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The (Harry) Gold standard: angina, suggestion and the path to the 'double-blind' test and clinical pharmacology. Part 1: angina relief and suggestion

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> It is idle to attribute the relief of pain to a substance given in a series of injections when the ritual of the treatment itself, as well as numerous other factors that have not been excluded, could have been responsible for the change. (Gold,[1] p. 6)

In his seminal history of blind assessment, Ted Kaptchuk traces the history of 'intentional ignorance' in medical research from the 18th-century sceptical evaluation of mesmerism, through the attachment of double-blinding to the mid-20th century randomised controlled trial as the embodiment of the hard science of clinical medicine.[2] Having focused attention on the late 19th-century and early 20th-century European concern with 'suggestion' (and its likely impact on such early 20th-century German researchers as Adolf Bingel and Paul Martini), Kaptchuk nevertheless suggests that such concerns regarding suggestion were slow to cross the Atlantic. He thus grounds the Anglo-American interwar incorporation of blind assessment into clinical research not in terms of 'continental concern with suggestion', but rather as 'technical organizational problems (Kaptchuk,[2] p. 422)'.

And yet, Anglo-American studies of the treatment of angina pectoris – the debilitating chest pain considered by then to accompany coronary artery disease – would not only play the key role between the 1930s and 1950s in the formal advent of the 'double-blind'[a] study within American clinical pharmacology, but would be grounded from the 1930s onward in concerns over 'suggestion' and the impacts of anxiety, context and the apparently alleviating effect of the act of providing medication itself on the course of the experience and evaluation of anginal pain.

No one would be more central to the ascendance of the 'double blind' as a key component of angina evaluation, and of rigorous clinical trial methodology more generally, than Cornell clinician and pharmacologist Harry Gold (1899–1972). And Gold saw the double blind as only one methodological component – albeit a crucial one – that helped to elevate therapeutic evaluation beyond mere 'clinical trials' to what he termed 'clinical pharmacology' (or 'human pharmacology'), approximating the rigour of the laboratory and capable of separating pharmaceutical wheat from chaff. Yet, Gold, focused on the internal validity of the experiment, was not without his own blind spots concerning the larger therapeutic ecosystem in which such drugs were introduced and evaluated.

This series of three articles, with angina and Gold as its focus, situates the advent of the double blind amid such clinical, academic and industrial concerns during a crucial period in the history of the controlled clinical trial. This first article introduces studies of anti-anginal remedies and presumed patient suggestibility as a key stimulus to patient blinding in Anglo-American clinical trials. The second article will focus on the advent, especially through the work of Gold and his colleagues (themselves concerned with the 'unconscious bias' of researchers), of researcher blinding and the double-blind method as a second measure for ensuring unbiased outcomes. The third article examines the incorporation of double-blinding within the broader domain of 'clinical pharmacology', while drawing attention to the remaining 'blind spots' inherent in such efforts.

Angina and suggestion

From the 1920s through the 1940s, the scattered Anglo-American application of patient and/or researcher blinding extended to therapeutic domains as diverse as the common cold, psychiatric disease and tuberculosis.[2–6] Yet, by mid-century, the most sustained flow of such interventions related to

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angina pectoris. Angina, by this time, was largely considered to stem from coronary artery disease. Still, hearkening back to earlier notions, anginal pain continued to be considered by many as modified by the nervous system and other 'constitutional' aspects of the patient.[7] As New York clinician Harlow Brooks stated in 1935 at a New York Academy of Medicine symposium: 'Physical factors are often much subordinated to emotional ones in this complex and the social obligations and psychic reactions of the individual sufferer are usually of equal if not greater import than anatomical ones' (Brooks,[8] p. 442). In turn, those evaluating the efficacy of treatments of anginal pain, even if those interventions were geared towards the coronary anatomy, would have to grapple with the overlay of such 'psychic reactions'.

This would play out initially with respect to the apparently vasodilating xanthine drugs, though would extend to other pharmaceutical interventions as well. As far back as 1896, in Königsberg, Askanazy had alternated patients – in what would today be considered a 'crossover' design – to periods of treatment and no treatment, concluding that 'with the certainty of an experiment the attacks disappeared at once [Mit der Sicherheit eines Experimentes verschwanden die Aufälle sofort oder sehr bald nach der Aufnahme der Diuretinbehandlung, und traten ebenso prompt wieder auf, sobald das Mittel ausgesetzt wurde]' (Askanazy,[9] p. 224, Freedberg et al.,[10] p. 495). By 1929, researchers at St. Luke's Hospital in Chicago and Northwestern University Medical School administered xanthine preparations to 86 patients, with no comparison periods or patients, finding relief in 72 of them while acknowledging the difficulty of evaluating 'a symptom complex so readily influenced by nervous factors' (Gilbert and Kerr,[11] p. 203). A year later, the American Medical Association's Council on Pharmacy and Chemistry favourably reviewed the 'therapeutic claims' for such agents, based on in vitro evidence of coronary artery vasodilation, animal studies of increased coronary blood flow and such clinical data.[12]

Three years later, however, William Evans and Clifford Hoyle, at the London Hospital, noted with respect to anti-anginal drugs that 'there has scarcely been a methodical attempt to compare the relative values of the many drugs that have been recommended, and uncontrolled and isolated observations have too often guided opinion' (Evans and Hoyle,[13] p. 311). It is unclear exactly what motivated their study. Such origins do not appear in Evans' own autobiography or in later biographical accounts,[14,15] while John Gaddum, in his Walter Ernest Dixon Memorial Lecture delivered in 1954, expressed that 'this important paper probably owed something to Dixon's influence, since one of the authors was a close colleague of his' (Gaddum,[16] p. 197). At the time, Evans and Hoyle stated concerns with both 'natural variations' in the course of the disease, and with the likelihood that 'mental suggestion' could add 'bias' in favour of a positive response to a medication (Evans and Hoyle,[13] pp. 313, 315, 334, 335). As such, and admittedly focusing more on the former concern while setting the precedent for decades of studies to follow, they employed in their study of multiple purported anti-anginal drugs a crossover design in which patients were exposed for periods of time to the active drug or to placebo (one of several mixtures of sodium bicarbonate, gentian +/− liquor carmine) (Evans and Hoyle,[13] p. 313). They found that with one exception, 'a measure of improvement appear[ed] to result from every remedy tried, and at least as great an improvement during treatment with placebo', with placebos yielding a 37.5% overall chance of improvement (Evans and Hoyle,[13] pp. 336, 317).

Harlow Brooks likely spoke for those who were uninspired by such studies. Not only did he (perhaps surprisingly) consider that 'suggestion and autosuggestion' were irrelevant to 'true angina pectoris', but swiping at the very aspiration to controlled studies of angina, Brooks observed that the 'syndrome does not permit of a standardized scientifically based treatment, for the individual patient is not standardized but is a very pleomorphic biological and emotional integer' (Brooks,[8] pp. 447, 443). Yet, others, appreciative of the subjectivity of the experience and reporting of anginal symptoms, were more impressed.[17] At Mount Sinai Hospital in New York, Arthur Master could already report by 1935 that he and his team at their 'special anginal syndrome clinic' had 'fully corroborated' Evans and Hoyle's findings (Master,[18] p. 880). However, while Evans and Hoyle focused a good deal on natural variation as a confounding issue, Masters and his team focused far more on suggestion. Continuing their study, and finding their own placebo, milk sugar, useful to some degree 52% of the time, they concluded in 1939:

> It was not a particular drug, but merely the factor of receiving a medication, that gave relief. . . . Obviously one cannot ascribe a specific effect to a drug when its action is no better than that of an inert substance. The improvement noted must depend on psychological factors. (Master et al.,[19] p. 777)

Such psychological factors – 'the nervous makeup and emotional status of the patient' – were not

incidental (Master et al.,[19] p. 780). On the contrary, they were of 'paramount importance', to the point that 'a new medication, a new physician, a new type of therapy may bring relief' (Master et al.,[19] p. 780). Indeed, at their clinic, 'the average patient feels improved during the first few weeks of attendance . . . no matter what drug he receives' (Master et al.,[19] pp. 780–781). That was the (temporary) good news. The flip side was that it likely explained 'the reports of good results with numerous drugs' (Master et al.,[19] p. 781). As a final display of pharmaceutical scepticism and patient concern, they concluded: 'It is the physician who spends half an hour talking to a patient gaining his interest and confidence who is most apt to help the patient' (Master et al.,[19] p. 781).

Gold and colleagues' application of the 'blind test' to anti-anginal evaluation

Perhaps the most visible display of such scepticism, however, appeared in Harry Gold, Nathaniel Kwit and Harold Otto's use of the 'blind test' (quote in the original) to evaluate the xanthines in particular (Gold et al.,[20] p. 2178). Gold's team, throughout the middle of the 20th century, would be largely based in the Department of Pharmacology at Cornell University Medical College, and the cardiology units at New York's Beth Israel Hospital and Hospital for Joint Diseases (though Gold would hold affiliations with a number of other clinics and hospitals throughout this time). Claiming in 1937 that their study had already been in progress when the Evans and Hoyle paper was published (per Arthur Shapiro's interviews with Gold and Kwit in the late 1960s, the study began in 1932) (Shapiro and Shapiro,[3] p. 142) – and apparently continuing while the Master study was ongoing uptown – Gold and his colleagues framed the need for such a patient-blinded study against the backdrop of the multiple factors that could influence a patient's anginal symptoms (see especially numbers 9 and 10):

'1. Spontaneous variations in the course of the pain.
2. Change in the weather.
3. Change of occupation or amount of work.
4. Change of diet.
5. Change in eating habits with increase in the amount of rest before and after meals.
6. Condition of the bowels.
7. Emotional stress.
8. Change in domestic affairs.
9. Confidence aroused in the treatment.
10. Encouragement afforded by any new procedure.
11. A change of the medical advisor.' (Gold et al.,[20] p. 2177)

After initially hoping to exclude (through a comparison of the response to glyceryl trinitrate vs. placebo) a subset of patients especially vulnerable to expectation, Gold and his colleagues deserted such a plan, finding that patients across a wide range of clinical severity seemed susceptible (Gold et al.,[20] p. 2173) and lacking in apparent insight. When patients were asked to 'disclose their own belief regarding the influence of the drug', some 'insisted' on the efficacy of the lactose placebo, seemingly justifying 'all the circumspection one can exercise in accepting a patient's judgments in a study of this sort' (Gold et al.,[20] p. 2175). From their study, Gold and his colleagues themselves determined 'that the xanthines exert no specific action which is useful in cardiac pain' (Gold et al.,[20] p. 2178).

Later, in that very issue of *JAMA*, citing Evans and Hoyle, as well as Gold and his colleagues, the AMA's Council on Pharmacy and Chemistry would reverse its prior stance and report on the 'Limitations of Claims for Aminophylline and Other Xanthine Derivatives'.[21] And Gold would not only go on to become the foremost advocate for blinding within clinical research more generally, but would become the acknowledged pioneer of 'clinical pharmacology' in the United States, with blinding a central component of such rigorous trial methodology. Yet, in the domain of anti-anginal evaluation, this was not a simple, linear path, and the shared and differing commitments and findings of various groups from this time are telling.

Patient blinding and the complexities of anti-anginal evaluation

At one level, equally patient-blinded crossover studies could still yield diverging results. Several such reports from Chicago seemed to favour the use of xanthines, starting with Hyman Massel's from the Michael Reese Hospital in 1939.[22] Across town at Northwestern, George LeRoy, in studying aminophylline, took care to ensure that 'like-appearing placebos' were used, dispensed in envelopes and 'always designated by number' (LeRoy,[23] p. 923). As he continued: 'Care was taken not to discuss with the patient the nature of the drug used. It was felt to be good practice to lead the patient to believe that all the drugs were good'. With this, LeRoy found aminophylline to be far more effective than placebo, and with no 'injustice' intended, wondered aloud whether 'the poor results with xanthines reported by other workers may well be due to the fact that the patients were attended in hospital or medical school dispensaries with shifting personnels whose

diagnostic acuity and criteria varied' (LeRoy,[23] p. 924). Back at the Michael Reese Hospital, Stephen Elek and Louis Katz, studying papaverine, took pains, in acknowledging the size difference between their larger papaverine and smaller placebo pills, to assure patients 'that a small pill may be as potent as a large one by virtue of concentration' so as to offset 'any bias that might arise in the patient's mind because of a difference in size of the two pills' (Elek and Katz,[24] p. 435). Yet, in finding in favour of papaverine, they wondered aloud if Evans and Hoyle, in reporting negative results, had simply employed too small a dosage of the medication (Elek and Katz,[24] p. 436). In Vermont, Wilhelm Raab extended patient blinding past such vasodilators, studying thiouracil, under the premise (and drawing upon the treatment of angina through thyroidectomy) that the recently identified thyroxine-suppressing nature of thiouracil might be effective in lowering overall stimulation of the heart and thereby reduce symptoms. Again, while employing a small crossover study that included periods of what he termed 'unconscious placebo intake', Raab came out not only in favour of thiouracil, but of a reorientation of the understanding of angina around its neurohumoral influences (Raab,[25] p. 252). Thus, patient blinding was not just for sceptics, even as researchers sought to eliminate subjective enthusiasm.

At another level, certain researchers acknowledged such patient subjectivity, but attempted to eliminate it beyond blinding alone. At Boston's Beth Israel Hospital, another hub of angina research, Joseph Riseman and his colleagues (from their own 'special clinic' (Riseman,[26] p. 670) for angina) certainly acknowledged the subjective component of anginal pain. Even after attempting to exclude from study those 'patients with financial, domestic or social difficulties which were important factors in precipitating attacks', and while taking care to disguise their 'inert' placebos through sugar-coating them or painting them with a tincture of cudbear, Riseman's group still found that several patients 'felt better with every drug administered'. This led the clinicians to believe that 'the improvement apparently consisted of a sense of well-being, induced not by specific medication but by the fact that medical supervision was being given' (Riseman and Brown,[27] pp. 101, 102). Yet, Riseman and his colleagues felt that they could go beyond Evans, Gold and their studies by substituting for subjective reporting an 'objective' test, namely a standardised exercise-tolerance test, with electrocardiographic monitoring. Here, and still through pharmacologically blinded studies, they found that certain medicines (including several of the xanthines) seemed more effective than placebo in terms of exercise tolerance. For them, the real-world environment of the patient could not be adequately 'controlled or observed by the patient', and thus the exercise-tolerance test made it possible to 'differentiate real improvement due to therapy and apparent improvement unrelated to it'. As Riseman concluded, aspiring to a mechanical objectivity that itself dated back to the 19th century: 'Objective measurements are essential' (Riseman,[26] p. 672, Daston and Galison,[28]). Notably, however, even in this 'controlled' setting, Riseman and his colleagues employed patient blinding, though never explicitly discussing the potential for enthusiasm or suggestibility to creep into even such a seemingly decontextualised setting (discussion of the potential for suggestibility to influence exercise treadmill test outcomes *would* develop decades later).[29]

Gold and his colleagues took issue with both the outcome measured and the very decontextualisation that Riseman was attempting with the exercise-tolerance test. With respect to the former, Gold, focusing on the patient's subjective symptoms, would later note that 'the patient's complaint is clearly pain and not something wrong with his T-wave' (Gold,[30] Gold,[31] p. 10). With respect to the latter, the clinical goal was the treatment of patients in their 'natural habitat', where

> the total distress expressed as pain depends not alone on the intensity of the pain perception but on feeling states that may exist or may be aroused by factors associated with the pain perception, such as anxiety, frustration, fear, and panic. (Greiner et al.,[32] pp. 152, 151)

As Gold and his colleagues continued:

> There is interaction between pain perception and such feeling states, each possessing the power to diminish or intensify the total experience expressed as pain. In the usual exercise tolerance tests in which the exertion is carried out in a special environment under artificial conditions, and with concentration on a particular set of rules, the patient's usual attitude toward his illness may well be erased. (Greiner et al.,[32] p. 151)

Patient blinding seemed to level the specific playing field concerning suggestion and the impact of the receipt of medication on pain perception; but further control of the environment ran the risk of conflating the artificial world of the investigator with the real-life world of patients and their subjective symptoms.

Instead, Gold focused on a second measure introduced to ensure unbiased assessment of outcomes: researcher blinding. Part 2 of this series will focus on the incorporation of such blinding in Gold's work as a prelude to its advent in clinical studies more generally.

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Note

a. Note that as an indication of the fluidity of the term during its emergence in the 1950s, it remains unclear whether 'double blind' should be hyphenated or not. It was not hyphenated in its initial published appearance in 1950 (Greiner et al.,[32] p. 146), but was hyphenated in Harry Gold's classic articulation of the method as a key component of clinical evaluation in 1954 (Cornell Conferences on Therapy,[33] p. 724). In this article, I will hyphenate it in its adjectival and verb forms, and not hyphenate it in its nominal form (though this admittedly does not follow its usage in the two papers cited).

References

1. Gold H. Drug therapy in coronary disease. *JAMA* 1939; 112: 1–6.
2. Kaptchuk TJ. Intentional ignorance: blind assessment and placebo controls in medicine. *Bull Hist Med* 1998; 72: 389–433.
3. Shapiro AK and Shapiro E. *The Powerful Placebo: From Ancient Priest to Modern Physician*. Baltimore: Johns Hopkins University Press, 1997.
4. Rasmussen N. The commercial drug trial in interwar America: three types of physician collaborator. *Bull Hist Med* 2005; 79: 50–80.
5. Rasmussen N. *On Speed: From Benzedrine to Adderall*. New York: New York University Press, 2008.
6. Gabriel J. The testing of sanocrysin: science, profit, and innovation in clinical trial design, 1926–1931. *J Hist Med Allied Sci* 2014; 69: 604–632.
7. Aronowitz RA. *Making Sense of Illness: Science, Society, and Disease*. New York: Cambridge University Press, 1998.
8. Brooks H. The treatment of the patient with angina pectoris. *Bull N Y Acad Med* 1935; 11: 442–452.
9. Askanazy S. Klinisches über Diuretin. *Dtsch Arch Klin Med* 1896; 56: 209–230.
10. Freedberg AS, Riseman JEF and Spiegl ED. Objective evidence of the efficacy of medicinal therapy in angina pectoris. *Am Heart J* 1941; 22: 494–518.
11. Gilbert NC and Kerr JA. Clinical results in treatment of angina pectoris with the purine-base diuretics. *JAMA* 1929; 92: 201–204.
12. Council on Pharmacy and Chemistry. Therapeutic claims for theobromine and theophylline preparations. *JAMA* 1930; 94: 1306.
13. Evans W and Hoyle C. The comparative value of drugs used in the continuous treatment of angina pectoris. *Q J Med* 1933; 2: 311–338.
14. Evans W. *Journey to Harley Street*. London: David Rendel Ltd, 1968.
15. Mendel D and Silverman M.E. William Evans. *Clin Cardiol* 2001; 24: 487–489.
16. Gaddum JH. Clinical pharmacology. *Proc R Soc Med* 1954; 47: 195–204.
17. Levy RL. Management of the patient with anginal pain. *N Engl J Med* 1934; 211: 392–397.
18. Master AM. Treatment of coronary thrombosis and angina pectoris. *Med Clin North Am* 1935; 19: 873–891.
19. Master AM, Jaffe HL and Dack S. The drug treatment of angina pectoris due to coronary artery disease. *Am J Med Sci* 1939; 197: 774–782.
20. Gold H, Kwit NT and Otto H. The xanthines (theobromine and aminophylline) in the treatment of cardiac pain. *JAMA* 1937; 108: 2173–2179.
21. Council on Pharmacy and Chemistry. Limitations of claims for aminophylline and other xanthine derivatives. *JAMA* 1937; 108: 2203.
22. Massel HM. Clinical observations on the value of various xanthine derivatives in angina pectoris. *J Lab Clin Med* 1939; 24: 380–383.
23. LeRoy GV. The effectiveness of the xanthine drugs in the treatment of angina pectoris. *JAMA* 1941; 116: 921–925.
24. Elek SR and Katz LN. Some clinical uses of papaverine in heart disease. *JAMA* 1942; 120: 434–441.
25. Raab W. Thiouracil treatment of angina pectoris. *JAMA* 1945; 128: 249–256.
26. Riseman JEF. The treatment of angina pectoris. *N Engl J Med* 1943; 229: 670–680.
27. Riseman JEF and Brown MG. Medicinal treatment of angina pectoris. *Arch Intern Med* 1937; 60: 100–118.
28. Daston L and Galison P. *Objectivity*. New York: Zone Books, 2010.
29. Benson H and McCallie DP. Angina pectoris and the placebo effect. *N Engl J Med* 1979; 300: 1424–1429.

30. Gold H. Clinical Pharmacology of Cardiac Drugs: 23rd Series of Friday Afternoon Lectures at the New York Academy of Medicine [March 25, 1949]. Box 7, ff 74, Harry Gold Papers, Medical Center Archives of New York-Presbyterian/Weill Cornell, 1949.
31. Gold H. Some recent developments in drug therapy. *North End Clinic Quarterly* 1941; 2: 5–17.
32. Greiner T, Gold H, Cattell M, Travell J, Bakst H, Rinzler SH, et al. A method for the evaluation of the effects of drugs on cardiac pain in patients with angina of effort: a study of khellin (visammin). *Am J Med* 1950: 9: 143–155.
33. Cornell Conferences on Therapy. How to evaluate a new drug. *Am J Med* 1954; 11: 722–727.