

▶ PAUL MARTINI: THE FIRST
CLINICAL PHARMACOLOGIST?

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THE MAN

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In 1932, Paul Martini (figure 1), professor of medicine at the University of Bonn, published a monograph entitled *Methodology of Therapeutic Investigation*.¹ In this slim volume of 69 pages Martini summarised his 3 years as professor of medicine in Berlin, and his experience of the scientific investigation of drug action.

▶ FIGURE 1:
PAUL MARTINI (1889-1964)

He not only coined the phrase „clinical pharmacology“ but also described procedures for „n of 1“ trials, use of matching placebos, establishment of baseline conditions before the institution of treatment under study, consideration of sample size in treatment and control groups, stratification, the use of rating scales, dose-response associations, and a mathematical approach to calculating probability of efficacy with respect to the endpoints used.

The monograph was reviewed in the German medical press² but not in *The Lancet*, the Bri-

tish Medical Journal, or the *New England Journal of Medicine*; thus his contribution escaped the attention of the English-speaking world. Neither Doll³ nor Armitage⁴ referred to Martini's contribution in their historical surveys. Although Martini's work on the scientific evaluation of drug treatment was overlooked, his *Principles and Practice of Physical Diagnosis* (*Die unmittelbare Krankenuntersuchung*) had been painstakingly translated and appeared in English in 1935.⁵

Our aim here is to draw attention to the principles of evaluation of drug efficacy laid down by Martini and to put his work into the context of the practice of therapeutics at the time of publication of his monograph.

▶ THE MAN

Paul Martini was born in Frankenthal in the Rhine-Palatinate in 1889. His doctoral thesis (1917) in cardiac physiology was supervised by Otto Frank, and he graduated in medicine in Munich in 1922, where he worked with Friedrich von Müller until 1927. Martini moved to Berlin and in 1932 became professor of medicine at the University of Bonn, where he remained (despite pleas for him to return to Munich) until he retired in 1959.

From 1933 onwards Martini was in trouble with the new regime for supporting his Jewish colleagues (such as Leopold Lichtwitz) and for his independent views, which were underpinned by his devout Catholicism. By 1936 the local party hierarchy could no longer tolerate him and tried to dismiss him from his professorial position and exile him to Erlangen, but they failed. In 1939 Martini worked briefly in a supervisory capacity in the army medical service in Poland and France, but with the onset of progressive and crippling arthritis he was discharged and returned to Bonn. His courage in continuing a full clinical programme while in great distress was widely admired. After the

war he supervised the rebuilding of the medical school and was also personal physician to Konrad Adenauer and Theodor Heuss.

On his death in 1964 Martini was described as „the conscience of German medicine“,⁶ not only for his contribution in the fields of cardiology, infectious disease, diabetes, heavy metal poisoning, neurology, and chest disease, but also for his 1948 address to the German Society of Internal Medicine on the question of German guilt and the Nuremberg trials.

His presidential address began: „Dark memories, heart-felt concerns, much anguish and few hopes, beset our hearts today. A whole philosophy of life has been shattered. The unconditional belief in progress has shown some value in material things, spiritually however it has led to a state of breakdown ...“

He went on to describe how the craving for progress in medicine had become detached from ethical considerations and rode roughshod over the laws relating to its particular concern, man: „The doctors who sat at Nuremberg were in part criminals and we wish to have nothing to do with their deeds. But they were also in part the product, the flesh and spirit of the medicine of their time, the medicine of the late nineteenth and twentieth centuries, and not just German medicine. Any of us who tries to dissociate himself from the wrong direction of that discipline can only be compared with the whited sepulchres (the Pharisees) of the Gospels“.

► HIS WORK

Martini's monograph is bursting with ideas, all of which are relevant to the practice of drug evaluation today. The principle aim of the monograph was the promotion of the scientific method, to replace collections of clinical impressions with scientific investigation. Although recognising that the inductive method can only be realised in a pure science like physics, Martini believed that by control of extraneous variables and standardisation procedures, valid comparisons (of a new drug with placebo or standard) could be achieved.

Martini was also a pragmatist who felt that therapeutic research and the practising physician could not wait until all physiological and pathophysiological knowledge was complete, so that therapeutic understanding fell like ripe fruit into one's lap. Careful experimentation, with reliable endpoints, would pave the way to reliable conclusions. He was very critical of generalised statements such as „Every organ maintains its own form and function through the hormones that it produces“⁷ – which he thought was not only unhelpful but also dangerous.

At the time that his monograph was published, English academics were arguing over whether therapeutics „was drowning in its own excreta“;⁸ had Martini met these protagonists they would have certainly agreed on the plethora of useless if not dangerous medicines available, but there is no other contemporary evidence of the approach espoused by Martini during 1931-1933.

Martini believed that in any comparative study the pre-treatment observation period should determine the degree of variability, which will in turn dictate the duration of observation and the size of the sample. The duration must also relate to the intended treatment period. During this control period, treatment should be stable if an essential drug is indicated (he lamented

how few drugs fell into this category) or symptomatic treatment exhibited. Most studies examined the course of a disease, not the outcome. The quality of the data obtained at this time (and subsequently) depended on the rigour of the methodology of measurement and the frequency of measurement. Once stable baseline conditions were achieved (or degree of variability known) comparative studies could begin. Martini believed that the information obtained in this way was infinitely more valuable than historical data.

He also thought that the switch to the investigative drug or placebo should be made without the patient's knowledge with a drug identical in form matched for its physical characteristics (and with a comparable mode of action). Alternation (not random assignment) of treatments was made more than once and the case strengthened by the use of a post-treatment control period. The selection of the investigative drug depended on: homogeneity of effect, knowledge of the minimal effective dose, and the dose-response relation.

In an interesting example, Martini showed how the minimal effective dose of a cardiac glycoside was determined using pulse rate, urinary output, fluid balance, and body weight as criteria (using strophanthin as standard). If the minimal effective dose of the drug was not known and the drug effect ill defined, many months would be wasted in illusory studies despite every effort to achieve baseline conditions. Martini contrasted the futile studies of tuberculin in tuberculosis with those of insulin in diabetes.

Although Martini discussed the determination of sample size for group comparisons, the examples given in the monograph related mainly to studies in individuals. Recognising that patients react both to disease and to treatment in an individual manner, he devised protocols for „n of 1“ studies. Single patients follo-

wed the same sequence described above. After steady-state conditions were achieved, identical placebo, standard, or investigative drugs were given, again by alternation. His reasons supporting this concept were echoed in the much cited paper published 54 years later by Guyatt and colleagues,⁹ although these authors used random allocation of treatment.

Figure 2 illustrates such a case. Note the use of a five-point rating scale for anginal pain, and the use of trinitrin as an indirect measurement of efficacy of the investigative drug (which Martini inferred was inactive). Martini did not use standardised exercise to induce angina and this method was published in the following year.¹⁰ In situations where the time course of the disease was short, patients could be matched by severity to produce what was, in effect, a series of paired comparisons. Here equipotent doses of standard and investigative drug were used.

► FIGURE 2:
60-DAY STUDY WITH FOUR TREATMENT PERIODS IN A PATIENT WITH ANGINA

L is a so-called cardiac hormone. Distilled water was coloured and flavoured so that the two treatments were indistinguishable. Treatment periods began from day 12 after admission when the patient had been stabilised.

There was no suggestion in the monograph that the proposed programme of experimentation would be universally applicable; neurological diseases and cases where there was a marked psychosomatic element were not suitable. Martini thought it was unscientific to break down admittedly ill-defined disorders into constituent symptoms and plot the course of each (during pretreatment and treatment periods). Although he used rating scales for pain severity (as in angina) and other scoring systems, he always emphasised physical or laboratory measurement.

Martini used mathematical models to calculate probability of the drug effect relative to the probability of spontaneous improvement, and this was expressed as an absolute or relative ratio. Since any control group is never completely homogeneous, the size of the group depended on random variability and the order of magnitude of the drug effect. Martini plotted the course of averaged values of selected endpoints of the disease under study (such as basal metabolic rate in thyrotoxicosis, pulse rate and fluid balance in congestive heart failure, blood pressure in hypertension) during the pretreatment control periods and during subsequent stages. By comparing the gradients, he measured the incremental angle of change during treatment and attempted to validate the degree of change by probability estimates. Again, the rigour of the methods and the need for adequate periods of study were emphasised.

In a review of all (German) published studies in angina in the preceding 11 years, Martini outlined their deficiencies using his probability calculations and other criteria. All of the 27 studies cited were defective in some way or another. The sample was too small, the pretreatment observation inadequate, the methodology poorly described, or there were no controls, so that no valid conclusion could be reached. He concluded: „The difficulties are innumerable and without doubt the large proportion of published therapeutic studies would never have seen the light of day if their authors had observed and followed the laws of methodological investigation“. This need for some knowledge, however imperfect, falsified the situation and brought further confusion. Martini was very cautious with respect to the application of findings in individual patients to large populations. He did not use randomisation; his method of alternation would be later described as: „A fascinating forerunner of randomisation, in which investigators have sought to impose a

deliberate, rather than a haphazard, system of treatment allocation.“⁴

Alternation in allocation of treatment has had an honourable history. It was used by Fibiger¹¹ to evaluate the efficacy of diphtheria serum, by Park and colleagues¹² in the serum treatment of lobar pneumonia (and later by Evans and Gaisford¹³ using sulphapyridine in the same condition), and in Wagle and colleagues' comparison of sulphonamide with iodine in a plague epidemic in Bihar.¹⁴ Martini's achievements were considerable, all the more so in view of the limited range of drugs available at the time.

► THE HISTORICAL CONTEXT

What was the state of the therapeutic research in the UK when Martini's monograph was published? In his address to the British Medical Association in 1932, Gunn¹⁵ unconsciously echoed many of Martini's complaints.¹⁶ Medicine was faced by an accumulation of useless and inactive drugs. „The question we have to ask ourselves is whether this process of elimination of useless drugs has proceeded with reasonable speed; whether, if only from the point of view of economy, there has ever been a deliberate and concerted plan to rid medicine of the incubus of spurious remedies. The answer to this question is No“. But Gunn had other beliefs: „At no period has treatment by means of drugs been on so sure a foundation or so amply justified“. He proposed that pharmacology should be brought to the bedside, and that teaching facilities should be increased (Edinburgh was the only medical school with a chair in therapeutics). He also drew the attention of the meeting to the establishment of the Therapeutics Trials Committee by the Medical Research Council in the previous year.

It is worth examining the background to the formation of this elite committee, the task of which was: „To secure trustworthy clinical trials of products produced by manufacturing

firms.¹⁷ The Medical Research Council noted: „Conspicuously in Germany, physicians of good reputation are ready to publish the results of new and patented substances over their own names.“ One result was that drugs produced in the UK came into general use on the basis of reports of studies conducted in Germany. Leading British physicians were reluctant to associate themselves with the pharmaceutical industry, so the committee was instituted with a „formidable representation of clinical, pharmacological and statistical expertise“.¹⁸ From 1933 to 1939 the Therapeutic Trials Committee published the results of studies on calceferol for rickets, digoxin for atrial fibrillation, and sulphanilamide for septicaemia, and it was the forerunner of the specialist groups set up to study penicillin and to conduct randomised trials with pertussis vaccine and streptomycin. Thus, it is tempting to suggest that the rigour of the experimental method that Martini advocated found its expression in the establishment of the Therapeutic Trials Committee in the UK.

► THE PAUL MARTINI FOUNDATION

In its entirety, Martini's monograph is greater than the sum of its parts. Ethical issues of drug investigation were also addressed, and the work is much more than a historical curiosity. At the time, Martini did not receive the international recognition he deserved (although he was made an honorary member of the Rudolph Virchow Society in New York in 1959). His name, however, is commemorated through the foundation that bears his name. The Paul Martini Foundation was established in 1966 to promote clinical pharmacology in Germany through stipends and investigational grants. The foundation also awards prizes, nominates invited speakers, and publishes reports of proceedings. Prize winners and speakers have been drawn not only from Germany, but also from the UK, Sweden, Switzerland, USA, Canada, and Denmark.

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► CONCLUSION

In his address, „The practice of experimental medicine“, McCance observed: „The medical profession has a responsibility not only for the cure of the sick and the prevention of disease but for the advancement of knowledge upon which they both depend. This third responsibility can only be met by investigation and experiment...“.¹⁹ Martini's career upheld these responsibilities, and his contribution should be a lesson to all those involved in drug development. He was truly the father of clinical pharmacology.

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