

Did John Stuart Mill influence the design of controlled clinical trials?

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John Stuart Mill and causal inference

The writings of the 19th-century British philosopher John Stuart Mill contain logical analyses relevant to causal inferences about effects but not specifically to assessing the effects of medical treatments. However, because Mill's analyses are relevant to the evolution of thinking about how to assess the effects of treatments, some passages from his writings are included in the James Lind Library.¹ For example:

In the spontaneous operations of nature there is generally such complication and such obscurity, they are mostly either on so overwhelmingly large or on so inaccessibly minute a scale, we are so ignorant of a great part of the facts which really take place, and even those of which we are not ignorant are so multitudinous, and therefore so seldom exactly alike in any two cases, that a spontaneous experiment, of the kind required by the Method of Difference, is commonly not to be found. When on the contrary, we obtain a phenomenon by an artificial experiment, a pair of instances such as the method requires is obtained almost as a matter of course. (p. 431)¹

The 'Method of Difference' to which Mill refers in that passage is one of the methods he sets out in his *System of Logic* (bk. III, ch. 8, p. 429).¹ Mill's 'Method of Difference' states:

If 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 circumstances in which alone the two instances differ, is the effect, or the cause, or an indispensable part of the cause, of the phenomenon. (bk. III, ch. 8, p. 483)²

One can appreciate the relevance of these ideas to thinking about how treatments should be tested. However, it should be noted that Mill's differences

appear to refer implicitly to differences resulting from comparing a treatment ('instance') with no treatment and not to differences resulting from comparing two treatments.

Was Mill influenced by earlier writings on fair comparisons of treatments?

Mill makes one reference to the application of this logic to assessing the effects of medical treatments, acknowledging that uncertainties can remain:

Suppose that mercury does tend to cure the disease, so many other causes, both natural and artificial, also tend to cure it, that there are sure to be abundant instances of recovery in which mercury has not been administered: unless, indeed, the practice be to administer it in all cases; on which supposition it will equally be found in the cases of failure. . . . Neither, therefore, will the instances of recovery agree in the administration of mercury, nor will the instances of failure agree in its non-administration. It is much if, by multiplied and accurate records from hospitals and the like, we can collect that there are rather more recoveries and rather fewer failures when mercury is administered than when it is not; a result of very secondary value even as a guide to practice, and almost worthless as a contribution to the theory of the subject. (p. 494)¹

He does not refer to any features of the design of the 'artificial experiments' that he deems necessary and he appears not to have conceptualised controlled trials. Some earlier writers had addressed these issues. During early 18th century in debates about the safety of inoculation against smallpox, for example, Massey³ had pointed out that 'to form a just comparison' between inoculated and uninoculated people 'the circumstances of the patients must and ought to be as near as may be on a Par'.

Proposals to draw lots (random allocation) to generate fair treatment comparison groups were made at

least as early as the 17th century.^{4,5} Alternation was used to create unbiased treatment comparison groups at least as early as the beginning of the 19th century,^{6,7} and some prominent doctors had started to use alternation during Mill's time.⁸

However, we are not aware of any sources indicating that Mill was aware of any of these developments in thinking among doctors or that he saw its relevance to his analyses.

Did Mill's writing influence the development of fair comparisons of treatments?

Some philosophers have claimed that Mill's writings are relevant to the evolution of controlled clinical trials. The most specific claim has been made by Cartwright and Hardie⁹:

An RCT [Randomized Control Trial] is a study design based on John Stuart Mill's method of difference for making causal inferences.

Other philosophers, while drawing attention to Mill's methods, have been less specific, perhaps because they are aware that random allocation for controlled trials was not widely adopted until a century after Mill and that alternation had been used to create similar treatment comparison groups 50 years before that.¹⁰ Examples of these less specific statements include the following:

Mill's 'method of difference'...seems to lie at the heart of EBM [Evidence-Based Medicine] because it lies at the heart of clinical trials. (ch. 6, part 3)¹¹
Comparative clinical studies have been referred to as Mill's methods..., the 'numerical' method..., the 'statistical' method..., and 'difference-making' evidence. (p. 124)¹²
Mill's method of difference can be seen as the basic principle behind the controlled clinical trial. (p. 212)¹³

Neither Cartwright's claim or any of the above statements is accompanied by references to supporting evidence that Mill's 'Method of Difference' had any subsequent influence on those promoting or doing controlled trials. Had Mill been influential in the evolution of controlled trials one would have expected to find references to him in the writings of pioneers of controlled trials using alternate allocation during the first half of the 20th century – Haffkine, Choksy, Cecil, Bullova and Hill, for example – and of random allocation during the second half of the century. As it is, not even Alexander Bain¹⁴ (p. 362), a Scottish philosopher and close friend of Mill, referred to Mill's writings in his emphasis on the use of

statistics and the importance of the elimination of chance as an element in his '*Logic of Medicine*'.

The only evidence of Mill's influence on medical writers of which we have been made aware has been communicated to us by Ulrich Troehler (personal communication, October 2017). In 1852, Friedrich Oesterlen, a German physician, referred to Mill and aimed to transfer his teachings to medicine in his book *Medicinische Logic*.¹⁵

I am indebted, however, to J. Stuart Mill's excellent work for the greater part, the true pith and thread of my system, and the following is, in a great measure, but an application of his doctrines to the particular questions and objects of our department of science. (p. X)¹⁵

Oesterlen referred to the significant contribution of statistics in general terms as 'the essential link in our research on truth based on experience'. He further emphasised that this held, provided one kept to the rules of extremely precise observation, compared like with like, considered the natural course of diseases, collected large numbers, and was appropriately cautious in making generalisations (pp. 129–140). Oesterlen's book dealt with medical observation and thought: the concepts of induction, deduction, generalisation, experiment and statistics. However, although Oesterlen's book made a major contribution to methodological discussions in Germany,¹⁶ Ulrich Troehler has not found any evidence that it penetrated the clinical world (personal communication, October 2017).

Conclusion

Mill's writings are important in their own right, regardless of whether they were influenced by prior writings on controlled trials or whether they have influenced the subsequent development of controlled trials. However, commentaries on and examples of prototype controlled trials antedated Mill; there does not appear to be evidence that he was aware of them. Nor does there appear to be evidence that Mill influenced the development of controlled trials, even if the way they are conducted is in keeping with his methods. Of course, it may be the case that evidence of these possible influences on and of Mill remains to be discovered. Yet until such evidence is discovered, philosophers should acknowledge the lack of it.

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Also at the two Sugar-loaves over against St. Antholins Church at the lower end of Watling Street, 1657.