Editorial

Reflections on Two Modern Medical Research Ideas

One of the main tenets of modern clinical therapeutic trials is that the double blind method must be used. Anything else is called anecdotal, in a pejorative sense. One of the main tenets in evaluating research publications is that the methodology and the final manuscripts must be reviewed by peer committees. Although they have never been scientifically established, both these beliefs are politically correct, so correct that anyone who questions these beliefs immediately runs into massive opposition from the defenders of the faith.

Double Blind Controlled Therapeutic Trials

Fortunately double blind methodology is facing more opposition recently, and it is about time. About forty years ago Sir Lancelot Hogben, the English mathematician, exposed it as an inappropriate way of conducting human therapeutic trials. His analysis led him to conclude that the two fundamental prerequisites for randomized sampling where missing. These are (1) that it is possible to obtain representative samples from the human population that have to be tested and (2) that the phenomenon being tested is invariant. His first objection is that contrary to trials in agriculture in which millions of plants can be compared, large scale human studies are so costly that they are not done and most trials are on a small scale. With such small samples it is impossible to be sure that it truly is a representative sample of any larger population from which it is drawn. I have raised several objections to the double blind randomized methods.[1,2] My main objections are (1) that it removes faith, that psychological healing benefit so essential in treating anyone, from the therapeutic process. It creates an unreal situation that has no relevance to clinical practice of good physician healers. It is like studying the natural behaviour of gorillas by observing them in a cage. (2) It is dishonest and unethical. To be truly double blind the patients must be kept in the dark, i.e. told lies. They are allowed to believe that they are being treated with some active compound They are not told they maybe getting nothing, i.e. placebo. If they are told it will be double blind they will not trust their physician any more. Many years ago I tried to conduct a double blind trial comparing a well know anti-depressant against a new anti-depressant which had fewer side effects. I had complete faith that the new compound would be as efficacious. I advised my patients, asking them to think carefully about whether they would like to enter this double blind and added they would not have to pay for the new antidepressant. If they were reluctant I did not enter them in the trial. Most of them agreed, but there was a tremendous fall out. We always expect a certain number of no shows, like in the airline industry; but from this study I have never seen such a massive fall out. These patients showed me, by not appearing anymore, that they did not trust the double blind trial and/or no longer trusted me as their psychiatrist That was my last attempt to run this type of study.

A major criticism of the double blind, which is usually not discussed, is that it often shows compounds to be not effective when in fact long usage has shown that they are effective. The best examples are the early double blind experiments which showed that L dopa was not therapeutic for Parkinson's disease. A more recent example just appeared in which it is shown that imipramine is no more effective than placebo in treating depression. Physicians and psychiatrists know from long usage that this anti-depressant does have anti-depressant properties.

Kapser, Moller, Montgomery and Zondag[3] reported on a well designed double blind therapeutic trial comparing Imipramine, fluvoxamine and placebo on 338 depressed patients with five North American centers cooperating. Their conclusion

was "Fluvoxamine but not imipramine was significantly superior to placebo in severely depressed patients" and "No significant improvement was observed with imipramine."

Modern attempts are being made to bypass the double blind method by using what is called meta-analysis. With this technique single studies which are considered not adequate standing alone are simply lumped together into a large statistical table using mathematical formulae and then conclusions are drawn from these.

The powerful adherence to this flawed methodology reminds me of a meeting I attended in Prague about 30 years ago. This was the first international meeting held in Czechoslovakia during the communist regime, when the iron curtain was just beginning to come down. Most speakers were from the communist controlled countries. As each speaker presented their report I was struck by a uniformity in the structure of their presentation. Each began with a statement that communism was of course the superior system. Then they would report their medical or scientific findings. Finally after their conclusion they would finish by stating that their conclusions of course proved the superiority of the communistic system. I turned to one of my neighbors and asked him bluntly what was going on. He answered cynically, "they have to live."

Communism was overthrown and I am certain the same scientist today would present papers that are very much like those presented by western scientists. Isn't it about time we forced all the defenders of the double blind to stop bowing to the double blind methodology, to seriously have another look, to let us know why they insist on using a method that has never been validated and which contains so many inherent defects that it is probably one of the worst ways of doing clinical experiments? I must make clear I am not against controlled experiments. These are essential but they do not have to be double blind and they must take into account the many errors generated by sampling techniques.

An example of a recent major trial which in my opinion should never have been published is the Finnish double blind controlled experiments using as subjects heavy drinkers and smokers The effect of beta carotene and vitamin E was studied using randomized groups. The randomization was not good and the group given beta carotene had been smoking on average one more year than any of the other groups. The authors concluded that the beta carotene group had slightly more patients with lung cancer but that these results were probably not of from a statistical point of view. Actually, the fact they had been smoking one year more probably did make a difference since lung cancer is progressive and may take years to fully develop. They should have concluded only that the beta carotene did not inhibit the development of cancer. Yet they allowed the conclusion that beta carotene had increased the incidence of lung cancer to be publicized widely. There were many other points about their design which have been severely criticized by others. The public not being aware of the niceties of this statistical technique assumed simply that beta carotene increased the incidence of lung cancer. In my opinion the double blind method best serves not the interests of science or medicine, but the interests of editors of journals, and those who evaluate research grant applications, for the double blind removes the need to really think about the subject matter. All is left to the holy $P < .005$

About Peer Review

It is widely believed that peer review committees maintain the purity of science and prevent bad science from penetrating into our medical journals or in obtaining research grants. I do not think that there is much evidence that this is true. The orthodox journals who depend so heavily on peer review committees published many fraudulent articles over and over. And any com-

petent editor can manipulate his peers in such a way as to eliminate any paper with which he does not agree or which goes against the policy of that journal. For example the *New England Journal of Medicine* had a firm policy of not publishing anything that provided some evidence that vitamins in large doses were useful. If such a paper arrived it would be simple to send it to peers who are part of the vitamin-as-prevention establishment who would then automatically reject it. Linus Pauling could not get his vitamin C papers accepted by that journal.

Several years ago a professor of Medicine at McGill Medical School found that all of eight patients with idiopathic thrombocytopenic purpura (ITP), were markedly benefitted by vitamin C. There is no effective orthodox treatment for this disease. Here we have a disease which has a zero response rate to treatment but when given vitamin C there was a 100% response rate. This paper was submitted to the *New England Journal of Medicine* and was rejected because it was not done double blind. The difference in results was so striking that any one with any common sense would know that even with this small series the therapeutic value of this vitamin was established. I have used it for three such patients with equally good results.

The paper by Zelek Herman in this issue (please see p. 225) describes how they avoided publishing Pauling's analysis of a previous paper they had published which concluded that vitamin C was not therapeutic for cancer.

In fact the term "peer" can not be applied to a new science until it has had a chance to develop scientists who are familiar with it. They can then become the peers. Even then I do not think it is a good idea because, as I see it, the main function of peers is to maintain the purity of the current paradigm. I like Linus Pauling definition of peers. Peers, he said, are people who pee together!

I find that the best and most interesting journals are those where the editor is wide open to new ideas and does not send the manuscripts to any peers. This is why many physicians turn to the letters section of any journal for only here will they find uncensored letters with ideas that may be good or bad but at least they are interesting. Dr. Fleming was such an editor and his journal the *British Journal of Mental Science* was very interesting. The current *British Journal of Psychiatry* is as dull as any other psychiatric journal.

Double blinds do not ensure that effective drugs will be found to be effective and that ineffective drugs will be ruled out as ineffective. They do not serve the needs of science or of patients. Peer Review committees do not serve the needs of science either. They serve the needs of editors, and of grant evaluators. There main function is to protect the status quo of any science.

References

1. Hoffer A, Osmond H: Double blind clinical trials. *J Neuropathol*, 1961; 2: 221-227.
2. Hoffer A: A theoretical examination of double blind design. *Can Med Assoc J*, 1967; 97:123-127.
3. Kasper S. Moller HJ, Montgomery SA; Zondag E: Antidepressant efficacy in relation to item analysis and severity of depression; a placebo controlled trial of fluvoxamine versus imipramine. *Int Clin Psychopharmacol*, 90,1995; Suppl 4:3-12.