THE INTRIGUING TRANSMOGRIFICATION OF
THE PLACEBO

AND

ITS ROLE IN MEDICAL RESEARCH

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Submitted for the degree of Doctor of Medicine

The University of Edinburgh

2001
DECLARATION

In accordance with the postgraduate degree regulation 1.2.7 of The University of Edinburgh, I declare that this thesis has been composed by myself and describes my own work together with that published by others as referenced.

Dr R A P Burt
15 February 2002
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DEDICATION

This thesis marks the culmination of a medical career which has been considerably shaped by contact with three men. My early interest in drug action and evaluation was stimulated by Dr. Garnett Davey, the discoverer of the dihydrofolate antagonist proguanil (Paludrine), still one of the safest and most widely used drugs for malarial prophylaxis and treatment. In the early 1950s Dr. Davey used to stay with us in East Africa while he conducted clinical evaluations of the anti-malarial properties of the drug. Some years later, when he was the Director of Research for the I.C.I. Pharmaceuticals Division, Dr. Davey encouraged me as I contemplated a career in the pharmaceutical industry and during my time as a house surgeon, invited me to spend four days as his guest at Alderley Park, the I.C.I Research Centre. This was highly instructive and opened my eyes to the opportunities and activities of physicians in the pharmaceutical industry, particularly when I was able to spend time with scientists of the calibre of Dr. James Raventós who discovered the general anaesthetic properties of halothane, and a young physician who was using remote, single channel ECG telemetry in dogs to study a new class of drugs that slowed the heart rate and lowered blood pressure. He later became Sir James Black and the drugs, of course, were the β-adrenergic blockers.

There is a little known aside to the β-blocker story: after the concept of α- and β-adrenergic receptors had been proposed in 1948 by Alquist, the first β-blocking drug was synthesised not at I.C.I. but at Eli Lilly in Indianapolis, by Irving Slater, Ph.D. His compound was a dichloro analog of isoproterenol which, unfortunately, was not clinically useful because it also possessed potent sympathomimetic properties. His
data were published in 1958 and he kept a sample of the compound on a shelf in his office until he retired. In their 1962 paper describing the first clinically useful β-blocker, 'Alderlin', Black and Stephenson acknowledged the precedence of Slater and his colleague Powell. In those days I.C.I. were attempting to establish 'name recognition' for these new compounds, so the next two β-blockers were named Eraldin and Inderal, all semi anagrams and a play on the word Alderley.

While a medical student at Edinburgh in the second half of the 1950s I had the immense good fortune to be taught therapeutics and materia medica by Professor (later Sir) Derrick Dunlop. His teaching was memorable for its style, quips and bon mots with which he peppered his presentations, and for the common sense that he attempted to instill into our practice. Following the thalidomide disaster he left Edinburgh at the Government request to create the Dunlop Committee, the drug watchdog committee as the British press dubbed it. As a house physician in Ward 28, I had prescribed thalidomide to elderly in-patients as a sedative, until my Chief, Sir James Cameron, who was President of the Royal College of Physicians of Edinburgh at the time, pointed out the reports of neuropathy that had been associated with the drug, so the creation of this eponymous committee to regulate the evaluation and marketing of new drugs was intriguing. Later still, when Sir Derrick had become 'Gamekeeper turned poacher,' as he put it on joining Sterling-Winthrop as a corporate Director, I, as Medical Research Director for Winthrop in Europe, came to know him from a different perspective as we discussed new drug evaluation and the regulations surrounding these activities.
During my training in Edinburgh I realised that with anaesthesia I was practicing applied clinical pharmacology, at that time a fledgling and barely recognised speciality. Anaesthetists have an advantage over physicians (Americans call them 'internists') in that we give our drugs and watch them take effect, whereas physicians prescribe drugs but very seldom see the patient actually take them or see the immediate or delayed effects.

By this stage in my training I had developed considerable interest in the subject of pain and its relief, so I joined Sterling-Winthrop to learn more about drug discovery and drug evaluation in general, but more particularly to work with their newly synthesised analgesic pentazocine, (Fortral in the UK, Talwin in the US). As a result, at the 1966 Annual Meeting of the Scandinavian Society of Anaesthetists in Copenhagen I first met Dr. Henry Beecher, Dorr Professor of Anesthesia at Harvard University, and at that time the doyen of analgesia and analgesic research world wide. In addition to articles describing his observations on the effect of pain in United States soldiers wounded during the Anzio beachhead landings of World War Two Beecher had published, in 1955, one of the most widely quoted papers on placebo (which, incidentally, he pronounced playseebo) and a book on the measurement of subjective responses, of which pain is perhaps the most subjective of all. He had also written articles and a book (my copy has a generous inscription from him) critical of many practices in the United States which had been performed under the banner of medical research. As I came to know Beecher we had many discussions about clinical research, drug evaluation, subject protection and subject abuse and, no surprise, the
role and place of placebo in medical research. Many of the study designs which I have
employed for the evaluation of analgesics and other drugs grew from these discussions.

With this background perhaps it is hardly surprising that I developed an interest
in all aspects of drug development, and I date my interest in the use of placebo from
my meeting Beecher. I believe that, at some time or another, I have read everything
that he published on the subject and I hold him in high esteem, quoting from him
frequently and extensively.

To these three senior colleagues, who at different times and in different ways,
befriended, stimulated the interest of and encouraged a very junior colleague, I owe
an enormous debt. As I come to the end of my own career I hope to make a
compelling argument for the retention of placebo as a research tool for the evaluation
of new drugs. If this goal is achieved then credit is due to these three men, to whom
I dedicate this thesis as a belated token of thanks for their guidance, encouragement,
willingness to teach and share ideas.
Dr. Garnett Davey.

Photograph supplied by, and used with permission of, AstraZeneca, Cheshire, England.
Professor Sir Derrick Dunlop.

Photograph supplied by, and used with permission of, The Royal College of Physicians of Edinburgh.
Professor Henry Beecher.

Personal photograph taken outside Boodles Club, St. James, London, 1970.
ACKNOWLEDGEMENT

In 1945 Dr. Pepper bemoaned the almost total absence of papers with placebo in the title. Since 1950 there have been published over 1,000 such papers and I myself have made a very modest contribution to this list. Many of these papers quote from others or are repetitive and I make no claim to have reviewed or quoted from every publication. From those which I have read, and from the large stack of copies of publications on placebo which I have collected over the past 30 or so years, I have attempted to select the first, the most comprehensive or to my mind the most relevant and interesting, publications to support my arguments and position in this thesis.

In this task I have received and gratefully acknowledge the unstinted and enthusiastic help from the Library staff at the Royal College of Physicians of Edinburgh, the Royal Society of Medicine in London and the College of Physicians of Philadelphia, of which institutions I am a Fellow, Philadelphia University where I lecture, the public library in Radnor, PA., which I support with my state taxes and the Bodleian Library in Oxford with whom I have no connection but nonetheless received willing help.

These people allowed me to read, or provided me with copies of, the references that I did not already possess and from which I have quoted. It was interesting to see how transcription errors have occurred: for example, Pepper misquotes the definitions of placebo by Motherby and Quincy, substituting OF instead of OR and thereby considerably changing the meaning: Johnson, by inserting an extra NOT, reverses Beecher’s original comment on the placebo effect of surgery, and Shapiro disagrees with Encyclopaedia Britannica on Queen Anne’s success with the
Royal Touch, claiming that she was unsuccessful. All of these are discussed and referenced in the text.

I make these points not to claim superiority but because I have learned just how easy it is to misquote or incorrectly transcribe. I have taken pains to check the original references that I have used, but I accept that if there be any such transcription errors in this thesis then they are mine and mine alone.

As previously stated, my interest in the various facets of the placebo started when I met Professor Beecher, but numerous colleagues have given me ideas, listened to the discussions and provided assistance and guidance in ways too numerous to mention. Work on this thesis, I suppose, could be said to have started in the late 1960s when I began to read and collect articles on the topic, but most of the task has been performed during the 25 years that we have lived in the USA. I should be remiss if I did not acknowledge the opportunities for research in study design and the encouragement to pursue my interests that were offered by Sterling-Winthrop and Eli Lilly in the UK, Lilly Research Laboratories in Indiana, Syntex Research in California, Elan Pharmaceuticals in Georgia and Covance Inc. in Pennsylvania.
AN EXPLANATION

I recognise this thesis is somewhat unusual in that it does not follow the conventional pattern of describing and presenting results and interpretation of direct experiments in the basic sciences or clinical medicine. It does, however, examine and discuss a subject that is critical to almost all direct clinical evaluation and assessment.

Advances in medicine depend upon the results of clinical investigations. If these investigations are not well conceived or designed, if they lack scientific rigor or assay sensitivity, then the ethics of conducting the investigation can be questioned. If the results are flawed or do not lend themselves to valid interpretation then they become misleading, at best, possibly dangerous and probably useless. Fortunately, there is available an agent which can help to avoid many of these problems: unfortunately, this agent and its effects are misunderstood and misinterpreted by many critics, to the extent that the placebo has become a divisive cause célèbre in modern medical research.

The Hypotheses

a) Primary

Throughout this thesis my primary hypothesis is that the use of placebo is essential for most clinical investigations in modern medical research. To support this position I have developed several secondary hypotheses, as outlined.
b) Secondary

My secondary hypotheses concern:

i). the misunderstanding of what placebo was and has now become;

ii). how the concept of placebo entered the medical lexicon and how its use in medical practice was heavily influenced by the dictionary definitions;

iii). how physicians in the 19th. and early 20th. century used placebos in their practice and understood how the placebo effects could be used to benefit their patients;

iv). how the modern therapeutic revolution has created effective drugs so that use of the placebo as a treatment is no longer necessary or acceptable;

v). how modern medical practice, although rightly abhorring placebo as treatment, fails to understand and appreciate the ever present ubiquity of the placebo effects;

vi). how this has created confusion so that critics attribute to placebo problems which should more accurately be aimed at other targets such as the informed consent process;

vii). how use of placebo is not synonymous with 'no treatment' and how imaginative study design permits all patients in the study to receive standard medical care even with the inclusion of a placebo; and
viii). how omitting placebo may invalidate the study by reducing assay sensitivity so that Type I and Type II errors are undetected, leading to erroneous interpretation of the results.

It is true that my thesis is not concerned with a single study, but instead I have reviewed and described a range of studies, covering several different therapeutic areas, including many studies that I either designed or with which I was closely involved, to support my contention that the critics are wrong and that placebo is an essential tool in many aspects of modern medical research.
INTRODUCTION.

“When I use a word,” Humpty Dumpty said, in a rather scornful tone, “it means just what I choose it to mean – neither more nor less.”

“The question is,” said Alice, “whether you can make words mean so many different things.”

“The question is,” said Humpty Dumpty, “which is to be master – that’s all.”

Through the Looking Glass.
Lewis Carroll, 1832 - 1898.

Controversy, argument and criticism are strangers neither to medical practitioners nor to the practice of medicine. The great advances in medicine since the end of the Second World War have generated new ethical arguments and divisive controversies far beyond anything conceived in that first code of ethics for physicians, produced approximately 2,500 years ago in the form of the Hippocratic Oath. These impressive changes have demanded reconsideration of, for example, the ethics of access to patient records, rationing of medical care, resuscitation of patients, continuing treatment of comatose patients, genetic manipulation and pharmacogenomics, to name only a few topics of current discussion. The role of ‘alternative’ medicine, the treatment of members of religious sects who refuse blood transfusion, and the availability of organ transplantation have expanded the religious, ethical and moral aspects of medical treatment with consequent impact on the
responsibilities of the physician. Finally, resulting directly from the Nazi atrocities committed on prisoners during the Second World War, there has been increased scrutiny of all aspects of patient protection when they are subjects in clinical trials and experiments.

In this maelstrom of discussion there remains *Placebo*, which is the first person singular, future indicative of the Latin *placere*, meaning "I shall please." Just how this word came to evolve into one of the most divisive enigmas of modern medicine is an interesting tale.

Parts I – IV of the thesis provide an historical review of the transmogrification of the word and conclude with a review of the medical use of placebo from the 19th. and 20th. century. Part I starts with the early translations of the Bible and explains the background that led to the confusion and criticism. Part II describes how the meaning of the word changed from Biblical days through its appearance as a noun in the Middle Ages, with examples from the works of Chaucer. Part III is concerned with the appearance of definitions in medical dictionaries towards the end of the 18th. century, and considers the changing definitions through the 19th century, up to present day dictionaries.

While there is no doubt that placebos were used extensively for treatment during the 19th. and early 20th. centuries there is a marked paucity of publications describing this use, but even in these days there were obvious differences of opinion among members of the profession as to the ethics of this use and whether physicians who prescribed placebos were not being inherently dishonest with their patients. In the aftermath of the Second World War, placebos were still being used as treatment,
but now practitioners were more willing to discuss openly their practice, some defending the placebo as a useful therapeutic tool.

Part V considers what the placebo is and what the components of the placebo effect, or response, may be. Understanding of the concepts and use of placebo has not kept pace with the monumental advances in the science of modern medicine in the last half century, and physicians tend to treat the concept of placebo with disdain or disparagement. Their own role as a component of the placebo effect and their ability to induce huge variability in the placebo response or how this can be affected by the interactions of patient and physician, seem not to be appreciated.

These effects are discussed in Part VI, and although there may be no role for the placebo in modern medical practice the placebo effect pervades every kind of patient-physician relationship. These same components impact every clinical research project at least as much as they impact daily clinical practice, probably more so.

Criticism of the use of placebo in clinical research is not lacking and Part VII presents each criticism or facet of the criticism, discusses its rationale and the factors that provoked it. I then attempt to answer each criticism, to disprove the validity or at least to offer an alternative explanation or interpretation.

The important role of placebo in medical research is addressed in Part VIII and subsequently. Placebo can make contributions that are directly applicable to medical practice, solving problems and providing answers to patient queries. Examples are presented, emphasizing the blurred line that separates medical practice from medical research. Part IX describes the different phases of a clinical development programme for a new drug, briefly looks at study designs and finds roles for placebo in different
designs. However, it is the use of placebo as a comparator in clinical trials that draws the ire of the critics and in Part X examples are offered from Phase I and II studies in which I had substantial involvement in the planning, monitoring, conducting and even as a participating subject, to show the different functions of the placebo as well as recognising that it is not always necessary to have placebo as a study component.

The expanded studies of Phase III and IV create different problems which are identified and discussed in Part XI, and the distinction between placebo effect and the perceived placebo effect is introduced. Part XII examines specific studies, including several of my own, to explain the use of placebo in providing assay sensitivity. Because a full reference is provided for each study I have not repeated all the study details but have concentrated on that aspect which illustrates the point to be made and suggested some study designs that can be used to limit exposure to placebo. Regarded as ineffective and putting patients at risk, placebo is usually seen as a villain, but the truth is somewhat different, and in Part XIII I suggest that placebo actually reduces the number of patients exposed to risk in studies.

Throughout the thesis each Part builds on the previous Parts, so there is constant cross referring, in the form of a musical Rondo, but finally, in Parts XIV and XV the arguments against placebo are challenged once more, leading to the conclusion that exclusion of placebo would invalidate much of the data obtained from clinical trials while wasting resources and putting at risk patients for no benefit to themselves or society in general. In short, I submit that placebo, when used in studies with full, informed consent of the participants, is an essential and integral
component to provide the assay sensitivity without which many studies would not be ethical.
THE TRANSMOGRIFICATION OF PLACEBO

Confusion and controversy

I. THE BIBLICAL ORIGINS

a) ‘In the beginning was the word.’

Borrowing the opening line from the Gospel according to St. John seems appropriate because *Placebo* first appeared in a Biblical translation of Psalm 114. In later translations the word was moved to Psalm 116 and modern interpretation has it that the original translation may have been incorrect. However, to appreciate the problems faced by translators of the original texts and explain how the various changes in location and meaning came about it is necessary to embark on a short Ecclesiastical journey.

The Greek language Septuagint version of the Bible, so named for the 72 linguists who were sent to Alexandria by Ptolemy II Philadelphus (285 – 246 BC) to translate the Hebrew Biblical texts, is the earliest extant translation of the Bible (1). The translators encountered great difficulties with the original Hebrew language as they had incomplete texts from which to work and no knowledge of the Hebrew technical terminology which had become obsolete over time (2). Additionally, in ancient times there was no fixed or uniform system of chapter divisions and often there was no indication of transition from one psalm to another, so varieties of verse groupings were possible. For example, in the Hallelujah Psalms, numbers 111 – 117, the Septuagint
translators combined 114 with 115 and divided 116 into two. By the 3rd. century, as a result of accidental corruptions and errors by scribes and copyists, versions of the Septuagint text varied from copy to copy. Although Latin translations of the Septuagint had existed from the 2nd. century textual confusion in these Old Latin versions had made them unacceptable to the Church (3). This situation had to be remedied, so towards the end of the 4th. century Pope Damasus commissioned his secretary, Eusebius Hieronymous (c. 347 – 420, later to become St. Jerome), to produce a new, acceptable, Latin translation of the Bible.

b) The translations of Saint Jerome.

St. Jerome was extremely well qualified for this commission. Born in Stridon in Dalmatia, he was the outstanding scholar of his age, remembered for his erudition and understanding of the Bible. Regarded as the most learned of the Latin fathers of his day, fluent in Latin and Greek, he learned Hebrew so effectively that he was able to give lessons on the Hebrew text of the Psalms.

St. Jerome started with a translation of the Psalms and the Book of Job and eventually produced three distinct Latin translations of the Psalms, all still extant (4). His first was a translation into Latin from the Greek Septuagint version. Although not totally accepted, this translation was incorporated into the liturgy by the Catholic Church at Rome and is known also as the Roman Psalter. The second translation, again into Latin from the Greek, and published in Palestine, was based on the Hexaplaric Septuagint. This version, popular in Gaul, became known as the Gallican Psalter, and was adopted into the third translation. St. Jerome found the same
difficulties with translating the Psalms as were found by his predecessors, and although he brought the Latin closer to the Hebrew, the Gallican version still differs from the Hebrew version in many places. For example, in the Gallican version Psalm 14 includes the addition of three verses from St. Paul's Epistle to the Romans, which obviously could not have been in the original Hebrew text.

After these two attempts St. Jerome realised the futility of continuing to translate into Latin from the Greek text. Between the years 391 – 406, making a fresh translation directly from the Hebrew, he produced a Latin version of the Old Testament which is known as the editio Vulgate, or common version (5). Initially this was received with suspicion because it diverged significantly from the Old Latin version and seemed not to be in accord with the then traditional versions. By the 8th century however, the superiority of the third translation led to its ultimate acceptance. With the passage of time and continuing copyist errors the Old Latin and Vulgate versions tended to become composite, as might be expected with a new revision of an existing text, although scribal corruptions and variations have been found (5) in the more than 8,000 surviving manuscripts.

c) The Introduction of Placebo.

The first appearance of placebo is in Psalm 114, verse 9, of the Gallican version, based on the Greek Septuagint (6). This translation divides the Psalms in a different manner from the other Bibles and it has been noted that, in addition to the translation difficulties already described, the Psalms created additional problems for a translator because the Psalter was not only a book to be read, but also a song to be
sung (6). The first line of the verse appears as *Placebo Domino in regione vivorum* and this has been translated into English as "I shall please the Lord in the land of the living." Confusion has occurred because in other translations, in particular the Vulgate, this verse has been moved to Psalm 116 verse 9, with Psalm 114 reduced to 8 verses. It has been suggested (7) that this change occurred because the original Hebrew line *ethalekh liphnay adonai b'artzot hakhayim* (translated as "I will walk in Yahweh's presence in the land of the living") was attracted to Psalm 116: verse 8 under the influence of the parallel Psalm 56, where verse 13 is very similar to verses 8 and 9 in Psalm 116 ("For you have rescued me from death to walk in the presence of God in the light of the living").

Controversy has arisen also because of St. Jerome's use of *placebo* ("I shall please") for the Hebrew word *ethalekh* ("to walk"). This anomaly has been reported by several authors (8, 9, 10) and defended or explained by others. The Latin has been accepted as an accurate, direct translation from the original Greek in the Septuagint, *Ευαφρέστησα ενω πιον Κυριον εν χειρα ζωντον* and also as a meaningful interpretation of the Hebrew (6). Jacobs suggests that while the simple Hebrew *elech* means "I will walk", the reflexive grammatical form *ethalech* has a more purposeful meaning in keeping with "I will be in step with" or "I will please." He further notes that this use of "walking" is translated several times in the Septuagint version of Genesis as "pleasing" (6). Support is provided by Pepper (10) who notes that the Hebrew can be translated as "to walk habitually" and this is used in phrases such as "he walked before God" and therefore by implication, was pleasing God. However, an alternative translation of the Greek (11) proposes "I will be
pleased in the company of the Lord in the land of the living.” Another explanation as to why St. Jerome should have chosen *placebo* for his Latin translation is that he may have believed that anyone who walked before the Lord would please Him and perhaps used the word for euphony or metre (9).

In the 15th century the development of printing made possible the production of consistent and stable texts without corruption of scribal errors from copy to copy. Taking advantage of these benefits, a new version of the Vulgate was produced in 1592, under the auspices of Pope Clement VIII. In 1611 the King James VI version in English, the first translation under Royal patronage since the Septuagint, was published. Forty seven scholars participated in this effort which understandably shows a lack of consistency, but it is generally accepted that the Jewish sources involved in the translation helped to produce a version that is the most faithful to the original Biblical language (5). In the King James’ version, Psalm 116 verse 9 is translated as “I will walk before the Lord in the land of the living.” and this is consistent with Psalm 56 verse 13. It would seem that this time the scholars did not agree with or accept St. Jerome’s interpretation.

It is worth noting that even with the advantages of printing these ‘modern’ translations, versions were still published which contained differences or errors. For example, in 1611, the Book of Ruth 3: verse 15, contained the “He” and “She” versions. In 1631, publication of the ‘wicked’ Bible in which the word *NOT* was omitted from the seventh Commandment (Exodus 20: verse 14) cost each of the printers a penalty of £300 and in 1717 the ‘vinegar’ Bible resulted from a copyist error in the heading for Chapter 20 of the Gospel according to St. Luke.
The discovery of new documents such as the Dead Sea Scrolls has expanded and changed interpretations of the Hebrew, Greek and Latin words so it is hardly surprising that St. Jerome's interpretation of \textit{placebo} has been challenged, deemed incorrect, altered and generally surrounded with controversy.

d) \textbf{Was the best word chosen?}

Reviewing the proposals, suggestions and difficulties described above, I prefer to believe that St. Jerome, with his detailed and extensive knowledge of Latin and Greek, deliberately chose \textit{Placebo} to convey the impact, nuance and shade of meaning that he wanted to impart. With his linguistic skills he surely would have used \textit{ambulato} ("I will walk") if indeed he thought that was what the Psalmist intended. Words change their meaning, emphasis and implication over time and similar subtle changes occur frequently even in the same language, as we see today between modern British English and American English (12). To take a few examples starting with one from medicine, the term Sister in Britain is used properly and respectfully to address the senior member of the nursing staff. Such an appellation in the United States, however, is likely to be greeted by the recipient with much less enthusiasm! In Britain the word stupid is regarded as a very mild rebuke, encompassing a hint of the bizarre, but in the United States it is regarded with much more gravitas and with strong overtones of insult. Instead, Americans use dumb for the mild rebuke.

Perhaps the biggest change in recent years has seen the word gay pass from being a lighthearted, happy adverb or adjective to a noun that describes a particular life style. Other words may change their meaning less dramatically, for example the
implication of presently changes from the British procrastination of some time in the near future to the American imperative, right now. Momentarily changes from the British starting and then abruptly stopping to the American interpretation of starting in a moment.

So, how will a translator in the future be expected to know these subtle differences and nuances and would it be considered incorrect if one translation refers to a female sibling of a member of staff, the second to a person who is mute, the third to express an emotion and the fourth....?
II. IN THE MIDDLE AGES

a) Changing the verb to a noun

Sometime in the 13th century the word *placebo* entered the English language, variously translated as 'to please', 'to give pleasure', 'to be approved', 'to be pleasing', 'to be agreeable', 'to suit', 'to satisfy', (13). Acceptance of St. Jerome's translation *Placebo Domino in regione vivorum* by the Roman Church led to the incorporation and first use of the word into the first antiphon of Vespers for the Dead. In the 13th. and 14th. centuries these Vespers, or Lauds, were recited and sung after the Mass at the graveside (13). In time this service came to be known by the first word, and family members and mourners attending the Burial Mass would sing the Placebo (9). Towards the end of his life, John Wyclif (1330–1384), theologian, church reformer and promoter of the first complete translation of the Bible into English, perceived a change in Ecclesiastical outlook when he wrote 'Prelatis ben more bounden to this prechynge......than to sei matyns, masse, evensong or placebo.' This quotation is only one example of several similar quotes from religious leaders and writers, including John Knox, provided by the New English Dictionary (14).

At funerals Priests and Friars would pester the populace for money to sing these prayers, often joined by professional mourners who attended the interment and also sang Placebos at the bier, sometimes in lieu of the family and always in the hope of being remunerated by the grateful family members (13, 15). For those Friars known as Limiters this was an important source of income because, as the name suggests,
they were granted by the town and city fathers the right to beg for alms only in certain limited districts of the town or city. Figure 1 shows a *memento mori* of the Placebo in the Middle Ages (16). A corpse has been buried in a grave. The mourners in black, with a child present, are probably the family members while the two men beside the Priest may be Friars or professional mourners. The text, clearly headed *Placebo*, exhorts the Christian man to contemplate death steadfastly and remember his own impending end.

By the 14th century the word *placebo* had taken on a secular meaning, becoming derisive and meaning ‘to sing, be servile, time-serving or to play the sycophant’ (15). In the Parson’s Tale, Chaucer writes ‘Flatereres been the dueles Chapellyns that syngen eure Placebo’ and in a modern translation, ‘Flatterers are the Devil’s Chaplains, always singing *Placebo.*’ (9). It is not difficult to understand this transition, given the role of the Priests, Friars and other mourners and easy to see the low regard in which certain members of the clergy were held in Chaucer’s time.
Figure 1  Office of the Dead.

Photograph supplied by, and used with permission of, The Bodleian Library,

b) Geoffrey Chaucer (c. 1340 – 1400) and The Canterbury Tales.

The Canterbury Tales is regarded as one of the greatest books in the English language, written by an acute and accurate observer. Chaucer was well connected and well schooled: after school he was hired as a page in the household of the third son of King Edward III. John of Gaunt, the Duke of Lancaster, was a faithful patron and protector throughout his life, and when Chaucer, a soldier, was captured in France during the 100 years war, part of his ransom was contributed by the King himself. When he returned to England Chaucer was employed by the King on foreign missions.

Chaucer read widely in Latin, French, Italian and Anglo-Norman. He became an expert in science, especially astronomy, physics, alchemy and medicine. He knew senior churchmen and, blessed with a prodigious memory, he quoted frequently from every book in the Bible. Clearly an intelligent, highly educated and extremely observant recorder, it is likely that Chaucer was totally familiar with changes in meaning, nuance and interpretation of words in the languages of his day. *Placebo* appears in three of the Tales. As already quoted, it appears in the Parson’s Tale, which was written in prose. It also appears in the Tales of the Summoner and the Merchant quoted below from a modern English translation (17).

The Summoner’s Tale describes the murder of the son of a knight and the quandry in which the speaker finds himself when advising his friend how to break the news to the father:
What should I answer of the knight

His son was slain, there is no more to say,

Dealing with Lords be careful in your play:

You sing Placebo! I shall if I can,

The Merchant’s Tale is a discussion concerning marriage and the perceived fickle nature of women and wives, between two friends and an elderly knight who seeks to court a much younger maiden. The two friends are named Justinus and Placebo, with Placebo clearly a flatterer and sycophant throughout the discussion.
c) The absent placebo: Chaucer's error of omission?

In the search of the Tales for a mention of placebo in a medical context, there is a curiosity on a par with the dog which didn't bark and thus attracted the attention of Sherlock Holmes. In the Prologue to the Tales, Chaucer describes the characters who are about to undertake the pilgrimage to Canterbury. One of the pilgrims, a Doctor of Physic, was based on John of Gaddesden who trained at the then world leading Montpellier School of Medicine, of whom Chaucer states:

He gave the man his medicine then and there.

All his apothecaries in a tribe

Were ready with the drugs he would prescribe.

And each made money from the other's guile,

In extolling the virtues of the Doctor in the Prologue Chaucer includes a promotional twist by listing John of Gaddesden among the classical physicians with whose work the Doctor of Physic was familiar, but there is no mention of placebo in the drugs that were prescribed. In itself the Physician's Tale is a story of unrequited love between another old knight, an untrustworthy judge and another young maiden, and contains no medical information and no mention of treatment or placebo.

With his knowledge, erudition, language skills, foreign travel, contacts and remarkable memory, it seems to me very unlikely that Chaucer simply overlooked, or forgot to mention the medical use of placebo, if this had been introduced into medical practice by this time. It is also likely that John of Gaddesden would have been familiar with placebos, and mentioned them to Chaucer, if indeed these were a part of
medical practice of the time. It is more likely that at this time the concept of a placebo in medicine simply did not exist.
III. PLACEBO JOINS THE MEDICAL LEXICON

In fact, it was some four centuries later before the word was to be introduced to medicine.

a) Dictionaries Ancient

From the beginning it is clear that the arrival of placebo as a noun in the medical lexicon, was varied and incomplete. A reference to each from the plethora of dictionaries published in these early years would become repetitive, boring and not particularly illuminating. I have attempted to follow the changing definitions in the medical and general dictionaries, concentrating on those changes which I find significant for the practice of medicine and the development of placebo as a research tool. Equally intriguing however, are those many dictionaries that I reviewed which made no mention of the word when others did. Was this an immediate indication of the arguments and disagreements that have since followed the word?

Placebo was not mentioned in the Latin-Greek medical dictionaries published in the 16th, 17th. or 18th. centuries, nor in the early German, French, Italian or Portuguese dictionaries (18). It was not mentioned in the first English language medical dictionary published by Blanchaart in 1684 (18) and it was not included in the first edition of Quincy's Lexicon Physico-Medicum (19). Quincy published subsequent editions of his dictionary with the 9th. edition appearing in 1775, all without any mention of placebo. In the same year George Motherby published the first edition of his dictionary and again, placebo was not included (20).
Ten years later the story changed. In 1785 one of the most famous dictionaries in the English language, that of Dr. Johnson (21), published its 7th. edition and in keeping with the previous editions, there was no mention of placebo. However, in the same year, the 2nd. edition of Motherby’s dictionary was published (22), and this defined placebo as a common-place method or medicine. Two years later the same definition of placebo appears in the 10th. edition of Quincy’s dictionary (23). Interestingly, in his presentation to the College of Physicians of Philadelphia (10), Dr. Pepper incorrectly quoted this definition as a common-place method OF medicine, which altered the meaning considerably. Obviously the problem of transcription errors which dogged the early Biblical translations remains even with modern printing techniques.

Two other medical dictionaries (24, 25) published shortly after the appearance of placebo in the dictionaries of Motherby and Quincy do not mention placebo, suggesting that the word was still not in common or frequent use in medical practice at the end of the 18th century. In 1795 an expansion of the earlier definition with an added note of derision appeared in a revision of Motherby’s medical dictionary (26): a common place method or medicine calculated to amuse for a time, rather than for any other purpose. This definition persisted for another edition and was repeated in other dictionaries of the time until 1803 when Fox, (27) for the first time, clearly defined placebo as a medicine and toned down the derisive note: I will please: an epithet given to any medicine adapted more to please than benefit the patient. This definition was accepted and repeated by a well known Philadelphia physician of the time in his own dictionary (28) and was also used verbatim by Professor Hooper when
he revised Quincy's Lexicon in eight London editions and 13 American editions between the years 1811 and 1841, (29, 30, 31 for example).

From about this time placebo became a fixture in medical dictionaries, almost all using the same definition as used by Hooper, with some refinements and minor changes. In 1833 Dunglison (32) defined it as: Placebo: *I will please: an epithet given to any medicine, intended rather to satisfy the patient than to cure the disease.* and stuck to his definition in a 3rd. edition, published in 1842 (33). This definition enraged Oliver Wendell Holmes, physician, attorney, poet, medical school Dean, Supreme Court Justice and humorist, and he disagreed so strongly with this definition that he told a Harvard medical student class '.....the learned Professor Dunglison is hereby requested to apologise for his definition of the word Placebo or expunge it from his Medical Dictionary.' (34). This is one of the earliest times that we get some indication that placebo was being used in medical practice and that this use was not received with universal approbation. Further indications of disquiet with the earlier definitions came from Hooper himself for in his last revision of Quincy (35), he expanded his definition: *An epithet given to any medicine administered rather to amuse the mind of the patient than to fulfill any definite therapeutic intention. It must not be supposed that such administrations are useless: the sensorium often exercises great influence on disease.*

Although the author of an English publication (36) took issue with part of the definition, seeking to correct the Latin translation: *Placebo: Literally, though incorrectly, I will please, applied to any medicine given to please or humor the patient.* it seems that medical dictionaries published for the next century continued to
use the definitions that differed hardly at all from the earlier ones. For example, Dunglison's son, also a physician, undertook a revision and enlargement of his father's Dictionary (37) but disregarded Holmes' request and retained his father's definition of placebo unchanged. Another popular English language medical dictionary (38) again slightly modified the definition: Placebo: *a medicine adapted rather to satisfy, than to benefit, the patient.* (*L. I will please*). These many minor variations are reviewed in great detail by Shapiro (18) and they show a consistent pattern, sometimes with an embellishment such as the identification of the formulation of the placebo, *-water colored with cochineal*. However, there is one further definition from the end of the 19th. century (39) which merits consideration because it offers the first suggestion that placebo was considered to be devoid of pharmacological activity; *a make-believe medicine, sometimes administered for its effect on the patient's imagination rather than because it is of medicinal value.*

There is no doubt that by the end of the 19th. century placebo was firmly established in the medical lexicon and in medical practice and for the first half of the 20th. century it would seem that no major change took place. Nevertheless, there were differences in the way in which medical dictionaries defined placebo, giving hints that some authorities were not entirely satisfied with then current interpretations.

**b) And modern**

In the early part of the 20th. century there were published in the United States three medical dictionaries whose modern descendents are published today. The first, by Dorland (40), followed the previous definitions of placebo as: *a medicine given to*
please and gratify the patient. The next dictionary, by Stedman (41), provided the definition: *an indifferent substance in the form of a medicine, given for the moral or suggestive effect.* and this remained in the next 19 editions. Perhaps the most interesting definition was in the Medical Digest of Taber (42): *Placebo, inactive substance given to satisfy patient's demands for medicine: such as bread pills.* This was the first occasion in a medical dictionary that placebo was limited to inactive substances although Webster's, a non-medical dictionary (43), had used the same definition some four years earlier: *a medicine, or preparation, especially an inactive one, given merely to satisfy the patient.* It is also worth noting that the lawyers had become involved (44), with their own definition *an inert medicine given to please and satisfy a patient who thinks medicine is required.* In 1947 Dorland (45) republished the definition used by Foster: *a make believe medicine given to please and gratify the patient.* and in 1949 Blakiston (46) provided: *a medicine having no pharmacologic effect, but given for the purpose of pleasing or humoring the patient.*

The next significant and totally different definition came from the 22nd. edition of Dorland (47) which introduced the concept of placebos in research: *an inactive substance or preparation formerly given to please or gratify a patient, now also used in controlled studies to determine the efficacy of medicinal substances.* A decade later Stedman (48) expanded and clarified this: *an inert compound, identical in appearance with material being tested in experimental research, where the patient and the physician may or may not know which is which.*

After this time definitions in medical dictionaries became more or less standardised, although many of the non-medical dictionaries maintained the earlier
religious definitions and meanings in addition to the secular ones. Webster’s the oldest, largest and most widely quoted American dictionary (49), currently offers three definitions:

a) *In the Roman Catholic Church*, the Vesper hymn for the dead.

b) *A medicine*, given mainly to humor the patient, a preparation containing no medicine but given for its’ psychological effect.

c) *Something said or done to win the favor of another*. To sing *Placebo*: to agree, to humor someone by agreeing. [Archaic].

The Oxford English Dictionary, largest and most comprehensive dictionary of the English language (50) offers four definitions, in chronological order of the appearance of each meaning:

*Placebo* [a L. I shall be pleasing or acceptable. 1st. sing. fut. indicative of placere].

a) *Eccl.* The name commonly given to Vespers in the Office for the Dead.

b) *In allusive phrases*: to play the sycophant, flatter, be servile or time serving.

c) A flatterer, sycophant, parasite. In Chaucer as a proper name.

d) *Med.* A substance or procedure which a patient accepts as a medicine or therapy but which actually has no specific therapeutic activity for his condition or is prescribed in the belief that it has no such activity.

The most recent edition of Dorland’s (51) has considerably expanded the medical definition in line with modern conceptions of the placebo: any *dummy treatment*: originally, a medicinal preparation having no specific
pharmacological activity against the patient's illness or complaint given solely for the psychophysiological effects of the treatment; more recently, a dummy treatment administered to the control group in a controlled clinical trial in order that the specific and nonspecific effects of the experimental treatment can be distinguished — i.e. the experimental treatment must produce better results than the placebo in order to be considered effective.

Active p. inactive p. a substance having pharmacologic properties that are not relevant to the condition being treated.

Finally, the latest edition of Stedman's (52) provides two definitions, the second of which relates directly to the use of placebo as a research tool:

a) An inert substance given as a medicine for its suggestive effect.

b) An inert compound identical in appearance to material being tested in experimental research, which may or may not be known to the physician and/or patient, administered to distinguish between drug action and suggestive effect of the material under study. SYN. Active p. [L. I will please, future of placeo].

I find it interesting that even the modern definitions continue to refer to placebo as a treatment and as a medicine, while clarifying its role in research activities. Is this meant to indicate that the use of placebo as a treatment continued as the 20th. century closed?
IV. THE PLACEBO AS TREATMENT IN MEDICAL PRACTICE

a) The 19th. and early 20th. centuries

In 1892 *The Principles and Practice of Medicine*, written by Sir William Osler (53), became the standard textbook of medicine, yet only 10 percent of the entire book dealt with treatment. This was not willful therapeutic nihilism but a reflection that practitioners of the day had very few practical choices. Most of their treatments were symptomatic remedies of herbal origin, largely inactive and ineffective, a view shared by another influential physician of the time. In his address to the Massachusetts Medical Society (54) Oliver Wendell Holmes made his famous criticism concerning ‘......the whole materia medica, as now used,......’ but he did not call them placebos, even though he had railled against the definition of the word in Dunglison’s dictionary. Of course, not all the drugs of the time were ineffective. For example, synthetic derivatives of the Poppy, Cinchona and Willow form a major part of modern therapeutics and one of the more enduring of medical advances was the discovery in 1775, by country doctor William Withering, of the action of digitalis when taken as Foxglove tea (Figure 2) in curing dropsy. Although Withering recognised the effect he did not identify the inotropic mechanism of action: even so, it is hard to understand why one hundred years later Holmes told his Harvard class that ‘Digitalis has gone out of favor.’ (55). Perhaps he was expressing frustration at inconsistent formulations and doses, but even if it fell out of favour with the physicians of that time, the drug has undoubtedly returned to favour and today remains an important part of our materia medica.
Figure 2  Purple Foxglove  (Digitalis purpurea)

Personal photograph from the Herb Garden of the College of Physicians of Philadelphia.
Given the state of medical knowledge in the 18th. and 19th. centuries it was probably prudent to believe that the treatments were effective drugs and that the placebo was something else. Thomas Jefferson, the 3rd. President of the United States, for example, criticised what he called the pious fraud of bread pills, coloured water and ash pills (56) so it would have taken a courageous and very secure individual publicly to categorise the remedies of the day as placebos.

One such was Austin Flint, Professor of Medicine at the Bellevue Hospital Medical College in New York for whom the unusual soft cardiac diastolic Flint Murmur is eponymously named. Flint described what is probably the first assessment of sham treatment when he wondered if the current drugs used for treating rheumatism had any effect on the natural course of the disease. Thirteen of his patients 'Were placed on the use of a placebo which consisted, in nearly all the cases, of the tincture of quassia, very largely diluted. This was given regularly, and became known in my wards, as the placeboic remedy for rheumatism. The favourable progress of the cases was such as to secure for the remedy generally the entire confidence of the patients.' Placeboic in italics, and the English spelling of favourable appear as such in the original reference. Interestingly, this paper, which does not mention placebo in the title, was published posthumously, a year after Flint died (57). Coincidence, publication delay or to escape criticism? In Britain also, some were openly talking about placebo and in a popular textbook published a few years later, the authors discuss the treatment of pyrexia using a simple febrifuge and dismiss this as 'probably a mere placebo, but there is every reason to please as well as cure our patients.' (58).
In a review of medical practice in New York around the 1860s, Rosenberg (59) acknowledges the 'routine use of placebos by practitioners in this period.' Others, however, were less comfortable and in 1885 an editor wrote (60) 'Physicians and intelligent laymen know that the former cannot always tell the plain facts to a patient without injuring him. It should be the rule of his life however, to be straightforward and candid. Therefore we say that placebos should be, and need be, rarely prescribed.' He also commented that physicians should 'not find it necessary to keep a polychromatic assortment of sugar pills in his closet.'

Perhaps the most impressive and courageous review of the role of placebo up to this time came at the end of 1902 in a lecture given to the prestigious New York Academy of Medicine by a highly respected Harvard Professor of Social Ethics who admitted that he had often used placebos in treating his patients (61). In his talk Cabot reviewed both the good and the bad aspects of placebos in medicine, and given the setting, the role and the status of the speaker, it is worth considering his comments in some detail. He started by stating 'I approach the subject of truth in medicine, not from the point of view of scientific method, nor of metaphysic analysis, but of professional ethics.' Then in a way which could not be contemplated today he lambasts two physicians, Drs. Munyon and Trutt, for their cancer cures, cures for weakness and all-healing handkerchiefs sent through the mail. I could find no response, riposte or defence from either of the named physicians in subsequent issues of the journal in which Professor Cabot's lecture was published, so maybe his comments were accurate and valid!
Turning to placebo Cabot states: 'Now I was brought up, as I suppose every physician is, to use placebos, bread pills, water subcutaneously, and other devices for acting upon a patient's symptoms through his mind.' He accepted that the frequency of placebo use would depend on the individual practitioners, but doubted 'if there is a physician in this room who has not used them pretty often.' No challenge to this statement by the audience is recorded. Then he shifts his position a little, as if preparing for criticism of his comments. 'No patient whose language you can speak, whose mind you can approach, needs a placebo. I give placebos now and then (I used to give them by the bushel) to Armenians and others with whom I cannot communicate, because to refuse to give them would create more misunderstanding, a false impression, than to give them. If an interpreter is available I tell no lies in the shape of placebo.'

Well into his talk, Cabot starts to review the other side of placebo use. 'It never occurred to me until I had given a great many placebos that if they are to be really effective they must deceive the patient. I had thought of them simply as a means of getting rid of a symptom and no more a lie than hypnotism or any other form of frankly mental therapeutics.' He stressed that in order for a placebo to work the patient must believe in it, but he cautioned that giving a placebo is '...a form of deception which if detected will destroy the patient's trust in the physician.' He gave an example from his own practice where a patient saw him preparing water for subcutaneous injection as a sedative, and asked 'How am I to believe anything you say from now on?' He then asked, is it acceptable to use a placebo if one is not found out? Answering his own question he continued, 'The majority of placebos are given
because we believe the patient will not be satisfied without them. He has learned to expect a medicine for every symptom, and without it he simply won't get well.’ In this statement Cabot was echoing Wendell Holmes (54) who spread the blame more evenly, ‘Part of the blame for over-medication must, I fear, rest with the profession, for yielding to the tendency to self delusion, which seems inseparable from the practice of the art of healing. Another portion of the blame rests with the public, which insists on being poisoned.’

Finally, Cabot generalises: ‘It is we physicians who are responsible for perpetuating false ideas about disease and its’ cure.’ He offers another evil of the use of placebo as giving the patient the harmful idea that every symptom can be cured with a drug: thus it is impossible to convince the patient of that ‘most fundamental principle of therapeutics – to remove a symptom remove its cause.’

Four years later Cabot (62) returned to the subject of the use of placebos with a presentation at the Annual Meeting of the American Medical Association, and on this occasion he was more critical of their use. ‘.....the educated physician gives his drugs as placebos. In my opinion, the placebo habit does more harm than the habit of giving drugs to every patient with full faith in their pharmacologic action.’ And again, ‘Placebos have another bad result. They weaken the confidence of the patient in the physician, because every placebo is a lie, and in the long run the lie is found out.’ Finally, ‘Placebo giving is quackery.’

Following this presentation by Cabot there was a lively discussion from the floor which the Journal editor saw fit to print immediately following Cabot’s article. Dr. H.A.Hare of Philadelphia ‘vehemently denied the truth of any statement made that
members of the medical profession, particularly of Pennsylvania and of Philadelphia, had deliberately given placebos to patients with the idea of fooling or deluding them.' Another speaker, Dr. Cohen asked for the 'intelligent use of drugs, that is to say, the use of known drugs under suitable conditions.' A statement that is hard to criticise today!

From the comments of the various sources quoted above it would seem that the placebo was well recognised and widely used in medical practice during the latter half of the 19th century and the first half of the 20th. century, even if most practitioners did not talk or write about it. In 1938 at the American College of Physicians meeting in St. Louis, Houston (63) gave an extensive review of placebo use in medical practice. He identified three types of placebo, that which is an 'effective drug sometimes', 'The second sort of placebo, the type which the doctor fancies to be an effective medicament, but which later investigation proves to have been all along inert, is the banner under which a large part of the past history of medicine may be enrolled.' And the third which is 'believed in by the physician'. Perhaps Dr. Hare was deceiving only himself when he made his comments.

b) A passing glance at homeopathy

Founded by C.F.S.Hahnemann (1755 – 1843) this system of therapy is based on the principle that a medicinal substance giving rise to certain symptoms in healthy individuals may be effective in the treatment of those illnesses that produce the same symptoms. Although not strictly a part of any discussion on placebo I was able to find
comments on homeopathy from two of the physicians and authors already mentioned. Wendell Holmes (64) stated 'So long as the body is affected through the mind, no audacious device, even the most manifestly dishonest character, can fail of producing occasional good to those who yield it an implicit or even partial faith.' A few years later in his textbook, the younger Dunglison (65), who refused to remove from his father's dictionary the definition of placebo despite the call from Holmes, wrote, 'I consider the doses ordered by the homeopath are too small to be of use.' And later on, 'Can a medical man honestly meet a homeopath in consultation? To this I can only say, certainly not.'

These show the disdain in which two physicians held homeopathy, at a time when most of their own prescribed medicines were of doubtful consistency and efficacy, yet neither author labeled the homeopathic treatments placebo. Might they have recognised that placebo therapy had some utility and was widely used by their colleagues in the medical profession, whom they would not wish to expose or embarrass?

c) After the Second World War.

At this stage two important events occurred, the start of 'The Therapeutic Revolution' which produced new drugs and the Declaration of Helsinki which provided guidelines for patient protection in treatment and research. For the first time there were available drugs that were consistently potent and effective and these had to be evaluated and compared with existing therapies which entailed patient enrollment in clinical trials. Placebo still played a major role in therapy as evidenced by the
increasing number of publications that discussed the role and use of placebo and practitioners seemed more willing to discuss their use of it. Pepper (10) called placebo 'a valuable item of our therapeutic armamentarium.' As Dr. Pepper practiced in Philadelphia, was a highly regarded teacher and clinician who also was President of the College of Physicians of Philadelphia, the oldest society of that ilk in the United States, his comments cast some doubt on the validity of Hare's earlier vehement denials to Cabot. In addition to his accolade to placebo, Pepper supported Cabot saying 'Every one of us has often used the word and often prescribed the placebo, yet how many of us realize how little has been written and how little is known of the history of this word and this type of treatment.'

In contrast to the paucity of papers on the subject in the first half of the 20th. century, the second half has seen a plethora of publications on placebo. Among the earliest was a conference sponsored by an Ivy League University with a major academic medical school (66). The conference was opened with Dr. H.G.Wolff describing the placebo as a 'very important therapeutic device' while Dr. E.F.DuBois lamented that 'They have been considered the humblest, the most unscientific and the most dishonest of drugs.' There followed a lengthy series of case and anecdotal reports from several speakers, all laudatory, describing the success of placebo, its importance in their practice and giving advice on the patients who might best respond. In summarising the conference the Chairman gave three conclusions: there was general agreement on the utility of placebo in practice, there was disagreement on the best agent to use and that successful management with placebo depended on the
proper selection of cases and choice of placebo material. Clearly no reticence on the part of the practitioners here.

In the same year Platt (67), who would become President of the Royal College of Physicians, was in turn scathing and accepting of placebos: 'The frequency with which placebos are used varies inversely with the combined intelligence of patient and doctor.' followed by: 'The point is that the prescription of a placebo should be a deliberate act and not a conditioned reflex, and it should be an invariable rule that it must be something which can do no good.' Again, 'It must be clearly understood that a placebo is given for the mental comfort of the patient, not of the doctor, and that whereas it may occasionally be expedient to deceive the patient it should never be done at the risk of deceiving oneself.'

An Editorial in the British Medical Journal (68) quoted a family practitioner who found that 10% of general practice patients were treated with placebo and added 'There is no question about the usefulness of placebos in therapeutics, nor about the fact that they have in some cases a more powerful effect than known pharmaceutical agents.' The writer heaped on more praise pointing out that there are 'many real symptoms and diseases in which placebo is often justified and works wonders.' Not to be outdone Lancet, perhaps detecting the start of a shift against placebo stirred the controversy with two papers a few years later. Carter (69) discussed the use and abuse of the placebo and warned against prescribing the placebo to please the doctor rather than the patient. He then showed his support with his final statement, 'Nevertheless there is a not inconsiderable place for placebo in medicine and, if intelligently used, I will defend it to the last drop in the bottle.' This was followed by
another senior British physician (70), who was less enthusiastic and wondered why 'placebos are so widely used - are placebos part of the Art of medicine or a necessity?' He saw the placebo as 'a form of deceit initially of the patient ultimately of the doctor.' But like Platt he found for placebo a 'small place when no effective treatment is available, and for re-inforcing patient confidence in his recovery.' Presumably so long as the patient did not discover the deceit! Not every one agreed with these sentiments and two highly critical Letters to the Editor were published in the next week! (71, 72).

American physicians were also providing support. Findley (73) thought that placebo 'should be accorded more respect than it gets. For the vast majority of his patients it and himself are all that the modern physician has to offer.' a statement that showed an understanding of the placebo effect as well as the placebo itself. Earlier, an American textbook (74) noted that 'The most frequent method of psychotherapy is the giving of placebos.' adding '....giving the placebo is at least a recognition that the patient is suffering and the patient appreciates and gets better out of gratitude. The physician who prescribes placebos, in whatever form, is not consciously dishonest.' Leslie (75) quoted Plato 'A lie is useful only as a medicine to men. The use of such medicines should be confined to physicians.' and he also believed that 'deception is completely moral when it is used for the welfare of the patient.' He drew a fine distinction between deception and deceit and offered that if deception was to be used then it must be wholehearted and efficient. He believed that 'there are circumstances where placebos constitute the therapy of choice.' He even offered advice on the types, appearance and formulations of placebo to be used.
In 1970 an Editorial (76) again took doctors to task for 'failing to make effective use of the considerable body of scientific evidence on the placebo effect,' and added 'There may be many occasions when an appropriately presented placebo will be less harmful and perhaps more beneficial than a complex and incompletely understood drug.' The writer also lamented that there was 'little evidence that placebos were being employed in a systematic way.'

i) Personal experience

Whether or not these comments encouraged the use of placebo as treatment is not recorded, but I know from personal experience as a medical student, when I followed tradition by taking locum tenens appointments for medical and surgical residents who were on vacation, and then as a House Officer, that placebos were commonly used as sedatives at the Edinburgh Royal Infirmary in the late 1950s and early 1960s. In the bustle and noise of the wards many elderly patients had difficulty falling asleep at night, even when sedatives had been prescribed and given to them. At such moments it was routine for nurses to give these patients one or two tablets of vitamin C, together with the assurance that these were effective sedatives, and they nearly always fulfilled the promise. In part, the deception was justified by the nurse's knowledge that additional doses of barbiturate, the most widely used sedative at that time, carried risks which a tablet of vitamin C did not, but the active sedatives also required a prescription which entailed finding the physician to write it. Vitamin C was quicker, easier and apparently just as effective! It is worth pointing out that because vitamin C did not require a prescription or written hospital order there was no record of
its use and although the practice was common knowledge among the Residents we did not have to admit to the deception which we condoned. I suspect that we were not unique among the medical profession in this respect.

ii) Practice in general

Thomas (77) has suggested that by the end of the 20th century placebos were deliberately given only rarely as treatment, and he offered a possible explanation that this may be a result of the association with charlatanism. He went on to describe a study which he undertook (78). In 1,656 of 3,848 patients seen in general practice, no firm diagnosis could be made. These patients all had a consultation and discussion of the complaint, received a physical examination and reassurance that there was no serious illness and that they would soon recover. Most patients received a placebo, a few received nothing at all, yet at the follow up visit 82% claimed to have recovered.

That deliberate use of placebos for real life treatment was still practiced towards the close of the century was accepted by a pharmacologist (79) although, like Houston (63), he made the point that some of this may arise because the physician innocently believed that the prescribed drug possessed the relevant pharmacological activity when it didn't! This would fit with the third type of placebo already discussed (63). Even after the close of the 20th century a rheumatologist has described (80) the successful treatment of osteoarthritis in a patient for whom modern conventional therapy had failed to provide relief, using golden raisins soaked in a particular brand of
Bombay gin. However, I believe that this would not qualify as an inert placebo devoid of any pharmacological action.

Modern textbooks offer mixed advice on placebo use. In 1982 one textbook (81) informed its readers that 'Placebo effects are important' but did not advocate the actual use of placebo. Instead the authors emphasised that the physician's enthusiasm and reassurance were important. Another major textbook from a year later also concentrated on the placebo effect pointing out that approximately one third of patients obtain benefit for a variety of illnesses when given therapeutically inert substances (82). Ten years later another edition of the same textbook fails to mention placebo or placebo effects, at all (83). In the United States The Merck Manual has been in continuous publication since 1899 and the pocket sized convenience makes this probably the most widely used medical reference text. Several modern editions refer to the placebo, discussing the nature of placebo effects and also the deliberate use of placebo in treatment (84, 85). The Centennial edition (86), however, while retaining most of the text from the earlier editions, has dropped the deliberate use of placebos, pointing out the deceptive nature of this use and the harm that can accrue if the deception is discovered. Mention is made of the practice of prescribing, say vitamin B₁₂ injection, when this clearly has no relevant therapeutic benefit for the patient, noting that physicians would not prescribe sterile water for injection. If the patient is informed and agrees the authors suggest that placebo could be used as a diagnostic tool in particular circumstances. Placebo effects are also discussed in most recent edition of the first textbook on Clinical Pharmacology (87) with the comment that these
effects can be exploited to supplement pharmacological effects and thus represent the
difference between success and failure of therapy.

So, at the end of the 20th century does placebo have any role at all? Clearly there are different opinions and several authors have suggested that even with modern medicine occasionally we will need placebo as a treatment. Thus some can justify using a placebo under certain circumstances while others decry its use under any circumstances. Is only one choice correct or does some of the confusion arise from misunderstandings of what a placebo is and how it performs: can modern medicine and research actually afford to do without a placebo? I believe not and from this point offer my thesis as to why placebo is still an essential and indispensable part of the modern medical research scene.
THE PLACEBO AND THE PLACEBO EFFECT

Setting the Scene

From this review of the history of placebo and the many definitions that have been created it is easy to see that there can be disagreement and misunderstandings. An Editorial in Lancet (88) referred to placebo as not quite respectable in the context of treatment and the modern connotation of placebo is one of disdain, harking back to the Middle Ages. Hardly surprising that placebo has wound up as an object of derision and embarrassment.

Could the reason be, as Leslie has suggested (75), that modern medicine has become so concerned with scientific advance, the growth of Evidence-Based Medicine and cost driven efficiencies, that too little attention has been paid to the Art of Medicine? Thus, for most practitioners the knowledge, understanding and application of placebo has not advanced and there is confusion between the placebo and placebo effect.

If the case is to made that placebo is an essential research tool in the process of drug evaluation then it is equally essential that the confusion and misunderstandings be dispelled and replaced with consistent interpretations.
V. WHAT KIND OF PLACEBO?

a) Active or impure

When physicians today talk of using placebo treatment they are usually thinking of one of the types described by Houston (63) or along the lines defined by Shapiro (18) as ‘any component of therapy deliberately used although it is without specific pharmacological activity for the condition being treated.’ This component may be, say, tablets of vitamin C or injection of vitamin B12, both of which have clearly defined inherent pharmacological activity but lack specific therapeutic activity against the disease or illness in question. It may also be the use of a drug that is effective in the required therapeutic area, but given at a dose that is known to be ineffective. These are generally referred to as an active or impure placebo.

b) Inert compound

It is important to distinguish the active or impure placebo from the inert placebo, used in clinical research studies. These specially formulated preparations are compounded from inert ingredients such as lactose, starch, isotonic physiological saline or sterile water. Once formulated they are presented as tablets, capsules, ointments, creams or solutions for injection that are identical in appearance to the comparator drugs being evaluated in the double blind (also called double masked) studies.
c) Selecting the placebo

Advice has been offered by several authors (75, 89, 90, 91) as to the most effective formulations for maximizing the effectiveness of the placebo. Route of administration is important: although intravenous injection provides the most impressive psychotherapy with intramuscular injection next in order, in most instances the oral route is preferred for simplicity and convenience. Tablets and capsules should be shaped and coloured red, yellow or brown, should taste, smell and look like medicine and should not look like tablets or capsules that are available at the pharmacy without a prescription. It seems as though green tablets are the most effective anxiolytics, yellow tablets work best in depression (92) and round white tablets tend to be the least effective in all situations. Tablets should be either tiny, implying great potency, or very large, impressive for size alone. Finally, the chosen placebo must never be toxic or noxious, the objective being to help, not harm, the patient.

Cutaneous application of placebos can be made more impressive by incorporating some dissolved substance such as Epsom salts or magnesium sulphate, which although not absorbed through intact skin, cools as it evaporates. Patients with coryza or blocked sinuses often seek relief by inhaling steaming water containing tincture of benzoin. Even though it is only the steam which is therapeutic the smell of benzoin adds verisimilitude. If these suggestions seem facetious or cynical that was not the intent. The placebo effect is a multifaceted phenomenon of which the placebo formulation is but one component, and the spectrum of efficacy of placebo is extremely susceptible to manipulation by outside factors, as we shall see.
Nevertheless, the drive for science in medicine has led to attempts to explain how an inert or impure compound might actually produce a pharmacological response.

**d) A possible mechanism of action**

.........we are not ourselves

When nature, being oppress'd, commands the mind

To suffer with the body.

*King Lear, Act II. 4.*

*William Shakespeare, 1564 – 1616.*

To attempt to explain the mechanism of action as through the mind at first sounds trite, dismissive and even patronising, yet this was the explanation given in all seriousness by Hooper (35) in his last, expanded definition, while Holmes (64) in his dismissive comments on homeopathy also acknowledged the importance of the link between mind and body.

Placebo produces the best effects when used in patients with illness of a subjective nature, particularly pain, disorders of autonomic sensation such as nausea, anxiety, depression and phobias or in disorders of factors under neurohormonal control such as blood pressure and bronchial air flow (93). Beecher (94) described the two phases of pain, the original sensation (nociception) and the patient's reaction (awareness and cognition) and pointed out that placebo modifies only the second, cognitive, phase which may reside in the thalamus (95). Anxiety activates the hypothalamic-pituitary-adrenal (HPA) axis and increases the perception of pain while
removal of anxiety decreases pain. Anxiety also increases blood pressure in a conditioned response that has been described as White Coat Hypertension (96).

The suggestion that placebo might actually have an identifiable pharmacological action followed the demonstration by Lasagna and others (97) that naloxone, a potent opioid antagonist, had hyperalgesic effects in humans. Subsequent studies in animals identified a group of endogenous opioid peptides (often referred to generically as endorphins) in the brain, and showed that these mediated some types of somatic pain (98). Later, these endogenous opioid peptides were linked with regulation of the HPA axis although the precise manner in which these links function remains unclear (99).

Using the dental pain model Levine et al. (100, 101) found that patients who received naloxone reported significantly more pain than did those who received placebo. Also, the patients who obtained pain relief from placebo given first, had an increase in pain level following an injection of naloxone whereas patients who did not have an analgesic response to placebo when given first, did not get an increase in pain level following naloxone. These findings led the investigators to postulate involvement of endogenous opioids in the human placebo response. At the time these studies were criticised (102, 103), and other investigators (104) produced conflicting results, but a recent systematic review of six published studies (105) has concluded that the endogenous opioids do have a role in placebo analgesia. Whether or not the endogenous opioids are involved in the mechanism of placebo analgesia this does not necessarily explain the mechanism of placebo effects, as Wall has discussed (106).

This lack of a clear cut explanation as to how or why placebo works is a disappointment to those who demand a science based justification for their actions.
For these scientists the unexplained mechanism makes placebo an embarrassment but it is worth recalling the experience of William Withering with digitalis. He knew that digitalis worked, he just didn't know how it worked. Perhaps the earlier comments and definitions on the mechanism of placebo were closer to the truth than we recognise. Our science has made clear that so far we barely understand the workings of the brain and the extent of brain-body interactions, so perhaps we should accept that as yet we cannot explain the mechanistic conundrum of the placebo itself and examine instead the response to placebo, the so called placebo effect. Separating these two is something that leads to continuing confusion and misunderstanding.
VI. THE PLACEBO EFFECT AND ITS COMPONENTS.

a) The placebo effect, or response

Even if it is not yet possible to satisfy the scientific demands for an explanation as to how the placebo exerts its effect, at least it is possible to understand how and why these effects, or responses, may be brought about. The placebo effect is a multifaceted, multicomponent response, of which the placebo itself is but one component.

Conditioning gives priority to learning from direct experience (107). In the classical experiments of Pavlov, the dogs started to salivate at the sound of the bell and before they could see the food container, because they had learned from experience that the tintinabulation was always followed closely by the arrival of food. This was a typical conditioning response. Expectation, on the other hand, requires a cognitive appreciation of the information which is then processed and organised for future reference. Expectation places priority on the importance of verbal conditioning (108).

Conditioned enhancement of the analgesic response to placebo, based on direct experience, has been shown to be greater and more important than expectancy, and that these conditioning responses can occur even when no placebo is given (109). An analgesic study (110) and a study in patients with hypertension (111) have shown that the response to the first drug, or dose, influences the response to the second drug, or dose, and these are examples of the conditioning effect. While conditioning from direct experience is a potent means of enhancing the effects of an intervention.
intended to reduce pain, it has been shown that there is also an expectancy interpretation of the conditioned response and that expectancy plays a role in potentiating the placebo effects (112).

Clearly there will be many more investigations into the psychological role of conditioning and expectation and the impact these have on the placebo effect. It is likely that both will be found to be important and possibly combined in most instances but it is not part of this thesis to examine the interaction further. I included this part only because I believe that to understand the role of placebo as a research tool it is necessary to understand how and why the placebo response occurs. A review of the components of the response, which include faith, previous experience, learning, reputation and expectation, will show how these interact to produce conditioning and expectation. The placebo effect, or response, is variable and inconsistent between different patients and within the same patient at different times and circumstances, changing synchronously with changes in the components, recent experience and further learning, changing expectations and reputations. At any one time it is a complex amalgam of interactions between the patient and the physician. Beecher (113) commented that 'However inert a placebo may be in the usual physical sense, it is not inert in its effect.' while Kabler (114) wondered whether placebo, which has produced objective physiological responses when used to treat patients, can truly be called inert? He concluded that while a placebo may be inert people are not. To which can be added with confident assurance, and neither is the physician!
b) The patient and faith in the healer

Faith in the healer is probably the major and most underrated component of the placebo effect. In our society this faith has been inculcated since infancy and our history is replete with tales of miraculous cures or healing.

One of the earliest reports of this faith and a miracle cure comes from the Gospels and tells of the woman who had uncontrolled haemorrhage for 12 years. She had consulted physicians and St. Mark was highly critical of the way in which she was made to suffer at their hands. St. Luke, himself a physician, probably understood the medical difficulties better and was less critical, confining himself to noting that she had spent all her money on the physicians without being cured. The woman had heard of the miracles performed by Jesus and she was cured merely by touching his garments as he walked. Greenblatt, a professor of endocrinology, has noted (115) that although functional uterine bleeding can readily be explained scientifically as a disturbance of pituitary-ovarian balance, psychosomatic disturbances play a role in uterine bleeding more frequently than is commonly acknowledged. He notes also the words of Jesus to the woman, ‘Daughter, be of good comfort: thy faith hath made thee whole: go in peace.’ These produced such a degree of faith that the cessation of the woman’s bleeding was more rapid than can be induced by progesterone today.

In the Middle Ages this faith was transferred to people of high standing or ecclesiastical position, and monarchs in particular (116). The disease known as scrofula or The King’s Evil, was in fact cervical tuberculous adenitis and it was supposed to be cured by a touch from royalty (117). The Monarch’s, or Royal, Touch was practiced in France by Philip I but it was Edward the Confessor (1006 – 1066)
who first adopted this form of therapy in England and the Monarch’s Touch was accompanied with great ceremony. Buchanan (118) notes that James VI (1603 – 1625), who united the kingdoms of England and Scotland and commissioned the Authorised translation of the Bible, was sceptical of this traditional practice. Charles II (1660 – 1685), supported by his personal surgeon Richard Wiseman who affirmed his belief in the therapy, set aside one day in the year to touch those afflicted with scrofula. Holmes (64) while mentioning the practice by Edward the Confessor pointed out that William III (1689 – 1702) abandoned the practice completely. However, his successor, Queen Anne (1702 – 1714) who was the daughter of James II and the last of the Stuart monarchs, reinstated the practice, and with some success, for it is recorded that she cured the scrofula in a young child who grew up to be………………Dr. Samuel Johnson of Dictionary fame. Surely a reliable recorder of the event even though he would not be able to confirm the accuracy of the original diagnosis? Our own establishment of faith started young for who, as a child with a minor knock or bruise did not trust Mother to ‘kiss it better’?

When patients seek medical help in treatment there is already an established faith based on past experience and in part the patients’ responses to a new treatment will be based on their responses to the success or failure of previous treatments, and success breeds success.

c) The role of the patient

The psychological components of medical practice and the patients’ expectations should not be ignored or underestimated. Patients with a positive,
optimistic approach invariably have a better response to treatment than do those who are fearful or pessimistic. Mira (119) has described the malignant anxiety that occurred among the civilian population during the Spanish Civil War and which led to death in a few days. Beecher (120) tells of two surgeons at Johns Hopkins hospital who refused to operate on any patient who acquiesced in their suggestion of an operation but then expressed firmly that death would result, and of the Army officer at Walter Reed Hospital facing surgery for an inguinal hernia who stated that he would die if operated on. The surgery was uneventful but the patient developed ileus and died. When his personal effects were collected it was found that he had laid out his dress uniform and left instructions for his funeral. Beecher makes the point, in italics, that an 'understanding of the role of these non-specific forces is essential to the full understanding of the possibilities inherent in the disease situation.'

d) The role of the physician

After the patient, the second most powerful influence on the placebo effect is the physician and at least one author has described the doctor himself as an important therapeutic agent (63). More recently a number of authors have emphasised the role of the physician and identified factors in this role which can affect the overall placebo response (66, 89, 121, 122). These factors are:

1) the amount of time spent with the patient;
2) the time spent in a careful, thorough examination;
3) the explanations about the disease and the prognosis;
4) explanation and expectations on the proposed treatment particularly reinforcing a positive approach;
5) an explanation that dose titration might be required;
6) a discussion of possible adverse secondary effects from the treatment;
7) ensuring continuity of care;
8) discussing other treatment options, especially if the first treatment is not fully effective. To this I add an exhortation of my own, to 'follow the failures' (123); and
9) creating an impression of authority and control over the situation. The late Dr. Henry Matthew, in his day with the largest private practice in Edinburgh, used to tell his patients 'It is probably going to get worse before it gets better, but we will be able cope.'

The impact of a positive approach, as outlined above, was shown in a study reported by Thomas (124) when he found that a successful outcome to treatment was reported by 64% of patients who were given a positive consultation with a firm diagnosis and treatment plan, compared with 39% of those patients who were given a negative consultation in which the physician implied some doubt as to the diagnosis and outcome of treatment.

The instructions outlined above require considerable time to execute properly and in medicine today, driven by cost effectiveness, the need to see as many patients as possible in a limited time and the fact that more patients are seeking to see fewer
physicians, it is doubtful that many physicians can accomplish more than a few of the suggestions. The importance of the physician's personality has been examined and explained by Balint (125) and the physician's role in the psychological component of the placebo effect should not be minimized. A study was undertaken in patients with bleeding ulcers, all of whom were treated with placebo and all of whom received in the same words the message that this new medicine would undoubtedly produce relief (126). In the group of patients who were given the message by the study physician, 70% had excellent results. When the message was given by the study nurse only 25% of the patients reported an excellent result. Every opportunity must be taken to increase the patient's faith in the physician, the treatment and the outcome and although these findings are important in practice, more relevantly, they are a critical, and often overlooked, factor in clinical research. The presence and involvement of the study physician is supremely important. When study patients are evaluated by different team members their results tend to be different, which is why the first statistical analysis is always to look for the presence of inter-observer differences.

e) The environmental impact

Beyond those already considered there are other, often unappreciated, components of the placebo effect namely the impact of the visit to the physician. The anticipation, perhaps concern, the waiting room, the medical smell of a hospital or clinic, the overheard conversations of others reflecting the speaker's faith and expectations or the reputation of the physician, clinic or hospital. During the consultation the furnishings and accoutrements of medical practice, the examining
couch, the scales, the sphygmomanometer, possibly an ECG machine, kidney dishes, bandages and tapes and those 'special' medical scissors all combine to create powerful images and build positive expectations.

f) The prescription

At the end of the consultation comes another great placebo effect, the writing of the prescription. Although no longer yesteryears' impressively arcane, illegible mystery written in Latin (Figure 3), this remains a potent psychological stimulus.

During the Cornell Conference (66) Dr. DuBois stressed the placebo element of this activity. A prescription cannot be written without an element of the placebo effect and a warning has been offered that this task should not be taken lightly (68). It has the weight of 2,000 or 3,000 years of medicine behind it. The prescription has to be written by a doctor, it has to be signed by a doctor and it has to be taken to a pharmacist to be filled, both respected figures representing education, authority and power. If the prescription is written in a perfunctory way it may have the effect of increasing the faith in the disease rather than the remedy and the physician.

g) Surgery as a placebo

If a visit to the doctor is fraught with so many opportunities for psychosomatic overlay and placebo effects then these are eclipsed by the aura and opportunities that surround the process of a surgical operation (127). Expectations are influenced by friends, television programs, newspaper reports and magazines, especially with the
increasing call to publish Rankings listing hospitals in order of death rates from various surgeries etc.

Figure 3  A prescription from R. Cheston, MD.  1892.

Photograph supplied by, and used with permission of, The Marvin Samson Center for the History of Pharmacy, Philadelphia University.
The detailed preliminaries to surgery, preparing for the operation, admission to hospital and the attention paid by large numbers of people involved in the admission and preparatory processes, the pre-surgery examinations and assessments, the unfamiliar anaesthetic room, the anaesthetic and going to sleep, invasion of one's body and then waking in an intensive care/recovery room with the attendant monitoring devices, provide a powerful combination of components. No wonder that Beecher (113), an anesthesiologist not a surgeon (and misquoted by Johnson), concluded that 'It would be surprising, if in this charged atmosphere, surgery did not have a powerful placebo action in addition to what it may or may not accomplish physiologically.' He also went on to examine the different results obtained by the enthusiastic surgeon as compared with those obtained by the sceptical surgeon. Enthusiasm on the part of the surgeon was better!

The placebo effects have been shown in unwitting surgical trials as when the operation had to be halted because of uncontrolled hypotension or because the surgeon discovered that the disease was so widespread as to make the planned procedure impractical. Wall reports (90) that there are several such instances where the patients, unaware that the surgery had not been performed as planned, nevertheless had an excellent result. Despite the inherent difficulties there have been a few planned studies conducted to examine the placebo effect of surgery. An evaluation of the benefit of ligating the internal mammary artery in an attempt to improve circulation to the heart had patients allocated at random to either artery ligation or skin incision only, both performed under local anaesthesia (128). The results showed some benefit for both groups but no benefit for the ligation group.
beyond that seen in the skin incision group. More recently there have been reports of surgical procedures performed in patients with Parkinson's disease (129). Patients were allocated at random to have human foetal tissue implanted in the brain or to undergo the same surgical procedures but without the implant. As might be expected there were several patients who did not get the implant but nevertheless reported improvement. Publication of this study was followed by an editorial (130), a series of critical letters and even merited a report in a newspaper (131). It would seem that Finneson (132) was absolutely correct when he wrote 'Probably surgery has the most potent placebo effect that can be exercised in medicine.'

h) No role for placebo in practice

Despite the earlier Editorial exhortations I do not believe that it is ethical to use a placebo in patient treatment. The major reasons are two, namely the deception involved and the question of beneficence, and as both are used by critics of the use of placebo in clinical research they are addressed in more detail in the next Section.

Briefly, patients are autonomous agents, capable of making their own decisions, deliberating about personal goals and entitled to make choices based on the information they are given. Deception by the unexplained inclusion of a placebo in their treatment repudiates the autonomy of the individual. Beneficence requires that the patients must be protected from harm and their well being ensured. Use of a placebo could impede early diagnosis of a potentially serious illness for should the patient respond to the placebo then the physician might be deceived into believing that the illness had been cured and stop further evaluation or investigation.
Some physicians (91) claim to use placebo to differentiate between functional and organic disease, but given the pervasiveness of the placebo response this is a dubious test and may lead to the problems listed above. Physicians who use a homeopathic dose of active drug as an active placebo seem to me to be guilty of not respecting patient autonomy and of ignoring beneficence, in addition to deceiving themselves. In 1945 Pepper (10) commented that 'giving of a placebo....is not to be mentioned in polite society,' and I suspect that most physicians today would echo his sentiments.

i) **But the placebo response is different**

No place for placebo perhaps, but the placebo response is another matter. This distinction and the component factors making up the response can be influenced by physicians. A pharmacologist has noted (133) that 'placebo effects are probably the most relied upon aspects of pharmacotherapy today, however unintentional this may be on the part of the physician.' This author quotes one of the physicians who founded Clinical Pharmacology as writing 'The question is not whether the physician should or should not use placebo, but how he should best utilize the omnipresent effect.' The British Medical Journal two years later (134) weighed in with 'Placebo response has served doctors well. Because of it they have throughout the centuries been held in high esteem, despite the dearth of medicines with beneficial therapeutic effect.' Although these comments are not particularly flattering to the physicians, they may have been correct at the time of writing, given the available pharmacopoeia.
These comments not only have relevance for clinical practice but also encapsulate the main reason for including placebo comparators in clinical studies intended to evaluate or demonstrate the effectiveness of new drugs and therapies. Like the Biblical poor, the placebo effect, or response, is with us always, but not always consistently. As in clinical practice, it also has an immense, important and undeniable role in clinical research.
PLACEBO IN MODERN MEDICAL RESEARCH

The critics attack

It is an interesting anomaly that around the time that some journals were promoting the rational use and better understanding of placebo and the placebo effect in clinical practice, criticism of the use of placebo in medical research was gathering steam. Support for the role and use of placebo was mustered by the publication of a series of papers (135–139) and a Conference on the topic reported in the same journal (140).

Perhaps the most consistent and strident critic has been Rothman, a professor with academic titles at two Boston Universities (141) but he has not been alone (142–146). Although these different critics have their own choice of topics, in general their criticisms include some or all of the following variants: poorly designed trials, patient deception, infringement of patient rights and the Codes of Ethics such as the Helsinki Declaration, problems with informed consent, denial of effective therapy, impact on benefit-risk equation, putting patients at risk, deleterious effects on the quality of life and unreasonable demands from the Regulatory Agencies for the evaluation of new drugs.

Feinstein, a statistician, has commented (147) that many of the critics are confused about their target and the criticisms are ill aimed, attacking components of the clinical trial process other than placebo use itself. Perhaps the critics hope that this shotgun approach will hit at least one target somewhere, but it seems to me that the best way to defuse the criticisms and make the case for placebo use is to consider
each logically and attempt to refute it, so I begin with a consideration of the clinical trial itself, what it is and how it resembles or differs from clinical practice.
VIII. CRITICISMS AND ANSWERS

a) The clinical trial

A clinical trial is a carefully and ethically designed experiment with the aim of answering some precisely framed question.

*Principles of Medical Statistics* 1971.

Hill, A.B.

Many critics claim that the use of a placebo is unethical in a clinical trial because the trial is thus poorly designed. Sackett (148) agrees that a badly designed trial is always unethical and Beecher (149) makes the point that 'an experiment is unethical or ethical at its inception: it does not become ethical post hoc – ends do not justify the means.' so there would seem to be no argument on that score. However, this criticism is aimed not so much at placebo as at the components of clinical trial design, namely randomisation, the double blind technique and the manner in which the study results are presented. Critics claim that trials deny the physician the ability to choose the best treatment for the patient and also infringe the ethical stance that the interest of science and society must never supercede the well being of the individual patient.

The definition makes it clear that a clinical trial is an experiment: in a trial a patient with a disease is seen by a physician at a clinic or hospital, but from that point on there is little resemblance between clinical trials and clinical practice. In fact, trials more closely resemble a game, played on a designated field, with limits to the number of players and substitutions, rules governing conduct of play, and the whole under the
control of referee or umpire who impose penalties for infractions of the rules. Such penalties have included refusal to accept the study and its results as part of a new drug application and suspension of investigators.

Clinical trials differ from clinical practice because they limit the physician's options to those described in the protocol. Only a specific number of patients who meet all the criteria for inclusion may be enrolled and these criteria usually exclude patients with concomitant diseases or treatments. Treatment options are limited to those of the study, commonly two or three different drugs or placebo. Because of the randomised, double blind design, now the recognised standard for clinical trials and particularly for evaluations of new drugs, selection bias is minimised because neither the patient nor the physician knows or can influence which treatment is allocated to the patient.

The various measurements to assess the patient's response to treatment, the specific laboratory variables and the times at which they are to be monitored are specified in the protocol, and are usually much more numerous and frequent than they would be in routine practice. Finally, the duration of treatment is specified and this stops at the end of study date whereas in routine practice treatment may be continued for months or years.

It is correct that at the end of the study the statistical analysis and data presentation commonly compare the patients' response rates by comparing the values across the treatment groups, but during the conduct of the study each patient receives individual treatment and monitoring of an intensity far greater than occurs in regular practice so I do not see how the interests of science and society are superceding the
individual’s well being. If anything, there is greater care of the individual in a clinical trial. A decision as to whether the trial is ethical or unethical and an assessment of risk inherent in the study is made by the Institutional Review Boards in the United States and the Independent Ethics Committees in Europe.

b) The Institutional Review Board

Critics complain that the institutional bodies set up to oversee and approve proposals for clinical research have inconsistent and differing standards for assessment, do not understand the ethical problems with placebo and are failing in their responsibility to protect the patients.

As reviewed by Levine and Lasagna (150), the impetus for establishing independent committees came from the first Declaration of Helsinki in 1964. In the United States this was followed by a memorandum from the Surgeon General (151) establishing independent review of all grant proposals submitted to the Public Health Service. Beecher’s article (149) exposing ‘unethical or questionably ethical procedures in subjects research’ provided further stimulus and was followed by publication of the Belmont Report which in turn led to the Federal Regulations that now govern medical research in the US.

In the United States the Food and Drug Administration (FDA) have formally defined (152) the role, functions, composition and operations of the Institutional Review Board (IRB). The requirements for Independent Ethics Committees (IEC) proposed by the International Conference on Harmonisation (ICH) are very similar (153). Under these mandates the IRB/IEC is charged with reviewing the proposed
study protocol, suggesting changes and ensuring that these are made, assessing potential risks from the study, ensuring patient protection and conducting periodic, usually annual, reviews of study progress and recommending changes to the protocol.

Of course, having regulations does not guarantee that they will be followed and the critics have some validity in their complaints. In the past three years the Office for the Protection from Research Risks (OPRR) has audited IRBs in the US and shut down half a dozen academic boards (154). In the main they found that the boards lacked sufficient evidence to make determinations required for approval of research proposals and performed inadequate continuing review of research projects. As a result several members of University staffs were fired or suspended from their jobs. Critics admit that IRBs are clearly overloaded with protocols for review (155) but also charge them with unethical behaviour and endorsing unnecessary new research (156). Others have called for an overall improvement in medical research standards and noted that the IRB process, imperfect though it may be, is the only safeguard available in research (157). There have been calls for education opportunities for the IRB members (158) and also for the setting up of a national committee (159). In the United Kingdom a two tier system has been introduced in which regional IEC approval is followed and supplemented by expedited local approval, but so far the results appear mixed. While there have been some reductions in the time to get approval this has been inconsistent and offset by increased demands for paper copies with consequent increased costs (160, 161, 162, 163).
Clearly there are multiple difficulties and opinions as to the effectiveness of the approval process brought about by diverse perceptions of the roles and responsibilities of the IRB/IECs.

i) A reflection of one

For the past three years I have had the privilege of managing the Administrative Support Group for an IRB and the experience has been illuminating. The work load has expanded to the extent that in this period the IRB has increased the number of members and now meets at least once each week, instead of every other week. The dedication and seriousness which the members bring to each task is exemplary and often in marked contrast to that of the investigators who are asked to respond to queries, provide explanations or make changes to their documents. The concept of patient protection dominates each protocol evaluation and I have heard discussions as to whether a placebo was ethically justified in one study while another study was challenged because the absence of placebo might invalidate the study results and therefore it was deemed unethical to enroll patients. As Sackett reminded us (148) a poorly designed study is always unethical.

Perhaps the last word as to who should decide whether or not the use of placebo in a particular study is ethical can be left to Hoffenberg (164) 'The whole point about ethical decisions is the inherent difference of opinion. If there were total agreement it would cease to be an ethical problem.' No doubt IRB members benefit from continuing education as to their responsibilities but in my experience the IRB review and evaluation of proposed studies to ensure patient protection is effective and
much more attention needs to be directed towards educating the investigators about their roles, responsibilities and performance.

c)  **Deception and Informed Consent**

Critics who claim that the use of placebo always entails patient deception are perhaps ignoring or misunderstanding the concept of Informed Consent. Or perhaps they are confusing clinical trials with clinical practice wherein informed consent does not exist even for invasive procedures such as phlebotomy or lumbar puncture, because patient consent is assumed from the fact that the patient has voluntarily consulted the physician for diagnosis and treatment. It is true that major procedures such as surgery require written consent, but most times this is driven by the need for legal protection of the hospital and surgeon rather than a genuine desire to inform the patient.

The concept of Informed Consent is in recognition of and respect for patient autonomy. It provides the opportunity for the patient to make a considered decision as to whether or not he or she should participate in the study, based on a full explanation of the study goals and procedures, the potential risks and benefits, especially if the latter are more likely to accrue to society in general rather than the patient in particular. In the United States the FDA have provided specific requirements as to the information, protections and other treatment options that must be included in the consent form (165). They also specify that the Principal Investigator must be the person who obtains the consent, that this should usually be written but must always
be witnessed (165, 166) and that the IRB must approve the proposed consent form before it is used (152). The international requirements specified by the ICH are similar to the FDA mandates (167). Interestingly, both groups allow waiving of consent under specifically defined circumstances (Sections 50.23 and 4.8.15, respectively) and this may have given rise to many of the subsequent problems. Some other groups have weighed in with their own guidelines and laws all of which broadly encompass the same scope of respect for the autonomy of the patient with voluntary informed consent (168, 169, 170).

i) Do all investigators follow the rules?

Two authors have noted recently that there has been a substantial erosion in public confidence in the medical profession and particularly in medical research, as a result of some recent disclosures. For example, in the gene-therapy study at the University of Pennsylvania in which a young man died, the consent form which he signed did not disclose the fact of primate deaths after receipt of the gene-therapy vector that he was to receive (171). The outgoing Head of the Department of Health and Human Services has suggested that researchers may not be doing enough to ensure that subjects fully understand the risks and benefits or may misinterpret the nature of the trial to patients (172) and the Office for Protection from Research Risks has found investigators downplay the risks of the study and enroll inappropriate patients (171). It also seems that many investigators fail to mention the inclusion of a placebo in the trial when informing patients about the trial (173).
ii) Is informed consent always necessary in clinical trials?

Even Beecher had some doubts about this writing, 'Informed consent is the goal towards which we strive. There may be a modest exception to this in circumstances in which there is no discernible risk and where discussion with the patient would vitiate any possibility of success ..........' (174). More modern authors also find occasion when consent can be waived (175) and cast doubt on the claim that informed consent provides protection against patient exploitation in research. They made a well reasoned case but found little support for their views in the subsequent correspondence sections of the journal. Still others claim that to provide full information may be harmful to patients, or that it is inhumane to physicians and patients to insist on full disclosure, and believe that clinical judgement should determine the need for disclosure. Further, they propose that individual investigators themselves should decide if formal consent is necessary in their trial (176, 177), presumably on the principle that the fox can be trusted to guard the chicken coop. Others espouse beneficent paternalism even further, suggesting that if the trial is ethical and scientific (they don't explain who decides this) the issue of informed consent need not always arise (178).

The possibility that full appreciation and knowledge of the trial may inhibit patient recruitment has been suggested as a justification for avoiding informed consent (175, 176, 179), and it has been suggested that telling patients they might receive placebo reduces the effect of the active drug in the study (180). Withholding from patients information that a placebo would be included in the study was discussed as part of an extremely comprehensive review of placebo presented to the Medical Ethics
Institute, but when Brody (181) said that not all patients expect the physician to tell them the name of the prescribed drug and that a vague comment like ‘this will make you better’ would often suffice, his remarks did not elicit any challenge, at least as far as I could ascertain.

In my opinion none of these arguments have validity. As we have seen, clinical trials are experiments, not an extension of patient care. By agreeing to participate in a trial the patient is giving up the right to treatment which is specifically tailored to the patient by the physician, relinquishing freedom of choice in many aspects of treatment and subjugating personal beneficence for social good. For these reasons I believe that the informed consent process, including the explanation of the study, must be intense, stringent and scrupulously applied.

iii) How comprehensible is informed consent?

Beecher posed this question (149) and suggested that consent in a fully informed sense may not be obtainable. Can we ever be sure that the patient has completely understood the information provided and how can this be understanding be assessed? Many physicians have difficulty in admitting to patients their uncertainty which justifies the conduct of the study (182). More worrying still is a study showing that only about one third of all patients believe that physicians explain things well (183). These concerns have been addressed in the context of patient enrollment in a study and how this affects the physician–patient relationship, possibly leading patients to believe that the suggestion to take part in the study is actually a recommendation that this is the best course of treatment for them (184).
When patients talk to a physician they are usually anxious and concerned about themselves or their relative so they do not always comprehend what the physician is telling them, they misinterpret words and have difficulty separating the major from the minor. It is easy to overestimate the degree of comprehension that patients and relatives take from our medical information and instructions and I learned this lesson when a House Surgeon, listening as the Chief attempted to explain to a patient's wife the difference between *possible* and *probable* risks of the proposed surgical procedure. Sensing that the subtle difference was not being grasped he pointed out of the Infirmary window and said,

"Suppose I told you that the Moderator of the Church of Scotland and the Pope were holding hands and dancing in the street. Now, you might agree that this could be possible, but do you think that it would be probable?"

The lady considered the problem for a moment then replied

"I really couldna say doctor; ye ken, I'm no a Catholic."

iv) What should we do?

A recent report (185) has noted that problems with informed consent are among the most frequent adverse findings recorded during audits and inspections of clinical trials and in a recent survey 40% of the respondents, from the USA and Europe, claimed that they had come across questionable informed consent practices such as backdating documents.

Shalala (172) recommends increased training in bioethics for IRB members and investigators. Others want to strengthen the IRB/IEC role (186) but do not explain
how the IRB/IEC is supposed to monitor each patient enrollment, while another group has suggested how the Boards could conduct better reviews (187). Unfortunately, the Boards are already overworked and any further increase in the workload might produce an effect that is the opposite of that intended. It certainly does not help to restore confidence and encourage participation in the IRB/IEC functions when law suits are filed against the individual members (188) but perhaps these will have the benefit of increasing awareness of the difficulties faced by the Boards.

A patient who has taken part in clinical trials (189) and a researcher who has also been a patient in a study (190) recommend that input from potential patients should be obtained at the design stage of a clinical trial. They also make a plea for more education of the public so that there would be greater understanding of the need for clinical trials, the rationale for the different designs and the relevance of trials to 'root out useless and harmful drugs and assess new ones'.

A report from the House of Lords suggests that physicians who wish to practice Alternative Medicine should have proper training in the techniques they employ (191) so why should the same standard not be applied to those who wish to undertake clinical research? Education and training in the ethics, regulations and methodologies of clinical trials for all their physicians who wish to be involved in clinical research is now being introduced by a number of the Managed Care and University Hospitals in the US, driven by the fiscal/legal pressure to safeguard the hospital and employees from lawsuits.

We also must address the training of those who take part in the informed consent process, so that they explain things clearly and establish a two way dialogue
with the patients to ensure that they really do comprehend what they are being told. What the physician says is not as important as what the patient hears and interprets.

Given these difficulties I can understand the critics who claim that placebo use is unethical because the informed consent process offers no protections, but I think that they are aiming at the wrong target. They should be concentrating on improving the consent process, because the weaknesses in the process apply to all studies, medical and surgical, and not exclusively to use of the placebo.

If, without these steps, critics of placebo continue to insist on full comprehension by each potential participant, then soon we will be limited to enrolling only medical or surgical colleagues! Perhaps this will help to increase understanding of the placebo effect and quell some of the criticism, but as matters stand at present, the critics' concerns about the adequacy of the informed consent process are absolutely valid, even if their criticism of placebo is not.

d) Infringement of rights and codes of ethics

Critics usually like to claim that the use of a placebo denies the patient's rights as laid down in the Hippocratic Oath, infringes the concepts of beneficence and autonomy as defined in the Belmont Report and is prohibited by the Declaration of Helsinki. These broad generalisations have elements of truth but once more they apply to all forms of clinical research rather than to placebo in particular.
i) The Hippocratic Oath

Familiar to all physicians from graduation, this is the first code of medical ethics, originating in ancient Greece with Hippocrates, the Father of Medicine. The biography in Encyclopaedia Britannica suggests that Hippocrates as a character was possibly a combination of several physicians from the same period rather than a single person, but no matter, the Oath remains as the accepted standard of physician behaviour and ethics today. The original oath, of course, was written in Greek and for an English translation I turned to the Encyclopaedia (192). The relevant sentences seem to be that the physician 'will abstain from whatever is deleterious and mischievous' and 'will strive always for the benefit of my patients'. Critics point out that the use of a placebo is deleterious and mischievous, particularly if deception is involved, and that substituting ineffective therapy for effective therapy is not a patient benefit.

Another frequent criticism that is usually wrongly attributed to the Hippocratic Oath claims that the use of a placebo contravenes the dictum of *primum non nocere* 'First do no harm'. There is an echo here of the early Biblical translation difficulties in that the original Greek oath was translated into Latin and thence to English, but I could find no part of the English translation that matched *primum non nocere*. Lasagna undertook a more thorough search (193) of different translations and concluded that this admonition did not come from the Oath.
ii) The Belmont Report

Although not invoked so often as the others by the critics of placebo, this uniquely American code is a guide to the IRBs in their review of research projects, informed consent and institutional compliance, and is neither aimed at individual research projects nor does it address the place or role of placebo itself. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was formed after the revelations of patient abuse described by Beecher (149, 174). Concerns also had been expressed over some behavioural studies, the government sponsored Tuskegee Study and some radiation studies, so the Commission was formed in 1974 by the National Research Act, met at the Smithsonian Institution’s Belmont Conference Center in 1976 and their report (194) was published in the Federal Register in 1979. The length and complexity of the Commission’s name guaranteed that this would always be known as the Belmont Report!

The Report highlights three basic principles,

Respect for persons,

Beneficence and

Justice.

Respect for persons incorporates the ethical dictates that individuals must be treated as autonomous agents and that persons with diminished autonomy, for example the very ill and the institutionalised, need especial protection by virtue of their being particularly dependent and therefore may have a reduced capacity to give consent. Beneficence implies first that no harm be done and second that possible benefits be maximised and
risks minimised. Justice requires fairness in selection of research subjects so that certain classes, ethnic minorities and welfare participants are not unduly represented simply because they are easily available.

If these precepts are followed by the IRB/IECs then critics of placebo use should have no case to argue.

iii) The Declaration of Helsinki

This has become the dominant code of ethics world wide and has superceded the Hippocratic Oath as the code for medical research. Almost all critics of the use of placebo complain that such use is a direct and unethical contravention of Section II, Medical Research Combined with Professional Care, and specifically disallowed by paragraph 3. The paragraph was added to the Declaration in 1975 and reads: 'In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.'

According to Rothman and Michels (141) this statement 'effectively proscribes the use of placebo as control when a "proven" therapeutic method exists.' and in response to the flurry of Letters to the Editor that followed their article, these authors state again ‘As we noted, the requirement of placebo controls violates the Declaration of Helsinki.' (195). Stephens (196) believes that placebo-controlled studies should be the exception and are justified only in exceptional circumstances, while Rothman (145) hopes that such studies will rapidly become obsolete. Michels
has been quoted (146) as stating that placebo-controlled trials are unethical and immoral while at another meeting the editor of the journal IRB, Bette Crigger, commented that there is increasing polarity in the research community over the placebo issue (197). So, what is this document that has come to dominate and give rise to such bitter divisions in the pursuit of medical research?

In 1964, following the Nuremberg Trials that disclosed the extent of the Nazi atrocities committed in the guise of research, the World Medical Association (WMA) at their General Assembly meeting in Helsinki put forward recommendations drafted only as guide to physicians all over the world (198). The authors acknowledged that their recommendations would require modification and should be constantly reviewed. This has occurred at the General Assembly meetings in Japan 1975, Italy 1983, Hong Kong 1989, and South Africa 1996. At none of these meetings since the paragraph was added in 1975, was any change or addition proposed for Section II, paragraph 3.

The 2000 General Assembly meeting was held in Edinburgh and the delegates clearly took account of the advice that was submitted from various quarters (199 – 204) before producing their fifth amendment to the Declaration (205). It was clear that this was the most comprehensive revision since the inception of the code; the framers made clearer reference to the IRB/IEC rights and obligations, and strengthened the requirements for informed consent (206, 207, 208). The text concerning placebo use was slightly expanded but left the intention almost unchanged: 'The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods.
This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.’ (208).

It is worth pointing out that from the beginning the WMA recognised that their recommendations were not going to result in a global consensus. Differences in ethical standards, variations in perception and medical interpretation, availability of diagnostic techniques and treatment choices, differences in culture and language were bound to produce differences of opinion. Not surprisingly several countries have produced their own modifications applicable to their own requirements and circumstances (209 – 211) to complement the Declaration.

I believe that those critics who insist that a strict interpretation of paragraph 3 prohibits the use of placebo as unethical, are mistaken. After all, a strict interpretation requires that every patient, including those of a control group, if any, must receive the best proven therapeutic method. Thus a new drug cannot be evaluated at all, because, by definition, it cannot be the best proven current prophylactic, diagnostic and therapeutic method without comparison and proof, and thus it is excluded by the demands of the code. So, strict interpretation rules out ALL therapeutic research and precludes the evaluation of any new therapeutic agents or methods. Fixed dose studies, which means almost all studies, are also excluded because best therapy often requires dose titration for maximum effect.

Although I would like to claim that this argument is original and my own, it isn’t. It has been put forward by several authors, Collier (142), Stephens (196) and Lasagna (199) to name only three that we have already discussed. Curiously,
given the vehemence with which they defend their absolutist position, the critics of placebo have offered no rebuttal to these three, at least none that I have been able to find.

e) The Regulatory Agency makes me do it

On several occasions the critics of placebo have blamed the various regulatory agencies, particularly the US Food and Drug Administration (FDA), for demanding placebo-controlled studies for evaluating new drugs and regarding this design as the gold standard (144, 145, 195, 212). Even Lancet, in an otherwise impassioned defence of the FDA suggests that their acceptance of placebo-controlled evidence in preference to an active comparator is a serious flaw (213). In my opinion these statements suggest an inadequate reading of the Code of Federal Regulations and are intended to obfuscate the issues so that the critics can portray the FDA as bureaucratic and inflexible, forcing everyone to undertake unethical studies. Do the FDA and other regulatory agencies in fact demand placebo use and is there coercive pressure applied?

The term “gold standard” was applied by the Editor of the New England Journal of Medicine (214) to the clinical trial design in which systematic selection bias has been reduced by the double blind presentation, random allocation of treatments and a placebo control. The words “gold standard” do not appear in the Code of Federal Regulations and it is an intellectual stretch to apply them only to the placebo component of the required triad.

In the Code the FDA ‘requirements and procedures for submission to and review by the agency of applications to market a new drug.’ are clearly stated (215).
The relevant section for our consideration here is 314.126a which defines adequate and well-controlled studies needed to 'provide the primary basis for determining whether there is "substantial evidence" to support the claims for effectiveness for new drugs.' The FDA suggest and discuss no less than five possible choices for the control:

- Placebo concurrent control
- Dose comparison concurrent control
- No treatment concurrent control
- Active treatment concurrent control
- Historical control

The Guidelines published by the International Conference on Harmonisation (216) list the same possible choices, but with reservations concerning the Historical control.

What is undoubtedly correct is that there is a need to include a placebo control in studies where the response is either totally or mainly subjective, the classic example being the evaluation of putative analgesics in patients with pain. As we have already seen, in such circumstances there is potential for a large placebo effect and the only way in which this can be discounted is by including a placebo control. As a member of the Analgesiology and Headache Section of the American Society for Clinical Pharmacology and Therapeutics I took part in several discussions between the members and the FDA as guidelines for the evaluation of analgesics were prepared and reviewed (217). Placebo control was discussed extensively and the recommendation is that 'The study design should include a comparison of one or more dose levels of the test drug with a placebo and, generally, with a standard analgesic.' The purpose of the placebo is to provide validation of the downside assay sensitivity and if placebo is
not used then some other method to verify assay sensitivity must be found to provide substantial evidence of efficacy of the test drug.

Patients with rheumatoid arthritis have pain as one of their major symptoms and the FDA guidelines for the evaluation of new anti-inflammatory drugs (218) also address the use of placebo control. In trials to demonstrate superiority of the new drug in patients with mild disease and who are taking say, an NSAID, the guidelines recommend that a placebo control should be used but with all patients continuing to take their NSAID therapy during the study. Patients who are responding poorly on NSAIDs alone are usually not candidates for placebo-controlled studies.

Obviously the regulatory agencies see a need for placebo-controlled studies and the various available study designs will be discussed in more detail in another section, but I am not convinced that any of the written guidelines specify placebo use in every study or that there is coercion or pressure to use placebo. However, there is pressure to ensure that the studies are so designed that they are ethically and scientifically valid and that the data are interpretable.

f) Denial of effective therapy

Critics who claim that inclusion of a placebo is unethical because it denies effective therapy to the patients, in my opinion are making three specious assumptions.
i) Withdrawal of active treatment

Michels is quoted asking emotionally 'if the patient was your son or your mother, would you withdraw active treatment for the sake of science?' (146). But is her question valid? Although she implies that the son or mother was receiving a drug which had pharmacological activity this may not have been an effective treatment or even well tolerated by the patient. In other words, Michels has glossed over the possibility that there might be a sound medical reason for withdrawing the active drug.

When a patient is receiving treatment for a disease which is responding to this treatment, and the treatment is well tolerated, I can see no ethical justification for withdrawing this treatment. Protocols that I have written insist that a patient who is already receiving treatment for the relevant disease may be enrolled in the study only if there is a sound, ethical, medical reason for withdrawing this treatment — say because of unacceptable secondary effects of the drug. Withdrawing successful treatment simply to enroll a patient in the study is to my mind unethical, and one can imagine that the indignation stirred up by Michels’ question probably dominated the discussion and overlooked the illogicality of her question.

ii) Active drugs are always effective

The second specious assumption is that all active drugs, at all doses, are effective treatments in all patients all the time. If life were that straightforward then such a concept would simplify therapeutics, but unfortunately it isn’t and it doesn’t!
iii) Placebo is synonymous with no treatment

The third specious assumption equates placebo with no treatment and indeed Rothman and Michels (141) and Hill (219) pose the question 'So what if the new treatment is better than nothing?' in the clinical trial.

By definition an inert placebo is devoid of any inherent pharmacological activity and if the critics were to claim denial of a specific therapeutic effect, for example that placebo has no antibacterial action, then their assumption might become more persuasive.

**Objective responses:**

Although we do not understand the mechanism by which they are produced, objective responses to placebo have been documented. In a series of experiments that have now become classics Wolf (220) was able to observe changes in the gastric mucosa and gastric secretion in Tom, a patient who had a permanent gastric fistula through the abdominal wall as a result of a gunshot wound. Wolf recorded changes in gastric secretion and vascularity occurring in response to emotional stimulus and showed that these could be blocked by placebo treatment. Tom hated injections of any kind and an intramuscular injection of distilled water would be followed by an increase in gastric blood flow, confirming that placebo effects on end organs could be measured. Neostigmine given repeatedly induced hyperactive gastric motility, abdominal cramps and diarrhoea as would be expected, but on other days when the neostigmine was withheld Tom would experience the same gastric effects in response to atropine, lactose tablets or distilled water. A modern review of
studies describing the treatment of gastric ulcers (221) showed that after eight weeks 48 – 58% of patients treated with placebo were cured, whether or not they had also taken antacids. Treatment of duodenal ulcers showed a cure after four weeks in 24 – 45% of patients who took placebo with antacids and in 29% of the patients who took placebo without antacids.

In a 28 year old female patient with persistent hyperemesis, Wolf (220) effected a cure by initial treatment with repeated doses of ipecac which produced nausea and vomiting. Once she was conditioned he treated her with ipecac together with a placebo which she was told would cure her, and it did. A recent review of studies in patients after surgery (222) showed that 20 – 99% of those treated with placebo did not have nausea or vomiting while other investigators (223, 224) reported no vomiting after laparoscopy in 55 – 68% of patients treated with placebo.

In patients with angina pectoris, placebo treatment has improved exercise tolerance, reduced consumption of nitroglycerin and been associated with ECG changes (225). In studies performed to evaluate nicardipine similar findings were reported in patients with angina (226) while patients with hypertension who received placebo had a reduction in mean diastolic blood pressure although this was significantly less than that seen in the patients who received the active drug (227, 228).

Placebo treatment has produced objective changes in diabetic patients (229), changes in blood sugar, serum lipoproteins and white cell counts (230): in patients with anxiety, injection of isotonic sodium chloride mimicked the response to an injection of corticotrophin, increasing neutrophil counts and the uric acid/creatinine
ratio, decreasing lymphocyte and eosinophil counts and changing serum levels of potassium, sodium and 17-ketosteroids and blood lipids (94).

**Subjective responses:**

In his review of 15 published studies Beecher (94) found that 15 – 58% of patients with pain reported relief after placebo treatment, and in his own studies (231) showed that 53% of patients with severe post surgical pain obtained relief following a single dose of placebo. Jellinek reported that 82 – 87% of patients with headaches obtained relief from analgesics but found that 60% of patients being treated with placebo also obtained comparable relief (232). A review of studies in patients with anxiety suggest that 24 – 71% of patients treated with placebo show a beneficial response (233).

**Nocebo responses:**

Given the objective and subjective responses described above it would not be surprising to find that these carried over to mimic the adverse events seen with active drugs. In a series of 109 Phase I, pharmacokinetic studies involving 1,228 healthy subjects (234), reports of headache, asthenia, drowsiness, nausea and vomiting, abdominal pain, impaired concentration, dry mouth and sleep disorders were made by 0.4 – 12.5% of the subjects. Beecher recorded (94) reports of dry mouth, nausea, headache, the sensation of heaviness, impaired concentration, drowsiness, warmth, relaxation, fatigue and sleep disorders from 9 – 50% of 1,082 patients with pain who received placebo in 15 studies. In patients with anxiety and tension (235) there were three major adverse events recorded in patients who received placebo. One reported weakness, palpitations and nausea, one reported
epigastric pain, diarrhoea and developed angioneurotic oedema of the lips and the third developed a diffuse rash, diagnosed by a dermatologist as 'dermatitis medicamentosa,' which cleared up when the patient stopped taking the lactose placebo.

Placebo can induce protean objective and subjective effects and responses which should not be ignored simply because we cannot yet provide a scientific rationale to explain how they occur. With these well documented effects and responses to placebo it seems hardly reasonable to claim that placebo is truly synonymous with no treatment: Beecher (236) was more succinct when he wrote 'The concept that placebos are inactive indicates considerable misunderstanding.' and it seems that at least one cartoonist has understood well the concept of placebo effects (Figure 4).
Figure 4.

Cartoon

"Now that is a Breakthrough-- a placebo with side effects."
MEDICAL RESEARCH AND THE ESSENTIAL PLACEBO

So far the placebo has been considered only as a treatment and the arguments for and against such use have been reviewed. Today there are very few, if any, reasons to even consider using placebo as sole treatment but there are some genuine questions in modern therapeutics that can best be answered by incorporation of a placebo.

The line that separates medical practice from medical research is not unremittingly straight but wanders from one side to the other, in a narrow and blurred manner so that often it is not possible to be certain exactly on which side of the line one is placed. This was recognised, with caveats, in the revision of the Declaration of Helsinki (205); 'The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value.'

Like many foot soldiers in the history of warfare who played a significant and major part in individual battles and then became anonymous and overlooked when the leaders received the glory and the laurels of victory, the contribution of placebo is often anonymous and overlooked and the essential role that it sometimes plays in improving medical practice is ignored. As we have seen there are plenty of critics who claim that placebo use in medical research is also unethical. In my opinion this
absolutist view is not only untenable but also overly simplistic and if implemented unthinkingly would add to the unanswered questions in modern therapeutics.
VIII. SOLVING PROBLEMS IN MEDICAL PRACTICE

Placebo to the rescue

Keep watch also on the fault of the patient which often makes them lie about taking of things prescribed.

*Hippocrates, ca. 460 – 377 BC.*

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a) **Missing doses**

Patients do not always take their drugs as prescribed. The phenomenon of missing doses is known as 'lack of compliance', and it seems that practitioners overestimate their ability to recognise the frequency and ubiquity of this problem (237).

Modern drugs, unlike their predecessors so disdained by Holmes (54) and whose lack of efficacy and therapeutic value was bemoaned by Sir Derrick Dunlop, are so potent, powerful and effective that the latter referred to them picturesquely as the ‘Therapeutic Thunderbolts of Jove’ (238). However, no matter how potent or powerful, not even a modern drug can produce a therapeutic effect if it isn’t taken and a drug that is taken irregularly cannot produce its full therapeutic effect.

The reasons that patients miss doses range from simple forgetfulness, resolution of symptoms being interpreted as ablation or cure of the disease, the occurrence of adverse secondary effects, a difficult or inconvenient dosing schedule which conflicts with work or social activities and, increasingly for older patients on a fixed income, the desire to save money by skipping doses and prolonging the lifetime
of the current prescription. Unfortunately, missing doses can have serious consequences beyond the fact that the patient is not getting effective treatment.

i) The oral contraceptives

The successful extraction of diosgenin from the Mexican yam by the chemists who founded Syntex Corporation, Drs. George Rosenkranz, Alex Zaffaroni, Carl Djerrassi and Bert Bowers, enabled them to create the first synthetic progesterone and oestrogen compounds, and led to their development of the first oral contraceptives and topical steroids. To suppress ovulation successfully it is necessary that the contraceptives be taken on a regular basis: in clinical trials of one current product, Ortho-Cyclen, for example, 1,651 subjects were studied for 24,272 cycles. During this time only 18 subjects became pregnant, most of these because they did not take the drug consistently, as prescribed (239).

The necessity for good compliance with the dosing schedule became even more critical in the 1970s when the ‘mini’ pill, with lower doses was introduced and physicians needed an answer to the question ”How many doses can I miss before being at risk of becoming pregnant?” In the 1980s there were five clinical studies including one by Edinburgh colleagues (240 - 242), which used the placebo substitution design, in which placebo tablets were substituted at different times in the cycle and for different duration, during and after which suppression of ovulation was measured.

Clearly this is medical research but it meets the requirements spelled out in the Declaration and it has direct applicability to everyday clinical practice and life in
general. Physicians can answer patient concerns and provide advice based on good science and the patient gets the information written in simplified lay language and enclosed in the drug package (243). As a bonus there is the pack itself in which placebo, the humble foot soldier plays a crucial role. As can be seen from the photograph of the pack (Figure 5) blue tablets are to be taken for the first 21 days of the cycle: these contain norgestimate and ethinyl estradiol, colouring agents and the inert ingredients lactose, magnesium stearate and starch. For the next seven days the woman takes only an inert green placebo, described in the package insert as made up of colouring agents, lactose, magnesium stearate, cellulose and starch. Inclusion of these placebo tablets has simplified the dosing sequence to one pill once daily throughout each month which makes the schedule acceptable, convenient and more likely to be remembered, in other words improving compliance, openly and free of all deception.
Figure 5

The Ortho-Cyclen pack

personal photograph
ii) Drug holidays and forgiveness

Patients being treated for life long, chronic diseases do not always take their treatment regularly or as prescribed, stopping or adjusting the dose and frequency as they learn what best suits them. A large study in the United Kingdom (244) found that almost half of the 37,643 hypertensive patients either changed or discontinued their treatments within six months of starting. More recently, using electronic monitoring devices placed in the bottle cap, (237, 245, 246) researchers were able to confirm that lapses in compliance with antihypertensive drugs were mirrored by an increase in blood pressure and concluded that up to half of all “therapeutic failures” seen in hypertensive patients may simply be due to a lack of compliance in taking the prescribed treatment. Another author (247) has suggested that while 50 – 60% of hypertensive patients almost always comply with the recommended treatment and 20 – 40% usually comply, there remains a core of 5 – 10% who never comply.

A study of patients with ankylosing spondylitis showed that only 22% of the patients complied strictly with the prescribed schedule (248) and in another study of psychiatric outpatients doses were missed on 19% of the days while 48% of the patients failed to take their medications at all (249). It might be assumed that doses would be skipped predominantly over the weekends but Rudd has shown that most of the skipped doses are errors of omission and occur randomly, not in a systematic pattern (250). Using the electronic monitoring device Urquhart has shown that they seem to occur approximately monthly in one patient in six and about three to four times a year in a further one patient in six (245, 246). Drug Forgiveness, defined as
the post dose duration of effect minus the prescribed interval between doses, provides an indication of how long drug efficacy remains following the last dose. Again using the placebo substitution design, a study compared two β-blocking drugs in patients with hypertension (251). Control of blood pressure was maintained for up to six hours after atenolol was replaced by placebo and for up to 48 hours after betaxolol was replaced by placebo.

Clearly betaxolol is a more "forgiving" drug and a patient who missed one or two days of dosing would be at less risk of loss of blood pressure control than would be a patient taking atenolol who also missed the same number of doses. This information might be of considerable help to a physician planning to treat a patient with a β-blocking antihypertensive and would also enable the physician to recommend a course of action if a dose should be missed.

   iii) Rebound and first dose effects.

When doses are missed the control of disease which had been exerted by the drug is no longer present and this release of control can lead to rebound effects such as the vasoconstriction that follows withdrawal of β-blocking drugs. It may be necessary with some drugs that treatment be started with an initial small dose, well tolerated although probably not fully effective, and then the dose be gradually increased to a level at which it is well tolerated and fully effective. After missing a few doses it is usual for the patient to restart taking the drug at the same dose level as was last taken and this may lead to the sudden appearance of those secondary
pharmacological effects which were avoided by the initial careful upward dose titration, the so called first dose effects.

It has been suggested (246) that the problems described above could be identified early in the drug development program if the placebo substitution design were to be used more frequently and that it should be used also to extend monitoring of patients beyond the end of study treatment and into the post treatment period to ascertain the risks of rebound and breakthrough phenomena. With informed consent there would be no deception, only the date of the change from active to placebo being in doubt. Such studies would provide useful information to the practitioner intending to prescribe the new drug, an explanation of the possible consequence of missing doses and how this should be corrected.

iv) Single patient (N of 1) studies

Another role in which placebo has contributed to medical practice by improving the therapeutic efficacy of drugs has been described recently (252). Although Evidence-Based Medicine relies on the results from double blind, randomised, controlled studies not all patients in such studies respond optimally, equally, or even at all. When a new drug becomes available for widespread clinical use it is likely that some patients will fail to respond or will report the appearance of secondary adverse events. If the results of the double blind, randomised, controlled studies are to be extrapolated to clinical practice then the single patient, or N of 1, study becomes indispensable (253).
This again employs the double blind, cross over, randomised design, but with placebo substituted for the less than active, or suspect drug, which may be restored later or replaced by another with similar activity but perhaps a different pharmacokinetic profile. It is necessary to identify a target response for each patient, say a sign or symptom which is particularly troublesome and such that would be expected to respond rapidly when the stimulus is removed (dechallenge) and to return equally rapidly if the stimulus is reintroduced (rechallenge). The technique may require multiple active drug – placebo substitutions to be completely successful (254) and experience over two and three years has been described (255, 256). The technique is feasible, it increases the likelihood that that the prescribed treatment is actually the best for that patient and helps to increase the physician’s confidence if there had been any initial doubt about the proposed treatment.

Although the single patient study is a formal clinical trial most of the usual ethical issues do not arise because the objective is to identify the best treatment for a specific patient and no other patients are involved. However, as with all trials, informed consent is required from the patient who is free to withdraw from the exercise at any time, and the same issues of confidentially apply to this design as they do to any other trial.

An Editorial in Lancet (257) has described the single patient trial as an innovation which, if widely used could be a powerful tool for physician and patient education. Thus, it is difficult to understand why the concept has not been more widely used, particularly as one author has drawn attention to the biases inherent in open evaluations, namely the natural history of disease, placebo effects and the
expectations of the patient and physician (258). Others have asked for research into the reasons for this lack of acceptance of the technique (259). The Lancet Editorial commented that even in 1986 ‘placebos are in everyday use.’ but at least one practitioner has called for the abandonment of placebo (260) on the grounds that placebo effects ‘cannot be clearly distinguished from specific treatments or therapeutic skills.’ Perhaps this concept requires more vociferous support and clarification of the role and utility of placebo.

In these examples it is obvious that placebo is being used as a research tool to answer specific questions and obtain information that is directly applicable to medical practice, improving the effectiveness of treatment and enabling the practitioner to respond to patient queries and concerns. This crossing of the line between practice and research is an early indication of the essential role played by placebo in what might be called practical medical research. The overall benefits are increased physician and patient understanding, possibly better therapeutic efficacy as a result of better compliance and almost certainly greater patient safety. Not an insignificant achievement for a scorned tool.
IX. CLINICAL TRIALS AND THE PLACEBO

In their haste to condemn placebo in all its forms the absolutist critics do not challenge the need for the evaluation of new drugs to be carried out in anything other than a rigorous, unbiased and scientific manner, but they fail to realise that their position mitigates against exactly the requirements they espouse. To appreciate how this occurs let us briefly review the steps in a clinical development programme for a new drug and the most common study designs that are used at each step, to see how placebo plays a major role in such development.

a) The clinical development programme

Traditionally this has been divided into four phases, but there is considerable overlap of the lines of separation which are neither rigid nor fixed.

i) Phase I, clinical pharmacology

This is the first administration to humans, intended to assess tolerance, define the pharmacokinetic/pharmacodynamic (PK/PD) profile, identify the metabolic pathways and the excretion pattern in healthy volunteers. These studies usually start with a single, low dose and progress with dose escalation and multiple dosing and typically involve less than 100 subjects. The data from these studies are immediately relevant in planning the starting doses, frequency of dosing and steps for increasing the dose in the next phase.
ii) Phase II, therapeutic exploratory

Patients with the relevant disease but free from other, concomitant disease or medications, are involved to establish the 'no-effect' dose, and explore dose-response relationships. Usually of fairly short duration with surrogate or pharmacological endpoints in addition to clinical measurements, these studies provide proof of concept by establishing that the new drug has some efficacy, and provide guidance for study designs in the next phase. Usually up to 500 patients may be involved.

iii) Phase III, therapeutic confirmatory

Again involving patients with the relevant disease and free from concomitant diseases and medications, these studies involve 2000 - 3000 patients and are intended to confirm efficacy, refine the dose-response relationships and assess safety. Involving larger numbers of patients than the previous phases these studies are all double blind with random allocation of treatment and they form the majority of the 'adequate and well controlled' studies required by the FDA and other regulatory agencies.

iv) Phase IV, therapeutic use

Conducted after the new drug application has been filed and continued long after the drug is marketed these studies involve patients with the relevant disease. The study design still involves the double blind and random allocation of treatment but the criteria for inclusion and exclusion are substantially relaxed so that patients with
underlying diseases or taking concomitant medications can be enrolled. By this phase the most effective, well tolerated dose will have been established and the duration of these studies is considerably longer than in phase II or III. The object is expansion of the safety information on the drug, particularly identifying the less common secondary adverse events, and to assess comparative efficacy and additional endpoints.

b) Study designs

The same basic study design is used in phases II – IV, namely a comparison between the new drug and the comparator(s), either placebo and/or active drug(s), presented as identical in appearance to maintain the double blind, and allocated according to a random code. The difference is whether groups of patients are compared or each patient in the study receives each of the drugs.

i) The between patient design

This is the most widely used design and compares groups of patients, one group who receive the new drug and the other(s) who receive the comparator drug(s). Although it is most usual to have two groups it is not unknown to have both a placebo and an active comparator group or even a 'no treatment' group. It is also possible to compare two or three different doses of the same drug using this design.

ii) The cross over, or within patient design

With this design each patient in the study receives both, or all, the study treatments allocated in random order. If three or more drugs are being compared the allocation is usually balanced as a Latin Square to ensure that all possible
order combinations are evaluated. At first glance this design would seem to offer the most advantages by having the drugs evaluated in the same patient but the design is unsuitable for any study in which the first period of treatment cures the disease and is really only suitable for evaluating drugs to treat chronic diseases. Other drawbacks include the occurrence of unacceptable adverse effects during the first treatment period which lead the patient to withdraw before the second period and the difficulty of exactly matching the presentations of the drugs being compared so that the patient cannot identify the switch by a difference in shape, colour or taste. It was this latter difficulty which led Sir Austin Bradford Hill, widely accepted as the father of the modern clinical trial, to publish the following anecdote as a brief caveat on "that most sacred cow, the prospective double blind randomised controlled trial." (261).

"Doctor," said the young lady patient, "Why have you changed my pills?"

"What makes you think I have?" was the cautious reply.

"Well last week when I threw them down the loo they floated, this week they sink."

c) Several roles for placebo

Within these two basic designs there are several reasons and roles for placebo.

i) Matching the new drug

In the early phase studies most new drugs are presented in the simplest formulation, in a capsule for oral consumption. This is unlikely to be the final formulation selected for marketing but it recognises that the easiest comparator to
produce is an inert placebo which can be formulated in a similar way and presented as identical matching capsules. If capsules are unavailable or unacceptable, say for reasons of stability, then tablets, with matching placebo tablets, are almost as straightforward to produce.

ii) Placebo and the double dummy

When there is no possibility of the new drug and the desired comparator being presented in identical appearance, for example when one is a solution for injection and the other a tablet or capsule, the double blind can be maintained by the double dummy technique. With this technique two placebos are used, one to match the injection and one to match the oral product, so that each patient receives both formulations, one active and one placebo. There is a disadvantage to this in that each patient is required to receive ‘double medication’ which some patients may find difficult to accept, and it also creates potential for non-compliance or confusion as to which dose is to be taken.

iii) Starting from the same point

Whenever two or more objects are to be compared it is important that the comparison should start from the same point and contain the same evaluations. With an acute intervention, say the assessment of post surgical pain, there is obviously no problem, all the patients start after the surgery, but with chronic diseases, such as hypertension or rheumatoid arthritis, patients may be at different disease stages and even have received a variety of different treatments before entering the study. For these reasons it is common to use a placebo ‘run in’ period during
which any active treatment that the patient may have been receiving can be washed out. This run in period also provides an opportunity to check that the patients do not have pre-existing biochemical or haematological abnormalities and that the inclusion and exclusion criteria are met. Once the disease has ‘flared’ to the defined level for starting study treatment the placebo is withdrawn and the patient receives the assigned study drug, which in appearance is identical to the placebo, so that the patient is unaware of the start of active treatment.

It will be apparent that when the cross over design is used these caveats apply not only at the start of the first period of treatment but also must be applied before the start of the second period, to ensure that the disease state is at the same level at the start of both treatments and that there are no carry over effects from the first drug which might be attributed to the second drug. Without this second run in period the study is invalid, and therefore by definition it is unethical. The crossover design appears beguilingly simple but it was incorrectly used so often that in the late 1970s the FDA announced that they would not accept data from cross over studies in the new drug submissions. Fortunately they have since modified their stance and will accept this design provided that the study has been conducted correctly.

The run in period has been criticised as incompatible with informed consent (262) on the grounds that fully informed consent and placebo go together only where the treatment allocation is randomised. I disagree because when the concept of the study is being discussed with the patient, the reason for the run in period and fact that the time of the switch from placebo to active drug will not be
apparent, can be explained. There should be no deception involved and the risk to the patient should be minimal.

Brief withdrawal of active treatment in a study, provided that there is no subsequent threat of morbidity or mortality, is no different from that often used in practice for patients with hypertension, depression, anxiety, insomnia, congestive heart failure or epilepsy, to assess whether or not the patient still needs it (199). A recent systematic review of short term randomised, placebo-controlled trials in patients with hypertension (263) found no difference in the incidence of those secondary effects usually associated with untreated hypertension, death, stroke, myocardial infarction and congestive heart failure, between patients treated with placebo and those treated with active therapy. The authors acknowledge that these studies included only patients with mild or moderate hypertension and the duration of exposure to placebo was limited. In addition, because they were enrolled in a study, all patients were closely monitored, probably considerably more closely than would have occurred in routine practice, and this may also have contributed to the absence of serious adverse events.
X. PLACEBO AS A COMPARATOR IN CLINICAL TRIALS

So far we have reviewed the various reasons and roles for placebo as they affect the design features of clinical trials, but this is not the use that upsets the critics and leads them to disparage the studies. Their criticisms concern the use of placebo as a comparator treatment in the clinical trial which, as we have seen, they deem unethical and increasingly unnecessary (144 – 147). To consider and rebut these criticisms it is probably best to look at studies as they are performed in Phases I – IV and to consider with specific examples, including my own involvement and experience, studies of different disease states.

At the outset it is worth recalling that even the most ardent opponents of placebo insist that all drugs must be evaluated and compared in the most scientifically rigorous manner compatible with patient safety, for only then can the results truly identify the best possible treatment.

a) Phase I studies

These early studies generally represent the first human exposure to the new drug and their purpose is to identify the PK/PD pattern. The subjects in these studies are all healthy volunteers free from underlying disease, medications or drugs of abuse, traditionally in the 20 –40 years age range and predominantly male, although this latter is changing. As would be expected the informed consent process is detailed and lengthy so that the subjects are fully cognisant of the procedures and the potential
risks. It is common for the subjects to be confined to a residential facility where resuscitation equipment is available and where they can be intensively and carefully monitored throughout.

i) Pentazocine

At the start of my involvement in the pentazocine programme Professor Beckett and I designed a series of studies to identify and compare the PK characteristics of the drug given by different routes, intravenous and intramuscular injection, oral solution, tablets and suppository (264). Four subjects took all doses and a physician colleague and I were not only subjects in the study but also administered the injections and collected all the samples of blood, urine and faeces.

ii) Benoxaprofen

This study was the first administration of the drug to humans, and another medical colleague and I, although not participating as subjects on this occasion, were available to monitor the subjects throughout the study (265). Once again we were concerned only with identifying the PK pattern following single and multiple oral doses, in fasting and fed subjects and also using oral formulations with different particle size.

iii) Cinoxacin

This PK study (266) involved patients about to undergo transurethral resection of the prostate who agreed to take four doses of cinoxacin in the 24 hours
before surgery. At the time of this study we were well into the development programme for cinoxacin and several hundred patients had taken it as treatment for urinary tract infection. Because the patients scheduled for surgery did not have a urinary tract infection at the time of the study and there was no reason to give the drug beyond our need to measure plasma and prostate tissue levels, it was critical to ensure that the informed consent process was unimpeachable. The surgeon and I discussed the study with the patients, separately and on two different occasions, before enrolling them and again before the first dose of cinoxacin was taken.

iv) A role for placebo?

Many of the early Phase I studies are designed so that a few of the subjects actually receive placebo, while the majority get the drug being studied. One, and perhaps the most obvious, reason for including placebo involves adverse events and has already been alluded to (234). The potential for clinical trials to generate placebo effects is much greater than that in routine medical practice so there is a need to separate those adverse events reported during the initial human administration of the new drug from the non specific placebo responses. When the subjects are confined in a dedicated facility there is always the risk that some will become conditioned and report adverse events that they have witnessed or discussed with other subjects.

The other reasons are more concerned with maintaining the integrity of the study. It is not unknown for subjects to exchange doses of their drugs, (this becomes difficult though not impossible, when the drug is given parenterally) and the identification of the drug in the blood or urine of a subject who was thought to be on
placebo indicates either drug swapping, a breakdown in the drug packaging and allocation system or deliberate fraud on the part of one or more of the study personnel.

In my studies described above there was no placebo because in each study I was working with a trusted colleague, I was present myself on each occasion and personally witnessed the drug administration or taking thereof. Except for benoxaprofen there was already considerable available data on adverse events reported in clinical trials so we deemed that requirement for placebo control was minimal.

v) Placebo isn't required for every study

There are also PD study designs where there is absolutely no requirement for placebo. Pentazocine is a benzomorphan analgesic that possesses both agonist and weak opioid antagonist properties. A single analgesic dose given intravenously produced respiratory depression but we wondered if there was ceiling effect or whether subsequent doses would produce cumulative depression as seen with the morphine derivatives. With some of my former anaesthetic colleagues a study was designed to investigate this question in a population of patients undergoing surgery (267). The results showed a difference between pentazocine and pethidine with no cumulative respiratory depression following a second dose of pentazocine. As all the patients were asleep and all the measurements were objective there could be no placebo response to be evaluated and therefore no reason to include a placebo in this study.
b) Phase II studies

As a general rule these studies are designed to show proof of concept, that the drug has at least some activity even if the initial dose, chosen on the basis of PK data, is not the optimum. With our understanding of the various components that make up the placebo response it is to be expected that in any study several participants will report improvement with the new drug, even if it is used at a 'no effect' dose. To compare a less than fully effective dose with an effective dose of a marketed comparator will inevitably lead to the conclusion that the new drug is ineffective. To compare it to no treatment may be unethical and this design introduces bias because the two treatments cannot be double blind. Provided that the patient's health is not put at risk by the short term withdrawal of specific treatment the only logical comparator in Phase II studies is the inert placebo.

Each new drug with which I have been involved has been evaluated for proof of concept in initial studies with placebo comparators. Subsequently we identified the no effect dose, the minimum effective dose and the dose response relationship. To support my contention that placebo is essential, I have chosen three studies of marketed drugs, in which I was involved, that required of proof of concept because we were evaluating different uses or formulations of the drug.

i) Oral versus parenteral administration

In the late 1970s and early 1980s there was a surge in the growth of outpatient day care surgery for minor operations, with patients returning home in the evening of the day of surgery. At that time post surgical analgesia was usually
provided by intramuscular (IM) injection of morphine or other opioid, but in many instances the patients remained drowsy, with nausea or vomiting, when it was time to return home. I wondered whether or not an oral analgesic could provide equivalent and acceptable analgesia, so I designed a single dose comparison of fenoprofen, morphine and placebo to evaluate proof of concept (268). As can be seen in Figure 6, IM injection of morphine provided the most rapid relief of pain, significantly better than placebo at all assessments. After two hours, oral fenoprofen was significantly more effective than placebo though less effective than morphine, but over the next four hours both fenoprofen and morphine remained significantly better than placebo and not significantly different from each other. The percentage of patients who requested rescue analgesics because of lack of efficacy of the study drug was 80% of those who received placebo, 37% of those who received fenoprofen and 23% of those who received morphine, showing that even a drug with specific activity is not effective in all patients all the time.

These results confirmed the proof of concept that an oral analgesic could be a practical and successful alternative to parenteral opioids for outpatient day care surgery even if the doses in this study might have been too low for maximum efficacy. That the statistically equivalent efficacy of oral fenoprofen and IM morphine was genuine and not the result of a Type II error --- wherein failure to reject the null hypothesis occurred because the methods of assessment lacked sufficient downside assay sensitivity --- was shown by the significant differences between the active drugs and placebo.
Figure. Mean pain intensity scores for patients with initial moderate pain. *Significantly different ($p < 0.05$) from placebo. †Significantly different ($p < 0.05$) from morphine and placebo.

Figure 6

Reproduced from reference 268
ii) Pre-emptive analgesia in outpatient surgery

The staff at infertility clinics use hysterosalpingography (HSG) as one of their diagnostic techniques. When I was an anaesthetist in the Royal Infirmary HSG was performed under general anaesthesia, but modern fiscal pressures and work load have made this less acceptable. The procedure produces excruciating pain at the moment of attachment of the tenaculum and instillation of the dye, even when the patient is encouraged to cough hard at the moment of attachment, but fortunately the pain dissipates rapidly, within 15 minutes or less. Rather than having to provide intravenous analgesia we wondered if an oral analgesic, taken approximately two hours before the patient came to the clinic, might obtund, or at least reduce the pain, so a small proof of concept study was designed to compare fenoprofen, aspirin and placebo (269).

The results showed that of the fenoprofen treated patients 30% (5/15) remained completely pain free at all times in the study, significantly more than the 7% (1/15) of the aspirin treated patients and none of the placebo treated patients. By 15 minutes there were 13/15, 10/15 and 9/14 patients free of pain, respectively in each group, and all patients were pain free by 45 minutes. Again, proof of concept was confirmed although it seemed likely that larger doses and an adjustment in timing of ingestion might make the oral analgesics more effective in even more patients. That the statistical superiority of fenoprofen was genuine was confirmed by the significant difference from placebo, inclusion of which also allowed an understanding of the natural course of the induced pain.
iii) Onset of analgesia

The anti inflammatory analgesic naproxen has been available world wide for approximately 30 years and although it remains one of the better tolerated of this class of drugs (270) a reformulation using the Intestinal Protective Drug Absorption System® (IPDAS) not only provided even less gastro intestinal upset but also enabled the drug to be taken only once daily (271). The sodium salt of naproxen is rapidly absorbed after oral ingestion and is widely used as an analgesic so we were interested to see if the IPDAS formulation, from which 30% of the dose is rapidly released and the remaining 70% has delayed release, would be as effective as the conventional formulation.

In a double blind, analgesic study using the third molar extraction dental pain model (272) patients with pain of moderate intensity received either 500mg or 1000mg of naproxen in the IPDAS® formulation, naproxen conventional formulation 500mg, codeine 30mg or placebo, allocated at random. In the three groups who received one of the naproxen formulations 70 – 73% reported onset of pain relief within 30 minutes, compared with only 35% and 45% of those who received codeine or placebo, respectively. PK analysis showed that by this time approximately 35% of the drug had been absorbed from the IPDAS formulation. These results confirmed proof of concept, namely that the new formulation was still a rapidly acting, effective analgesic.
XI. SOME CONSIDERATIONS FOR PHASE III AND IV STUDIES

Phase III studies provide the bulk of the clinical data on which a new drug submission is based, usually involving approximately 2,000 – 3,000 patients, most of whom are treated as outpatients. Obviously the intense monitoring that is available for phase I and II studies cannot be available in phase III but nevertheless the regulatory authorities require scientific rigor and a study design that permits collection of accurate and complete data so that the interpretations and conclusions that are drawn are scientifically valid and can stand scrutiny.

Phase IV studies, starting after the filing of a new drug submission and continuing throughout the life of the drug, move a little closer to resembling day to day practice by loosening many of the inclusion and exclusion restrictions, reducing the number and frequency of measurements and visits to the investigator. Nevertheless, phase III and IV studies are still experiments and should be regarded as such when being explained to patients who might enroll. Unlike the earlier phase studies these later studies bring ethical considerations of their own in matters of equipoise, uncertainty, superiority and equivalence studies and the presence or lack of assay sensitivity and internal controls.

a) Equipoise and uncertainty

Given that it is the primary duty of all physicians unfailingly to promote the welfare of their patients, the question arises, under what circumstances may a physician ethically offer and suggest to the patient enrollment in a clinical trial? In the
United States it is the principle of equipoise, meaning that there must be *collective uncertainty* and doubt among the general medical community as to the best treatment, before participation in the trial can ethically be offered (273). Rothman (145) notes that without equipoise any therapeutic study is unethical. Recent examples of such collective uncertainty include the debates over the treatment of breast cancer and prostate cancer, lumpectomy or radical mastectomy, irradiation or radical prostatectomy?

The principle of uncertainty, on the other hand, is widely endorsed in the United Kingdom, where substantial uncertainty on the part of the *individual practitioner* as to which trial treatments would be most appropriate for the particular patient, is deemed sufficient to make offering the study completely ethical (274). Another suggestion is that there must be uncertainty not only on the part of the practitioner but also on the part of all the study participants, and if the answer is already known then there is no need for the study at all (275).

Regardless which of these principles the practitioner prefers, there is the moral imperative that the study design must meet all the previously discussed requirements of scientific rigor, otherwise the study itself becomes unethical. The information for the patient must make it clear that there is genuine uncertainty as to the best treatment and so long as there is genuine uncertainty as to the best treatment, then patients are not being asked to subjugate their autonomy for the good of others (276).
b) **Trials to show superiority**

In clinical trials of new drugs efficacy is most convincingly shown by a dose response relationship or superiority to a placebo or active comparator. A well designed trial that shows clear superiority of one treatment over another offers the strongest evidence of effectiveness and no other information is required to support this conclusion (277), the study report will be accepted for publication somewhere and the sponsor's marketing department will be ecstatic. In a patient with serious disease or where there is risk that the patient's condition may deteriorate rapidly in the absence of specific treatment, or when previous studies have identified a specific, effective therapy, then placebo use is almost always unethical (278, 279).

It is worth noting, as a caveat, that the US Code of Federal Regulations (215), in paragraph 314.126 defines the need for 'Adequate and well-controlled studie$\textsuperscript{S}$ (emphasis added) which is commonly interpreted as meaning that the FDA require at least two such studies to be included in the new drug application (144). Presumably this acknowledges the observation of the gambler Nathan Detroit in 'Guys and Dolls', that once could be happenstance, twice is coincidence, but the third time is deliberate.

c) **Trials to show equivalence or noninferiority**

Strictly speaking these are two separate concepts but in practice they tend to be synonymous. Equivalence is generally limited to studies that assess bioequivalence, where different formulations or routes of administration are compared, and the term noninferiority is usually confined to clinical comparisons.
In noninferiority studies the hypothesis to be tested is that one drug is superior to the other, that is the opposite of superiority studies in which the more usual null hypothesis postulates no difference between the treatments being compared. Noninferiority studies seem easy to design but often there is not a clear understanding of the principles behind the design so the studies fail to achieve their objective. Frequently these studies have insufficient patients in the treatment groups and contain design biases that may permit inappropriate conclusions to be drawn (279). Unlike superiority trials in which the sample size is calculated on the basis of the expected difference between the treatment groups, in noninferiority studies there is no expected difference, hence difficulty in calculating the sample size. When the study is completed the results may indeed show no difference between the treatment groups, but were the treatments equally effective or equally ineffective?

d) Type I and Type II errors in data interpretation

In evaluating the results from clinical trials there are two potential errors. The Type I error, in which the null hypothesis is actually true but is rejected (one treatment is declared better than the other although in fact both are the same) and the Type II error in which the null hypothesis is actually false but is not rejected (the treatments are actually different but they are declared to be the same). Type II errors are common in studies that lack assay sensitivity and in this case it is well to remember that absence of evidence of a difference should not be construed as evidence of absence of a difference (280).
e) The perceived placebo effects

Earlier we considered the components of the placebo effect in practice. To these components in a clinical trial setting must be added responses that are often mistaken for placebo effects, but are more accurately described as perceived placebo effects (281). It might be supposed that this is purely a semantic argument but as the authors point out, the true placebo effect is highly variable and depends on a number of factors that are as yet not fully understood. Therefore it is important to distinguish the true placebo effects from perceived placebo effects that are reported in a clinical trial, and the best way to achieve this distinction, according to the authors, is by the inclusion of an untreated control group in addition to a placebo group. Exactly what these perceived placebo effects may be is discussed below.

i) The Hawthorne Effect

This intriguing effect was first observed in studies at the Western Electric Company plant located at Hawthorne, IL. Workers, manufacturing and checking equipment for the Bell Telephone Company, were assessed to see if their efficiency varied as a result of differences in available illumination. The answers seemed clear, increased illumination led to increased efficiency, although several workers praised the increased illumination when in fact it had not been altered, and other factors were also identified which confused this simple interpretation (282). First, it was found that when the workers knew that they were being observed their actions and work patterns changed compared with when they were unaware of being observed. Secondly, they were so called piece workers and their earnings depended on how much work was
accomplished. When given feedback at the end of each day as to their output, workers increased this the next day so that they would earn more. This is known as the consequence of responding.

Thus the Hawthorne effect in experimental research is the unwanted effect of being in the experiment itself, which leads to changes in behaviour patterns, particularly apparent when the participants know that they are being observed or when they are rewarded for their performance. A second study, assessing the performance of Emergency Medical Technicians in ambulances, found the same effects, with the participants’ response depending on the perceived demand for service (283).

ii) The patients

Patients who agree to take part in a study are motivated by a desire to succeed, perhaps because they have a chronic disease and grasp any potential improvement. The sudden attention paid to them, the measurements and study requirements and having more people interested in them than is usual in their routine treatment, creates a powerful Hawthorne effect. For example, patients with rheumatoid arthritis frequently show improvement in the first two or three weeks of a study. Some patients, stimulated by the study and the interest shown in them may add interventions of their own, particularly hypertensive patients who decide to reduce their salt intake or lose weight. In some studies where compensation is offered to participants, with more money being ‘earned’ if patients complete the study as per the protocol, there is an obvious consequence of responding.
iii) Regression to the mean

Patients enter the study when their disease is active or has flared, either because of natural fluctuation, their existing treatment no longer works or is no longer tolerated so they stopped it anyway or as a result of withdrawal of active drug during the run in period of the study. For whatever reason, the study variables measured at the start (baseline) are likely to be at the high end of a scale so knowledge of the natural fluctuation in the disease state would suggest that improvement will follow.

iv) Good compliance

As Urquhart has demonstrated in clinical trials (245, 246) compliance with the treatment schedule is generally excellent for the first week or two, acceptable in the third week and then deteriorates. Any Hawthorne induced change in behaviour which leads to an alteration in the pattern of compliance will introduce unconscious bias into the study and either exaggerate or diminish the response to the study drug so the inclusion of a placebo may be necessary for the valid interpretation of the results.

v) Investigator's enthusiasm

Just as the practitioner generates an inherent placebo response, so does the investigator who has his or her own motivation to conduct the study and see it succeed. Payment to the investigator who participates is always a powerful motivating influence, although this is often not disclosed to the patient. Enthusiastically talking up the new treatment, describing the study and potential risks
and benefits, encouraging the patient to take part because of genuine uncertainty as to the best treatment, stressing the importance of adherence to the protocol and the treatment schedule, all convey a sense of excitement and commitment for the patient. Add a desire to provide the result that seems to be expected to support the investigator, and bias becomes unavoidable.

vi) Passage of time

In studies of chronic disease, patients change as the study progresses. One of the best documented changes is the acclimatisation seen in newly diagnosed hypertensive patients who are susceptible to the 'white coat effect' and in whom the early hypertension subsides as they become familiar with the staff and practice procedures. This problem is so prevalent that a newspaper advertisement has drawn attention to it (Figure 7) and home measurement of blood pressure is now recommended to distinguish between pathological, sustained hypertension, and the white coat version (284).
Ruling Out: “White-Coat Hypertension”

By John J. O’Hara, Jr., MD
Cardiologist
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“My blood pressure is always normal at home.” If I’ve heard one patient say that, I’ve heard 100. Or how about the popular “That’s normal for me?” As a member of the cardiology team at the Main Line Health Heart Center, I can safely say that there is no such thing as “normal for me.” Blood pressure guidelines, as defined by the Joint National Commission on Hypertension, are crystal clear: Optimal blood pressure is 120 (systolic) over 80 (diastolic), normal is less than 130 over less than 85, high normal is 130-139 over 85-89 and needs to be watched carefully. A blood pressure reading equal to or greater than 140 over 90 is considered high. With undetected, uncontrolled hypertension the first step to increased risk of stroke, heart attack, heart failure and kidney failure, knowing your blood pressure couldn’t be more important.

It is true that some people experience what is called “white-coat hypertension.” In other words, their pressure spikes when they are in their doctor’s office. A simple plan can reveal their actual blood pressure. First, buy a home blood pressure cuff. Second, take and record multiple readings at different times of the day. Finally, bring that record, along with your blood pressure cuff, in to see your doctor. Your blood pressure will be taken both on your home cuff and the one in the office, to see if they correlate. That is the only way “white-coat hypertension” can be eliminated as a factor, allowing us to focus on what your true blood pressure reading is.

When I started practicing medicine 25 years ago, we had three drugs available to treat hypertension. Today, numerous drugs are available, administered alone or in combination, to safely control high blood pressure with minimal side effects – even for pregnant mothers.

In America, some 5 million Americans live with hypertension, with 31.6 percent of those people unaware of the problem. Since high blood pressure is easily detected and is usually controllable through a combination of diet, exercise and therapeutic drugs, the more you know about your blood pressure, the better.
Investigators' skills improve subconsciously as the study progresses so that small differences in the study variables, perhaps missed in the early stages, are detected by the end of the study. One investigator with whom I worked, the late Walter Norris, MD, FFARCS, a consultant anaesthetist in Glasgow, would revalidate annually his own study evaluation technique. In the 1960s anaesthetists were evaluating oral forms of pre-anaesthetic medication to take the place of the Omnopon and scopolamine by IM injection, and Walter had devised a rating scale to assess the sedation and anxiolysis achieved. His first standard had been IM morphine compared with IM placebo and each year he would repeat this comparison in a small group of patients and compare the consistency of his current evaluations with those of the first study, as a form of internal control. His repeatedly checked consistency was the reason I asked him to perform evaluations of IM and oral pentazocine (285, 286).

**f) Assay Sensitivity: an absolute necessity**

There is no clear indication as to who was the first to use placebo as a control in clinical studies. As long ago as 1801 John Haygarth, describing a traction apparatus, reported what may have been the first placebo-controlled trial and noted the 'wonderful and powerful passions of the mind upon the state and disorder of the body.' (287). Flint gave his placeboic remedy in order to study the natural course of the disease and noted that it worked (57), but this was not a controlled trial. Shelley, an Edinburgh graduate and former Winthrop colleague of mine, has suggested that Martini was the first to recognise the need for placebo to control extraneous variables in order to obtain valid comparisons (288). Gold, who edited the Cornell Conference on Placebo (66),
was the first to emphasise the importance of placebo control to differentiate placebo effect from pharmacological effect (289). He planned an evaluation of treatments for angina pectoris and at first he attempted to enroll only those patients who could distinguish glyceryl trinitrate from placebo. Unfortunately, he found that a large number of his patients obtained benefit from both and that they could not separate the active drug from the placebo.

The first use of placebo as a concurrent control came in 1938 in a study of vaccines to treat the common cold (290). Using students from the University of Minnesota, the investigators compared the prophylactic effects of a vaccine, given by subcutaneous injection or by mouth, with those of matching placebo given by injection or by mouth. At the conclusion of the study there was a small advantage for the vaccine, a difference which, although statistically significant, was so small as to be deemed by the investigators to be of no practical relevance or value. In the discussion which followed Dr. W.A.Sawyer commented that many physicians claimed that 50 – 70% of their patients remained free from cold after receiving the vaccine, but these claims were based on a few cases and an absence of controls, while he himself had been guilty of jumping to the conclusion that because patients reported no colds after taking the vaccine this was probably the result of the vaccine. He expressed a debt of gratitude for this valuable investigation with controls.

As we have seen, superiority studies showing clearly that the new treatment is better (or worse) than the control treatment, are the easiest to interpret. With noninferiority studies, showing the new treatment to be not worse than the control treatment is less helpful because both could be equally effective or equally ineffective.
Henry, a former classmate of mine, has quoted Robert Temple MD, of the FDA, describing such a situation by saying, 'If the new drug seems indistinguishable from the active control you don't really know what you have got.' (144). Lasagna (136) discussed the difficulty when the new treatment seems to be inferior, writing, '..in the absence of placebo controls, one does not know if the inferior 'new' medicine has any efficacy at all, and equivalent performance may reflect simply a patient population that cannot distinguish between two active treatments that differ considerably from each other, or between active drug and placebo.' Exactly what was found by Gold.

Temple has for many years been a Senior Division Director at the FDA, and has access to the data from all new drug submissions that come to his Division, a number far in excess of any that a physician in a pharmaceutical company will ever see, so his opinion is to be heeded and valued. In discussing the use of active control treatments in equivalence trials (ACETs) he has stated that to conclude a new treatment is effective because it is similar to control assumes that the active control was effective and would have been superior to placebo. Support for this must come from outside the study, that is, previous comparisons with placebo (277). If we are not confident that the trial could have separated active drug from placebo then we cannot be confident that it would have separated a more effective drug from a less effective drug.

The FDA experience shows that of all modern antidepressant studies submitted by the manufacturers, a third to a half fail to show separation of a known effective drug from placebo. Results from studies of treatment for depression are difficult to interpret because drug effects tend to be delayed and the spontaneous improvement rate is high: these problems do not arise in studies of responsive cancer or infectious
disease, for example, two therapeutic areas in which the critics claim no one would contemplate using a placebo, but they might be wrong. No one denies that to use placebo as the only treatment for patients in such studies would be unethical, yet new treatments for these therapeutic areas deserve the same rigorous evaluation as any other if bizarre episodes such as the laetril debacle are not to be repeated. Placebo controls are needed even here, but the study design has to be more imaginative to prevent any harm arising as a result of its use.

g) Placebo effects are not constant

Beecher's seminal publication (94) propagated a myth that the placebo response is constant in approximately one third of patients. This occurred because Beecher averaged the response rates from his 15 studies and emphasised this figure. Subsequent misreading and misquoting of the paper perpetuates the myth that about 33% of patients in pain will always respond to placebo, and yes, I am guilty also, but I am in good and substantial company. Evans (291) has added to the myth by quoting data from a further 13 double blind studies of analgesics and showing an average placebo response rate of 36%. The error of interpreting the data as an average, rather than as a median, has been pointed out by others (287, 292, 293). The danger thus created is twofold, first it obscures the most important finding, namely that there is a range of variability to placebo response in the different analgesic studies, from 15 – 53% in Beecher's studies and 7 – 37% in those discussed by McQuay et al. (293), and second it suggests that the placebo response rate is constant.
Other disease states in which there is a subjective overlay, for example in psychiatric studies, show a similar pattern with the placebo response in depressed patients ranging from 0 – 68% and from 35 – 76% in patients undergoing psychotherapy (294, 233). In a review of studies involving ondansetron, an antiemetic used in post surgical patients, it was found that the active drug was no better than placebo in 19/52 studies, with success rates in the range of 1 – 80% for those who received placebo and 10 – 96% for those who received ondansetron (222). These studies showed an overall efficacy for the active drug but in several of the trials the incidence of nausea and vomiting was so low, or nonexistent, that there was no opportunity to show a drug benefit. Had these been ACETs without the placebo control, interpretation of the results would have suggested equal efficacy from the two treatments, a classic Type II error.

**h) Can placebo responders be predicted?**

It would be surprising if Beecher’s group in Boston had not considered this possibility, and indeed they did so (231). Using psychological tests, they were able to identify some differences in attitude, habits and educational background between those who had reacted to placebo and those who had not, but they also found a total inconsistency of responses following both single and repeated doses, and could not predict the reactors in advance (295). They suggested that this probably reflected the operation of multiple factors in the determining the placebo response, since it was unlikely that the patient’s personality was changing so rapidly in such individuals.
There is general agreement that, despite many attempts by different investigators, it is not possible to predict placebo reactivity (296), to specify patient characteristics, particular study populations, treatment protocols or sample sizes that will consistently identify or allow predictions as to who will or will not respond to placebo treatment (277, 297). Patient expectations clearly have an effect (122) as we have seen. Others have concluded that response to placebo cannot be predicted, either for groups, patients or healthy volunteers, and that no 'clear, typical "placebo reactor" has been found.' (298).

Beecher was aware that his averaging of results in his early paper was regularly misquoted, and some time around 1970 - 71, in Hyde Park as we attempted to walk off the effects of lunch at Boodles, he mused that not only was it impossible to identify or predict who would respond to placebo, he had also changed his assessment to believing it likely that all of us respond to placebo, but inconsistently, given the changing circumstances and alterations in the impact of the various components of the placebo response at any one time.

i) Some differing opinions

Rothman (145) concedes that a placebo provides control for non specific effects which are often highly variable, but so long as two active treatments can compared in a blind assessment he challenges the need for a placebo group. He does not discuss how this is to be achieved if the active comparator is marketed and formulated with an unique identification, but if the presentation is to be altered to provide the matching to maintain the double blind there may be substantial alteration to the PK and thus the PD
characteristics (299). It is possible to leave the marketed formulation unaltered and have all evaluations and assessments performed by an observer who has no knowledge of the treatment allocation (300), but strictly speaking this then becomes a single blind study because the patient and the prescribing physician are well aware of the identity of the treatment.

Despite the slightly misleading title of their paper, Henry and Hill (144) accept that the placebo controlled studies ‘generally provide us with good evidence that the drug works under specified conditions.’ Their request for ACETs comes from the Australian requirements to show comparative cost effectiveness for new drugs: obviously this can only come from comparison with marketed, active controls, but will they be satisfied with equivalence studies lacking assay sensitivity or will “no evidence of difference” be construed as “evidence of no difference”? Simon (301) believes that Rothman’s claims overlook many of the problems of data interpretation from clinical trials particularly those trials involving active controls with limited or inconsistent efficacy, and in the absence of assay sensitivity, such trials might be considered unethical, comments with which I agree.

A final comment is thrown in by Michels (146) who reportedly stated that ‘Nobody would think of using placebos for such treatable diseases as cancer and AIDS.’ She was referring to placebo controls in trials and not to the treatment of these diseases, but as we shall see, she is wrong, people do, they most certainly do.

I wonder if, in their haste to condemn the placebo control as a fixation with statistical significance on the part of the FDA, Rothman and Michels are showing a
willingness to accept conclusions that cannot be verified because the measurements lack confirmation of sufficient assay sensitivity? They seem to have fallen for a common syllogism by believing that if a drug was once shown to be superior to placebo it will always be superior to placebo so there is no need to have further placebo controlled studies with this drug. By extension, if any other drug is shown to be noninferior to the first then it can also be considered to be superior to placebo and so, without equipoise and this certainty, any such comparison of the second drug with placebo is unnecessary and unethical.

I noticed that recently Hearts were able to defeat Dundee United by 2 – 0, and the next week United beat Rangers by the same score. Using Rothman’s syllogism it is obvious that, two weeks later Hearts should easily beat Rangers and earn three points --- but alas, they lost 0 – 1. Perhaps the combined impact of different times of the comparisons, the different venues, the different participants and the different observers was to blame. Under more ‘controlled’ circumstances, I recall in 1956 watching with great delight as the Hearts defeated Rangers at Tynecastle, by 4 – 0, on their way to winning the Scottish Cup. The next year, as a result of the luck of the draw, I watched the same two teams meet again, on the same ground and in the same competition with most of the same players, but this time it was Rangers who won, also by 4 – 0. Same teams, same ground, same competition, same observer, same score but a totally different outcome and, as might be imagined, a totally different response from the observer! What would Walter Norris make of this?

We need to be cognisant that, for rigorous, scientific evaluations of new drugs and treatments, direct comparisons are necessary and that they do not always provide
outcomes that match predictions and expectations. Even if there have been previous studies using placebo, further placebo controlled trials may be required to provide assay sensitivity, particularly if other relevant outcomes appear or have not been adequately evaluated, or if different observers, measurement techniques and assessments are being employed.
XII. SPECIFIC STUDIES: INCLUDING SOME OF MY OWN.

a) Analgesics and anti-inflammatory drugs

   i) Not so good

   The first study that I helped to design and monitor compared benorylate, an ester of aspirin and paracetamol, with aspirin, at that time the treatment of choice for patients with rheumatoid arthritis (302). A previous study using the third molar dental pain model had shown benorylate to be superior to placebo. In several respects ours was a well designed study embodying many of the points that have been raised thus far, but it had a fatal flaw. Dr. Bain, the rheumatologist, even undertook a small pilot study with benorylate which developed familiarity with the protocol and confirmed that a dose of 4g. daily was an effective analgesic in rheumatoid arthritis.

   To remove the problem of inter observer errors there was only one observer and the duration of treatment was four weeks, to minimise natural disease regression to the mean. There was a treatment free run in period of one week then patients started the double blind, random allocation of study treatment. After two weeks patients could increase the dose of the study drug if they so wished. At the end of the study 29% (4/14) of the patients who received benorylate had increased their dose compared with 54% (7/13) of the patients who received aspirin. This was the only objective difference between the two treatment groups. Subjective improvements
were seen in the reduction of the duration of morning stiffness and increase in grip strength, but these were of equal degree in both treatment groups.

In the absence of a placebo group the study lacked any internal assay sensitivity so we were left to conclude that the new drug appeared to be as effective as aspirin at the doses used, but questions remained. Could this have been a Type II error or were both drugs genuinely equivalent? With the benefit of hindsight and more experience I wonder if the study was truly ethical, given that the design made a definitive result unlikely. Incorporation of a placebo would have been considered ethical because of uncertainty concerning the efficacy of the new drug, the duration of exposure was sufficiently short for no harm to come to the patients (263, 303) and at that time the first line of treatment in RA was aspirin or other mild anti-inflammatory drugs such as ibuprofen. At this distance I cannot recall if we considered having a placebo treatment arm, but the omission proved to be a major disadvantage.

ii) A better effort

The reformulation of naproxen using the IPDAS® system and the results of an analgesic study have already been described (272), but it was expected that this formulation would be used more widely for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). The objective was not to prove that naproxen was an effective analgesic and anti-inflammatory drug, that had been known for 30 years, but to ascertain whether or not the new reformulation altered or impaired the drug performance.
Two identical studies were undertaken (304, 305), one in OA and one in RA with study participation for 12 weeks. After a run in period during which all patients received placebo, they were randomly assigned to receive either Naprelan once daily, Naprosyn twice daily or placebo twice daily. The Naprelan treated patients also received a placebo tablet in the evening, using the matching dummy technique to maintain the double blind. In both studies, global assessments of disease state by the physicians and patients, joint pain and stiffness showed significantly greater improvement after one week of treatment with the active drugs compared with the placebo. At the end of the study, after 12 weeks of treatment, both groups that received the active drugs showed significantly greater improvement than did the placebo treated group. In addition, the OA patients who had received active drugs required significantly less 'rescue' paracetamol compared with the placebo treated group, and in the RA study, the 'marked responder analysis' (306) showed significant advantages for the patients who received the active drug. For all assessments in both studies the two active drugs were equivalent, except in the RA study where pain relief, evaluated during the day and into the evening as a check on the continuing efficacy of the once daily Naprelan formulation, showed Naprelan to be significantly superior to both Naprosyn and placebo.

I had not taken part in the design of this study but I became responsible for the data analysis and presentation. Ethically, there was justification for the study with genuine uncertainty over the efficacy of the two part release system in the formulation, the time to onset, and duration, of action being paramount. The
placebo run in period for each patient was of particular significance in this study because of the need to assess onset of action of the new formulation. It was essential that any effectiveness observed in the first week of study treatment come from the study drug and not as a carry over from the previous therapy, which has been shown to occur (307). Thus, the run in was continued only until the complete absence of previous active treatment was shown by the flare in disease state. The inclusion of active comparator and placebo groups provided assay sensitivity for the comparison of two active drugs, as we had used previously (268).

iii) Measuring dose responses

In an attempt to identify the most useful oral dose of pentazocine, a study (308) which I did not design but monitored, compared four doses of the drug, 25mg, 35mg, 50mg, 70mg, in patients in general practice. No placebo was included and the results showed no significant differences between the three larger doses, with 35mg and 70mg being indistinguishable. The 50mg dose was only marginally more effective than the 25mg dose although it was better tolerated than the 35mg and 75mg doses.

These data did not prove to be helpful in answering the question as to which dose should be developed further, so to obtain a clearer assessment I designed a second study. This compared single doses of 50mg and 70mg, and included a placebo, in patients who had undergone abdominal or thoracic surgery, but were now able to take oral analgesics, and once more I asked my anaesthetic colleague to help (309). The results are shown in Figure 8 and a statistically significant trend of
increasing effectiveness with increasing doses is seen. It is interesting that both doses of the active drug were ineffective in 30 – 35% of the patients, confirming again that even pharmacologically active drugs are not effective all the time in all patients, and that an inert, lactose placebo was partially effective in 25% of these patients who were in moderately severe pain. Although not shown in the Figure, there was also a dose response effect seen in the incidence of adverse events with 8%, 13% and 26% of patients reporting events in the placebo, 50mg and 70mg treated groups, respectively. The placebo provided the required assay sensitivity that confirmed these results as valid, and after the injectable formulation of pentazocine had been marked it was the 50mg oral tablet form that was developed.

### Analgesia Obtained by Patients in Moderate Pain (expressed as percentages)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pain Relief</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Placebo</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>Pentazocine 50 mg</td>
<td>30%</td>
<td>49%</td>
</tr>
<tr>
<td>Pentazocine 70 mg</td>
<td>35%</td>
<td>23%</td>
</tr>
<tr>
<td>Total</td>
<td>43%</td>
<td>34%</td>
</tr>
</tbody>
</table>

**Key:**
- 0 = nil
- 1 = partial
- 2 = considerable or complete

**Figure 8**

Reproduced from reference 309.
iv) Comparisons with effective drugs still need placebo

As we have seen comparisons with effective, currently used comparators are required and that some critics believe that these should be the only comparisons performed (144, 301). However, if we are to avoid the problems already discussed at length, and ensure the validity of the study results, then placebo is still required for assay sensitivity.

When the NSAIDs were shown to be effective analgesics for women with dysmenorrhea we thought that it would be useful to compare fenoprofen with ibuprofen, one of the first of the modern NSAIDs, and placebo, in a double blind, randomised study (310). The results showed that fenoprofen 200mg and ibuprofen 400mg were equivalent and both active drugs were more effective than placebo, as assessed by the patients' reported pain scores. Internal assay sensitivity in this study was provided by the placebo so the results could be considered valid, and that these doses of the active drugs were genuinely of equivalent efficacy.

Following this study we wondered if a larger dose of fenoprofen would be more effective, so a second four arm, double blind, randomised study was designed, comparing fenoprofen 400mg with aspirin 650mg and placebo, with a fourth arm being fenoprofen 200 mg, again, to check and confirm the superiority over placebo seen in the previous study (311). Thus the study combined double assay sensitivity by inclusion of the placebo and two different doses of the drug under evaluation. The results showed several interesting aspects. Using the patients' reported pain scores, fenoprofen 200mg and 400mg were equally effective, with no significant difference
between them, but both were significantly more effective than aspirin and placebo, the latter two being indistinguishable.

The similarity in effect between the two doses of fenoprofen might seem like a possible Type II error or the result of inadequate sample size in the study, but the significant separation from placebo confirms the validity of these results. In fact, these findings indicated a plateau effect with increasing doses of fenoprofen. This led to the clinically useful recommendation that if 400mg. of fenoprofen fails to benefit a particular patient then it may be more appropriate to switch to another NSAID rather than simply increase the dose of fenoprofen. That aspirin was no more effective than placebo came as no surprise to the gynaecologists who performed the study as apparently they had been aware of this for many years.

v) Add on placebo comparison with standard therapy

Patients with sickle cell disease have frequent vaso-occlusive crises which are excruciatingly painful and in many US Hematology Centers the standard treatment is IM injections of pethidine. The investigators were concerned about the attendant secondary opioid effects of constipation, respiratory depression, injection site fibrosis and addiction potential which accompanied chronic and repeated use of pethidine, and they had previously evaluated an oral NSAID in the treatment of these patients, hoping that the analgesic properties and the inhibition of platelet aggregation by this class of drugs might be more advantageous. Unfortunately the results had been disappointing, raising the question as to whether the NSAIDs as a class were not effective analgesics in this setting or whether the problem was the oral administration
of the drug. With this experience there was considerable uncertainty as to the value of an injectable NSAID, ketorolac, but this seemed to be worth studying. It would have been cruel and completely unethical to treat these patients with placebo alone so an add on design was used for a double blind, randomised study to compare ketorolac with placebo (312).

In the study centre the routine analgesic care for patients with sickle cell crisis was IM pethidine at least every three hours or on demand, until relief was obtained, and as these were regular patients at the centre all were familiar and experienced with this regimen. There was no question of withholding standard, best available care.

On enrollment to the study patients received either a continuous infusion of ketorolac or placebo (normal saline) allocated at random, and their injections of pethidine as per usual practice. The results as measured by reduction in pain intensity showed that ketorolac plus pethidine was significantly more effective than placebo plus pethidine. More striking, perhaps, was the finding that patients who received ketorolac required 33% less pethidine than their counterparts who received placebo plus pethidine. Recalling that all patients were used to receiving pethidine every three hours, they were asked to comment on the combination that they had just received and again the ketorolac plus pethidine was significantly preferred over their usual care. The most surprising finding was that the patients who received ketorolac, on average spent three days in hospital compared with the other group who spent, on average, seven days in the hospital. A survey of the hospital records for all the patients in the study showed that previously their average stays in hospital had been about seven days also, providing confirmation that in this study there was no Hawthorne effect and the
group who received placebo plus pethidine were not responding in an abnormal manner.

The use of the add on technique permitted all patients to obtain standard effective therapy in a clinical trial of a new drug and also allowed a comparison with placebo to provide assay sensitivity. There can be no doubt about the validity of this study and no criticism that one group of patients were denied standard, effective treatment.

b) Placebos and infectious disease

Growing concerns with resistance resulting from inappropriate antibiotic overuse are being increasingly addressed (313) and despite the assertions of critics placebo controls are used in clinical trials involving patients with infectious disease where the risk of mortality and morbidity are minimal.

i) Treatment with antibiotics

A study comparing aureomycin and placebo in military recruits with coryza showed that after 24 hours of treatment 44% who received the antibiotic had improvement or cure compared with 45% of those who received placebo (314). A more recent, similar study compared an antibiotic combination with placebo and showed that 34% of the patients with coryza were cured in five days regardless of which treatment they had received (315).

A pediatric study comparing amoxicillin and placebo in children with acute otitis media showed that after four days the children who received the antibiotic
had significantly fewer symptoms than did those who received placebo, but after 11 days both treated groups had the same rate of clinical failure (316).

ii) Prophylaxis and placebo

Low dose antibacterial prophylaxis for patients with recurrent urinary tract infection (UTI) came into vogue about twenty years ago and I designed a study to compare cinoxacin, then recently introduced, with placebo. This might have been a study in which the critics would demand an active comparator, but UTI is not immediately life threatening, the patients were seen at regular intervals for urine culture and there was minimal risk of an infection actually going untreated, so it seemed that the benefit of assay sensitivity was worth obtaining (317). Patients who had suffered at least three UTI in the previous year but were free of infection on enrollment, received either cinoxacin 500mg once daily or placebo. After 220 days of treatment 90% of those who received the antibacterial drug were asymptomatic and microbiologically clear, compared with 52% of those who had received placebo.

I had no involvement in a second pediatric study (318) of malaria chemosuppression but it was of interest to me because it was performed in an emerging country, used a double blind, randomised design with placebo control and involved proguanil. All the children had initial curative therapy with atovaquone plus proguanil and were free of *P. falciparum* and *P. malariae* at the start of the chemosuppression phase. They then continued to receive the combination product, at one fourth of the dose, or placebo, for 12 weeks. At this time 25/140 of the children who received placebo had positive blood smears for parasitaemia compared
with 0/125 of the patients who had received the active combination, leading the authors to conclude that this combination should replace current regimens to which resistance was becoming more common.

Results from the studies described above that had assay sensitivity offered proof that prescribing of antibiotics for coryza is an ineffective exercise which is specifically not recommended (319), but that early antibiotic treatment in pediatric otitis media offers the advantage of rapid symptom resolution. Prophylaxis for UTI and malaria, together with identification of a more convenient and equally effective dosage schedule or a combination associated with less developed resistance, would seem to me to be worthwhile information that has direct clinical application, but would these results stand up to scrutiny without the assay sensitivity provided by placebo or totally objective measurement?

iii) Different treatment schedule

In another study of UTI we were interested to learn if the standard dose of cephalexin, 1g daily, would be as effective if given in the more convenient schedule of twice daily rather than four times a day (320). As the assessment was to be entirely objective, based on urine culture and the microbiological response, the same drug in the same dose was being evaluated and because untreated UTI is associated with significant morbidity, we did not believe that a placebo comparison was justified in this study. Results showed that the microbiological cure rate was 93% in the patients who took the drug twice daily and 91% in those who took it four times daily. The results from this study, together with other similar studies, resulted in a change
to the product prescribing information, in which the more convenient, less frequent dosing schedule was recommended for the treatment of uncomplicated cystitis (and skin infections, which were studied later).

iv) Add on placebo for AIDS and transplantation studies

As Michels points out, of course no one would countenance using a placebo as sole treatment in studies of these diseases. However, the add on technique can be used and placebo plus best supportive care has been suggested as inevitable for the reliable assessment of the benefit-risk ratio in these life threatening diseases (321). Although not particularly informative about the use of the new treatment as monotherapy, this design is appropriate if the new treatment is likely to be used in practice as part of combination therapy (277). As the laetril debacle in cancer patients showed, there are also ethical concerns over the recommendation of useless nostrums that have never been properly evaluated or have shown efficacy only in poorly designed, anecdotal investigations that lack both controls and assay sensitivity.

I had nothing to do with a major double blind, randomised study of over 1,000 patients with HIV infection, in which ritonavir, a new protease inhibitor, was compared with placebo, using the add on technique (322) but this shows that placebo can, and is, being used in trials of these serious diseases. All the patients continued to receive their standard HIV therapy which could include up to two nucleosides (zidovudine and stavudine were used by 71% of the participants), and to this was added either ritonavir or placebo, allocated at random. Any patients who developed
an AIDS-defining outcome, for example CMV retinitis, were switched to open label ritonavir while those who did not develop this outcome remained on the blinded study medication. At the end of the study all patients received ritonavir on an open label basis.

Addition of ritonavir reduced the risk of AIDS-defining illness or death, which occurred in 22% of the patients who received active drug and in 38% of those who received placebo. On the risk assessment however, 21% of the ritonavir treated patients withdrew from the study because of drug related adverse events compared with only 8% of the placebo treated patients. Clearly the add on design contributed to the knowledge base for ritonavir in the treatment of AIDS.

My therapeutic group was not directly involved in the studies of mycophenolate mofetil (MMF), an immunosuppressant used to prevent organ graft rejection but I was involved in the early phases of the trial design. Recognising that the drug would never be used as sole treatment the add on technique was the only choice if assay sensitivity was a requirement. Three trials were performed (323, 324, 325), all following the same principles of design and all using active drugs or placebo as an add on to the supportive therapy of cyclosporin and corticosteroids. All the patients had renal allograft transplants and two doses of MMF, 2G or 3G daily by mouth, were evaluated.

The results were similar in all three studies with MMF 2G daily offering the best protection against graft rejection and also being the best tolerated of the active drugs. Rejection rates were greatest in the groups that received the standard therapy plus placebo but patient withdrawal because of adverse events was the lowest
in these groups. There is a high incidence of mortality and morbidity associated with renal transplantation, but placebo was used to provide assay sensitivity in these studies and contributed to the overall assessment of benefit and risk of the new treatment.

c) Designs to limit placebo exposure

Provided that it is undertaken honestly and correctly, the informed consent process should provide sufficient safeguards for any patient who agrees to participate in a study, and for him or her to understand the need for and role of a placebo. Nevertheless, investigators should not take advantage of these patients by expecting them to tolerate pain or discomfort for prolonged periods, remembering of course, that even therapeutically active drugs are not effective in every patient every time. For these reasons designs to limit exposure to placebo have been considered.

i) Rescue medication

In most analgesic studies, patients are told that rescue medication is available should the study drug fail to provide the required relief. During the informed consent process, and at subsequent discussions, the patients should be encouraged to give the study drug a chance to be absorbed, say waiting for an hour following an IM injection and say two hours after oral ingestion, before they ask for rescue medication, although stressing that they are free to withdraw at any time. Once the rescue medication is given the patient has to be withdrawn from the study if it is a single dose design, but if the study is of longer duration then requirement for repeated doses of
rescue medication does not mandate withdrawal from the study. In fact, the requirement for rescue medication can be used as a method of assessing comparative efficacy. For example, in our study (268), 24/30 patients who received placebo required rescue medication compared with 11/30 who received fenoprofen and 7/30 who received the IM morphine. The difference between placebo and both active drugs was statistically significant while that between the active drugs was not, a further emphasis of the assay sensitivity.

ii) Early escape

In some study designs a well defined treatment failure point is identified and established in the protocol, say exacerbation of the disease beyond a defined level, at which point the patient is withdrawn from the study and given the active study drug in an open label fashion. This occurred in the ritonavir study when, at the end of the second period assessment, 147/545 patients who received placebo and 79/541 patients who received ritonavir had developed an AIDS-defining outcome and were switched to open label ritonavir (322).

iii) Post study treatment

In the ritonavir study all patients who had received placebo during the study were ultimately treated with the active drug on completion of the formal study. The protocol for the surgical implantation of foetal tissue in patients with Parkinson disease stated that those patients who underwent the sham procedure would receive the ‘active’ implantation after conclusion of the study (129). Unfortunately this did not
happen for each patient, leading to substantial criticism and opprobrium being leveled at the investigators (130, 131).

Whether or not placebo is involved, offering treatment beyond the conclusion of the study is not common, and as an aside, this raises an ethical problem in my mind. If a patient has responded well to the study drug, particularly for a life threatening illness, say cardiac arrhythmia in which a new anti arrhythmic drug has been evaluated, I believe that it is unethical for this treatment to be withdrawn simply because the study has ended. Ideally, treatment should be made available for as long as the patient continues to respond or the drug is marketed and thus readily available.

iv) Randomised withdrawal

If the desire is to compare a new and an established treatment in an ACET, yet assay sensitivity is required, this design allows all patients to receive active treatment to start with, but for placebo to be substituted for active drug in a double blind fashion. The timing for the substitution is allocated at random so that patients will continue with active treatment for different periods. This design provides information on the duration of continued drug effect after it has been taken for different lengths of time and then withdrawn. If any patient deteriorates the drug code can be broken, the study drug identified and the patient switched immediately to active treatment.
v) Planned withdrawal

A variation on the randomised withdrawal has also been described, in part based on the paper by Gold (289) who found that only 4% of his patients with angina who had coronary artery disease responded to placebo, compared with 25% who responded to placebo but did not have coronary artery disease.

In this design (326) all patients entered a period of open label treatment with the active drug, during which the dose could be titrated as necessary. The protocol identified a time point at which all patients were to be evaluated. At this evaluation, those patients who had failed to respond to the open label, active drug, were removed from the study and treated in the usual manner. Patients who had responded to the active drug then continued with the active drug or switched to placebo, in a double blind, randomly allocated manner. The advantage of this design is that all the patients receive active drug and those who fail to respond are not exposed further, either to the drug or to placebo. The null hypothesis is thus tested only in the second, double blind phase, enabling an assessment of the effects of the new, active drug: were these genuine or a placebo response?

vi) Two doses of active drug

Provided that the two doses are sufficiently separated for any difference in response to occur, this design can be used with an active comparator and no placebo. However, if one of the doses is known to be too low to produce an effect then this design involves self deception on the part of the investigator who claims that all patients will receive active drug and that placebo is not involved. All the study
drugs may indeed be active, but one group of patients is being denied effective therapy. If there is genuine uncertainty as to the best dose then instead of homeopathic doses of the active drug, why not use an inert placebo to provide assay sensitivity, provide validity to the results and ensure that any lack of difference will be not be casually accepted as equivalence?

vii) Unbalanced distribution

A compromise between the need for assay sensitivity and limited exposure to placebo can be achieved by getting the statisticians to provide a random distribution of the study drugs so that say, there are two or three patients who receive the active drug for every one who receives placebo. Provided that the unbalanced distribution is planned at the start and did not develop as an afterthought or as a consequence of some failure of the patient enrollment or drug allocation process, my statistical colleagues assure me that the data analysis is straightforward.

viii) Smoke and a mirror

One interesting study in which I was closely involved (327) concerned the switch, from a prescription only to 'over-the-counter' non prescription status, of a nicotine patch as an aid to smoking cessation. The FDA had requested placebo controlled studies (a genuine instance of the regulatory authority making us do it!) and also a study in which the participants would be asked to pay for the patch, to see if payment improved the success rate. This would be a sort of an inverted Hawthorne test in that the participants were not rewarded for increased performance but penalised
by paying when they did not succeed. It was universally agreed that asking participants to pay for placebo patches would be unethical, but the problem was how to retain assay sensitivity for this group. The dilemma was solved by combining the data from the two studies so that the placebo control group was a mirror for both the groups that received the active nicotine patch.

In response to a newspaper or radio advertisement potential participants telephoned a central service and, according to a random code, were told either about the double blind placebo-controlled study or about the study in which they would be asked to pay for the patches. If they agreed to take part in whichever study had been described to them they were referred to the nearest study site for screening and enrollment if suitable. Study personnel knew to which of the two studies each participant had been assigned, but not the actual treatment in the double blind, randomised comparison with placebo.

All participants were seen at the same sites with the same investigators and study staff, in accordance with the study protocol requirements (328). Patients were asked to record their smoking cessation in a daily diary and at each visit this was checked biochemically using a carbon monoxide monitor. After treatment for six weeks the point prevalence quit rates were 9.6% in the placebo treated group, 16.8% in the group that received the active patch double blind and 19.0% in the group that received the active patch and paid. After a further eighteen weeks without the patches the point prevalence quit rates were 4.3%, 8.7% and 10.8% respectively in the three groups. At both assessments the quit rates in the groups that received the active patches were significantly greater than the quit rate in group that received placebo, but the 2%
difference between the two groups that received active treatment was not statistically significant.

All patients were told at the initial telephone interview that they had the option of declining to participate in the study, so those who did choose to participate probably were representative of the real world in which they would select patch use as an aid to quitting smoking. Thus these were probably the best results that could be obtained with the patch and the quit rates seen in the placebo treated group were probably the lower limit for patch efficacy. The small difference in the quit rates seen in the two groups who received the active patches suggest that there was no Hawthorne effect in this study, and that paying for the patches was not a greater stimulus to quitting.

ix) Historical control

In one of the hoariest clichés heard in connection with new drug development the critic points out “No one needed formal trials to show that penicillin worked.”, ignoring that even so there was a comparison of sorts because the results of treating infections with penicillin were evaluated against the results of previous treatments in which an antibiotic had not been used because none existed. In the 1980s my therapeutic group was involved in a similar situation as the AIDS epidemic took off.

Burroughs Wellcome (BW) and Syntex had both developed ganciclovir which could be used to treat the cytomegalovirus (CMV) retinitis that rapidly led to blindness in these immunocompromised patients. At the suggestion of the FDA, BW
had started an initial Compassionate Use program in which all physicians treating AIDS patients could obtain free drug. For business reasons, BW soon withdrew from the scene leaving Syntex as the sole supplier and developer of the drug.

I became the Director of the therapeutic group into which ganciclovir was placed and about this time my colleagues published their preliminary findings (329) describing dramatic results in 26 patients with virologically confirmed CMV infections, some involving more than one body system. Stabilisation of the disease was seen in 11/13 patients with CMV retinitis and 5/8 with CMV gastrointestinal disease. Of the seven patients with CMV pneumonia, four died and the response in this disease group could only be described as poor, but overall, these results made all conventional, future comparative study designs unethical.

This publication was rapidly followed by three others, all concentrating on the treatment of CMV retinitis, for which ganciclovir appeared to be particularly effective (330, 331, 332), showing disease stabilisation and even some regression of the retinitis in approximately 88% of the treated patients. These publications, predictably, led to demands from the AIDS community that the drug be approved for marketing so all the clinical data obtained up to this point, without any comparative studies, were included in a new drug application to the FDA. The Agency, with whom we had been working closely, recognised the difficulties involved and perhaps would have accepted the study results for what they were, and approved the drug, but the Advisory Committee were unimpressed. They recommended that the drug application be rejected and that FDA and ourselves design further studies which would incorporate comparator groups. The Committee members themselves offered no
guidance on how these groups should be gathered nor what study design would be acceptable to them, but in discussions with the FDA group we came up with two designs.

We settled on one historical control design and a second study that compared two different treatment regimens. The first study (333), at one site with a large patient population, compared fundus photographs from patients who had been treated either before ganciclovir became available or in the early days when doses and dose schedules were at personal discretion, with photographs from new patients treated prospectively according to a formal protocol. A standard for assessing disease progression from fundus photographs, with gradings of new lesion, enlargement of existing lesions and opacification of the border, was devised and all photographs were read by a single ophthalmologist who was unaware of the treatment. Photographs had the patient identity and date masked and coded and they were presented for assessment in random order. Once each photograph had been assessed the scores were sent to Syntex, the code was broken and the scores tabulated for each patient.

The results were convincingly in favour of treatment with ganciclovir, but as always, there were questions over the systematic bias in selection and comparability of the control group. For various reasons there had to be some selection of patients, for example only those in whom photographs were available could be included in the control group: there could be no random allocation of treatment: there was no standardisation between the two groups as to intervals between diagnosis of CMV retinitis and the start of treatment: there were different intervals between evaluations of disease progression: some of the early treatments had been deliberately
delayed and not all the patients had been photographed. In other words, the control group was typical of an historical group collected post facto, and in the end, data from 67 potentially suitable patients had to be discarded.

The second study compared two groups of patients all receiving zidovudine, with peripheral retinitis that was not immediately sight threatening, who were prospectively treated with ganciclovir (334). Ganciclovir is by no means a non toxic, well tolerated drug in all patients, particularly when given in combination with other antiviral compounds. The uncertainty here concerned questions as to whether immediate ganciclovir treatment, with zidovudine withdrawn, was more effective than continuing with zidovudine until the retinitis had started to show progression. The results showed clear benefit: immediate treatment with ganciclovir, in the absence of zidovudine, delayed progression of retinitis by a median of 49.5 days, compared with a median time to progression of 13.5 days in patients who received standard best therapy of the time, zidovudine with ganciclovir therapy delayed. When these results were submitted to the FDA and considered by the same Advisory Committee, the vote to approve ganciclovir was unanimous.

However, historical control studies are always questionable because there is considerable doubt as to whether the same diagnostic criteria were used to identify the control group. Are patients who were previously excluded now entered because of a change in disease diagnostic definition or the advent of new diagnostic techniques? If an important variable was not recorded for the historical group does
that mean that it was absent, or simply not measured? Absence of evidence cannot be assumed to be evidence of absence. If multi therapeutic regimens are required, say the anti cancer regimens, have the components been changed since the control group was treated? However, as with penicillin, when there is evidence that a new treatment can prevent or delay the onset of serious complications, the ethical justification of comparative study designs becomes problematic. Falling back on an historical control may be the only choice.
XIII. PRIMUM NON NOCERE: PLACEBO REDUCES THE RISK!

In his attack on placebo controls in clinical trials Professor Rothman admits that 'Because the placebo effect is usually considerably different from that of an effective treatment a study does not have to be very large to find a significant difference.' (145). To admit to this advantage for placebo is an enormous concession from one of the strongest critics and endorses the need for placebo controls in studies that are seeking proof of concept. If the new drug really does not work at all then this should be discovered as quickly as possible while exposing as few patients as possible to ineffective therapy, while still remembering that even effective drugs do not work in all patients all the time, despite Dr. Michels' apparent beliefs.

Using data from a recent paper by friends and colleagues in the Oxford Pain Relief Unit (293) let us accept a placebo response rate of 37%, and a hoped for response rate from a new analgesic of say 75%. To show a difference between the two treatment groups at the 5% level of significance will require 15 patients per group, of whom 10 (63%) of those who receive placebo and 4 (25%) of those who receive the new drug, that is a total of 14 patients, will not obtain effective analgesia, yet the study objective of proof of concept will have been achieved.

If now we take an established analgesic which, using the Oxford data, might be effective in up to 63% of patients (recall that the study with oral pentazocine (309) showed a response range of 65 – 70% for the two doses) and compare it with the new drug which is again effective in 75% of the patients, 150 patients per treatment group will be required to demonstrate a statistically significant difference at the 5% level. Of
these, 56 (37%) who receive the established analgesic and 38 (25%) who receive the new drug, that is a total of 94 patients, will not obtain effective analgesia. This seemed to me (335) to be a disappointingly large number of patients on which to inflict the torture of pain that Rothman agrees is not a good idea (197) but it is the price that has to be paid in order to assess comparative efficacy with best available treatment rather than placebo. Should the difference between the new analgesic and standard therapy be less marked, say a response rate of 70% for the new and 65% for the standard, which was in fact the difference between the two doses of pentazocine in our study (309), then approximately 500 patients per group will be required to show this as a statistically significant difference, with a total of 325 patients obtaining inadequate analgesia. With approximately one third of the patients showing no response to treatment and in the absence of assay sensitivity, could this be a valid result or an error of Type I or Type II?

The late John Harter, MD. who was the FDA Division Director responsible for the approval of analgesic and anti inflammatory drugs, and who was prominent in the rewriting of the Guideline for the Evaluation of Analgesics (217), applied a simple proof of concept test. ‘If,’ he said, ‘your new analgesic cannot be shown to be significantly better than placebo in a study of no more than 30 patients, who needs your drug?’ Actually, his comment seems to ignore the extreme variability in placebo response, ranging from 25 – 60% depending on the study and disease being evaluated, but this itself is a reason for always including a placebo control.
XIV. PLACEBO REDUX

As the Art of Medicine gives way to the Science of Medicine and Evidence-Based decisions dictate the choice of drug or treatment for our patients, there are loud demands that all new therapies undergo rigorous scientific evaluation before being approved for marketing. From this it might be supposed that the need for assay sensitivity would have universal acceptance, but apparently not.

We have seen that since earliest history placebo has been on a roller coaster ride as it passed from being a word of respect to a major role in a religious ceremony, through derision in the Middle Ages to widespread use, if not publicity, in the practice of medicine, to a role in modern medical research. Definitions in medical dictionaries do not always provide consistent help in interpretation or understanding and members of the medical profession have seemed to be unsure of what role, if any, placebo should play. Some senior physicians have openly proclaimed the usefulness of placebo in their practice while others have been more diffident and perhaps regarded it as akin to charlatanism. Even today there appears to be considerable confusion as to what placebo is. In an exercise that owed something to the comments of Dr. Pepper, 318 published articles with the words ‘placebo’ or ‘untreated’ in the abstract, were recently evaluated (336). In 188 of these articles the word ‘untreated’ did not refer to an untreated control group. In the remaining 130 articles, 52 used ‘untreated’ as synonymous with placebo, and differences between the placebo itself and the placebo effect, or response, seem to pass unrecognised.
Thus, it has been easy for Rothman and Michels, with their fellow critics, to make sweeping statements about placebos to stir the emotions and cloud the rational appreciation of what is being said. Their major criticisms appear in 3-D, namely Denial, Disregard and Deception and perhaps should be addressed briefly once more.

Denial of effective therapy and reduction in quality of life are usually cited first, but we know that individual patients do not always respond equally even to the so-called standard doses of drugs, although this is more often disregarded than investigated and explained (123). As Dundee graduate Alastair Wood wrote recently (337), this inability to understand and predict the variability in patient response to treatment means that our prescribing of drugs is an iterative process in which treatment is started with the standard dose and then titrated up or down depending on the therapeutic response. Thus patients may receive ineffective therapy for varying periods, even from an effective drug given with the best of intentions. True, placebo may lack a specific therapeutic effect but it is a powerful intervention (338), and even Rothman acknowledges that it has the advantage of reducing the numbers of patients in a clinical trial put at risk of receiving ineffective therapy.

Critics claim that patients in studies of antidepressant or anxiolytic drugs are at a greater risk of committing suicide if they remain ‘untreated’ by receiving placebo, but a review of the data from controlled trials submitted to FDA found no increase in suicide or suicide attempts among placebo treated patients, and conversely, a review of national suicide rates has shown no decrease in suicides among depressed or psychotic patients who were treated with currently available ‘effective’ drugs (339).
Using a placebo comparator puts fewer patients at risk, as I showed in the analgesic example.

Michels seems unable to recognise that even when they achieve a satisfactory therapeutic response the quality of life of patients receiving active drugs can be markedly diminished by the appearance of adverse events such as nausea, vomiting and constipation. For example, cancer patients often complain that the constipation caused by opioid administration is more troublesome than the pain the drug is supposed to relieve. She also ignores the other more severe and serious secondary pharmacological effects that may occur, such as cardiac arrhythmia or blood dyscrasia, neither of which have been reported with placebo treatment.

Disregard of patient autonomy and beneficence is the second criticism, but this applies to any and all trials and not just to the use of placebo. Clinical trials are experiments designed to elicit a particular answer from a comparison of groups of patients, with consequent restrictions in catering for individual response. Patients must be informed before they are enrolled in a trial, but if they agree then presumably they understand what they are giving up in the way of autonomy.

The third criticism is Deception of the patient by placebo substitution, but this occurs only if the informed consent process is incomplete, ignored or dishonest. If, after a full and comprehensible explanation that a placebo will, or may, be introduced at some time unknown to the patient or investigator for the purpose of separating perceived placebo effects from placebo effects themselves and to validate the study results by providing assay sensitivity, and the patient still agrees to enter the study, I see no problem with the ‘deception.’
The critics seem to forget that we welcome and enjoy 'informed' deception in our everyday life. We are entertained by magicians and illusionists when they perform their tricks. We read detective stories and are delighted when we can successfully unravel the deceptions perpetrated by the author and identify the culprit, we go to the theatre, watch television or a film knowing that we are being deceived, that things are not necessarily what they appear to be, that the actors are not really killed or buildings spectacularly destroyed. We admire the work of stunt men who perform the tricks and we ponder the manner in which the deception is created, so that the deception is part of the enjoyment. Some patients may even derive the same pleasure from the study if they understand the nature and reason for the deception, but, failure to disclose the placebo means there is no 'informed' deception. This is unethical and indefensible.

It was a pity that shortly after publishing the instructive series of papers on aspects of placebo use, Lancet adopted a general policy of not accepting papers that describe placebo controls when an effective treatment is known to exist (340). Does this mean that the Editor believes that the only way to include a placebo is as sole therapy in the comparator group? If so then it seems to show a lack of appreciation that there are many different study designs that include placebo to provide the assay sensitivity and do not deprive the patients of effective therapy at the same time. If there are to be no placebo controls will Lancet accept reports of studies involving untreated control groups? While it is possible to have the patients allocated at random to study treatment or to no treatment, but it is not possible to make this double blind,
as scientific rigor requires, and there can be no doubt that the untreated patients will be denied effective therapy.

The Lancet Editorial stance is at variance with the recently published E10 report from the International Conference for Harmonization (341) which accepts as ethical the use of placebo-controls in clinical trials even if an effective treatment is available for the condition. The report contains the caveats that the placebo use must be for short duration only, that patients are unlikely to come to serious harm from the withholding of specific treatment and that full information is provided to the patients about available treatments outside the study and the possible consequences of delayed treatment. It is also relevant to note that the International Conference is comprised of representatives from the regulatory authorities and the pharmaceutical industry in Europe, Japan and the USA. In this recent report the ICH revisit the earlier list of five possible choices for control groups (215, 216) and add a sixth choice, Multiple Control Groups (paragraph 1.3.6) which has a placebo control in addition to an active drug control.

Critics demand maximum scientific rigor in the evaluation of new treatments with the double blind, randomised design, but they fail to consider the practical aspects of these demands, such as how the blinding of the study drugs is to be achieved when a marketed comparator is selected as the active control. Obviously the marketed formulation cannot simply be changed to match the new drug, nor can the latter be prepared to look like the marketed comparator, particularly if there are identification marks on the marketed drug. The easiest technique is to formulate the new drug as an opaque capsule and then put the marketed comparator into a matching
opaque capsule. However, frequently this over-encapsulation changes the PK and PD characteristics of the comparator drug and at the very least this requires a PK study to be undertaken to show that there is no alteration in these characteristics. Overall the placebo offers the best and most flexible options for matching formulations to maintain the double blind, even if the double dummy technique has to used on some occasions.

If the double blind, randomised clinical trial is truly the gold standard for drug evaluation then incorporating a placebo comparator, in one design or another, is necessary to provide validity of the results and for a reliable assessment of the benefit risk ratio (319, 342, 343). Among the scientists involved in the development of new drugs, the reviewing officers in the various regulatory agencies and the committees who evaluate the clinical trial data, there is a shared desire to have scientifically rigorous, assay sensitive and validated, clinical assessments and comparisons. That means placebo control, not necessarily as a sole therapy but in some form and using one of the more imaginative designs such as add on, or timed withdrawal, if these are appropriate. There is also a need to educate the medical community about the role of placebo and the separate area of placebo effects, often perceived merely as 'noise' to be eliminated without any understanding as to how these potentially desirable effects play a role in every interaction between patient and physician, or how they can be used to benefit the patient (336). The need for assay sensitivity in clinical trials must be understood if we are to eliminate trials that are unethical because they have no chance of showing a clear and scientifically valid answer.

Another advantage of placebo as a control is that generally, smaller groups of patients are required to demonstrate proof of concept with the new drug than would be
necessary with an active comparator, thus reducing the number of patients exposed to the potential risk factors. Placebos may be inert and lacking in specific therapeutic effect but this cannot be said of the patients or physicians, which partly explains the wide variability, ranging from about 25 – 60%, and inconsistencies in placebo response rates in different studies. Placebo is not devoid of therapeutic benefit, nor is it synonymous with nothing. Even if it were, it is well to recall that penicillin became widely used because it was so obviously more effective than the best available treatment for infections in the pre-antibiotic era, namely nothing. In other words, one could say that penicillin was used only because it was ‘better than nothing.’ In his derisive dismissal ‘who cares if the new drug is better than nothing?’ had Bradford Hill forgotten penicillin and why was Rothman so eager to quote him?
I began this thesis with a quotation from Humpty Dumpty concerning which particular definition of a word was to be the master. Placebo has been called many things, as we have seen. It has been a prayer, a ceremony, a sycophant, a treatment given only to please the patient, an unacceptable deception, a lie, a valuable item of the therapeutic armamentarium, an important therapeutic device and a respected tool in modern research. It has been described as quackery and in terms of derision, embarrassment and disdain, as having a not inconsiderable place in medicine, not to be discussed in polite society and unfit for publication. Quite a vocabulary from which to choose the word that is to be master.

In a recent article (344) the authors described their systematic review of 130 trials in which treatment with placebo was compared with no treatment, and attempted to understand the effects of placebo as a treatment rather than the effects of placebo as a comparator in clinical trials. They suggested that there is no justification for the use of placebo as a treatment, outside the clinical trial setting, and they are supported by the author of an accompanying Editorial who agreed that he would wish neither to prescribe nor receive a placebo, as treatment (345). Both note that within a double blind, randomised clinical trial setting however, the use of placebo is a precaution against many forms of bias and not simply a way of controlling for the placebo effects.

It must be clear, therefore, that choice of the word that is to be master must accept that there is no role in modern medicine for placebo as a therapy. We are
concerned only with the use of placebo in medical research, specifically in clinical trials of the double blind, randomised design.

'Where would the evidentiary basis of medicine be without the randomized, double-blind, placebo-controlled trial?' asked Desbiens (342) as he discussed the daunting problems of making matching supplies of marketed drugs for clinical comparison.

'Placebos still constitute an important methodological tool in establishing the internal validity of a trial.' stated some clinical investigators from London and Amsterdam (343) as they considered a specific study design.

'The reference treatment should consist of placebo and best supportive care.' proposed the clinical pharmacological assessor to the Dutch Medicines Evaluation Board (321) as he considered study designs for new treatments for cancer, HIV infections and other life threatening diseases.

'I have concluded that the placebo has made probably the single most important contribution to modern therapeutics of any drug.' wrote a clinical pharmacologist who is also the chairman of an academic department at Tulane University (346).
For a final word to the critics of placebo use in clinical trials I selected a quote from Lasagna (199), who trained under Beecher and with whom he published a number of seminal articles on analgesic research. Lasagna's contributions to all aspects of drug development are well known and respected world wide. On the subject of placebo he addresses Rothman and his supporters by recalling the words that Oliver Cromwell wrote in a letter to the Church of Scotland: "I beseech you, in the bowels of Christ, think it possible you may be mistaken."

My sentiments, entirely.

Oh yes, I have found the master word that defines the role of placebo in drug development and scientifically rigorous clinical research. It is ESSENTIAL.
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