

The (Harry) Gold standard: angina, suggestion and the path to the ‘double-blind’ test and clinical pharmacology. Part 3: the double blind and the rise of ‘clinical pharmacology’

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As described in Parts 1 and 2, Harry Gold and his colleagues at Cornell, concerned with the suggestibility of patients and the ‘subconscious’ or ‘unconscious’ bias of researchers, developed and deployed the double-blind method in their studies of anti-anginals in the 1930s–1950s as an attempt to ensure unbiased results. As Part 3 relates, amid the seeming enshrinement of the double-blind method, Gold saw the double blind as one key component (albeit a crucial one) in the larger task of elevating therapeutic evaluation to ‘clinical pharmacology’, approximating the rigour of the laboratory experiment. Yet, as Part 3 concludes, Gold was not without his own blind spots concerning the larger therapeutic ecosystem (influenced by commercial priorities) in which drugs were introduced and evaluated.

The dissemination of the double blind

Much as Gold the cardiologist used the double blind to examine the treatment of angina, Gold the ‘clinical pharmacologist’ used such angina studies to transform clinical evaluation more generally, especially around double-blinding. Not everyone was convinced of the necessity or even legitimacy of double-blinding. As Gold would lament by the late 1950s, ‘doctors seem to have little difficulty accepting the power of suggestion as applied to the patient’. However, ‘the notion that the same applies to the doctor has not had an equally cordial reception’. As Gold expanded:

Among the many reasons is the feeling that this requirement impugns their personal integrity, that it is an accusation rather than a point of fact that bias is a normal function of the mind, which may be mostly unconscious, and beyond the investigator’s control. (Gold,¹ p. 41)

Similarly, in the notes for a talk on ‘Planning Clinical Trials’ for the 1959–1960 meeting of the American Statistical Association and Biometric Society, Gold wrote:

I have known doctors who have taken offense at the notion [of their own bias]. They regard it as an attack on their character; charged with dishonesty. . . . What they fail to appreciate is that bias is a normal state of the mind, and what is more, most of it is unconscious. ‘I try to be unbiased’[.] The trouble is you cant [sic] try because you don’t realize you are biased. It is unconscious [underlining in the original].²

Other would-be investigators simply could not believe the null results they obtained through the implementation of the double-blind method. One New York clinician-researcher, writing in *JAMA* in 1955 and refusing to accept the null answer he received through a double-blinded study, defaulted to the notion that ‘the future of a drug depends on what it can do in the hands of the general practitioner and not what it should do on the basis of experiments’.³ Gold was not the only one to scoff at such a seeming reversion to the play of biased impressions (Gold,¹ p. 42). As a University of Miami clinician-researcher replied in *JAMA*, the very ‘validity of the scientific method as applied to medicine’ was at stake in such deliberations.⁴

Despite such resistance, Gold was remarkably successful with respect to increasing attention to and usage of the double blind. As Shapiro and Shapiro have somewhat impressionistically written, ‘interest in the placebo effect and the double-blind procedure increased in the late 1950s, resulting in an avalanche of meetings, symposia, papers, and

books' (Shapiro and Shapiro,⁵ p. 154). A PubMed search (accessed on 27 July 2022) reveals 78 English-language articles with 'double blind' in the title by 1960. The *New England Journal of Medicine* would publish 36 uses of the term by that time, with its first two in quotes, and two in titles, including regarding its usage in Leonard Cobb and colleagues' sham-controlled internal mammary artery surgical ligation study of the treatment of angina⁶; by 27 July 2022, when this search was conducted, there had been 3643 uses of the term in the journal, including within 73 titles between 1957 and 2012. Double-blinding would indeed be discussed in the 'avalanche' of American and British books and symposia devoted to clinical trials by the 1950s and early 1960s.⁷⁻¹² By 1959, it had become the subject of a medical cartoon (see Figure 1).¹³ By 1960, it had become the title – and the central theme and ethical dilemma – of a popular British novel, in which (in some ways hearkening back to *Arrowsmith*) a clinician scientist applies the double-blind method (so as 'to eliminate unconscious bias when testing out a drug') to the evaluation of an active vaccine treatment for encephalitis in a British island colony (Shapiro and Shapiro,⁵ p. 155; Wilson,¹⁴ p. 12). Perhaps indicative of the seeming obviousness and ubiquity of both the term and methodology by 1960 – and of the capacity for historical foreshortening amid such ubiquity – the novel and clinical trial itself takes place in 1950, by which time, the author mistakenly writes of

double-blinded trials: 'It was a standard experimental method, and there were no doubt hundreds of trials going on throughout the world on the same basis. There was no need to make a drama out of it' (Wilson,¹⁴ p. 113).

Yet, this ascension came with limits and caveats. Donald Mainland would note that at an international seminar on medical records and statistics in 1961,

American and British speakers emphasized the importance of double-blind trials wherever possible, whereas the general European speakers thought that it was sufficient if the patient was kept in the dark regarding therapy... - an attitude which many of us 'converts' [in the United States and Great Britain] possessed not very long ago. (Mainland,¹¹ p. 28)

And Gold and his colleagues were moved to point out that the double blind technique was not 'magic', and could not otherwise 'convert a poor experiment into a good one' (Gold,¹ pp. 42-43; Modell and Houde,¹⁵ p. 2191). Janet Travell intended, in late 1959, to write an article entitled the 'Use and Abuse of the Double-blind Method' (it does not appear that she wrote the article),¹⁶ while Walter Modell and Raymond Houde, in their AMA Council on Drugs-authorized 1958 report in *JAMA*, would caution:

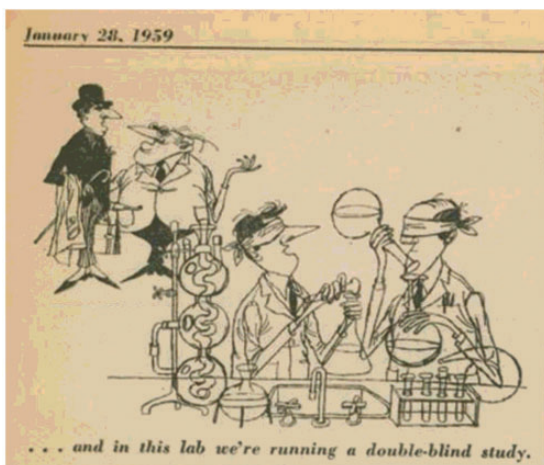
A large number of papers emphasize in the very title that this type of control [the double blind] was used, not only as if the use of a control in a clinical experiment were worthy of special mention, but also as if to warn the reader in advance that a special type of insurance had been taken out to guarantee that the results about to be recounted were beyond reproach. (Modell and Houde,¹⁵ p. 2191)

Instead, pointing to the discrepant results that could still be derived depending on the variable quality of the rest of the research methodology employed, they warned: 'No simple device such as the double-blind technique will correct astigmatism or myopia in the examination of drugs. The blind will not lead the blind to a valid conclusion unless the method somehow also provides vision' (Modell and Houde,¹⁵ p. 2191).

The rise of 'clinical pharmacology'

Rather, the double blind was to be one component – albeit a central one – of 'clinical pharmacology'. As early as in 1945, while ostensibly speaking on 'the pharmacologic basis of cardiac therapy', Gold had his sights set on broader evaluation and on elevating the status of

Figure 1. "And in this lab we're running a double-blind study."
Source: *Medical News: A Newspaper for Physicians*, 28 January 1959; as also found in Box 17, ff 42, Harry Gold Papers, Medical Center Archives of New York-Presbyterian/Weill Cornell.



the evaluation of remedies in people vis a vis seemingly more fundamental science. As he offered:

The term ‘clinical study’ doesn’t rate very high in scientific circles... but there is a vast area of pharmacologic investigation which may be developed with the human subject and which, if the experiments are suitably designed, may be counted on to yield important facts in a manner which complies with the strictest demands of scientific evidence. (Gold,¹⁷ p. 547)

Within two years, Gold would be named Professor of Clinical Pharmacology at Cornell, with clinical pharmacology expected to approach the rigour of laboratory and animal investigation, and to be juxtaposed to ‘therapeutics’, which represented more art than science (Gold,¹ p. 47; Gold¹⁸). As Gold reported to the New York Academy of Medicine in 1949:

I am inclined to believe that something more than nomenclature is involved. In the pharmacology laboratory, methods for planning and executing investigations on drugs have made great advances, and these are notable by their absence in most clinical studies on drugs.¹⁹

As he continued:

I recall a striking illustration in a recent series of papers. There was the most marked contrast in the criteria for scientific evidence made by one and the same investigator, a distinguished pharmacologist, working with one and the same drug, at one time in animal pharmacology, and at another time working on the same problem in humans in collaboration with a clinician. In the case of the human subjects, the laws of scientific evidence seemed to have been completely suspended.

As such, there was a pragmatic rationale to ‘cultivating the term, clinical pharmacology... as assurance, however feeble it may be, that the investigations may be bound by methods and laws which apply in pharmacology’.

By 1954, the nation’s first Division of Clinical Pharmacology would be launched, at Johns Hopkins and led by Louis Lasagna.²⁰ And by 1957, Gold (who by this time was beginning to use ‘human pharmacology’ interchangeably with ‘clinical pharmacology’, though it would be ‘clinical pharmacology’ that would stick) felt the time had come for a journal devoted to clinical pharmacology, as he wrote to Walter Modell (Gold,¹ p. 47; Gold,²¹

Greiner et al.²²). Yet, Modell’s journal, begun in 1960, would be entitled *Clinical Pharmacology and Therapeutics*, and such tensions concerning the relative roles of pharmacology, empirical studies of therapeutic outcomes and the application of such findings in the clinic would apparently continue to play out through the formation of the American College of Clinical Pharmacology and Chemotherapy in 1963, its amalgamation with the American Therapeutics Society to become the American Society for Clinical Pharmacology and Therapeutics in 1969, and the consequent splinter formation of the American College of Clinical Pharmacology that same year.^{23–27} Nevertheless, despite such internal tensions, by that very year, as the FDA attempted in 1969 to formalise the notion of the well-controlled clinical trial, the double-blinded, placebo-controlled method would be encoded as part of the ideal clinical study, unless there were clear reasons not to include it.²⁸ By the time Harry Gold died in 1972, no fewer than 144 papers would be published in English that year with ‘double blind’ in their title (as accessed on PubMed on 27 July 2022). It had indeed become ‘a standard experimental method’.

Enduring blind spots

Gold was well attuned to threats to the internal validity of controlled clinical trials, as evidenced, e.g., by his expenditure of effort regarding the proper appearance and taste of active and placebo tablets so as to ensure adequate patient blinding.^{29–32} Yet, he appears to have been less reflective concerning the academic–industrial relationships through which such studies and their results were funded, conducted and disseminated. Dominique Tobbell has examined the manner by which the emerging discipline of clinical pharmacology – dramatically underfunded and undermanned in relation to the number of drugs emanating from the post-World War II pharmaceutical industry – accommodated itself from the mid-1950s onward to the pharmaceutical industry.³³ This not only entailed seeking funds for its programmes, but manifested in joint efforts with respect to both pushing back against potential threats (as with enforced informed consent) to the research enterprise and concerning the seeming ‘education’ of physicians regarding pharmaceuticals. Gold’s relationship to the pharmaceutical industry in these respects prefigured or paralleled many of these accommodations. For instance, Gold’s opposition to informed consent in the early 1960s was both personal (and perhaps related to his comfort with paternalistically keeping patients ‘in the dark’ [‘I never did seek consent in

the 40 years I have been working in human pharmacology'] and publicly deployed by him (with some prodding from colleagues in industry) in the early 1960s, especially in relation to the proposed introduction of informed consent (a 'snare and delusion', in Gold's terms) into what would become the Kefauver-Harris Amendments, with such requirements perhaps watered down in response to his opposition.^{28,34–38} I will focus here, however, on the informational ecosystem emerging from double-blinded trials and clinical pharmacology.

This is not to paint a picture of uniform industry resistance to attempts to tame the marketplace, let alone of a uniform attempt to undermine the results of negative blinded trials. Joseph Gabriel has demonstrated Parke-Davis's support of the iconic blinded (and negative) trial of sanocrysin starting in 1926³⁹; and one of the most impassioned pleas in the medical literature in the 1950s for the uptake of the double blind came from the Department of Clinical Investigation at Upjohn, appearing in *JAMA* the same month that the negative double-blinded study of Upjohn's heparin for angina was being reported in the *American Journal of Medicine*.^{40,41} Similarly, as a member of Searle's Division of Clinical Research wrote in 1954 to Gold upon hearing of the latter's negative study of their potential diuretic: 'I must say that I was disappointed with the results but nevertheless one has to accept these trials'.⁴²

And yet, Gold himself was well aware of the role of industry in promoting the 'survival qualities' of seemingly ineffective drugs. This was especially evident in relation to khellin – the subject of his own first truly 'clinical pharmacological' study – in which certain industry staffers tried to either discredit or reinterpret the results, while one company seemed to entirely ignore Gold's team's study in its promotional literature concerning its commercial khellin product.^{43–46} On the opening page of this promotional brochure, Gold handwrote: 'No mention of our paper only positive papers'.⁴⁶

Despite such experience, Gold saw a central role for the pharmaceutical industry in the postgraduate education of physicians. Amid Estes Kefauver's hearings into the pharmaceutical industry, and at the same time that Charles May was decrying the blurred lines between pharmaceutical promotion and physician education,⁴⁷ Gold nonetheless proposed in 1961: 'The pharmaceutical group must add to their program what I believe is inevitable, Post-Graduate Education. ... [Industry] has things to teach and a method of communication with the practicing doctor which is unique and vital for good medical practice'.⁴⁸ This could especially entail, in anticipation of the expansion of reliance on 'key opinion

leaders' to come,⁴⁹ the funding of seemingly neutral 'qualified investigators or teachers to meet with practicing physicians at a more local level than is ordinarily accomplished by the big national (or even regional) investigative or clinical meetings'.^{50,51} Such tensions between pharmaceutical promotion and physician education – and especially concerning the role of industry in 'educating' physicians – would persist for decades to come.⁵²

Still more fundamentally, Gold appears to have had certain blind spots concerning the political economy of knowledge production by the emerging discipline of clinical pharmacology. In 1957, he and his colleagues reported on their double-blinded study of laxatives for constipation. Invoking the image of the epistemically and morally dubious 'testimonial', they noted that such humble preparations were chosen for study not for their representing the apogee of clinical or industrial pharmacology, but for being 'supported by the weakest series of studies' while representing the largest sales volume of any class of drugs (Greiner et al.,⁵³ p. 244). Finding some laxatives better than placebo, and others not, Gold and colleagues were admittedly less concerned with the consistency of stool than with ensuring the consistency of clinical investigative methodology. As they stated:

This presentation neither defends nor deplores the widespread use of laxatives by the public. Its concern is with methods for measuring the action of drugs in human patients. Laxatives are relevant only as a class of drugs sorely in need of the application of pharmacologic principles in their clinical trials. (Greiner et al.,⁵³ p. 252)

Pointing explicitly to the 'placebo effect, a shorthand way of saying that the patient's psyche induces responses to the doctor's interest and prescriptions', Gold and his colleagues again emphasised that 'the physician's psyche, too, may alter drug response by the unconscious attitudes imparted to the patient before the drug is taken and when the drug effects are being assessed' (Greiner et al.,⁵³ pp. 252–253). This all warranted a double-blind study conducted by a 'team' of physicians (Greiner et al.,⁵³ p. 253).

As it would turn out, Gold was not the only clinical pharmacologist invoking the spectre of the 'testimonial' that year. Harvard infectious disease specialist Maxwell Finland was similarly invoking the 'testimonial' as pertaining to the dubious testing and marketing of certain emerging antibiotics, arguing for the need for 'controlled clinical studies' to tame the therapeutic marketplace and helping set in motion a path that would lead to the passage of the Kefauver-Harris Amendments in 1962 (mandating

proof of drug efficacy by ‘well-controlled studies’), and the regulatory defining of the ‘well-controlled’ study in terms of the randomised, double-blinded, placebo-controlled study by 1969.²⁸

There are certain historical ironies to such outcomes. Gold and his colleagues, in their laxative paper, pointed to the economic waste of inefficacious remedies making it to the marketplace, and the potential capacity for

physicians with a mild inclination toward research [to] apply such [clinical pharmacological] methods within the structure of their own practice, break the ‘bottle jam’ on the pharmaceutical shelves, return most of these unknown compounds firmly and securely to laboratory limbo, and retain the few that offer particular promise. (Greiner et al.,⁵³ p. 254)

Perhaps Gold, who had long emphasised the complex, team-based notion of rigorous clinical research, should have known better. This rigorous approach, soon inscribed into the Kefauver-Harris Amendments and their aftermath, would create economic barriers to the conduct of such broadly disseminated research.⁵⁴ Instead, the chief source of funding for such team-based studies would eventually be the pharmaceutical industry itself.⁵⁵ While the shape of individual studies could conform to such rigorous methodological prescriptions, the shape of the overall marketplace would increasingly bear the impress of commercial industry needs and choices regarding which agents to study. Blinding at the level of the patient and investigator could only accomplish so much.

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