

THE USE OF CLINICAL TRIALS AS A MEASUREMENT OF EFFICACY IN TRADITIONAL CHINESE MEDICINE

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THE USE OF CLINICAL TRIALS AS A MEASUREMENT OF EFFICACY IN TRADITIONAL CHINESE MEDICINE

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Abstract

The use of clinical trials as a measurement of efficacy lies at the heart of the debate between Conventional and Traditional Chinese Medicine (TCM). The Irish Medicine Board (IMB) have voiced serious concerns about the safety of herbal medicine and over the past 2 years have classified many herbs including *Hypericum perforatum* (St John's Wort), *Gingko Biloba*, and *Tribulus Terrestris* (Bai Ji Li) in the same category as prescription only drugs. The IMB and many medical doctors argue that without clinical trials, the efficacy and safety of TCM cannot be demonstrated. The double-blind randomised controlled clinical trial is the 'gold standard' for the measurement of efficacy of orthodox drugs. Yet despite this, orthodox drugs are not without significant dangers. In addition, while clinical trials are designed to test the efficacy of treatment in a relatively unbiased way, they have many limitations. They are based on a view of the world that adopts relatively narrow descriptions of disease and treatment, and which does not always recognise the patient as a whole person. Furthermore, in standardising the treatment, the clinical trial may remove from it elements which are an essential part of it. The therapeutic relationship, for example, which lies at the core of every clinical practice, is completely ignored. The gold standard for measurement of the efficacy of single drugs may not be the best research tool to measure the efficacy of TCM where many herbs may be used in an herbal prescription and each disease episode and every patient is treated as being different from any other. A change in perspectives is required which facilitates research methodologies that understands and respects the integrative and holistic nature of TCM.

Introduction

Last year the Irish Medicine Board (IMB) decided to classify the herb *Hypericum Perforatum* (St John's Wort), *Ginkgo Biloba*, and many other herbs, in the same category as prescription only drugs. This action raised many old questions regarding freedom of choice, protection of the public, efficacy, quality control and the competence of a medical doctor or herbal practitioner to prescribe herbs. The IMB claims that any products, which claim to cure, alleviate, or prevent diseases will be considered to be medical products. In addition any herbal products which imply a claim by using such phrases as - heals, treats, helps with, calms, alleviates, or prevents disease is by definition a medical product and should undergo the same rigorous clinical research trials as any orthodox synthetic drug.¹ As these valuable herbs do not have Irish product licenses and very few doctors in Ireland have formal training in herbal medicine this ruling effectively amounts to a ban.² This is not in the interests of the public who are being driven to buy herbs on the Internet or from Northern Ireland where they remain on sale over the counter. The indignation felt by a large section of the Irish public, and protests from herbal practitioners about the effective banning of St John's Wort resulted in thousands of letters of protest to the Government. In response the Irish Government established, within the IMB, a Scientific Committee on Herbal Medicinal Products that is considering practical ways to allow herbs to be regulated and marketed in Ireland.

Traditional Chinese Medicine (TCM)

Over the past few years there has been an increase in the number of reports in both medical journals and national newspapers regarding the safety and efficacy of herbal remedies. Practitioners of herbal medicine would argue that the issue of safety and efficacy of Chinese herbs should not be considered in isolation from the principles and practice of Traditional Chinese Medicine. Traditional Chinese Medicine (TCM) has developed through extensive observation and clinical testing over the last 3000 years as a system of medical theory and practice. This is different from, but no less valid than, Western medicine. It has its own consistent theoretical concepts, philosophy of health and disease, theory of disease aetiology, system of disease classification and a coherent diagnostic and treatment framework. Disease is seldom thought as being the sole result of a single causative agent. Rather it is seen as due to a pattern of influences leading to disease and imbalance. Everything in one's internal and external environment can contribute to the development of a pattern of disharmony or dis-ease. Treatment is therefore aimed at restoring the balance or harmony of the whole person – psychological, social, physical and spiritual. This perspective has many correlations

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with modern quantum physics, systems theory, complexity theory, and ecology.^{3, 4} This TCM perspective also mirrors the World Health Organization (1947) definition of health as ‘a state of complete physical, mental and social well being’.⁵

Measurement of Efficacy

Measurement of efficacy is one of the issues that lie at the heart of the debate between orthodox drugs and herbal medicine. Many doctors reject user surveys, case studies, and anecdotal information regarding TCM.^{6,7,8,9} They argue that success is more to do with ‘magical thinking’ or the placebo effect.^{7,10,11,12,13.}

Serious concerns have also been voiced about the possible harm of herbal medicine and claims have been made that without clinical trials, the efficacy and safety of herbal medicine cannot be demonstrated. Despite clinical trials, however, conventional medicine is not without significant dangers. For example, according to one study by Lazarou et al. (1998) published in the JAMA, two million serious adverse drug reactions occur each year in the USA.¹⁴

In addition, while clinical trials are designed to test efficacy of treatment in a relatively unbiased way, they have many limitations. They are based on a view of the world which adopts relatively narrow descriptions of illness and treatment, and which does not always acknowledge the patient as a whole person. Furthermore, in standardising the treatment, the clinical trial may remove from it elements which are an essential part of it. The therapeutic relationship, for example, which lies at the core of every clinical practice, is completely ignored. This is despite the fact that considerable variability has been reported among doctors regarding different aspects of their practice.

For example, Anderson et al. (1983) reported that doctors differ in their diagnosis of asthma.¹⁵ Marteau et al. (1984) claimed that doctors differ in their treatment of diabetes.¹⁶ Bennette et al. (2002) reported that doctors vary in their treatment of heart disease.¹⁷ Mapes (1980) claimed that they also differ in terms of their prescribing behaviour with between 15% and 90% receiving drugs.¹⁸ These differences cannot be simply explained in terms of difference in knowledge and experience. The variability is explained by different health belief systems, variations in perceptions of the incidence and seriousness of various diseases,¹⁹ the doctor’s mood,²⁰ and to the whole process involved in communication between the doctor and patient as this interaction takes place in the context of these beliefs.²¹ Medical education now emphasises the importance and value of the doctor-patient relationship and studies show significantly different outcomes

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depending on how it is managed.²² There is much in the research literature on the value of communication skills as determinants of outcome and related psychological research suggesting that it is the doctor's qualities of personal presence (rather than any particular therapeutic techniques) that determines outcomes of the therapeutic interaction.^{21,23}

Is the type of clinical trial that is used for measurement of the efficacy of single drugs the best research tool to measure the efficacy of TCM where many herbs are used in an herbal prescription and each disease episode and every patient is treated as being different from any other?

Double-blind, randomised controlled clinical trials

The classical way to test efficacy in orthodox medicine is clinical trials. Ideally, the experiment follows certain criteria. It must: compare the effect of treatment with the effect of no treatment; ensure that people are randomly selected into each group; control for placebo effect; identify a clearly diagnosed illness and a standardised treatment; provide for a noticeable change; use measures that are precise, valid and reliable. The most common version of clinical trials, which satisfy these rules, is the **double-blind, randomised controlled clinical trial (RCCT)**, where neither patient nor the therapist giving the treatment knows who is receiving the actual treatment.

The search for a scientific basis to orthodox medicine has led to the double blind randomised controlled trial as the 'gold standard' for the evaluation of therapeutic interventions yet orthodox medicine still relies to a large extent on individual experience, opinion and invalidated treatment.¹¹ For example, there are approximately 30,000 biomedical journals in the world,²⁴ yet, according to David Eddy, professor of health policy and management at Duke University, North Carolina, only about 15% of medical interventions are supported by solid medical evidence.²⁵ This is because only 1% of the articles in medical journals are scientifically sound and partly because many treatments have never been assessed at all.²⁶

Limitations of RCCT

1) Reality is poorly reflected in the controlled clinical trial setting.

The systematic and controlled setting used in experiments is a poor model of the complex and dynamic real world of the clinical practice. Selecting and controlling variables means the exclusion of others that are influential and may involve disregarding some of those that are selected and controlled. Consequently the resulting findings have little relevance to understanding the real world where all the variables may be at work.^{23,27,28} In addition, with less easily diagnosed conditions, treatment does not necessarily follow diagnosis in a strict chronological sequence. Also, there are usually a variety of causes in illness, not just one, and many people have diseases which may defy classification.²⁹

2) Conventional classification of the diseases (such as the International Classification of Diseases) may not adequately describe the signs, symptoms and syndromes of illnesses that are more likely to be seen in a TCM practice.

For example, myalgic encephalomyelitis / chronic fatigue syndrome and irritable bowel syndrome, are not associated with any consistent, measurable physiological abnormality. Moreover in TCM there is a completely different system of disease aetiology, diagnosis, classification and treatment framework.

A TCM diagnosis of Liver Qi Stagnation, for example, is the most common of the Liver patterns. This single pattern may present with symptoms commonly seen in patients with migraine, irritable bowel syndrome, Pre-menstrual tension, dysmenorrhoea, irritability, hypochondriac pain and depression.³⁰

3) Measurements of change in clinical trials may not be adequate indications of a successful outcome from the patient's perspective.

The measures of change in clinical drug trials (e.g. changes in hormone and neurotransmitter levels) may not be adequate indications of a successful outcome from the patient's point of view. Since 1947 reliance on laboratory tests has increased while diagnosis from clinical signs and symptoms has declined significantly. Similarly, the frequency with which the emotional, psychological, occupational or social status of subjects has been reported has diminished with time.³¹ Most operational measures of

health are poor relations of concepts such as quality of life, ²⁹ and bear little relationship to a TCM definition of health as a state of physical, mental-emotional, social and

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spiritual well-being.³⁰

For example, a study published in the Lancet in 1986, on the efficacy of acupuncture in the treatment of chronic obstructive pulmonary disease showed that the subjective reporting of breathlessness in patients with this condition was significantly improved although objective indices of lung function (such as thoracic gas volume and expiratory flow rates) remained unchanged. This paper was the first to be published in the Lancet where traditional Chinese diagnosis has been respected. ³²

Many other clinical trials demonstrated this greater subjective perception of symptom relief by patients whilst there was only mild to moderate improvement in the 'objective' assessment indices. ^{33,34,35,36,37.}

4) In standardising the treatment, the clinical trial may remove from the treatment elements, which are an essential part of it.

The double-blind randomised controlled trials give us a statistical probability of the effect of treatment on a group of people. This probability is derived from a comparison of treated patients with control subjects. These groups are constructed on the basis of common shared criteria that should be as few, simple, objective and reproducible as possible if results are to be generally applied. In other words, there is a price to pay for the objectivity of these trials. Gain in objectivity is achieved by simplification and at the cost of completeness and wholeness. The whole philosophy of the trial is to exclude individual differences and concentrate on group similarities. Indeed, the exclusion should ideally apply to every aspect of the therapeutic encounter except the specific intervention under assessment.^{23,27,28}

In contrast, the TCM model is more dependent upon integration of a wide range of data, and a therapeutic decision is seldom based on one or two factors alone. The fundamental reason for this is that no symptom or sign provides a single objective reading that acts as a basis for diagnostic conclusion. In the TCM model any piece of information (symptom or sign) gathered from the patient can only be interpreted subjectively in relation to other symptoms and signs.³⁸ In other words, any one observation on the patient may hold several meanings dependent upon other observations made of the patient.

For example, a bright red tongue may be meaningfully interpreted as an excess heat (yang) patient constitution if there is also a thick yellow tongue coating and a strong pulse, or as a deficiency syndrome (yin xu) if the tongue coat is absent and the pulse is

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thin. The meaning of the red tongue is most clearly stated by observing other data. ³⁹

The double-blind, randomised controlled trial aspires to a world where effective medicine is so simple that the therapeutic relationship between the doctor and patient and patient's individuality are rendered unimportant compared with the objective probabilities established by rigorous evaluation. From the patient's perspective the deficiencies of the clinical trial approach is even more obvious since, more often than not, there is a genuine discrepancy between illness as actually experienced by the patient and as it is conceptualised in the reductionist biomedical mode. When patients tell their doctor their symptoms and medical history, they find that elements that they deem important are either ignored completely in favour of more objective physical signs and laboratory results, or at best filtered for those few discriminatory symptoms that have been subjected to group trials.^{23,27,28}

In contrast the practice of TCM is based on the evaluation of individualistic factors, so that no two patients are treated exactly the same. Of course, this requires time for full assessment on the part of the TCM practitioner rather than a seven-minute consultation by an overburdened general practitioner or an intervention by a hospital consultant who may put technology first and all too often ignore the patient as a person.

5) In TCM single herbal products are rarely used alone and each disease episode and every patient is treated as being different from any other.

TCM uses very complex herbal prescriptions tailored to the individual patient during particular stage of the disease process and the prescriptions may act over a long period, which may preclude single drug studies. As these TCM prescriptions are directed at promoting the body to heal itself, the time-scale for experiments needs to be sufficiently long. Many of these traditional prescriptions have been safely and successfully used by millions of people over thousands of years. ³⁰

One of the first clinical trials on Chinese herbal medicine that adhered to the traditional diagnostic and treatment process while using a double-blind randomised control trial protocol was carried out on irritable bowel syndrome (IBS) by a group of researchers in Australia led by Alan Bensoussan during 1996-7. Patients were recruited from two

teaching hospitals and five private practices of gastroenterologists. They received Chinese herbal medicine in three herbal clinics. Patients were randomly selected to one of three treatment groups: placebo (35), a standard Chinese herbal formulation (43) or

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individualised Chinese herbal formulations (38). Patients received 5 capsules 3 times a day for 16 weeks and were evaluated regularly by a traditional Chinese herbalist and by a gastroenterologist. Patients, gastroenterologist and herbalists were all blinded to treatment group. The study demonstrated that Chinese herbal medicine is effective in the management of symptoms related to IBS. In follow up assessment 14 weeks after completion of the treatment, only the patients who received individualized herbal formulas maintained improvement.⁴⁰

6) Clinical trials can be dehumanising.

Although the vast majority of studies are subjected to ethical scrutiny, this does not always guarantee the protection of individuals participating in clinical trials. In double-blind randomised controlled trials, there may be substantial ignorance on the part of the person being treated. The premise that there needs to be a high degree of objectivity on the part of the experimenter can lead to patients being treated as objects and their personal power being reduced to an object. This is a frequent complaint by patients participating on clinical trials.^{41,42,43,44,45}

7) Safety: The use of clinical trials does not guarantee protection against adverse reactions.

In 1990 the General Accounting Office in the US reported that over half the drugs approved as “safe” by the FDA between 1976 and 1985 caused such serious side effects as to require relabelling or withdrawal of the drug from the market. These side effects were described as “common” and resulted in hospitalisation, permanent disability or death.²⁸ A more research study to estimate the incidence of serious and fatal adverse drug reactions (ADR’s) in hospitalised patients published in the Journal of the American Medical Association in 1998 states that properly researched, regulated, prescribed and properly used drugs are the fourth most common cause of death in the USA. This is over 100,000 deaths per year. That’s equivalent to a Boeing 747 crashing every day. The study also reported that over 2 million serious adverse drug reactions (defined as requiring hospitalisation or causing permanent disability) occur each year in the USA.¹⁴

46 people die every day from Aspirin alone in the USA. Reilly (2001) states that in Britain last year 2,500 people died from bleeding due to non-steroidal-anti-inflammatory drugs.⁶⁰ A report by Professor Breckenridge of Liverpool University claims that up to 20,000 deaths a year in Britain may be linked to ADR's, that ADR's may be implicated in 5% of all hospital admissions and that they may occur in as many as one in five hospital in-patients. Among patients taking five or more drugs, there is a 50% chance of an adverse reaction.⁶¹

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In contrast, Maciocia (1999) claims that "the WHO monitoring centre in Uppsala, Sweden, issued a summary of reports on adverse reactions to herbs worldwide over a 20-year period. The total number of adverse reactions reported is 8984, a relatively low figure considering that it covers the whole world and extends over a period of 20 years. The reported adverse reactions in the all-herbal combinations, are only 368 this is only 4% of the total reports of adverse reactions." ⁶¹ These WHO figures should be treated with caution as systems for reporting adverse herb reactions are not in place in many parts of the world. However, they do show that combinations of herbs seem to cause fewer adverse reactions than single herbs.

A more recent extensive study by Prof Ernst, Director of Complementary Medicine at University of Exeter UK who surveyed the medical literature between 1992 and 1996 for reports concerning adverse effects of herbal remedies found a total of 35 fatalities and less than 200 other adverse effects involving herbal remedies during a five year period. That works out to an average of 7 fatalities and less than 40 adverse events per year ascribable to the use of herbal medicines.

8) The use of clinical trials does not guarantee bias-free research.

Sackette (1979) points out 56 known potential sources of bias in clinical research. Bias can creep into experiments at every stage of research, from reviewing the literature, through design, sampling, and analysis to interpretation and presentation of findings.⁴⁶ Klein et al (1994) demonstrated that the clinical trial might be compromised by poor physician compliance with trial protocol ^{47,48}. Other studies showed bias in selection and allocation.^{49,50,51} Numerous studies have shown that the value of the clinical trial may be undermined by negligence, dishonesty, fraud and other kinds of wrongdoing usually for purposes of academic or economic gain.^{52,53,54,55,56} In addition, Sapiro et al (1989) reported that the regulatory bodies such as the FDA never audit the vast majority of drug trials and penalties for unethical or fraudulent behaviour are lenient to nonexistent.⁵⁵ Plieffer et al (1990) have shown that fraudulent conclusions from clinical trials, later retracted, continue to live on and influence future clinical conclusions.⁵⁷

Researchers may have political bias and subvert the scientific process in order to discredit complementary medicine.⁵⁸ In educational, psychological and medical research publication bias favours research with statistically significant results over non-statistically significant results. In addition, publication bias may also discriminate against complementary medicine. For example, a study of 398 experts who review papers for publication, found that they were prejudiced against complementary medicine. This was a randomised, controlled double-blind study using two versions of a fictional report on obesity, which were identical except for the nature of the intervention

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(an orthodox drug as against a homeopathic remedy). One of the two versions and an assessment form were sent to each of the 398 experts. They were asked to rate the reports significance and publication potential. The findings revealed that the expert peer reviewers were three times as likely to favour an orthodox version over the unconventional version of the report. ⁵⁹

The Future

The dominant research model of disease today is biomedical, and its strictest manifestation leaves little room within its framework for the social, psychological, behavioural and ecological dimensions to illness. It leaves little or no room for complementary and alternative medicine systems. There are profound differences in the philosophical perspective of the proponents and opponents of clinical trials. These differences reflect the many different views of reality.

No one view of reality is more correct than any other. The premise that any one method of evaluation is right leads to scientific stagnation. No single method of evaluation should be expected to assess the effectiveness of all treatments. Indeed Austin Bradford Hill, the father of the controlled clinical trial, stated at the end of his life that:

“Given the right attitude of mind there is more than one way in which we can study therapeutic efficacy. Any belief that the controlled trial is the only way would mean, not that the pendulum has swung too far, but that it had come right off the hook” ²⁸

If there is to be greater integration between TCM and orthodox practitioners in terms of measurement of efficacy, there will need to be a paradigm shift which, facilitates research that understands and respects the holistic nature of TCM. We need to be cognizant of the many biases that currently limit the efficacy of the double blind randomised controlled trial. Lewith (1998) claims that research in complementary therapies does not in many cases require placebo controls, standardised treatment or objective outcome measurements.⁵⁸

We need more flexible clinical trials where the therapeutic relationship, which is at the very heart of every type of clinical practice, is not removed from the trial no matter how impersonal we may wish to be. There is a need for more research using single case designs that looks at changes within individual patients over time.⁶² Research of a collaborative kind between therapist and patient, rather than research by the therapist on the patient is required.⁶³ The philosopher John Heron recommends the use of a “participatory method of cooperative inquiry” where both researchers and subjects

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engage in democratic dialogue as co-researchers to design, manage and draw conclusions from the research.²³ The separation of the disease from the person loses those very qualities that we need to understand. Diseases may be treated as aggregates and submitted to statistical analysis, but it is the individual persons in whom these diseases are located and who confront us in our clinics. Consideration must be given to the fact that symptoms are located within individuals who perceive their symptoms differently.

TCM needs to develop its own research methodologies that take into account its own unique philosophical perspective of health and disease. The treatment method must be decided by the TCM practitioner based on traditional diagnosis therefore the number of treatments (acupuncture points or herbal formulas) should not be controlled. The practitioner should be allowed to give advice regarding relevant nutritional, physical, psychosocial, occupational factors that may aid in the treatment strategy. The clinical trial by Bensoussan et al (1996) on traditional Chinese herbal medicine for irritable bowel syndrome is an innovative effort that respects the integrity of a TCM paradigm yet simultaneously manages to adopt the methodological safeguards demanded by scientific research. Birch (1998) claims that research into the efficacy of TCM may require a more multidisciplinary approach involving the skills of philosophers, clinical researchers, basic science researchers, linguists, sinologists and TCM practitioners at various times during the research process. ⁶⁴

If research methodology is applied, simply as a formula, without becoming as familiar as possible with the subject matter under study, then no significant findings emerge. To do this relinquishes both responsibility in science and real discovery. Science is not methodology; methodology serves science. Tukey’s (1979) wise comments about quantitative measures can also apply to the development of new more integrative and holistic research methods:

“When the right thing can only be measured poorly, it tends to cause the wrong thing to be measured only because it can be measured well. And it is often much worse to have good measurement of the wrong thing - especially

when, as it is often the case, the wrong thing will IN FACT be used as an indicator of the right thing - than to have poor measurement of the right thing". 65

TCM practitioners agree with the Irish Medicine Bord that TCM needs to be able to prove its efficacy. However, the type of clinical trial that is used for measurement of the efficacy of single drugs is not the best research tool to measure the efficacy of TCM where many herbs are used in an herbal prescription and each disease episode and every patient is treated as being different from any other. We need to develop new research models so that, in future, we may have a **good measure of the right thing**.

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References

1. McCarthy P. The Use of Clinical Trials as a Measurement of Efficacy in Traditional Chinese Medicine. *Irish Medical Times*: Vol. 34. No18 April 2000. P.34
2. McCarthy P. Safety of Herbal v Orthodox Drugs – one of the key issues under consideration by the IMB. *Irish Medical Times*: Vol. 35. No31 Aug. 2001 P. 18-19
3. Fritjof C. *The Turning Point: Science, Society, and the Rising Culture*, Bantam 1983
4. Hyland ME, *The Intelligent Body: Conventional Medicine Will Never Cure All Our Ills. Our Bodies Just Don't Work That Way*. 26th May, *New Scientist* 2001
5. World Health Organisation: *Constitution of the World Health Organization*. Geneva: 1947.
6. *Magic or Medicine? Which?* 1986; Oct: 443-447
7. Moore J, Phillips K, Mercer D, and Lewith G. Why do people elect to be treated by alternative medicine? *British Medical Journal (Clin Res)* 1985; 290: 28-29
8. Hammond M. Public opinion regarding alternative medicine. *Curations* 1982; 5(2): 40-3.
9. Knight JF Miracle cures. *Med J Aust* 1982; 1(3):
10. Davies G. The hands of the healer: has faith a place? *Ethics* 1980; 6(4) 185-189
11. Peck ML, The therapeutic effect of faith. *Nursing forum* 20(2): 153-166
12. Fitzgerald FT. Science and scam: alternative thought patterns in alternative health care *New England Journal of Medicine* 1983; 3 1066-1067.
13. Semmes CE, Nonmedical illness behaviour: A Model of Patients Who Seek Alternatives to Allopathic Medicine. *Journal of Manipulative & Physiological Therapeutics* 13(8) 1990 JMPT
14. Lazarou J, Pomeranz BH, Corey PN. Incidence of Adverse Drug Reactions in Hospitalised Patients: *JAMA* April 15 1998.
15. Anderson HR, Freeling P, Patel SP. Decision making in acute asthma. *Journal of the Royal College of General Practitioners*, 33, 105-108. (1983)
16. Marteau TM, Johnson M. Doctors' view of Diabetes. *Archives of Disease in Childhood*, 56, 566-70 (1984)
17. Benette K. *Irish Medical Journal* July (2002) ((*Irish Times* 24/07/02)
18. Mapes R. (Ed.) *Prescribing Practice and Drug Usage*. London, Croom Helm 1980.
19. Weinman J. Diagnosis as problem-solving. In *An Outline of Psychology as applied to Medicine*, 2nd Ed. London: Wright. (1987)
20. Isen AM, Rosenzweig AS, Young MJ. The influence of positive effect on clinical problem solving. *Medical Decision Making*, 11, 221-7 (1991)
21. Ogden J. *Health Psychology – A Textbook* Open University Press. Buckingham 1996
22. Cousins N. *Head first: the biology of hope and the healing power of the human spirit*. Penguin, New York. 1990
23. Heron J. The Placebo Effect and the Participatory World View - in Peters D. Ed.

Understanding the Placebo Effect in Complementary Medicine – Theory, Practice and Research. Churchill Livingstone. 2001

24. Lock S. The future of medical journals. London BMJ 1991: 1-8
 25. Smith R. Where is the Wisdom...? The poverty of medical evidence. BMJ 1991: 303: 798-799.
 26. Williamson JW et al The quality of medical literature: An analysis of validation assessments. In: Bailar JC, Mosteller F. Medical use of statistics. Waltham, Holman H.R. Hospital Pract. 11, 11 (1976)
- 13.**
27. Charlton BG Medical practice and the double-blind, randomised controlled trial. British Journal Gen Practice 355-356 Sept 1991
 28. Coulter H.L. The Controlled Clinical Trial: An Analysis. Centre for Empirical Medicine Washington D.C. 1991
 29. Leibrich J. Measurement of Efficacy: a case for holistic research: Complementary Medical Research 1990 4(1) 21-25
 30. Maciocia G. The Foundations of Chinese Medicine, Churchill Livingstone 1989.
 31. Fletcher, R.H. & S.W. Clinical research in General Medical Journals. New England Journal of Medicine 301-4 (July 26 1979) 180-183.
 32. Jobst K, McPherson K, Brown V, et al Controlled trial of acupuncture for disabling breathlessness. Lancet Dec. 20-27 1986
 33. Dias PLR, Subramanian S, Lionel NDW, Effects of acupuncture in bronchial asthma: a preliminary communication. J R Soc Med 1982; 75: 245-248.
 34. Shao Jm, Ding YD, Clinical observation of 111 cases of asthma treated by acupuncture and moxibustion. Journal of Traditional Chinese Medicine 1985; 5: 23-25
 35. Berger D, Nolte D, Acupuncture in bronchial asthma: body plethysmographic measurements of acute bronchospasmodic effects. Comparative Medicine East and West 1975; 5: 265-269.
 36. Christensen PA, Laurensen Lc, Taudorf E, Sorensen SC, Weeke B, Acupuncture and bronchial asthma. Allergy 1984; 39: 379-385
 37. Tashkin DP, Kroenig RJ, Bresler DE, Simmons M, Coulson AH, Kerschmar H. A control trial of real and simulated acupuncture in the management of chronic asthma. J. Allergy Clin. Immunol. 1985; 76: 855-864.
 38. Chan Wing-Tsit, translator: A Source Book in Chinese Philosophy, Princeton, NJ 1963.
 39. Bensoussan A. The Vital Meridian a modern exploration of acupuncture: Churchill Livingstone; 1991 p2.
 40. Bensoussan A. Talley NJ, Hing M, Menzies R, Guo A, Ngu M. Treatment of Irritable Bowel Syndrome with Chinese Herbal Medicine – A Randomised Controlled Trial JAMA Nov.11. Vol. 280 No.18. 1996.
 41. Aakster CW. Concepts in alternative medicine. Soc. Sci Med 1986; 22(2): 265-273
 42. British Holistic Medical Association. Report on the Science Working Party on Alternative Therapy. BHMA, 1986
 43. Roberts H. Women and their doctors: power and powerlessness in the research process. in Doing Feminist Research, ed. H. Roberts, London: Routledge and Kegan Paul, 1981.
 44. Kingham S. Medical Research on Trial New Scientist : Sept.18 p.48-52. 1986
 45. Schulz KF. Unbiased Research And The Human Spirit: Challenges of Randomized Controlled Trials: J. Can. Med. Assoc. Sept 15. 153 (6) 1995.
 46. Sackett DL. Bias In Analytic Research: J Chron Dis Vol32, p 51-63 Pergamon Press Ltd. 1979

47. Klien MC, Gauthier RC, Jorgensen SH et al: Does epistomy prevent perineal trauma and pelvic floor relaxation? Online J Curr Clin Trials July 1 (doc 10) 1992.
48. Klien MC, Gauthier RJ, Robbins JM et al: Relationship of epistomy to perineal trauma and morbidity, sexual dysfunction, and pelvic floor relaxation. Am. J. Obstet Gynaecol 171: 591-598 – 1994
49. Schulz KF, Chalmers J, Hayes RJ et al: Empirical Evidence of Bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 273 408-412. 1995.

14.

50. Schulz KF, Chalmers J Grimes DA et al. Assessing the quality of randomisation from reports of controlled trials published in obstetrics and gynaecology journals. JAMA 272: 125-128 1994.
51. Altman DG, Dore CJ: Randomisation and baseline comparisons in clinical trials. Lancet 335:149-153 1990.
52. Cooper J.D. ed. Philosophy and Technology of Drug Assessment Vol.1 Decision Making on the efficacy and Safety of drugs. Washington D.C. interdisciplinary Communication Associates 1971.
53. Palmer P. ed. Controversies in Clinical Pharmacology and Drug Development. New York Futura 1972.
54. Vander Harr, T.A. & Miller M. Warning: your prescription may be Dangerous to Your Health New York 1977
55. Sapiro M.F., Charrow R.P. The role of Data Audits in Detecting Scientific Misconduct. JAMA 261:17 (May 5 1989) 2505-2511.
56. Wade N. Physicians who Falsify Data. Science 180 (June 8 1973), 1038.
57. Pleifer M.P., Snodgrass G. The Continued use of Retracted Invalid Scientific Literature. JAMA 263:10 (Mar. 9 1990) 1420-1423.
58. Lewith G. Misconceptions about research in complementary medicine in Examining Complementary Medicine: Vickers A.(Ed.) Stanley Thornes (Publishers) Ltd. 1998 P.174
59. Peer review Biases? News Section: The Journal of Chinese Medicine May 1999 quoting a publication in JAMA (19-9-97).
60. Reilly D. Some Reflections on Creating Therapeutic Consultations in Peters D. (Ed.) Understanding the Placebo Effect in Complementary Medicine – Theory, Practice and Research. Churchill Livingstone. P.96. (2001).
61. Maciocia G. Safety of Chinese Herbal Medicine: Su Wen Press (1999).
62. Fielding N, et al. Linking Data Beverley Hills, Calif: Sage publications (1986)
63. Denzin N. The Research Act: a Theoretical Introduction to Sociological methods. 2nd ed. New York; McGraw Hill, (1978).
64. Birch S. Diversity and acupuncture: acupuncture is not a coherent or historically stable tradition. in Vickers A. (Ed.) Examining Complementary Medicine. Stanley Thornes (Publishers) Ltd. (1998).
65. Tukey J W Methodology, and the statistician's responsibility for both accuracy and relevance. J Am Stat Assoc: (1979), 786-793.

