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Paul Martini's *Methodology of Therapeutic Investigation*, 1932

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'If you skim through a dozen volumes of our medical journals, you will be lucky if you find as many as two dozen reports of therapeutic studies that stand up to critical assessment. Even in reputed periodicals such as the various "Clinical Archives", therapeutic studies are extremely rare. For every 100 reports of basic research or diagnostic studies there may be only 3 or 4 reports of therapeutic studies, and many of these will be methodologically deficient. You will not be mistaken if you conclude that most authors of reports of therapeutic studies are not at ease in a more rigorously scientific context (that is, in which applying strict methodological criteria will be expected).'

These sentences are quoted from the chapter on 'Therapeutic research as science: Criticism on the current situation', in Paul Martini's *Methodology of Therapeutic Investigation*.¹ In his view, the volume and standard of clinical therapeutic research in Germany around 1930 were unacceptably low, and there was no obvious concern to improve this situation. What was to be done about it?

The eight chapters of Martini's book constitute a proposal for reform. In this 69-page book, Martini presents his ideas for what we call today n-of-1 studies, including unbiased creation of control groups, blinding, placebos, stratification and statistical methods. In brief, this book sets out the basic principles for studies to evaluate treatments.

Not much is known about the history of the book. The biographical data on Martini shows that he first came into contact with questions of mathematics and medical statistics during his military service in World War I. He subsequently graduated as a doctor after studying medicine in Munich, and became a medical registrar and then consultant under the supervision of Friedrich von Müller (1858–1941) in Munich.

It was not until he moved to Berlin in 1928 to take over the huge medical section of the private St Hedwigskrankenhaus that he began to intensify his work on the development of criteria to assess the effects of treatment. Apart from the fact that Martini had to face several difficulties in pursuing his ideas and carrying out his first clinical trials at that hospital, conditions there were otherwise ideal: he saw a great variety of diseases and a large number of patients. Adolf Heymer, one of Martini's pupils, reports:

*'His [Martini's] new duties consisted primarily of clinical work at the bedside of large wards with interesting cases. In those days, up to 20 or 30 cases of bacterial pneumonia could be found on a single ward. He was impressed by the large number of patients and the frequently depressing prognosis of some diseases [...]. He doubted the therapeutic efficacy of many of the medications used at that time. Such doubts led to considerations of test procedures for medications which could be applied at the bedside. He hoped, thereby, to replace subjective interpretation of drug effects with objective evaluation of therapeutic efficacy. Plans for such critical therapeutic trials, however, had to overcome great obstacles. These originated from the patients themselves, from insurance companies and from the hospital's administration. Understanding and conscientious collaboration had to be obtained from colleagues and nurses. Through tedious orientation sessions Martini labored to convince hospital administrators of the necessity of such trials, which were aimed solely at providing the basis for "rational therapy", and thus were in the interests of the insurance companies as well.'*²

Although it was published in 1932, shortly after he had moved to Bonn to become Professor of

Medicine at the Rheinische Friedrich Wilhelms-University, the first edition of Martini's *Methodology of Therapeutic Investigation* was based mainly on the results of his studies in Berlin. His theoretical standpoint was outlined in the one-paragraph Introduction:

'The ultimate aim of scientific methodology is the specifically designed experiment, the pure case. That [pure case] always asks Nature the same question, to which she will always give the same answer, due to her principles and causality; a single experiment, carried out rigorously, is thus of higher value than all other accumulations of facts. However, although the pure case is the ultimate aim, it is only achievable in the most exact branch of science – physics. Only there is exact induction possible. Apart from physics, the inductive method will always involve generalisations, especially in a discipline that is as scientifically complex as medicine. However, even in medical science, it is possible to achieve a high probability of valid induction if two conditions are fulfilled: firstly, experiments have to be arranged in such a way that secondary causes can be ruled out; secondly, a vast number of cases is needed to replace the lack of representativeness of single cases. In our view, everything is dependent on the question of whether claims in medicine, especially in therapeutic investigation, can be adequately justified. The answer will both reveal the conditions that have to be considered in therapeutic investigations, as well as the rules that have to be obeyed by the investigators.'

Martini's major ideas on the subject can be summarized as follows:

- (1) Acknowledging comparison as the basis of therapeutic investigation, by observing the course, duration and outcome of disease, with and without specific treatment:
 - (a) definition of a control group without specific treatment; or
 - (b) design of an n-of-1 study by observing a single patient during a longer time with defined periods (pre-treatment, during treatment, post-treatment).
- (2) Securing as much homogeneity as possible of the patients observed:
 - (a) comparability of the patients, not just in terms of diagnosis;
 - (b) comparability of other characteristics, such as age, sex and physical condition.
- (3) Treating alternate patients with or without specific treatments.

'Such problems resulting from epidemiological or other fluctuations are prevented by the so-called "simultaneous method" of Wagner-Jauregg. Patients suffering from the same disease under otherwise equal conditions will be alternately treated, one without any specific medication or at most with remedies whose effects are sufficiently known, the next with the medication to be tested; indispensable symptomatic remedies (e.g. analeptics) have to be given to both in the same way and amount.'
- (4) Securing quality in the observational criteria (reliability, validity):
 - (a) use of criteria as objective and exact (quantifiable) as possible;
 - (b) introduction of numerical rating scales where subjective criteria cannot be avoided.

'The number of cases, and even more so the duration of the observation, rise and fall with the quality of the observational criteria.

It is obvious that the more objective these criteria are the higher [the quality of the observation] will be; we might add: the clearer and the more important they are, the more quantifiable they will be and the lower their range of error.'
- (5) Blinding as a component of the experimental design:
 - (a) making different remedies (or placebos) similar in shape, colour and taste to conceal their special character or purpose;
 - (b) using placebos during pre-treatment periods in n-of-1 studies;
 - (c) concealing the start of treatment.

'The best way to avoid suggestive or other subjective factors is the unknown experimental design. In respect of our main therapeutic possibilities this means: the drugs must be given to the patient in such a shape or wrapping that their special character or purpose cannot be detected, it has to be disguised. This is especially important if the effect of different remedies is to be compared; even if only a single drug is to be tested after a

period of pre-observation, it is often useful to simulate a treatment with ineffective agents during the pre-observation period. In both cases, the aim of disguising treatments is so that the patient remains ignorant of the timing of administration of the remedy to be tested, possibly even that it has actually been administered. This aim can only be achieved if the different remedies to be compared cannot be distinguished by the patient (independently of the fact of whether one is a sham or not). To achieve this, the shape, colour and taste have to be as similar as possible; solutions have to be compared with solutions, tablets with tablets, suppositories with suppositories, injections with injections.'

- (6) Minimizing artefacts (for example, physical and psychological factors, other remedies given at the same time, changes in nursing care).
- (7) Using statistical methods to describe the outcomes; if necessary dividing the sample into subgroups.
- (8) Analysing outcomes by referring to probability theory.

Martini's ideas and his book did not have much impact on clinical practice and research. Judging from reviews of the book in German general medical journals, the first edition seemed to have been

quite well received, but it did not apparently lead to new methodological debates. Indeed, Martini's work was not even regarded as 'science' by some of his colleagues. There are no obvious reactions outside Germany, even in German speaking neighbouring countries (except for one review in the *Wiener Klinische Wochenschrift* in 1933), and there were no translations.

Shelley and Baur asked in their 1999 article in *The Lancet* whether Martini deserves to be regarded as the first clinical pharmacologist.³ As far as Germany is concerned, '*Methodenlehre der therapeutischen Untersuchung*' was the first and for a long time the only textbook of what we call 'clinical epidemiology' today.⁴ Whether we regard Martini as the father of clinical pharmacology or the father of clinical epidemiology in Germany, his book certainly merits much wider recognition as a pioneering work in the history of ideas about the fair assessment of therapeutic interventions.

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