

Professor Bo Holmstedt kindly provided the following introductory paragraph and letter sent to him by Dr. Harry Gold.

Having taught pharmacology for many years I wondered how the double-blind technique really came to be introduced and how one found out how the investigator influenced the results. Consequently, knowing that Harry Gold was the pioneer in this field, I wrote him a letter to which he kindly responded. I only met Dr. Gold once and this was at Cornell in 1959 but I knew of his work already at that time of course. His answer to my inquiry is published below.

June 27, 1970

Professor Bo Holmstedt
Department of Toxicology
Swedish Medical Research Council
Karolinska Institutet
Stockholm, Sweden

Dear Professor Holmstedt:

I received your letter of May 12th. I am embarrassed by the failure of my memory to recall our meeting at Cornell and I hope you will forgive me. It is pleasing to know of your interest in the "double-blind" element in a design in Clinical Pharmacology.

My preoccupation with it began about 1935; the first paper in which I wrote about the circumstances which led to it was published in 1937 [Gold, H; Kwit, N. T.; Otto, H. The xanthines (theobromine and aminophylline) in the treatment of cardiac pain. *J. Am. Med Assoc.* 108:2173-2179, 1937]. Psychological factors have always stood in the way when one wanted to evaluate the effect of a chemical on the feeling state in man, especially where there were no objective phenomena which could be observed or measured. To keep the patient without knowledge about the test agent, the "blind test" seemed to be the way the psychological reactions of the patient could be eliminated and leave the patients answers uninfluenced about

the effect of the chemical or the effect of one chemical as compared to another.

About 1935 we undertook a study to try to secure an answer to the question whether the xanthines relieve cardiac pain. The literature was chaotic. We started out with the conventional device to eliminate bias by keeping the patient in the dark as to the new medicine. The practice in our clinic called for a doctor to take the history and do the physical. Then the patient would come to my desk for medication. It was my practice to scan the chart, especially the answers to the questions in the history. I was struck by the fact that the answers to the same questions were often quite different from those the examiner recorded. There followed a consultation in which the patient often participated. A change in the answers was a frequent result. It soon became quite clear that the attitude of the examiner was an ingredient in the patient's answers to the questions. What followed was the "double-blind" method, namely to design the research so that neither the patient nor the doctor is aware of the identity of the drug at the time history is being taken. The idea and the purpose were described in the 1937 paper. An occasion to label the maneuver seems to have come years later. The term "double-blind" test appears in our Khellin paper in 1950. I am not sure whether we or anyone else made use of the term earlier.

The devices for insuring the "double-blind" element in the design of a research in Clinical Pharmacology are numerous and have undergone many changes, but the importance of the principle has received increasing recognition so that the validity of psychopharmacologic study, or any study in which the crucial data depend on judgements, comes into serious question if it is carried out without it.

I imagine others before us have used the same idea in the study of drugs in man, but as far as I know, it was in the middle thirties that that form of sophistication in research began to flourish.

Sincerely yours

Harry Gold, M. D.

Bo Gold
- DOUBLE

Dr. Gold

~~Harry Gold~~

Dr. Gold

Pharmacology
Date ?



TUFTS UNIVERSITY
Sackler School of Graduate Biomedical Sciences

May 22, 1996

Dr. David Healy
University of Wales
College of Medicine
Div. of Psychological Medicine
North Wales Department
Hergest Unit
Ysbyty Gwynedd
Bangor
Gwynedd LL57 2PW
United Kingdom

Dear David:

By now I hope you've received my letter of 8 May, which gives the pendulum reference and my first sleep study. I enclose a copy of a Harry Gold letter which appeared many years ago in "The Pharmacologist", which is probably not archival. Jachuk et al is in J. Roy. Coll. Gen. Prac. 32:103-105, 1982.

Sincerely,

Louis Lasagna, M.D.
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