung der Fall-Kontroll-Studie, insbesondere den Entwicklungsverlauf während des 19. und 20. Jahrhunderts. Die Fall-Kontroll-Studie geht wie andere klinische Untersuchungsarten aus Praktiken hervor, die ursprünglich dem Gebiet der Patientenpflege zuzurechnen sind. Die Fall-Kontroll-Studie, als Art der Krankheitsuntersuchung, kann als eine Verstrickung medizinischer Konzepte (Fallexistenz/caseness, Ätiologie der Krankheiten und Konzentration auf das Individuum) und medizinischer Praktiken (Anamnese; Gruppierung von Fällen zu Serien; Vergleiche der Erkrankten und der Gesunden) verstanden werden, die zwar altbekannt sind, aber bis ins 20. Jahrhundert selten in Zusammenhang gesetzt wurden. Die analytische Form der Fall-Kontroll-Studie ist in der medizinischen Literatur des 19. Jahrhunderts präsent, wurde aber offenbar nicht als spezielle oder exklusive Methode wahrgenommen. Mehrere klinische Untersuchungen sowie einige soziologische Studien der ersten Hälfte dieses Jahrhunderts können als Fall-Kontroll-Studien bezeichnet werden, wobei die best entwickelte Janet Lane-Claypon's Brustkrebs-Studie von 1926 war.

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**Résumé**

**Origines et premiers développements de l'étude cas–témoins: Partie 1, Première évolution**

Cet article retrace les origines et les premiers développements de l'étude cas-témoins, en particulier au cours du 19ème et début du 20ème siècle. Comme d'autres formes de recherche clinique, l'étude castémoins émergea de pratiques qui faisaient à l'origine partie des soins aux patients. Cette forme de recherche peut être considérée comme l'assemblage de concepts médicaux (diagnostic, étiologie de la maladie et centrage sur l'individu) et de procédures médicales (anamnèse, assemblage de série de cas; comparaison entre sains et malades) qui ont une origine ancienne, mais qui furent rarement mise ensemble avant le 20ème siècle. La forme analytique de l'étude cas-témoins peut être retrouvée dans la littérature du 19ème siècle, mais elle n'apparaît pas comme une entité méthodologique. Plusieurs enquêtes cliniques et études sociologiques, dans la première moitié du 20ème siècle peuvent être décrites comme des études cas-témoins. L'étude sur le cancer du sein de Janet Lane-Claypon en 1926 est celle où la méthode fut le plus pleinement développée.

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