INSTITUTE OF EDUCATION

UNIVERSITY OF LONDON

THE PROBLEM OF BIAS IN MEDICAL RESEARCH AND ITS RELATIONSHIP WITH MEDICAL EDUCATION

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Thesis submitted for the degree of Doctor of Philosophy at the Institute of Education – University of London

London 2005

ABSTRACT

Biases in medical research are becoming acknowledged as a serious and increasing problem for medicine all over the world. They compromise the evaluation of the real effects of drugs, and jeopardise the possibility of evidence-based decisions and knowledge in medical practice. The current measures adopted to attempt to reduce them, although important and necessary, seem to have had only a limited effect. The fundamental aim of this study is to be a piece of exploratory research on the possible factors involved in medical education that can be related to the existence of bias in medical research.

The randomised controlled trial, the main research method in much of medical research, is analysed concerning its strengths and weaknesses as a scientific instrument and the most common biases that may occur in this research method are evaluated. Questionnaires and interviews with students and teachers of five medical schools in Paraná State (Brazil) were used to appraise aspects of a potential connection between medical education and the aforementioned problems in medical research. Qualitative and quantitative analyses of the data obtained were performed.

The level of awareness about bias in research, in these schools, was evaluated as insufficient and fragmentary. Some critical obstacles, related to the transmission of knowledge about bias to the students, were identified. There is evidence that, at least in the schools involved in this research, the problem of bias is considered as a minor issue, when compared with other structural and educational problems. Possible solutions to the problem of low level of awareness about bias in research were collected by the research instruments employed, and are discussed in regard to their potential efficacy and feasibility.

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Abbreviations

BIREME	Biblioteca Regional de Medicina
CAU	Canadian Association of University Teachers
CHD	Coronary Heart Disease
CIM	Confidence Intervals of the Mean
CINAEM	Comissão Interinstitucional de Avaliação do Ensino Médico
CME	Continuing Medical Education
CNPq	Conselho Nacional de Pesquisa
CONSORT	Consolidation of the Standards of Reporting Trials
CPG	Clinical Practice Guidelines
CRO	Contract Research Organisation
DeCS	Descritores em Ciências da Saúde
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration Agency
GMC	General Medical Council
HERA	The Higher Education Research and Development Society of Australasia
HRT	Hormone Replacement Therapy
INEP	Instituto Nacional de Estudos e Pesquisas Educacionais
IoE	Institute of Education (University of London)
ISI	International Scientific Indexes
LILACS	Literatura Latinoamericana y del Caribe en Ciencias de la Salud
OPAS	Organização Panamericana de Saúde
PADAM	Partial Androgen Deficiency of the Ageing Man
PBL	Problem-based Learning

PE	Pulmonary Embolism
PUCPR	Pontifícia Universidade Católica do Paraná
QUOROM	Quality of Reporting of Meta-Analyses
RCT	Randomised Controlled Trial
SETI	Secretaria de Ciência, Tecnologia e Ensino Superior do Estado do Paraná
SQ	Student Questionnaire
S&T	Science and Technology
TQ	Teacher Questionnaire
UEL	Universidade Estadual de Londrina
UEM	Universidade Estadual de Maringá
UEPG	Universidade Estadual de Ponta Grossa
UFPR	Universidade Federal do Paraná
UK	United Kingdom
UNIOESTE	Universidade Estadual do Oeste do Paraná
USA	United States of America
WGWHI	Working Group for the Women's Health Initiative Investigators
WHO	World Health Organisation

Acknowledgements

Although writing a PhD thesis seems a rather solitary enterprise it in fact entails the contribution of many people and several institutions. Most of the contribution of these people and institutions will be amalgamated in the essay structure in a relatively anonymous manner, making it difficult to individualise their importance and their involvement in the final configuration of the thesis. However, some of these contributors played such an important role in assisting me to transform some erratic initial ideas into a reasonably well structured reasoning about the problem of bias in medical research and its relationship with medical education that they deserve to receive my public gratitude for their efforts.

One important person was undoubtedly Professor Michael Reiss, my supervisor who in the last few years also became my friend. I could never have asked for a better friend or a more efficient and always present supervisor.

Also fundamental to the development of the present study were Professor Ingrid Lund and Dr Charles E. Engel. They were responsible for the difficult task of supervising me in my first year as a PhD student, a crucial moment in any PhD thesis.

Furthermore, this study would be just a distant dream without the financial, technical and personal support of all the members of the IoE-SETI-UEPG programme. To all such members I here declare my most sincere gratitude.

The opinions of the many anonymous participants of my research in five Brazilian medical schools were essential to the development of the initial ideas of this study and also to its conclusions. I hope that my work can partially repay them for their outstanding contribution to my study.

Finally, I have to mention my wife Amélia, to whom I dedicate this thesis. In the last four years she gladly and efficiently took on the responsibility of becoming my proof-reader, assistant researcher and psychological support in the difficult moments. To her I here proclaim my love and respect.

Chapter 1

An overview of bias in medical research

1.1 Introduction

As a physician and a teacher, when I first had contact with the theoretical concepts of 'evidence-based medicine' and 'evidence-based medical education' about ten years ago they seemed rather relevant for improving medical practice. Although I had some reservations about the use of the term 'evidence-based medicine', because I believed that modern medicine was already based on current medical evidence, the forecast of being able to use straightforwardly the results of trials, systematic reviews and meta-analyses in clinical practice was quite appealing.

A posteriori evaluation of the problems of modern medical research and its methodological framework showed me that it would be extremely difficult to rely on existing 'evidence' due to the high number of biased studies. My initial reasoning about the problem was that the biased 'evidence' was jeopardising the progress of modern medical education. However, there was also evidence that many medical researchers were not being prepared for correctly using the new methods of medical research (Altman, 1994), and that many physicians were not equipped to critically appraise the results of such research (Kenny, 1997):

> The initial education of most physicians practising today was didactic and fact-oriented. Ironically, this fact orientation is inimical to the scientific enterprise and to the skills of inquiry essential to science. Such education does not help students develop skills for assessing and judging new knowledge or managing uncertainty. An element in physicians' difficulties in incorporating new information is clearly rooted in their initial education. (Kenny, 1997, p.35)

From such a perspective, contrary to my initial belief about the problem, current medical education could be one of the causes of the incidence of bias in medical research. Based on this assumption, the present study was structured focusing on one main objective: to evaluate and discuss the relationship between current medical education and the incidence of bias in medical research and the potential deleterious influences they might have over each other.

This chapter aims to introduce the concept of bias, and more specifically bias in medical research, as an initial step to the appreciation of the problems it represents to medical education and research. It also includes an evaluation of the most important research method of modern trials in medicine: the randomised controlled trial (RCT), considering its strengths and weaknesses.

Although 'bias' has many connotations, the Oxford English Dictionary defines it as 'a systematic distortion of a statistical result due to a factor not allowed for in its derivation' (Pearsall, 2001, p.130). In medical research, the definition most frequently used is 'any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth' (Sackett, 1979, p.60).

The discussion about bias in science (Martin, 1979), and in medical research (Jadad, 1998a), is not something new. It includes aspects of research from deviations conditioned by social and political forces (Martin, 1979) to pure methodological deviations. There is a whole range of factors that can lead to research results that differ systematically from the truth (Sackett, 1979).

The possibility of bias in medical research began to receive more attention by researchers at the end of the 1970s. The reason for this was a modification in the research methodology of papers published in general medical journals. This modification of methodology had taken place progressively since the publication of the paper 'The Clinical Trial', written by Sir Austin Bradford Hill and published by the New England Journal of Medicine in 1952 (Hill, 1952). However, in the 1970s, researchers were

increasingly adopting case-control studies methodology, since this allows the researcher to obtain rapid results, at a low cost, and using what were then new computer based statistical methods (Sackett, 1979). Moreover, the results of such studies were more reproducible under different research circumstances, which allowed researchers to compare their outcomes.

Case-control studies have a number of different methodological designs. However, the basic structure consists of submitting two or more groups of patients to different procedures or treatments and then comparing the outcomes. One of the problems of case-control studies is that they are very prone to showing biased results. In a pioneer paper in 1979, David Sackett presented a catalogue of 35 examples of bias that occurred in case-control studies which could distort the design, execution, analysis and interpretation of research (Sackett, 1979). He discussed nine of these, and described the prospects for the recognition and prevention of these biases. The most common source of bias was the lack of randomisation of participants.

The fundamental difference between the initial case-control medical trials of the 1950s and today's trials is that 50 years ago most of the studies lacked the present requirements of scientific standards, particularly with regard to the planning and conduct of the study, and the reporting of the results (Salzberg and Muller, 2003). This was the reason for the adoption of the Randomised Controlled Trial (RCT) as the gold standard research method in medicine. It seemed a natural evolution of the case-control studies, and provided an apparently perfect approach to correct the main cause of bias in these studies: the randomisation of participants (Jadad, 1998b). It also had more stringent methodological rules and quality requirements which, at least theoretically, allowed the researcher to be more confident of the results of his/her trials (Salzberg and Müller, 2003).

However, the RCT only solves the problem of randomisation of participants. As will be explained in the following sections, it does not offer any protection either against the other categories of bias that occur in case-control studies (Jadad, 1998a), or intentional (or unintentional) methodological deviations in all the phases of a study. Also, one must be aware that many trials comparing an intervention with a control group are not really

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RCTs, if they do not follow rigorously the principles of randomisation (Greenhalgh, 2001).

1.2 The randomised controlled trial (RCT) as the main research method in medicine

In order to understand why RCTs (and before them, case-control studies) are recognised as the standard method of research in medicine it is necessary to review some historical aspects of medical research. Most of the research done before the nineteenth century essentially consisted of descriptions of observations about some aspects of a disease in one or a few patients in a qualitative way. However, some before/after trials in the eighteenth century demonstrated that it was possible to obtain results that were reliable and reproducible (Bull, 1959). The structure of before/after trials became progressively more sophisticated during the nineteenth century, and became the most common research method in medicine in the first decades of the twentieth century.

According to Doll (1998), these studies suffered from a series of methodological weaknesses:

> When I qualified in Medicine in 1937, new treatments were almost always introduced on the grounds that in the hands of professor A... the results in a small series of patients... had been superior to those recorded by professor B... Variability of outcome, chance... and (the) selection of patients brought about apparently important differences in the results obtained... Standard treatments, for their part, tended to be passed from one textbook to another without ever being adequately evaluated. (Doll, 1998, p.1217)

The history of controlled trials according to some authors may be traced back to 1747. Since this year, there were sporadic attempts to use trials in medical research. At the beginning of the 1930's, the British Medical Research Council suggested the alternation of treatment among patients with treatment alternating between two different methods.

However, according to Doll (1998), the introduction of the controlled trial in its present structure only began after 1946. In spite of the obvious improvement for the comparison of two or more medical procedures, it only assumed its position as the standard of medical research several years after this date. This delay was due to the opposition of medical researchers to adopt it, and to accept its results (Everitt and Pickles, 2000).

In 1952, Daniels and Hill published their results on chemotherapy of pulmonary tuberculosis in the British Medical Journal using an improved method of trial (Daniels and Hill, 1952). An article by Hill in the New England Journal of Medicine (Hill, 1952) explaining the new structure of research used is considered today as the landmark of the modern RCT.

The straightforward design of the clinical trial described by Hill (1952) has subsequently been submitted to several changes, increasing its complexity and variety of applications in medical research. In addition, the number of categories of RCTs has increased, and a RCT is currently classified, according to Jadad, in relation to:

> The aspect of the interventions investigators want to explore.
>
> The way in which the participants are exposed to the interventions.
>
> The number of participants included in the study.
>
> Whether the investigators and participants know which intervention is being assessed.
>
> Whether the preferences of non-randomised individuals and participants are taken into account in the design of the study. (Jadad, 1998b, pp.10-11)

According to Jadad (1998b), using his classification, there were 16 different types of RCTs being employed in research in 1998. This is an indication of the importance and widespread use of RCTs in medical research.

As a quantitative and comparative approach to evaluate therapeutic interventions in medical practice, the RCT seemed to be a good research option. Additionally, it allows researchers to compare their results with the outcomes of other trials using a statistical approach. The random allocation of the participants theoretically permits researchers to balance unknown prognostic factors, a feature that no other study design ever had in medical research (Jadad *et al.*, 1996).

As the types and complexity of RCTs increased, the possibility of methodological deviations and the dependence of researchers on more sophisticated statistical tools also increased. Additionally, the difficulties of researchers to understand the ever-growing number of different research designs also became more profound (Sackett, 2001).

1.3 Strengths and weaknesses of RCTs

Swinscow states that the most powerful studies are the prospective studies (studies where the data are collected after the study structure is done), and in medicine the RCT is the paradigm of such a study design (Swinscow, 1996). If correctly designed, the RCT permits the researcher to do a rigorous evaluation of a single variable in a defined patient group. It also avoids the occurrence of selection bias by comparing two groups that, at least theoretically, only differ by the medical intervention under study. As a quantitative research method, it generally allows the combination of numerical results of several similar trials through meta-analysis (Greenhalgh, 2001).

This is an important feature of RCTs because most such studies have a limited number of participants, and the possibility of enhancing the external validity is undoubtedly a positive characteristic. As Egger *et al.* (2003) point out, one must remember that the smaller a study, the larger the effect of a medical procedure required for the results to be declared statistically significant. This methodological characteristic could prevent researchers from evaluating the real outcome of a procedure that has a small effect, unless an isolated RCT had the sufficient number of participants. This is seldom attainable due to financial and time constrains.

Depending on the research question, a RCT can be as reliable and less expensive than an observational prospective cohort study. Although cohort studies are a very powerful medical research method employed to evaluate the incidence and potential causes of a disease, they are extremely expensive and time consuming (Hulley *et al.*, 2001). As an example, the Nurses' Health Study (Fuchs *et al.*, 1999) had as participants 121.700 American nurses that were observed by the researchers for almost 20 years. Conversely, a RCT can be done in a much smaller period of time, especially if the variable under study is continuous and changes rapidly with the intervention (Hulley *et al.*, 2001).

The above mentioned characteristics of the RCT were undoubtedly fundamental to the acceptance of this method as the most important research design for medical research in the last 50 years. Actually, the apparent strength of RCTs as a controlled experimental design led some authors to recommend them to other areas of science, such as sociology (Oakley, 1998).

However, RCTs also have their limitations and problems, as does any research method, although many of them are not obvious to many researchers. Their strength is based on a correct interpretation of the problem, and a very stringent respect to a methodological schedule.

The first problem that must be solved before deciding to use a RCT design in a piece of research is related to the topic of the intended research project. As stated by Sackett, what determines the appropriate research model should be decided by the central research question (Sackett, 1997). Some research questions demand the use of a RCT; however, in several instances a RCT will not be the correct choice (this point is more thoroughly discussed in Section 2.2).

Furthermore, a RCT is based on a statistical theory that demands the correct randomisation of participants. As stated by Altman and Bland: 'We know how random samples are expected to behave and so can compare the observations with what we would

expect if the treatments were equally effective.' (Altman and Bland, 1999a, p.1209). Although the principles of correct randomisation have been extensively published in journals and books (Altman, 1990; Altman and Bland, 1999b), '… the technical meaning of the term randomisation continues to elude some investigators.' (Altman and Bland, 1999a, p.1209). The researcher must be aware of this methodological aspect, because there are situations in medical research where the correct randomisation of participants is simply not possible. This may happen for instance when random allocation may not be feasible due to ethical constraints, such as in cancer treatment trials. In this case, the use of a RCT design could lead to unreliable and invalid results.

Finally, as the RCT is a quantitative research method, it depends on a very cautious and correct statistical analysis. Many systematic deviations may occur in the data analysis, either through lack of statistical knowledge, or through intentional manipulation of data or results (Mills, 1993). Additionally, the interpretation and dissemination of results of RCTs is open to several biases that may distort the conclusions of the studies (McCormack and Greenhalgh, 2000; Chan *et al.*, 2001).

In summary, a RCT is usually considered the best approach to determine the effectiveness and safety of a new treatment. The correct use of its methodology may prevent several causes of bias that threaten a study's validity. However, the risk of bias continues to exist in a RCT, particularly during data collection, data analysis, and interpretation of the results (Hartman *et al.*, 2002). The occurrence of bias in medical studies became such a serious problem in medical research that it is the subject of the next section of this chapter.

1.4 Major categories of bias in medical research and their prevention

After the seminal paper by Sackett (Sackett, 1979), many examples of bias in medical research have been detected and analysed as to their importance and prevalence (Hartman *et al.*, 2002), especially in relation to their influence in systematic analysis and meta-analysis.

TABLE 1 – Types of bias that undermine research quality and validity

Bias	Explanation
Randomisation bias	Occurs when the randomisation method is less than ideal, e.g. using the day the participant was enrolled (even or odd)
Selection bias	Common when those that are recruiting participants are aware of the next assignment in the sequence of a trial
Performance bias	When there is a systematic difference in the care provided to the participants in the comparison group, other than the intervention under investigation
Attrition bias	Refers to systematic differences between the comparison groups in the loss of participants from the study
Detection bias	Occurs when there are systematic differences in outcome assessment between the comparison groups
Ascertainment bias	When the results or conclusions of a study are systematically distorted by knowledge of which intervention each participant is receiving
Publication bias	Comprises several different biases related to the publication and dissemination of results of medical research
Language bias	A common variation of publication bias, denoting a tendency of more studies with positive results to be published in English

(Adapted from Jadad, 1998b, and Clarke and Oxman, 2001)

In this section I will focus on eight representative categories of bias, which, according to the literature (Jadad, 1998b; Song *et al.*, 2000; Clarke and Oxman, 2001; Jüni *et al.*, 2001), jeopardise the quality and validity of RCTs, and systematic analyses. These eight categories are summarised in Table 1. These types of bias were chosen due to their prevalence in medical research. They share an important characteristic in that they are either correctable or avoidable at some stage of the research process (Jadad, 1998b).

The first category affects the proper randomisation of participants in a trial. As discussed in Section 1.3, although randomisation is an established method in Statistics, many papers fail at this stage of the research. A simple way to judge if total randomisation was performed is by comparing the 'baseline' characteristics of participants at the beginning of a trial (Jadad, 1998b).

There are several reasons for failure to fully randomise participants. Some of them are very common as in the example of randomisation bias of Table 1. In this case, the researcher is assuming that the possibility of a participant being enrolled in a research project is the same every day of the week. This is not true due to the daily variations in the availability of medical staff, and to the patients' personal preferences.

However, the most usual is that the randomisation sequence has not been concealed from the investigators (Chalmers *et al.*, 1983). Concealing the sequence ('double blind') is an important way to avoid the possibility that personal preferences or beliefs of researchers or patients might interfere with the randomisation process and, indirectly, with the outcomes of a trial. One must remember that in much research the physician is also the researcher. If the randomisation sequence is not concealed, there may be a tendency, either voluntary or involuntary, to do 'the best for the patient' and not for the research.

As stated by Day and Altman:

> Human behaviour is influenced by what we know or believe. In research there is
> the particular risk of expectation influencing findings, most obviously when

there is some subjectivity in assessment, leading to biased results... Blinding (sometimes called masking) is used to try to eliminate such bias. (Day and Altman, 2000, p.19)

However, one must remember that despite the best intentions, some treatments or procedures have side effects, or a specific methodological structure (such as a surgical action), that are so particular that blinding may be impossible. Medical staff, and even some patients, will undoubtedly recognise the treatment received by each participant (Day and Altman, 2000).

Errors in randomisation compromise the estimates of treatment effects in controlled trials, and can, independently of other causes of bias, overestimate the effects of interventions by as much as 40% (Schulz, 1996). However, various methods can be used to assess and correct most of the deviations caused by randomisation bias. There are at least two, which can identify the possibility of divergence between different presentations of data (Ohlsson and Lacy, 1995). Also, it is currently possible to perform a sensitivity analysis correlating the level of subversion of randomisation and the resulting bias in treatment effect estimation (Marcus, 2001).

Selection bias, performance bias, attrition bias, and detection bias are more difficult to estimate, and correct. The Cochrane Reviewers' Handbook, discussing the sources of bias in trials of healthcare interventions, asserts that:

Unfortunately, we do not have strong empirical evidence of a relationship among trial outcomes and specific criteria or sets of criteria used to assess the risk of these biases. There is, however, a logical basis for suspecting such relationships and a good reason to consider these four potential biases when assessing studies for a review (Clarke and Oxman, 2001, p. 62).

Several graphical and statistical methods to reveal and correct these biases have been tested (Egger *et al.*, 1997a), but the results are still inconclusive (Irwig *et al.*, 1998).

Nevertheless, in medicine there is an axiom: 'prevention is the best therapy'. If these biases are difficult to detect and correct *after* a piece of research is completed, it is asserted that they can be avoided by correct design and data collection (Jadad, 1998a).

A researcher can avoid ascertainment bias by preventing participants from knowing the nature of the interventions of a study, for as long as possible. 'Blinding' of all participants is also the centre of the prevention of selection, performance and ascertainment bias (Jadad, 1998b). Attrition and detection bias may be corrected by using accurate methodological procedures available to RCTs (Begg *et al.*, 1996).

Important causes of systematic deviations in medical research are publication bias and language bias. Publication bias is probably the form of bias most studied in medical research, and was the focus of a systematic review (Song *et al.*, 2000). It is important because systematic reviews and meta-analyses rely on the fact that all available data about a medical subject should be accessible at the time these studies are carried out. If not, their results will not reflect current medical knowledge in a specific area. This bias is caused by the tendency to publish positive findings more quickly, and in greater number, than negative ones (Dickersin, 1990, 1997).

Its significance to medical practice is undeniable:

> The important consequences of publication bias include the avoidable suffering of patients and the waste of limited resources. At the very least, it is arguable that under-reporting research is scientific misconduct that may cause inappropriate patient care. In addition, it is unethical to abuse the trust of the patients involved and to waste invested resources. (Song *et al.*, 2000, p.25).

The correction of this type of bias depends on a more ethical position of researchers, funding sources, and a permanent evaluation of possible conflict of interest by reviewers and medical journals.

Publication bias may also be linked to the financial relationships between researchers and the pharmaceutical industries, or other research sponsors, which may influence the kind of results that are published. These relationships may also lead to a subspecies of publication bias that is very difficult to evaluate and correct as Brian Martin asserts:

> In spite of rhetoric of openness in research, the practice is often quite different. There are numerous examples of suppression (*of data*), including pressures not to undertake research in the first place, institutional controls on dissemination of data, and attacks on researchers who produce unwelcome results. (Martin, 1999, p.334).

Although the idea of suppressing data generally presupposes their existence, the simple fact that a certain piece of research is not done by imposition or restriction to its implementation can be considered a kind of suppression of data. Blocking dissemination or distorting data also has the same effect on the availability of information in a particular area of knowledge (Martin, 1999).

Language bias reflects a tendency to publish more positive results in English than in other languages (Egger *et al.*, 1997b). Dissemination of results is important to all researchers, and the most important journals are published in English speaking countries. These journals also have a tendency to publish more positive results than negative ones. In a search at MEDLINE® (15/11/2001) looking for *bias* or *biases* in the title or abstract, I found 32,103 citations. Skimming through the papers, the number of publications in languages other than English is extremely low. The reason for this may be a form of publication bias, since researchers probably publish in English hoping for wider dissemination. Some authors also believe that there is a language bias against European journals from non-English speaking countries in medical publication databases (Pentti and Isohanni, 1999).

However, the same author who helped to create the idea of a language bias states in a recent systematic review:

...systematic reviews that are based on a search of the English language literature that is accessible in the major bibliographic databases will often produce results that are close to those obtained from reviews based on more comprehensive searches that are free of language restrictions...(*However,*) in some areas of medicine it is essential to broaden the search to include the grey literature and material published in languages other than English. (Egger *et al.,* 2003, p.47)

Finally, an important type of bias, the interpretative bias, is presently receiving more attention (Kaptchuk, 2003). It is related to the tendency that researchers and physicians have to interpret the data, or the evidence on medical papers, based on their preconceptions, traditions of research, disciplinary affiliations or personal experience. It is generally considered as an unintended bias, although it can happen also as a deliberate attempt to avoid evidence that may contradict one's expectations. Unfortunately, this is a type of bias which is ubiquitous in medical practice and research, and that has so far no easy solution or prevention.

The number of types of bias, and their incidence in medical research, became so pervasive that Horton stated that:

A clinical investigator is, to paraphrase Whitney Balliet, a bundle of biases held loosely by a sense of method. Bias and medical research are firm and rowdy partners. (Horton, 2000, p.959)

Why did a method of research that was so promising 50 years ago become so prone to bias? Is it a structural defect of the RCT methodology, or is it a problem that involves the behaviour of the researchers that are employing this method? As will be discussed in Chapter 2, it is possible that we are seeing a combination of both these factors in the high incidence of methodological deviations in current medical research. Many researchers seem to be unaware of a cornerstone of research using the RCT (or other methods):

The first step to minimise bias is to have a clear idea of the question, and what approach is required and feasible to achieve the answer. The second step is to prospectively design the study in detail before, or *a priori*, the investigation is undertaken. (Hartman *et al.*, 2002, p.27)

Several methods to avoid the occurrence of bias in RCTs have been discussed in this section. However, one of the fundamental strategies to reduce bias in medical publications may be that researchers should make a previous publication of their intents before the research data collection. In fact, several important journals of medicine now require that authors send their research protocols in beforehand, especially in the case of systematic reviews and meta-analyses. The rationale is to inhibit researchers from manipulating unintentionally (or intentionally) the structure and results of their research.

To summarise, the problem of bias in medical research is an important issue and is well diagnosed. Some authors even believe that it is over-diagnosed, and that bad reporting of results does not necessarily mean that defective methods were employed in the RCTs (Soares *et al.*, 2004). However, although most of the bias that occurs in medical research could be corrected or avoided, this seems not to be happening (Celermajer, 2001). The possible reasons for this will be discussed in Chapter 2.

1.5 The importance of bias in meta-analyses, systematic reviews, and evidence-based medicine

One aspect of RCTs that deserves consideration is that they can be performed with a relatively small number of participants and in a shorter interval of time than some categories of medical research studies, as discussed in Section 1.3. However, the reduction of the number of participants and time of observation in RCTs decrease their statistical power and precision (Egger and Smith, 1998). Actually, it is very rare that an isolated RCT can provide a definitive response to the solution of a health problem or treatment.

In fact, it has been known since 1978 that the calculated statistical power of RCTs shows that many studies did not have totally reliable conclusions drawn from them due to their sample size (Donner, 1984). Although there is a simple method to calculate the necessary size of a sample, there are occasions when its use is not feasible, as in the case of a rare disease or financial limitations.

Furthermore, as clinical trials are usually performed in different groups of people and in different settings, it is improbable that they will provide identical results, even when designed to focus on a specific medical subject (Jadad, 1998b). Incidentally, these features of RCTs are probably one the most important causes of conflicting publications in the lay media, or even in some medical journals.

The only way that small and isolated RCTs may provide adequate evidence to physicians and health policy makers is if their individual results can be combined to provide a more precise and trustful conclusion. That is exactly the aim of two important research methods: the systematic review and the meta-analysis (Greenhalgh, 2001). If correctly performed, these methods can enhance the precision and consistency of data about a particular procedure in medicine.

To be considered as systematic a review must comply with several rules that will be discussed in the following paragraphs. However, the first and most important one is:

> A systematic review, in its ideal form, is a review that includes an explicit and detailed description of how it was conducted so that any interested reader would be able to replicate it. ... (*And*) should incorporate strategies to minimise bias and to maximise precision. (Jadad, 1998b, p.81)

A review receives the name of meta-analysis if the results of a systematic review are combined statistically to generate one single estimate of these results. It must also use

statistical tools to verify the homogeneity (compatibility) of the results of the several trials, and an evaluation of the possible effects of publication bias in its conclusion (Greenhalgh, 2001; Hulley *et al.*, 2001).

There are some excellent books about the subject 'systematic reviews'; these include Iain Chalmers and Douglas G. Altmans' *Systematic Reviews* (Chalmers and Altman, 1995), and the *Cochrane Reviewers' Handbook* (Clarke and Oxman, 2003). Furthermore, a significant number of papers focusing the structure, problems, and evaluation of systematic reviews and meta-analyses have been published in the last 10 years in the most important medical journals.

The fundamental reason for so many studies and books about the matter is that systematic reviews are becoming one the most important components of the structure of evidence-based medicine. In contrast, there is a progressive reduction of the importance of 'journalistic reviews' (Greenhalgh, 2001), or the 'expert reviews' in medical research, because both suffer from serious risk of bias.

One common bias in 'journalistic' and 'expert' reviews is the interpretative bias. As discussed in section 1.4, this is related to the tendency that researchers and physicians have to interpret the data or the evidence of medical papers in the light of their preconceptions, traditions of research, disciplinary affiliations or personal experience. As these studies are primarily focused on the 'new scientific breakthrough' in the case of the 'journalist review', or in obtaining or maintaining the researchers' influence or status in the 'expert review', they generally do not obey the first rule aforementioned: to be replicable and avoid bias.

However, even when the first rule of a good systematic review is obeyed, any systematic deviations of one or more RCTs can influence future systematic reviews and meta-analyses (Moher *et al.*, 1999).

As summarised by Greenhalgh (2001), a researcher who desires to do a systematic review

should carefully carry out the following progressive stages:

- State objectives of the review of randomised controlled trial and outline eligibility criteria.
- Search for trials that seem to meet eligibility criteria.
- Tabulate characteristics of each trial identified and assess its methodological quality.
- Apply eligibility criteria and justify any exclusion.
- Assemble the most complete data set feasible, with the assistance from investigators, if possible.
- Analyse results of eligible randomised controlled trials by using statistical synthesis of data (meta-analysis) if appropriate and possible.
- Compare alternative analyses, if appropriate and possible.
- Prepare a critical summary of the review, stating aims, describing materials and methods, and reporting results. (Greenhalgh, 2001, p.121)

In each of these stages there is the possibility of introducing one, or more, systematic deviations that may compromise the final result of a systematic review or meta-analysis. As an example of the complexity of such a method, using only the evaluation of the impact of publication bias on meta-analysis, Sutton *et al.* (2000) estimated that a significant number of meta-analyses had missing studies. Most of the time this was due to publication bias.

Actually, the number of unpublished papers on a particular area of medical knowledge may vary from 7% to 41% (Dickersin, 1997). There are several probable reasons for this. However, independently of the discussion of the causes, one can imagine the potential impact this has in systematic reviews and meta-analyses.

To exemplify the problem caused by known or unknown bias in the structure of systematic reviews and meta-analyses, the introduction of a paper by Mathias Egger and George D. Smith can be quoted:

That meta-analysis holds potential problems can be illustrated by contrasting the conclusions of two meta-analyses comparing low molecular weight heparin and standard heparin in the prevention of thrombosis after surgery. One group concluded that "low molecular weight heparin seem to have a higher benefit to risk ratio than unfractionated heparin in preventing perioperative thrombosis", whereas the other considered that "there is at present no convincing evidence that in general surgery patients low molecular weight heparin, compared with standard heparin, generate a clinically important improvement in the benefit risk ratio."... (Egger and Smith, 1998, p.61)

Incidentally, both of the reviews evaluated by Egger and Smith (1998) were published in 1992, one in *The Lancet* and the other in the *British Medical Journal*. Although the possible causes for such a difference in the reviews' conclusions will be further discussed in Chapter 2, it is hardly surprising that many physicians and researchers are somewhat perplexed by such contradictory conclusions.

This is especially true in respect of the idea of 'evidence-based medicine' (EBM). This term achieved its place in the history of medicine in the 1990s. Its best initial definition was provided by Sackett *et al.* (1996, p.71): 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'. This should mean the use of medical research results to help physicians decide what should be the best procedure or treatment for individual patients.

In principle, this is what a physician should indeed do. However, using the aforementioned example of meta-analysis it is possibly the moment to ask, as Celermajer (2001) did, 'How good is the evidence?'.

Sniderman (1999) already pointed out one aspect of present medical research that will be important for evaluation and discussion in the present study in order to answer Celermajer's question, namely the current entanglement between modern medical research and the pharmaceutical companies. According to Sniderman:

Many trials have been completed using similar agents for similar problems, and naturally, each company will try to distinguish its products from its competitors, even when the overall results are reasonably similar. Similarly, investigators will try to distinguish their contribution from those other investigators who take part in similar trials. In this enterprise, the interests of the companies and the investigators can imperceptibly coalesce. The net result is that important scientific debates can become coupled – and sometimes be driven by – competitive marketing approaches. (Sniderman, 1999, p.328)

Sniderman (1999) concludes that both the scientific debate and the marketing competition are defensible. However, he suspects that there is also a risk that scientific advocates become the companies' advocates. He also asserts that as readers of such pieces of research, whether practising physicians or consumers, we should remember that 'our interests are not always identical with those who produce them' (Sniderman, 1999, p.328).

To summarise, the initial straightforward and comprehensible method of the RCT created 50 years ago has evolved into a very complex and statistically dependent one. This evolution has undoubtedly provided a reliable possible source of medical knowledge. However, it may have converted the RCT, and its derivatives, the systematic review and the meta-analysis, into a very cryptic matter to many physicians, health researchers, medical educators, and health policy makers. Additionally, its current complexity and its vulnerability to bias may endanger the possibility of using its conclusions to support evidence-based medicine.

Chapter 2

Factors that influence the existence of bias
in medical research

2.1 Introduction

As discussed in Chapter 1, modern medical research relies to a great and increasing extent on a quantitative research method, the randomised controlled trial, and its derivatives: the systematic review and meta-analysis. Although powerful, these research procedures, like any other scientific research approach, are prone to bias. Furthermore, subversion of results may occur due to errors either in the structure or in the data analysis of a RCT, systematic review, or meta-analysis. These somewhat contradictory characteristics of such a research method are evident in the final paragraph of a major text about the matter:

> The RCT is one of the simplest, most powerful, and revolutionary tools of research. Despite their extensive use as research tools over the past 50 years, most trials are biased, too small, or too trivial. It is essential that we make more efforts to protect ourselves against ourselves during the design, analysis, dissemination and use of RCTs. Such efforts will hopefully benefit patients, scientists, governments, industry, research institutions, funding and regulatory agencies, ethics committees, journalists, and other consumers of information. Overcoming the existing barriers will, however, require innovative research strategies, and unprecedented levels of commitment, participation, and contribution by us all. (Jadad 1998b, p.116)

The author's intention was undoubtedly to emphasise that, as happens with any research method, the results depend on the validity and reliability of the data one can obtain using such a method. Furthermore, the quality of such results in medical research has a strong relationship with the conduct of the researcher, from the design of a study to the final

report of the research. This connection between the researcher and the quality of research is in the opinion of Jadad (1998b) the weakest link in medical research studies.

However, the structural framework of a RCT study may also have its role in the occurrence of bias on medical research. One of the aspects that will be discussed in this chapter is that the centre of the statistical approach used in controlled trials is *hypothesis testing*. This relies on establishing if there is a certain degree of *significance* in the relationship between the variables under study (Campbell, 2001). As previously mentioned in Chapter 1, this process can be undermined at any phase of a study, particularly during the acquisition of data, statistical treatment, or discussion of the results, by the introduction of systematic deviations (Mills, 1993).

The rise in the number of published papers based on RCTs has also increased the dependence of health programs and policies, medical education, and medical practice, on their results. It has seemed reasonable to rely on a method that could give rapid answers to important questions in these areas (Evidence-based Medicine Working Group, 1992).

As the number of papers reporting randomised controlled trials has increased since the 1970s (Simini, 1998), the number of detected biases and flawed studies also multiplied. In 1994, an inspired editorial in the British Medical Journal by Douglas G. Altman summarised the problem:

> We need less research, better research, and research done for the right reasons ... When I tell friends outside medicine that many papers published in medical journals are misleading because of methodological weaknesses they are rightly shocked ... Why errors are so common? Put simply, much poor research arises because researchers feel compelled for career reasons to carry out research that they are ill equipped to perform, and nobody stops them. (Altman, 1994, p. 283)

This strong statement by Altman, combined with the support of some of the most important medical journals and researchers, provided the underpinning to the publication

of the CONSORT statement (Begg *et al.*, 1996). An amendment to the original statement was published in 2001 (Moher *et al.*, 2001). The Consolidation of the Standards of Reporting Trials (CONSORT) was a collaborative process between clinical epidemiologists, statisticians, journal editors and reviewers. It aimed to improve the practice of medical research by increasing the awareness of researchers on the methodological structure of a good trial.

The most important medical journals incorporated the original statement as part of their requirements for authors in 1997. In 1999, the QUOROM (Quality of Reporting of Meta-Analyses) report was published which aimed to establish the standards for improving the quality of reporting of meta-analyses (Moher *et al.*, 1999).

The positive response of journals, medical associations, and researchers to the CONSORT and QUOROM statements is an unequivocal demonstration of the importance of the problem of bias in medical research. However, both statements had an unforeseen side effect: the predominant focus on correcting the research structure rather than the researchers' habits. Additionally, the CONSORT statement has been criticised for failing to appraise the problem of the inclusion and exclusion criteria of studies, which is an important issue with regard to the external validity of RCTs (Gross *et al.*, 2002).

Revisiting the topic of his 1994 editorial in the *British Medical Journal* six years after the publication of the CONSORT statement, Altman asserts that:

> I suspect that many basic errors have become less common, but statistics has become more complex, and there is evidence of frequent misapplication of newer advanced techniques... Much research is done without the benefit of anyone with adequate training in quantitative methods. Many investigators are not professional researchers; they are primarily clinicians. (Altman, 2002, p.2766).

As will be discussed in Sections 2.3 and 2.4, the basic mental and scientific behaviour of

the modern physician-scientist is essentially shaped inside medical schools. The medical 'scientist-to-be' will face a long, arduous, and extremely competitive environment in which to accomplish successfully the following sequence: graduation – residency (specialisation) – post-graduation. These steps are mandatory to enable him/her to have some possibility of entering a research group, or being able to seek a grant from a research-funding organisation. However, there are perturbing signs that this process is being undermined by a tendency to acquire moral deviations due to the intense competition existent inside the medical schools (Young, 1997). Moreover, some authors assert that much medical research is being carried out only as a career necessity by physicians (Altman, 2002).

The main objective of this chapter is to evaluate to what extent the combination of the intrinsic methodological problems of the RCTs, the formation of a physician-scientist, and the problems of certain type of research funding, could be contributing to the present problems of modern medical research.

2.2 Intrinsic methodological problems of a RCT

According to Simes (2002):

> Hence, evidence from trials is most applicable in practice when the design and the outcomes chosen are directly relevant to real patients, the trials are undertaken against a background of standard medical care, patients in trial are broadly representative in the real world, and evidence from trials is integrated with individual patient characteristics for meaningful risk-benefit assessment. (Simes, 2002, p.407)

The above quoted statement is extremely sensible. However, as discussed in the following paragraphs, it is very rare to achieve all these qualities in a RCT. The reason is that the RCTs' basic structure was deeply modified, as they were adapted to the several fields of

medicine. Also, to the fact that RCTs are used nowadays to analyse small to moderate effects of medical procedures.

Ironically, the first methodological problem of a RCT derives from one of its strengths. The statistical approach of *hypothesis testing*, although powerful and dependable, relies on three fundamental assumptions.

The first is that one must have a question that can be answered in a very straightforward way: 'Are the results obtained equally in both of the groups that are under investigation?'. This is effectively the *null hypothesis* (Greenhalgh, 2001). The answer to this question is fundamental because if there is no difference between the groups, one cannot reject with confidence the hypothesis that the two treatments or interventions have the same effects. In order to accept or to reject the *null hypothesis*, the researcher must be certain that both groups are identical at the beginning of the trial. The only aspect that should be prone to manipulation is the variable under study. This is the foundation, and the requirement of randomisation, as discussed in Chapter 1.

Identical groups in humans are not possible, with the probable exception of groups of identical twins. Even when randomisation is used correctly, a researcher must still be aware that it is possible that the two groups under study will differ in some potentially important aspect. As stated by Jadad:

> You must understand that the risk of imbalance among the groups (*under study*) is not abolished completely, even if the allocation is perfectly randomised. (Jadad, 1998b, p.4)

This might not be a problem if one is exploring a procedure that has an evident effect on the outcomes with another that has no effect. However, this is seldom the reality in medical research. Generally, RCTs are used for the evaluation of the possibility that two or more interventions have a small to moderate difference in their outcomes.

In fact, it would be unethical to submit human beings to a randomised clinical trial which is comparing two procedures when the researcher already knows that one of the interventions is undoubtedly better than the other. Despite the fact that it might seem redundant, it must also be stressed that although researchers sometimes fail to remember, it is also unethical to submit groups of persons to procedures that are indubitably ineffective for their health problems.

The second assumption that is intrinsic to the statistical model of a RCT is that the outcomes will be evaluated in relation to the existence of a *significant* difference between the groups involved in the research. In a sense, a *significant* result only expresses that the difference between the groups was *statistically significant*. It does not necessarily indicate that this outcome is of clinical or scientific importance. For example, a reduction of 2 mmHg in blood pressure observed when a researcher is evaluating two different drugs may be *statistically significant*, on account of the large sample sizes. However, this reduction may have no practical *significance* in respect of the clinical management of people who are under treatment due to high blood pressure (Jekel *et al.*, 1996).

For such reasons, a medical researcher using a RCT design cannot be sure that her/his results may validly be extended to the whole population in a clinically meaningful manner. What he/she has is a statistical indication of the possibility that this may be done, with a certain degree of uncertainty. In order to evaluate this degree of uncertainty, some statistical tools can be used to avoid the problem of assuming that the results of a study are 'true in the real world' when they are not. The most reliable one is the *confidence interval* (Altman *et al.*, 2000).

According to Altman *et al.*:

> So when should confidence intervals be calculate and presented? Essentially confidence intervals become relevant whenever an inference is to be made from the study results to the wider world... (*because*) a single study gives an

imprecise sample estimate of the overall population value in which we are interested. (Altman *et al.*, 2000, p.4)

Although the mathematical basis of confidence analysis is beyond the scope of this study, the theoretical foundation is not difficult to understand. It is due to the fact that results from a single sample of the population are subject to statistical uncertainty, leading to an imprecise estimate of the effect of a procedure in the overall population, as already discussed. However, the extent of the imprecision may also be estimated, and presented in the conclusions of a study. In principle, this procedure would allow the reader of a paper to estimate how much she/he could depend on the results of one or more RCTs to support his/her clinical decisions.

However, calculating confidence intervals is not as widespread a practice in medical studies as perhaps it should:

> The uptake of confidence intervals has not been equal throughout medicine. A review of papers published in the *American Journal of Physiology* in 1996 found out that out of 370 papers only one reported confidence intervals! (Altman *et al.*, 2000, p.7)

The final assumption of the statistical model of the RCT is that the sample used in a study is representative of a population. In fact, a correctly randomised RCT, based on a direct question about a health problem, and using the necessary number of participants in its groups, should provide answers that could be considered as suitable to the whole population. However, this is seldom accomplished by an isolated RCT study.

Actually, the external validity of isolated RCTs has been subjected to severe criticism (Gross *et al.*, 2002). One of the main problem seems to be the inclusion and exclusion criteria of participants in a study, which may 'impede generalising from RCTs to real life' (Kennedy *et al.*, 2003, p.8).

The inclusion or exclusion criteria of participants in RCTs are of extreme importance for the possible outcomes of a study, and to the potential use of these outcomes as a guide to medical practice. If the inclusion criteria are too restrictive, the RCT result will not represent something valid for the population. Conversely, the inclusion within a single RCT of participants who have multiple medical problems may conceal the real effect of a procedure, and lead to invalid conclusions.

In fact, there is presently a tendency to classify a RCT as either *explanatory* or *pragmatic*. The objective of such a classification is to categorise RCTs according to whether their methodological frameworks were structured to enhance their internal validity (which reflects the efficacy of a certain medical procedure in an ideal situation), or the external validity (the generalisability of the results) (Godwin *et al.*, 2002).

An explanatory trial tries to maximise the internal validity by assuring rigorous control of all variables with the exception of the one under study. One of the characteristics of such a study is to restrict the inclusion criteria in order to evaluate a possible beneficial effect in an ideal situation: the participants have only one known medical problem. As this is seldom the reality in medical practice, one may have a result that is, to some extent, meaningless (or at least oversimplified) for medical practice.

Pragmatic trials try to keep a balance between their internal and external validity (reliability and generalisability of their results). The exclusion criteria in this kind of trial are kept to a minimum. They try to use as participants those who represent the full spectrum of the population to which the treatment might be applied (Godwin *et al.*, 2002). The central idea of a pragmatic trial is that if a medical intervention exhibits a beneficial effect in the trial it will probably be effective in the 'real world'. However, it is extremely difficult to establish the limits of what is meant by 'minimum exclusion criteria' in the multiple applications of RCTs in medical research.

Actually, according to Gross *et al.* (2002), many RCTs published in high impact journals

do not provide a comprehensive description of the participants' recruitment process. This makes it difficult for readers and reviewers to estimate the internal and external validity of these studies, and their level of relevance to medical practice.

For such reasons, even the results of a carefully randomised and controlled study may not be directly applicable to an individual patient or a population. In addition, the conversion of the evidence obtained in a study sample to a particular patient is problematic due to differences related to individual characteristics (age, sex, co-morbidity, cultural and genetic variations, etc.) (Mant, 1999).

According to Greenhalgh (2001), there are also some restrictions to the use of RCTs when the study is looking at the prognosis of a disease, the validity of a screening test, or when the study focus is the problem of 'quality of medical care'. In the three cases aforementioned, specific research methods are available that may be more appropriate than a RCT.

As stated by Greenhalgh:

> For example, an RCT comparing medical versus surgical methods of abortion might assess "success" in terms of the number of patients achieving complete evacuation, amount of bleeding, and pain level. The patients, however, might decide that other aspects of the procedure are important, such as knowing in advance how long the procedure will take, not seeing or feeling the abortus (*sic*) come out, and so on. For this analysis, the appropriate route to best evidence is a *qualitative research method*. (Greenhalgh, 2001, p.49)

These methodological problems of RCTs have a clear influence on systematic reviews. Much of the criticism of systematic reviews is based on the argument that reviewers construct conclusions based on a feeble structure, the RCT. Furthermore, they are allegedly assembling a result as if they were capable of asserting which of the several RCTs have a correct structure. As stated by Ioannidis and Lau:

The traditional review expert assesses data, giving more weight to some and less to others, throws some data out, and reaches subjective conclusions in a monarchy without laws, sometimes an enlightened one, commonly a tyranny. (Ioannidis and Lau, 1998,p.590)

Furthermore, some authors believe that most systematic reviews are a cause of frustration to research users when they recognise that these reviews are often unable to provide specific guidance on the efficiency of medical interventions (Petticrew, 2003).

As will be discussed in Sections 2.3, 2.4, and 3.3 of this study, there are several possible (and concurrent) reasons for the present situation of endemic occurrence of bias in medical research. However, one important source of problems is undoubtedly the various intrinsic methodological problems of RCTs.

2.3 Contemporary structure of medical courses in Brazil

Compared with medical education in Europe, the existence of medical schools in Brazil is more recent. Historically, the first medical school was established in Bahia State in 1808 based on the structure of the Portuguese medical schools. However, it only attained the status of a true medical school in 1815 (Lima-Gonçalves, 2002). Therefore, medical education in Brazil has a history of a little under 200 years.

In 152 years, from 1808 to 1960, 28 new medical schools were created mainly by the federal and state governments. According to Lima-Gonçalves (2002), the regional allocation of these schools was appropriate given the existent Brazilian population distribution.

However, from 1961 there was a rapid expansion in the number of schools (Lima-Gonçalves, 2002). By 1975, there were 73 medical schools in Brazil. In other words,

there was an increase of more than 150% in the number of medical schools, in the short period of 14 years. Between 1975 and 1999, 19 new schools were created, giving us a total of 92 schools. Unofficial data suggests that in 2003 there were 104 medical schools in Brazil.

Unfortunately, according to Lima-Gonçalves (2002), the establishment of medical schools between 1961 and 1975 served political and economic interests, which eventually did not coincide with the real needs of the Brazilian States as revealed by technical surveys. Lima-Gonçalves also asserts that these schools were created without the necessary evaluation of the existence of educational resources for their maintenance and development, especially in relation to qualified teachers and adequate teaching hospitals.

Although there were several isolated attempts by the Ministry of Education and the Regional and Federal Councils of Medicine to evaluate and control the Brazilian medical schools, these were all somewhat ineffective. Only after 1991, with the creation of CINAEM (Comissão Interinstitucional Nacional de Avaliação do Ensino Médico), could a rather methodical diagnosis of the real situation of the Brazilian medical schools be achieved.

CINAEM is a committee composed of members of the National Society of Medical Schools, the Brazilian Medical Association, the National Academy of Medicine, the Federal Council of Medicine, and several other Councils and Associations related to medical practice and education. The fundamental aim of this committee is to evaluate the structural and educational profile of Brazilian medical schools. Furthermore, it is meant to propose necessary modifications to medical education, and establish permanent mechanisms of assessment of medical schools.

The final report of the first two phases of the CINAEM project was published in 1997 (CINAEM, 1997), and much of the analysis of the contemporary structure of medical courses in Brazil summarised in the next paragraphs is based on this report.

The first phase of the CINAEM project focused on the evaluation of the structure of the medical schools. In order to obtain these data a questionnaire composed of 266 questions organised by the *Organização Pan-Americana de Saúde* (Pan-American Health Organisation - OPAS), and modified to some extent by the CINAEM working group was employed. These modifications were intended to adapt the OPAS questionnaire to the Brazilian situation and the CINAEM objectives. This questionnaire aimed to determine which variables were most strongly associated with the quality of the final product of these schools: the graduate physicians. The CINAEM committee sent the questionnaire to the 80 medical schools that existed in 1991, and 76 schools responded.

Although this initial survey did not have a quantitative or classificatory characteristic, the data obtained were worrisome. Using the OPAS criteria of evaluation of medical schools, the human resources (teachers), the physical resources of the schools, the pedagogic model, and the final product (physicians), were all assessed as being on average below what was expected. However, it must be emphasised here that the results do not apply to individual schools, as the CINAEM report does not provide this kind of information.

The analysis of the questionnaire also showed that, in 1991, 57% of the schools were entirely funded by the Brazilian government (the students do not pay any fees during their courses), while 43% of them were private. The total number of graduates produced by these medical schools was 7554 physicians per year in 1991, according to Lima-Gonçalves (2002).

The average number of teachers was 197 per school, and these teachers spent 51% to 99% of their time in activities related to teaching, administration and surgery hours. Full-time dedication of teachers to research only existed in 20% of the schools. According to the CINAEM report, in 1991 only 56% of the schools had a Teaching Hospital of their own, and most of the others declared that were using rented private hospital facilities. In addition, 25% of the schools stated that they had no specialisation (residency) programmes.

The second phase of the CINAEM project focused on the evaluation of the teachers and the final product of a medical school, the physicians. It is understandable that, after the initial results, several schools decided not to continue in the CINAEM project. Consequently, the number of medical schools that participated in the second phase of this project dropped to 47. Most of the schools that decided not to participate in the second phase of this study stated that they were implementing their own internal evaluation procedures. One must be aware that the results of the second phase of the CINAEM study may not adequately characterise medical schools in Brazil, as the schools that remained in the project probably had better structures.

In the second phase of the CINAEM study 4193 teachers and 2214 students were evaluated; some of the results are important to the present study. The teachers' opinions and personal information were collected using a questionnaire and data provided by the medical schools. The students were assessed by two evaluation tests, one at the beginning of their last year as students, and the other at the end of the same year. These tests focused on four main areas of medical knowledge: Internal Medicine, Paediatrics, Obstetrics and Gynaecology, and Public Health. In addition, 1637 observations of the behaviour of 769 students in their daily surgery hours were undertaken.

According to the CINAEM report, most of the teachers were male (67%), with ages between 30 to 49 years, and with on average less than 9 years of experience as medical teachers. The majority of them (80%) had a title of specialist due to a residency (specialisation) program, 31% had a Masters degree, and 20% a Doctoral degree. Furthermore, only 7% of them declared that their specialisation was in Education. These proportions are cumulative, and one must be aware that this question had five options (graduation, specialisation, Masters degree, Doctoral degree and Post-doctoral studies) which should be ticked in a sequence. Consequently, someone who stated that they had a Doctoral degree may also possess a Masters degree and a specialist certificate, or just the Doctoral degree as will be explained in Section 3.2.

The majority (70%) of the medical schools stated that they had a mechanism for some kind of assessment of their teachers. In 71% of the 47 schools that gave details of how

their teachers were assessed, the number of published papers was an important element. Furthermore, in 66% of these 47 schools participation in research projects (even without publication of the findings) was also taken into account in the teachers' assessment.

However, as stated by Basile (1998), and presented in the CINAEM report, for the majority of the medical teachers in Brazil teaching activities are only a small part of their professional lives. In fact, the CINAEM report showed that, on average, their salary as teachers corresponded to just about 25% to 50% of their total income. Most of them were satisfied with their total income, although not with their salary as teachers.

A condition for participating in the second phase of the CINAEM project was that the medical school would allow the evaluation of their teachers and students. However, while the evaluation of the teachers had a compulsory characteristic, the students' assessment was structured as a voluntary participation. It was based on two qualification tests undertaken in 42 medical schools and a behaviour analysis of students during their surgery hours in 14 medical schools. Only 14 medical schools participated in the behaviour analysis study due to the small number of trained personnel available to make and analyse these observations.

The results of the two CINAEM tests showed that in the first one 39% (standard deviation +/- 3%) of questions were answered correctly, while in the second, 51% (standard deviation +/- 5%). These tests were composed of multiple-choice questions, most of them with five alternatives. The behaviour analysis study concluded that 50% of the students manifested inadequate humanistic and ethical behaviour in their relationships with their patients. According to Lima-Gonçalves (2002), the outcomes of the first two phases of the CINAEM project revealed that at the end of their graduation course, a significant proportion of the Brazilian physicians had an evident inadequacy in their scientific, humanistic, and ethical education.

In 1998, based on the results of the two initial phases, the CINAEM committee started an action research project that aimed to correct the deviations disclosed by the initial studies

in the participating medical schools. Unfortunately, there are still no published data about the evolution and results of this third phase of the CINAEM project.

2.4 The relationships among pharmaceutical companies, medical research, and continuing medical education

This Section will evaluate the relationships of the pharmaceutical industries and medical research from two different points of view. The first will be the influence of pharmaceutical companies on the production of research, and on the behaviour of the physician as a scientist. The second point of view will appraise the importance of their influence in the formation and dissemination of medical knowledge, and their significance to the physician as a consumer of medical research and continuing medical education (CME).

There is no trustworthy evaluation of the impact of pharmaceutical companies on medical research and medical education in Brazil. However, it will be demonstrated that the available data from Europe and the USA show that these companies have an international policy, and that this policy displays only superficial differences when applied to different countries.

2.4.1 The influence of pharmaceutical industry on the production and dissemination of medical research outcomes

As stated by Richard Horton:

> Pharmaceutical industry bias is hard to study with any rigour. However, Benjamin Djulbegovic and colleagues did find evidence of substantial bias in randomised trials of patients with multiple myeloma. (Horton, 2000,p.960)

The paper cited by Horton (2000) was published in the same journal, and the authors were Djulbegovic et al. (2000). After analysing randomised trials about the subject (treatment of multiple myeloma), Djulbegovic et al. (2000) assert that comparing trials funded by non-profit agencies, and profit-making companies (mostly pharmaceutical companies), there was an evident disparity. Although 74% of trials funded by profit-making agencies favoured the new drug treatments, only 53% of non-profit funded studies showed that such a difference really exists. The authors even assert that the possibility of violation of the principle of 'maximum uncertainty' (equipoise) in the profit-making studies could endanger the survival of the clinical trial in medical research.

As stated by Djulbegovic et al:

> The uncertainty principle, or equipoise, states that the patient should be enrolled in a randomised controlled trial only if there is substantial uncertainty ("equal bet") about which of the trial treatments would benefit the patient most. (Djulbegovic et al., 2000, p.635)

According to these authors, it is possible that industry would only sponsor those research projects in a particular area of medicine that are likely to be positive. This selective sponsorship would violate the uncertainty principle, which is a fundamental scientific and ethical principle of RCTs.

Although we must assume that there will always be some differences among researchers in a delimited field of knowledge, the aforementioned results, and comments, are remarkable. Unfortunately, rather than being an isolated occurrence, the previously mentioned example seems to be the rule, rather than the exception (Lexchin et al., 2003).

Lexchin et al. (2003) carried out an extensive search of papers in MEDLINE® published between January 1966 and December 2002, at Embase from January 1980 to December 2002, and at the Cochrane methodology register. They used a combination of terms in this search based on the key words: 'clinical trials', 'conflict of interest', 'drug industry',

'financial support', 'publication bias', 'research design', and 'research support'. They also used the QUOROM criteria (Moher *et al.*, 1999) to justify their reasons for the inclusion or exclusion of papers in their study.

The conclusions of this study, published at the *British Medical Journal*, are summarised in a table in their paper:

What is already known on this topic

When pharmaceutical company funds research into drugs, studies are likely to produce results favourable to the sponsoring company's product.

What this study adds

Research funded by drug companies was more likely to have outcomes that favour the sponsor's product than research funded by other sources.

This cannot be explained by the reported quality of the methods in research sponsored by industry.

The result may be due to inappropriate comparators or to publication bias. (Lexchin *et al.*, 2003, p.1175)

These results are consistent with another systematic review published in the same year in the *Journal of the American Medical Association* (Bekelman *et al.*, 2003). These authors used as data sources the MEDLINE® database and the Web of Science database, and the inclusion and exclusion criteria were different from the Lexchin *et al.* study. In the conclusion of this review, Bekelman *et al.* assert that:

Strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions. By combining data from articles examining 1140 studies, we found that industry-sponsored studies were significantly more likely to reach conclusions that were favourable to the sponsor than were non-industry studies. (Bekelman *et al.*, 2003, p.463)

A still more recent systematic review by Bhandari *et al.* (2004) was published in the *Canadian Medical Association Journal.* Using data from eight leading surgical journals and five medical journals their results also showed that industry funding has a significant influence on the results of both surgical and drug trials. The authors also suggest that:

> Future exploration of the complex relation between industry-funded trials and authors' conclusions will shed further light on this issue. (Bhandari *et al.*, 2004, p.480)

In fact, such a relation should receive more attention from researchers. However, this may prove to be a very arduous task, as few researchers will probably be able to contribute with their comments about their associations with the pharmaceutical companies, as stated by Garland (2004):

> Pharmaceutical companies seeking regulatory approval are obliged to make the results of all clinical trials they sponsor available to regulatory agencies. However, there is no requirement for these results to be published or even made available to investigators. Those researchers, including myself, who *did* see results of negative paroxetine (*an antidepressant drug*) industry trials were prohibited by non-disclosure contracts from discussing them. (Garland, 2004, p.490)

Quick (2001) summarises well the problems of these relationships between medical research and the pharmaceutical industry:

> Clinical trials form the basis of effective research ... but their reliability is currently imperilled by three major flaws: conflicts of interest on the part of investigators; inappropriate involvement of research sponsors in their design and management; and publication bias in disseminating their results ... In a highly

competitive world, the pressures may be simply too great for individual researchers, universities, medical journals, or public agencies to stem the tide of commercial interest. (Quick, 2001, p.1093)

According to Quick (2001), if clinical trials become a commercial business enterprise, due to the relationships between researchers and the pharmaceutical industry, 'the social contract which permits medical researchers to use human subjects in return for medical advances is broken' (Quick, 2001, p.1093). In fact, this 'social contract' underpins the moral entitlement of medical researchers to use human subjects in their research, as far as the results of such studies revert free of further cost to the entire population. Transforming medical research into a commercial business enterprise would represent a further financial burden to the whole population, which would be ethically unacceptable.

One may argue that such a financial burden might be paid back from the eventual fruits of such research, making such a commercial business enterprise morally perfectly acceptable. However, the evidence that the results of research done under such conditions is being in a certain way 'censored' by sponsors (Garland, 2004) invalidates such kind of reasoning.

2.4.2 The influence of pharmaceutical industry on continuing medical education

Twelve years ago Lexchin (1993) did a systematic analysis of the influence of pharmaceutical companies on medical education. He used as data papers published in Australia, Canada, New Zealand, Britain, and the USA about the matter, between 1978 to 1993. His results showed that pharmaceutical companies sponsored continuing medical education (CME) courses could have what he called a 'commercial bias', 'even when conducted under guidelines designed to ensure the independence of the event' (Lexchin, 1993, p.1401).

In the Abstract section of his study he asserts:

Physicians are affected by their interactions with pharmaceutical industry. Further research needs to be done in most cases to determine whether such interactions lead to more or less appropriate prescribing practices. The CMA's [Canadian Medical Association] guidelines on this topic should be evaluated to see whether they are effective in controlling physician-industry interactions. (Lexchin, 1993, p.1401)

Ten years later Moynihan (2003) declared that doctors and the pharmaceutical industry are entangled in a ubiquitous and controversial web of interactions. Furthermore, he agrees with Lexchin (1993) that these interactions are widespread, and that evidence exists that these relations with industry influence physicians' behaviour.

Between 1993 and 2003, medical research and CME became too expensive for the governments of most countries. Due to this fact, there was an intensive and extensive pressure to establish relationships between medical schools and the pharmaceutical industry. The industry willingly accepted this task because, as we have discussed in the previous section, they already controlled much of medical research.

However, Baird (2003) asserts that we need to think about the possible consequences of the strong academic-industry partnership, because there is a potential imbalance in research and educational practices that may endanger public confidence in medical practices.

According to Collier and Iheanacho (2002, p.1405) "the pharmaceutical industry spends more time and resources on generation, collation, and dissemination of medical information than it does on production of medicines". These authors went on to assert that:

Through their investment on research, transnational companies have an

important effect on the direction of medical research generally; via their promotional and educational activity, they are probably the biggest individual influence on prescribing practice... However, the huge scale of work involved, lack of openness... and distortion of the overall research effort and resulting messages make the business of information-generation inefficient and threatens patients' interests. (Collier and Iheanacho, 2002, p.1408)

One of the most important methods of CME are the clinical practice guidelines that should be derived from the systematic analyses and meta-analyses of previous studies. However, the aforementioned studies suggest that this important medical educational mechanism may be biased at two crucial stages: the production of medical knowledge, and its dissemination.

These questionable interactions between the pharmaceutical industry and CME were revealed by Choudhry *et al.* (2002) in a cross-sectional survey of 192 authors of 44 Clinical Practice Guidelines (CPGs) endorsed by USA and European societies. These CPGs were published between 1991 and 1999 and are related to guidelines on common adult diseases.

The results of the survey of Choudhry *et al.* (2002) demonstrate that 87% of authors had some interaction with pharmaceutical industries, and that 59% had relationships with companies whose drugs were considered in the guidelines they produced. In the published versions of the CPGs, only two authors declared their financial interactions with these companies. Moreover, 7% of these authors declared that their connection with the pharmaceutical industry influenced their recommendations, and 19% of them believed that relations with the pharmaceutical companies influenced their co-authors' opinions expressed in the CPGs they created.

Choudhry *et al.* also state that:

Although the results of this study must be interpreted cautiously in light of the

relative low response rate, our results appear to indicate that most CPG authors have interactions with pharmaceutical companies and that a significant proportion work as employees/consultants for drug manufacturers. (Choudhry *et al.*, 2002, p.615)

According to Komesaroff and Kerridge (2002), physicians and the pharmaceutical industry share a number of interests. The current configuration of the relationships between them is the outcome of a long-established culture in which gratuities, gifts, and sponsorship of meetings and CME activities are both expected and provided. However, funding of conferences and CME programmes has been shown typically to lead to information bias in favour of the sponsoring pharmaceutical companies' drugs (Komesaroff and Kerridge, 2002).

An important problem of the domination of CME programmes by the pharmaceutical industry is well presented by Choudhry *et al.* (2002):

> Unlike relationships that individual authors or physicians have with the pharmaceutical industry, financial conflicts of interest for authors of CPGs are of particular importance since they may not only influence the specific practice of these authors but also those of the physicians following the recommendations contained within the guidelines. (Choudhry *et al.*, 2002, p.616)

Actually, such influence can be even greater due to the fact that Choudhry *et al.* (2002) reveal that in the majority of the guidelines they have investigated no declarations of a potential conflict of interest were made by the authors.

Several medical associations throughout the world recognise the threat of pharmaceutical industries' controlled medical education programmes. As stated by Moynihan (2003b):

> Many individual doctors, and their professional associations, are facing difficult

choices about whether they remain part of the industry's extended promotional machinery or should seek real distance in their relationships, to give prescribing, teaching, and advice that is truly independent. Growing moves towards genuine separation may well make previously acceptable conflicts of interest untenable. (Moynihan, 2003b, p.1195)

In fact, the present influence of the pharmaceutical industry over medical education programmes endangers two of the main ethical features of medical practice, which are the obligation of competence and the prudence of conduct of physicians. As stated by Allman (2003):

One of the stated benefits of the physician-industry entanglement is support for educational activities. Patient interest is threatened when that which is presented to the physicians as objective, scientifically rigorous, unbiased information is commercially slanted to the benefit of a particular manufacturer ... The physician who is the mere sum of mind-dulling marketing agendas is less than the beneficent and competent agent of the patient's good. (Allman, 2003, p.161)

An additional ethical issue would be that who in reality is paying for these continuing medical education programmes and guidelines 'sponsored' by the pharmaceutical industry are the patients, as it will be discussed in Section 7.6.3.

Chapter 3

Research purposes and methods

3.1   Introduction

The previous two chapters focused mainly on the subjects that are internationally recognised as important to the existence and prevalence of bias in medical research. This chapter centres on the research questions and on the discussion of the methodology that was employed to answer these questions. However, in order to explain the rationale behind the research questions, and even to underpin a posterior assessment of the results of this study, a prior discussion of two topics that are seldom examined in studies in this area is necessary.

The first topic is based on the fact that medical research and medical education have many common aspects in most countries. Nevertheless, the structure of research production and the formation of the physician-scientist may differ among countries. As this research focus on five Brazilian medical schools, it is necessary to discuss these aspects of Brazilian medical research, and this is done in Section 3.2.

The second topic is related to the existence of some ethical aspects of research that may play a role on the occurrence of bias in medical research. With the exception of Section 2.4, most of the previous discussion about the problem of bias in medical research was based on the assumption that:

> Unlike the lay meaning of bias, bias in health research should not be associated immediately with a malicious attempt of investigators, funders, or readers to bend the results of a trial. Although bias can be introduced into a trial voluntarily, it is probably involuntary in most cases. (Jadad, 1998b, p.29)

However, there is some disturbing evidence that moral deviations, which may be exacerbated by the training of the physician and the physician-scientist, could be related to the problem of bias in medical research. This is discussed in Section 3.3 due to its eventual role in the discussion of the outcomes of the present study.

3.2 Medical research in Brazil

In a recent publication, in a journal funded jointly by the Brazilian Ministry of Science and Technology and the Brazilian Academy of Sciences, Zago *et al.* (2002) state that it is a complex matter to try to carry out a survey about the structure of medical research production in Brazil.

This is undoubtedly true, since there is no real control over medical publications in Brazil, and most studies are not published in indexed journals. However, the aforementioned authors, due to their relationships with the Brazilian Ministry of Science and Technology and the Brazilian Academy of Sciences, had access to information that is not readily available to most researchers in the area of medical education. Consequently, much of the information about medical research production provided in this Section is based on their essay.

In order to envision correctly the real size and importance of Brazilian medical research, it is necessary to use some quantitative data. According to the *ISI Essential Science Indicators* (http://www.in-cites.com, last accessed 03/03/2004), from January 1992 to October 2002, the Brazilian clinical medicine research production totalled 12586 papers (60479 citations). This number of papers represents 0.5% of the global production of medical research. In the same period of time, the UK production corresponded to 10.6% of global medical research.

As stated by Zago *et al.* (2002), in 2002 Brazil had 95 medical schools, and 9349 physicians graduated from these schools. However, in only 16 of the schools there was evidence of an established structure of scientific research. Moreover, 115 of the 128 most valued Brazilian medical researchers, according to the evaluation of the Conselho Nacional de Pesquisa (National Council of Research – CNPq), were teachers and/or

researchers in only eight medical schools and four research centres. Not surprisingly, these eight medical schools were responsible for most of the papers mentioned in the previous paragraph. Incidentally, the Brazilian government funds all of the eight schools and three of these research centres.

Zago *et al.* (2002)'s data are consistent with the information presented by Pellegrini Filho (2000):

> Universities in Latin America utilise almost 50% of the (*total*) resources for S&T (*Science and Technology*) and account for 70% to 80% of the scientific output. (Pellegrini Filho, 2000, p.347)

Mari (2002), discussing the problem of the number and distribution of medical researchers among the medical schools in Brazil, concludes that a significant portion of the Brazilian medical schools' graduates are unprepared to deal with or even correctly assess the advances in medical scientific knowledge. He believes that there is an important relationship between the quality and quantity of research projects and the quality of the available medical education in Brazilian medical schools.

In relation to Brazilian research, Pellegrini Filho (2000) claims that it is possible that in all Latin American countries there is an important disparity between scientific production and the dissemination and application of the results. One possible reason for this is the isolation of the scientific community from the rest of the society, which makes the production and application of scientific research vulnerable to political manipulation of financial resources.

Furthermore, Pellegrini Filho (2000) asserts that MEDLINE® indexed in 2000 only 45 Latin American journals, while LILACS database, which is maintained by the Latin American and Caribbean Center on Health Sciences Information (BIREME), had 600 Latin American indexed journals. This fact would not certainly help in the dissemination of Latin American medical research results in Latin America and abroad.

Since medical research in Brazil is carried out mostly in medical schools, it is important to discuss the structure of medical post-graduation courses in this country because they will be responsible for the formation of the physician-scientist.

It is not necessary to have a specialist certificate in order to enrol in a Masters or Doctoral programme in Brazil. However, it is extremely rare that a Brazilian physician registered in a postgraduate course does not have a previous specialist certificate. This happens because almost all students on medical postgraduate courses in Brazil are teachers in medical schools. In order to be accepted as a teacher, even as a temporary teacher, medical schools require a specialist certificate as a minimum requisite.

Furthermore, according to Lima-Gonçalves (2002), the six years of medical education required for a physician to graduate in Brazil are not sufficient to guarantee an adequate medical knowledge. Consequently, a good residency course (specialisation) became progressively compulsory to assure the possibility of success for a physician in a very competitive environment. This is especially true if one remembers that, as discussed in Section 2.3, teaching is generally only a part of the professional life of a medical teacher in Brazil.

The rapid increase in the number of medical schools discussed on Section 2.3 and the escalating demand for a specialisation course, particularly after the 1970s, created a vicious circle which resulted in a decline of the quality of medical education in Brazil (Lima-Gonçalves, 2002).

Discussing the last available official data about residency programmes in Brazil, Lima-Gonçalves (2002) states that in 1998 there were already 1963 specialisation programmes, which is a very large number considering that the first programme was created only in 1945. This number of programmes indicates that a recently graduated Brazilian physician had a 70% probability of enrolling in one of them in 1998. As is discussed in the following paragraphs, this rapid growth of specialisation programmes was not congruent with the Brazilian capacity on the formation of medical teachers and researchers in its Masters and Doctoral programmes.

The evolution in the number of Masters and Doctoral programmes in Brazil occurred at a slower pace than the creation of medical schools and specialisation courses until the beginning of the 1970s according to Ramos (1998). From 1970 to 1979, there was a remarkable increase in their number due to two factors. The first was the increase in the number of medical schools. The second was the new policy of the Brazilian Ministry of Education in relation to the requisites that should be fulfilled by the schools (Ramos, 1998; Lima-Gonçalves, 2002).

Unfortunately, the rapid increase in the number of postgraduate courses caused a deleterious effect on the quality of these programmes. In 1998 there were already 296 postgraduate programmes in the medical area in Brazil (Lima-Gonçalves, 2002). However, only 44% of the Masters programmes and 56% of the Doctoral courses were classified as 'good' or 'very good' (Ramos, 1998).

Furthermore, as stated by Zago et al. (2001), the same eight Brazilian medical schools and four research centres aforementioned in the discussion about research production in Brazil were responsible for 87% of the 'good' or 'very good' programmes.

Despite the various problems of the graduate and postgraduate courses in Brazil, according to Zago et al. (2001) over the last 20 years Brazilian medical scientific production has increased proportionally more than the total scientific production of this country. The same authors also assert that, based on the percentage of world citations of the Brazilian papers in indexed journals there was also an increase in the quality of the medical research production over the same period.

3.3 Unethical behaviour in medical research: a potential problem

The discussion about bias in medical research in Chapter 1, and about the potential factors that influence its existence in Chapter 2, shows that it is possible that the common occurrence of these systematic deviations in medical research may be due to several causes.

Section 3.2 shows that in Brazil, from the specialisation programmes to postgraduate courses, the physician-scientist-teacher has been submitted to a progressive physical and psychological strain in order to maintain, or acquire, a position inside a medical school or research centre.

According to some authors, this could be an additional potential reason for the existence of bias in medical research. It could favour the existence of unethical behaviours among researchers (Smith, 1998; Rennie, 1999). Although these authors show that ethical deviations may indeed be a cause of bias, there is no evidence that this could be the main factor to explain the existence and persistence of bias in medical research.

However, there is some evidence that a change of attitudes is occurring during medical training, which may be responsible for part of the problem. Despite the fact that there is a limited literature in this field, the information it yields is frightening. Snodgrass reports that 88% of medical students at two Chicago (USA) medical schools, when interviewed, admitted that they had cheated at least once in their medical course in order to graduate (Snodgrass, 1991). She suggests that:

> Systematic investigation of the attitudes of medical students and practising scientists could yield promising information about the relationship between ethos and writing in actual situations (Snodgrass, 1991, p. 13).

Sykes reports that at least 10% of his colleagues, in a medical school in England, claimed to have falsified at least some of their research data to satisfy the requirements of their courses, even though they considered their projects as important (Sykes, 1994). Perhaps more worrying than the fraud itself is the fact that they considered this behaviour as normal and necessary.

These papers reveal something that is more important than the well-known 'publish or perish' problem. In the aforementioned papers, medical students are considering their unethical behaviour as a morally *acceptable* conduct, and we must be aware that a significant number of them are now researchers. The estimation of how profoundly this can affect the future of medical research is very important.

Glick (2001), discussing the case of a possible inappropriately lenient reaction by the University of London Royal Free and University College Medical School, in a case of student cheating in an examination, is helpful for our discussion. The author states that:

> Reviews of the literature suggest that we have insufficient reliable data about the extent of this phenomenon, its rate of change, its pathogenesis, its prevention, or its effective management ... Medical schools should be the major focus of attention for imbuing future doctors with integrity and ethical sensitivity. Unfortunately there are troubling, if inconclusive, data that suggest that during medical school the ethical behaviour of medical students does not necessarily improve; indeed, moral development may actually stop or even regress. (Glick, 2001, pp. 250-251)

According to Glick, this phenomenon can be attributed to, among other causes, overemphasis on grades, competition, negative role models, and institutional tolerance to cheating. He concludes that it is important to create an environment of peer pressure in which certain behaviour is not acceptable.

Glick's editorial is consistent with the opinion of some previous authors. Levy, for example, recognised that the most direct and immediate efforts to reduce publication bias in the clinical literature should be educational. In his article, he asserts that is necessary to "... discuss all facets of publication bias among us and with our students frequently and comprehensively, in its scientific and ethical aspects" (Levy, 1992, p. 118). In addition, Pencheon asserts that:

> At school, too many of us have been (and a few still are) exposed to a convenient and simplistic view of the world ...Too little emphasis is placed on helping to develop our critical faculties, to question assumptions, and to challenge dogma ... Being so poorly prepared to engage uncertainty positively, some of us develop our scientific approach despite our training rather than because of it (Pencheon, 1999, p. 2).

In fact, as is discussed in Chapter 6, one important aspect of current medical education is the undeniable influence of the 'hidden curriculum' (Snyder, 1991). According to Lempp and Seale (2004):

> Six learning processes of the hidden curriculum of medical education have been identified: loss of idealism, adoption of "ritualised" professional identity, emotional neutralisation, change of ethical integrity, acceptance of hierarchy, and the learning of less formal aspects of "good doctoring." Together they achieve the enculturation of students as they develop into both practitioners and members of the medical profession. (Lempp and Seale, 2004, pp.770-771)

At this point, we may have to review the traditional definition of bias because it is based on the assumption that most bias in medical papers is an involuntary occurrence. It is possible that part of the problems of medical research is a combination of a low level of awareness about bias and, possibly, unethical behaviour. Although scarce, the literature leads to the conclusion that the educational process on medical schools may be responsible, at least in part, for this combination.

3.4 Research questions: their rationale

As discussed in the previous two Chapters, bias in medical research and its correction was the subject matter of several studies over the last 20 years. The focus of the resulting publications was the methodological procedures for detecting and correcting bias. Although these studies were important in quantifying the problem and in developing research structures less prone to systematic deviations, these efforts have not eliminated bias in medical research (Horton, 2000).

One aspect of this field of study that has received less attention is how much of the knowledge about bias is really reaching medical education courses and the medical research community. A second aspect that deserves more attention is to identify how intensely the information about bias is influencing medical education and research. These are important issues because medical schools and postgraduate programmes are partly responsible for the conduct of physicians as research consumers, and for the behaviour of

future medical researchers (Pencheon, 1999).

This study has two different but complementary objectives. The first objective is to obtain data about the current level of awareness about bias in medical research among teachers and students of the last year of the course of medicine, in a sample of medical schools in Paraná State (Brazil). The second objective is to evaluate how these teachers and students perceive the question of bias (whether as a methodological and/or educational problem). Additionally, this study has gathered information about the opinion of staff and students about the possible educational measures that could help to minimise the occurrence of bias in medical research. To achieve these objectives, it was necessary to obtain both qualitative and quantitative data (Sackett and Wennberg, 1997), as discussed in Section 3.5.

According to these research objectives, the present study focuses on three research questions:

1. What is the level of awareness about bias in medical research among teachers of Internal Medicine, Surgery, Gynaecology and Obstetrics, and Paediatrics, and students of the last year of the course of medicine, in five medical schools in the state of Paraná (Brazil)?

2. In the participants' opinion, are the systematic errors that exist in medical research the result of factors related only to the methodology of research, or are they also a manifestation of habits acquired during medical education and postgraduate courses?

3. What can be changed in medical education in order to reduce systematic errors in research?

The expression 'level of awareness' in the first research question refers fundamentally to the general knowledge of teachers and students about the existence and importance of bias in medical research. It is a direct question and can be answered with a quantitative approach. However, the second and third questions involve individuals' values and experiences, and demand a qualitative methodology (Sackett and Wennberg, 1997).

Although assessment of the level of awareness about bias among the participants was important to this study, it was also necessary to obtain some complementary information. Basically, this comprised two subjects: the sources of information that participants were using to obtain their knowledge about bias, and the phase of their medical formation at which this was occurring. This information was important because, as discussed in Section 1.5, knowledge about bias is not only important to the physician-scientist but also to the physician as a consumer of the information contained in medical publications.

In order to fulfil the objectives of this research, three concurrent methods of data collection were employed: questionnaires, interviews and curriculum analysis. The proposed methodological structure had the aim of obtaining a complementary perspective of the problem, rather then a competing one as is usually attained in a traditional 'triangulation' method (Barbour, 2001).

This approach to the study of the possible relationships between medical education and bias in medical research is coherent with the opinion of Murphy et al. (1998). Their view is that there is a complementarity of qualitative and quantitative methods, which can be very useful when studying human resources behaviour in health technology assessment. These authors also suggest that the use of a qualitative approach may be useful in enlightening the factors that sustain professional practices that are suspect of being ineffective or inappropriate in healthcare settings.

Since the problem of bias is more prominent in clinical trials, I selected as participants the teachers from departments that are more involved in clinical and surgical teaching and research (i.e., Internal Medicine, Surgery, Gynaecology and Obstetrics, and Paediatrics departments). The theoretical basis to this sampling method is the 'purposive sampling' (Silverman, 2000).

This method was chosen because in purposive sampling, we can use groups and settings where the processes we want to study are expected to occur more frequently. As a non-probabilistic procedure, it has the disadvantage that its findings cannot be generalised quantitatively to a wider population. However, it is considered to be effective for exploring areas of study that are still underdeveloped, and for generating theories or

hypothesis (Baker, 1999), which is the case in the research presented here. The theoretical basis that underpinned the choice of purposive sampling is more thoroughly discussed in Section 3.8.

Combined with the fact that participation in this study was voluntary, purposive sampling was expected to enhance the quantity of data obtained in the qualitative data collection. This would be particularly important to the present study, as these data are related to the second and third research questions. These questions focus on the relationships between medical education and the transmission of knowledge about bias, which is the least known aspect about the occurrence and incidence of bias in medical research, as discussed in the previous two Chapters.

Therefore, the possible deficit of generalisability of the data obtained in the answers to research question one would be compensated by the improvement of the data acquired for the second and third questions responses, which are the main research objectives of this study.

3.5 The assembly and results of the questionnaires and interviews of the pilot study

3.5.1 Structuring the questionnaires

In order to obtain the data needed to answer the first research question, I decided to use a questionnaire for both teachers and students. This approach had a fundamental problem, because historically questionnaires have a low response rate when applied to physicians in England and in USA, especially if the questions are about sensitive topics (McColl *et al.*, 2001). Although I did not have information about similar research in Brazil, it was reasonable to assume similar poor response rates. In order to reduce this possibility, several measures were taken in order to enhance the response rate, as discussed in the next few paragraphs.

One obstacle to the use of questionnaires was that the problem of bias has received more attention in English speaking countries. Conversely, in Portuguese, the number of

publications about the matter is scarce. In addition, authors use a range of terms in Portuguese, principally 'viés', 'tendência', 'tendenciosidades', and even 'bias', to translate the English word 'bias'. This created a semantic problem for the construction of the questions that composed the questionnaires.

Another problem was that most of the terms used in Portuguese do not have the strong negative connotation that the term 'bias' has in English. To reduce the possible effects of these problems, the wording, design and sequence of questions was tested with a small group of Brazilian physicians who were not based in medical schools. This assessment was carried out before the pilot study in order to see if the questions were understood as intended by general practitioners. This permitted me to assume that an unanswered question, or a non-returned questionnaire, would not be the result of a lack of understanding.

Furthermore, in order to reduce the occurrence of the two aforementioned problems, the questionnaires only used Portuguese expressions that could be found in the Descritores em Ciências de Saúde (Health Science Descriptors – DeCS). This is an official glossary of Epidemiology in English, Portuguese and Spanish from the Pan-American Health Organisation.

A pilot study of the questionnaires was undertaken in July 2002 at a medical school in São Paulo State (Brazil). This school was selected for the pilot for three reasons. Firstly, as I had graduated from this particular school I supposed that it would be easier to contact people to participate in the pilot, without having to follow all the normal bureaucratic procedures which will be discussed in Section 3.7. Secondly, I anticipated that some of the teachers who participated in the pilot would give me some important additional information about their opinion of the questionnaire structure, as they would recognise me as a former colleague or student. Finally, this particular school does not have much contact with the Paraná State medical schools where the main data collection of this study was performed.

The questionnaires in the pilot study (Appendix 1) included closed and free-response questions, and were structured along the lines recommended by Oppenheim (1992) and McColl *et al.* (2001). The two questionnaires had three fundamental objectives: first, to

structure and test the questionnaires that would be used in the main phase of the research; secondly, to evaluate any flaws in the questionnaires design that could compromise the results of this study; thirdly to estimate the usefulness of the questionnaires in the development of the personal interview framework.

In July 2002, I had my first contact with the Heads of the Departments of Internal Medicine and Surgery, and the representatives of the students in these Departments, of the medical school selected for the pilot. These two Departments were chosen because they contained a significant number of teachers who had a more frequent contact with the students during their medical course. Thirty questionnaires for the teachers and the same quantity for the students were distributed in stamped addressed envelopes for return.

The central idea of the aforementioned approach was to permit teachers and students freely to decide if they wanted to participate in the pilot study, as a contribution to a future research project in another state. My intention was to engage them into the project not as participants but as collaborators. I did not want formally to present the piloting of the questionnaires as a research project because this would entail, in Brazil, several bureaucratic procedures between my university and the school of medicine where I did the pilot study. These procedures can be particularly intricate and time-consuming, as will be discussed in Section 3.7.

After the pilot was concluded, discussions with academic staff at the Institute of Education, University of London (IoE), the Universidade Estadual de Ponta Grossa, and participants in the pilot revealed that the wording, layout, and the structure of the questionnaires should be changed in order to improve them. These modified questionnaires, which were used in the main data collection of this study are discussed in Chapter 4, and are included in Appendix 3.

3.5.2 The questionnaires: their role in answering the research questions

In this section, I will discuss the structure and objectives of the questionnaires in the pilot study, and their potential role in providing the information discussed in the previous paragraphs. Furthermore, I will demonstrate how their results changed some methodological concepts that I had at the beginning of this research. The structure and

results of the questionnaires used in the main data collection phase will be the subject matter of a systematic analysis in Chapter 4.

The first three questions in the student questionnaire (SQ) and the first four in the teacher questionnaire (TQ) aimed to establish whether the respondents were producers or consumers of medical information. They were also intended to determine how many participants are involved in medical research and, in the case of the TQ, their academic background. An example is question 1 of the teacher questionnaire:

1 Your present occupation (Tick more than one if necessary)
   ☐ Teaching
   ☐ Research
   ☐ Extension
   ☐ Administration

This information would enable me to compare different responses to the questions that followed among the participants (or between different schools of medicine).

Questions 5-7 (TQ) and 4-6 (SQ) aimed to reveal how the participants acquire information about bias in medical research, and whether they use this information to evaluate papers, e.g. question 7 of the teacher questionnaire:

7 How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias? Please explain.

The next six questions were the same on both the TQ and SQ, and focused on the participants' views about bias, their level of knowledge of the basic principles concerning the subject of bias, and their opinion on how to deal with the problem within medical schools. In addition, the answers to these questions would be important for subsequent interviews. An example of these questions is reproduced below. The assertion I used in this specific question is considered as an important aspect of the effect of bias in the results of systematic reviews and meta-analyses.

9 In the statements below choose the alternative that is more compatible with your personal opinion:

b- 'Publication bias is a menace to the quality of systematic reviews and meta-analyses'

☐ I totally agree

☐ I partially disagree

☐ I totally disagree

☐ I do not have an opinion about the subject

The response rate was low: only eleven teachers and one student. The teacher response rate is compatible with previous studies, as international surveys demonstrate (McColl *et al.*, 2001). However, the exceptionally low student response rate was attributed to several factors. Firstly, distributing the questionnaires via student representatives proved inadequate, and in the main data collection the questionnaires were delivered to the Graduation Council of the medical schools. Secondly, although the use of personalised letters and envelopes is recommended by the literature (e.g. McColl *et al.*, 2001) I had decided, maybe incorrectly, not to personalise them. The fundamental reason was that in order to obtain an official list of the students I would have needed to contact the Graduation Council of the medical school. This contact would elicit the necessity for subsequent bureaucratic measures, as aforementioned. Thirdly, the last year of training is extremely time-consuming and stressful to the students, and they may have seen the questionnaire as yet another burden. Finally, the low response rate could have been related to their feeling that they have a low level of knowledge about bias.

The answers to the first four questions in the teacher questionnaire (TQ) revealed that all of the respondents had completed their doctoral studies and were involved in teaching and research. Additionally, ten of them had papers published in the USA and/or United Kingdom. These rates are very high for Brazil, as discussed in Section 2.3 and may reflect that more academic teachers were more likely to complete and return the questionnaire and/or could be caused by the methodology of contacting the possible participants for this pilot.

The answers to question five of the teacher questionnaire were quite interesting. Only three of the respondents reported that they used the Internet to acquire knowledge about the problem of bias. However, all of them sent me their email addresses. This discrepancy may be caused by a language impediment (most of the databases are in English) or a difficulty in coping with the technical hitches involved in an Internet search. Anyone who has used MEDLINE® for research knows that it is time-consuming and sometimes frustrating, because of the huge number of papers one has to evaluate, many of them only remotely related to the research question.

The teachers' answers also showed that information about bias might be extensive, however, the dissemination of knowledge about bias may be less efficient than it should. One can perceive this in their answers to questions 9-b and 9-c, which use two statements that are considered accurate according to the literature about bias. The answers to these questions showed that the participants have certain knowledge about bias, however it does not seem to be very accurate and well based.

The answers to the last two questions (12 and 13) gave me a pleasant surprise because eight of the participants agreed to participate in a tape-recorded interview. Although I could not expect such a high proportion in all schools involved in this research, it seemed that it would be possible to have a sufficient number of permissions for interviews.

Even with a small number of participants, the pilot study was important to demonstrate some shortcomings in the methodology initially proposed for this research. However, the pilot also revealed that the questionnaires could give me responses to the first research question, and could contribute to answering the other two questions (see Section 3.4). It also exposed the fact that, at least in the case of the teachers who participated in the pilot, a certain degree of knowledge about bias and experience as researchers were not sufficient to attain a clear image of the problem of bias in medical research. It also permitted me to structure the interview schedule as described in the next section of this chapter.

3.5.3 Structuring the interviews

The interviews in this research had three main objectives. First, to understand how teachers and students of five medical schools of the state of Paraná (Brazil) perceive the problem of bias in medical research. Secondly, to appraise which were their methods of acquisition of their perceptions, and how they were using their knowledge about bias. Finally, as described by Tierney and Dilley (2002), I expected that the data collected in the interviews could eventually be useful in the improvement of educational practices in medical courses.

Although Fontana and Frey (1998) consider that interviewing is 'the art of science', I believe that it is a method to obtain data in a somewhat 'natural' form. It seems to be especially useful when one has a problem that can not be solved by a questionnaire, as is the case in which the problem under study is too complex to be approached by closed questions. There are three basic modalities of interview style: structured, semi-structured, and unstructured. Each of them can be used depending on the context and aims of the proposed research.

As the research area I have chosen is underdeveloped, and I needed to collect data about people's beliefs and feelings, I have selected a semi-structured interview design for use. The fundamental reason for this choice is that it could grant me the possibility of modifying or adding particular questions in order to elicit richer information, according to the individual characteristics of the participants (Robson, 1993; Britten, 1995). This could also be useful if the results of the open questions of the questionnaires showed a significant difference among the schools in a specific topic. Such differences could be better explored with a semi-structured design that would allow me to add some probe questions in order to ascertain why these differences occurred in the questionnaires.

Fundamentally, the interview proposed for the pilot study was intended to allow me to obtain data about the participants' opinions about the structure of the questionnaires, their evaluation of the current level of awareness about bias in medical research inside medical schools, and the possible educational solutions to this problem. Therefore, each interviewee received a copy of their questionnaire before the interview, because I had to assume that several of them would not remember their answers to the questionnaire.

The basis of the organisation of the interviews was the participants' responses to the open questions of the previous questionnaires, and the central objectives of this study as discussed in Section 3.4. Since the teachers and students who were interviewed had completed the questionnaire, the first two questions in the interview were:

> "Would you like to make any comments about the questions you have answered in the questionnaire?"

> "Some/Few/Many of your colleagues did not answer the questionnaire. Could you please give me your opinion why that happened?"

A possible alternative to these questions was:

> "Your answers to the questionnaire are very important to my research. Could you please give me more information about question X?

The main function of these questions was not to collect data, although this did occur. Rather, their purpose was to create a 'link' between the interviewer and the respondent.

The next two questions had a more direct importance in the research:

> "Do you really think that bias in medical research is/is not related to medical education? Why?"

> "Which are/could be, in your opinion, the possible educational procedures to minimise this problem? Why do you think they can be effective?"

As a possible respondent could not feel comfortable in disclosing his/her opinion, I believed that an alternative question could be:

> "Are you satisfied with the current measures adopted by the medical community to deal with the problem of bias in medical research? Why?"

3.5.4 The interviews: their role in answering the research questions

In this section, the results of the interviews in the pilot study will be discussed. As will be demonstrated, these were important for the development of the interview schedule used in the main data collection, which will be the subject matter of Chapter 5.

The pilot interviews were carried out in the first week of December 2002. I interviewed two teachers and two students of the school of medicine that participated in the pilot study. One of the students (Student 2) had not answered the questionnaire, but agreed to do the interview.

These interviews lasted for less time than I expected, and I believe this was due to two principal reasons. Firstly, these were my first interviews, and I did not make as full use of alternative questions as would have been ideal in enhancing the data collection. Secondly, as this was a small pilot I did not have enough data available from the limited number of returned questionnaires to use as a motivation for the discussion. However, this small number of relatively brief interviews provided an interesting glimpse into the problem I was proposing to investigate.

One notable aspect of the pilot interviews was the range of opinions of the teachers in respect of what is happening to the students on their medical course. This becomes evident in their answers to questions that focused on improving the knowledge of students about bias in medical research:

> ... We are not giving an opportunity to our students to develop a critical thinking about research, results, uses, etc ... To try to correct these problems in the postgraduate courses is impossible, as far as I can see ... no chances ... There are some schools that are trying to do something about that, but I must confess that I do not know the results ... however, something must change ... (Teacher 1)

> ... Our students have a good basis on scientific methodology and ethics ... We are doing the best we can do under the circumstances... there is nothing to be changed, as far as I can see ... As I have said before, the objective of a good

medical school ... and our school is a good one ... is to provide a solid basis in medical practice. And that objective is being fulfilled by the present curriculum ... (Teacher 2)

The students suggested that the first teacher quoted above might be correct:

You see, our teachers ... physician teachers, I mean ... do not talk much about these topics on research. I do not know why... other interests maybe ... or lack of time ... Some of them really seem to have an excellent knowledge about medical research, methodology, etc. However, when they have contact with us they only talk about the specific discipline ... diseases, treatments ... do you understand? Of course, we have the discipline of scientific methodology, but ... who remembers that four or five years later? (Student 1)

Well ... you see ... that there is much research that have problems ... some that is not useful ... well ... this is not really a secret. What I mean is that these problems are not really discussed as they should be. There is a kind of ... how should I say ... strange feeling ... that this is not to be discussed openly, do you understand? It is not a rule ... just that strange feeling ... (Student 2)

These answers illustrate the possible existence of 'hidden laws' about the subject of bias in medical research in this specific medical school.

Another important point is that the need for a closer contact with the school members in order to overcome the natural resistance of the participants to commenting on the subject matter of this research became evident. As Student 2 summarised in his interview:

Researcher: ... do you think that your colleagues did not answer the questionnaire for the same reason?
Student 2: It is possible ... I do not know ... I am not sure I can tell you ... some teachers said to us that the results of that kind of research could be harmful to the school ... could be harmful to the research projects, you see ... You know we are in a difficult period ...for many of us what teachers say is law ...You should have stayed more with us ... explained ... it would probably have helped ...

The pilot interviews also showed that it would be difficult to achieve a consensus about the possible educational methods that could be employed to overcome ineffective transmission of knowledge about bias, at least in this particular school. The teachers who were interviewed are highly skilled physicians, and had very strong ideas about the matter, as shown by their answers:

Researcher: I see ... and ... what would be your personal opinion about what should change (*in medical education*)?

Teacher 1: Well ... my opinion is that we should try to adapt progressively to a structure focused on problem-based learning. However, if you ask me if our teachers can assume the task, I will have to tell you: no! In addition, we do not have financial support to do that ... big problem ... Now that you asked, I was thinking that we should change the teachers and not the students...

Conversely, Teacher 2 had a very different opinion about the matter:

Researcher: Of course ... So, you do not think that there are other possible educational measures to minimise the problem of bias in medical research?

Teacher 2: Well ... not in the graduation period ... I really believe that this issue should receive more attention in the postgraduate courses ... In the undergraduate phase, we do not have much time to use for that ... The time we have with the students in a medical school, as you know, is barely sufficient to teach them the basis of medicine ... To try to overemphasise this aspect of research methodology will not improve our students' chances of becoming good physicians. Only a small proportion of them will ever be involved in research ... and even these few only after their post-graduate courses ... so ... it is better for them as a group to receive a solid formation on the practice of medicine.

It is obvious that a small number of questionnaires, and four interviews, do not allow anyone to jump to definitive conclusions. However, I believe that these pilot interviews demonstrated that my research questions were coherent, and that the structure of the interviews of the main data collection could remain the same of the pilot. They also established that the interviews would not only be necessary to answer the second and

third research questions of this study (see Section 3.4), they would also be essential for collecting information about the various possible educational measures required to reduce the occurrence of bias in medical research.

3.6 Medical schools involved in this study

The grant that allowed me to start the doctoral programme at the Institute of Education, University of London, was from the Government of Paraná State (Brazil). One of the requirements to receive such a grant was that the proposed research should focus (and take place) on the educational structure and problems of this State. Therefore, although the organisation and results of the present study are not intended to be restricted to a specific Brazilian State, the main data collection occurred in the medical schools of Paraná.

A second but not less important aspect was related to the time and resource limitations of this specific doctoral programme. It was intended that it should be concluded in three years, and there was no provision of resources to help in carrying out the data collection. This meant that the possible contacts with the participants was forcefully restricted to the minimum necessary due to the time and resource restrictions.

The possible choice of participants in this research was restricted to the eight medical schools that existed in the Paraná State at the time of the initial research proposal. However, the State Government closed one of the medical schools before the main data collection, allegedly due to structural problems of the course and financial constraints, which reduced the possible participants to seven schools.

During the pilot study, it became evident that the opinions of the students of the last year of the medical courses were important for the central objectives of this research to be met. One of the Paraná schools was only recently created and still does not have students on the sixth year of its course, which further limited the number of eligible schools to six.

Finally, one of these six schools did not grant me permission to undertake the research on its premises (see Section 3.7), reducing the final number of schools that participated in this research to five.

Some details of the structure of the schools that participated in the research, and that will be important in the discussion of the outcomes of this study, are presented in the following paragraphs. This information was obtained from the official website (http://www.educacaosuperior.inep.gov.br last accessed on 25/03/2004) of the Brazilian National Institute of Educational Studies and Research (INEP), an official bureau of the Brazilian Ministry of Education.

The school of medicine of the Universidade Federal do Paraná (Federal University of Paraná - UFPR), was the first medical school of Paraná State and started its activities on 09/12/1912. The Brazilian Federal Government funds this university, and its medical course follows a traditional curriculum structure with 7150 hours of contact teaching over 6 years, including an internship of two semesters. It also offers to its students an optional one-semester internship in 24 medical areas in the last year of its programme. It does not have a course of Scientific Methodology during the six years.

Forty-five years later (11/03/1957), the Pontifícia Universidade Católica (Pontifical Catholic University of Paraná - PUCPR), a private university that has educational units in several Brazilian States, initiated a medical course in its branch in Paraná State. Until 1999, its curriculum was also traditional with 6319 hours of contact teaching over 6 years, including an internship of three semesters. There were no optional courses, and the students had a 70 hour module on Experimental Research Methodology in the fifth semester. Although this school has changed its curriculum to a problem-based one in recent years, the students that participated in this study were the products of the traditional structure.

In 15/02/1967, the third medical school in Paraná State, and the first one funded by the Government of the Paraná State, was created: the Faculdade de Medicina do Norte do Paraná. In 1970, this and the other faculties that pre-existed in that area of the State were discontinued, and their structure and teachers integrated within a new university, the Universidade Estadual de Londrina (State University of Londrina -

UEL). This school of medicine maintained a traditional medical curriculum until 1997. In the 1998 it changed its curriculum structure to one based on the problem-based learning (PBL) model with 8252 hours of contact teaching over 6 years, including 2 years of internship. There are no modules that focus specifically on Scientific Methodology.

The Government of the Paraná State also funds the last two medical schools that participated in this study. Both of them were established in previously existent state universities in 1988 (UEM) and 1996 (UNIOESTE), and share the common feature of employing a traditional medical curriculum in their courses, including 2 years of internship. The course of the Universidade Estadual de Maringá (State University of Maringá - UEM) comprises 8657 hours of contact teaching over 6 years and has no formal training in Scientific Methodology. Finally, the medical school of the Universidade Estadual do Oeste do Paraná (State University of the West of Paraná - UNIOESTE) has a programme of 7610 hours of contact teaching over 6 years, which includes a 60 hour module of Scientific Methodology and Research in the first year.

3.7 Obtaining the necessary permissions to do the research

After the conclusion of the pilot study, it became apparent that one of the main obstacles to the success of this study would be obtaining the necessary official permissions to do the research in the six universities.

The central problem was that although medical schools in Brazil are associated with universities, all of them maintain their own bureaucratic apparatus because they retain a significant administrative autonomy. Additionally, the Departments that compose the Brazilian medical schools also have their specific internal rules, which can vary considerably from one school to another.

Consequently, obtaining permission to undertake research within these schools in fact entailed obtaining three different consents: the first from the administration of the universities, the second from the Graduation Council (or Course Collegiate) of

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each of the medical schools, and the final one from each Department involved in the research project. Accomplishing all this is troublesome and time-consuming.

Since I was a member of a doctoral programme that was considered relevant to my university, to the Paraná State government, and to the University of London, the first phase was unproblematic, because my research was already registered in my university.

On 15/01/2003, I received via my supervisors the information that I could start the main data collection. One week later I had my first contact with the Dean of Research of the Universidade Estadual de Ponta Grossa (UEPG). He was aware of the IoE-SETI (Secretaria de Ciência, Tecnologia e Ensino Superior)-Universidade Estadual de Ponta Grossa programme, and agreed to make contact with the Deans of Research of the six universities that I expected would participate in this study. As this first contact would be done by mail, I added to his memorandum a letter explaining the research project and providing additional personal information.

After one month without any response from the Deans of Research I decided to contact them by e-mail, and some of them finally agreed to meet me in order to hear about my research project. This stage of interaction between the Deans of Research and the researcher only occurred due to the personal efforts of the Dean of Research of UEPG, and I was able to contact them personally at their universities at the end of February 2003.

At the beginning of April 2003, I finally received the initial approvals that enabled me to do the contacts directly with the medical schools. These contacts with the medical schools were done face-to-face, as the experience of using e-mails in the previous stage had not proved to be very effective. The contacts occurred directly with the Co-ordinator of the Graduation Council of each school, and the Heads of the Departments to be involved in this research. The result was that five schools gave me the permission to do the research in their premises, without restrictions. By the end of May 2003, I had received almost all of the lists of teachers and students I needed to start the second phase of this study.

To receive the permissions and the lists of teachers and students by the end of the first semester of the year was fundamental to this research, because in Brazil the academic year is divided in two semesters separated by one month of vacations in July. Therefore,

receiving them at the end of the first semester would allow me the five months of the second semester to apply the questionnaires and do the interviews before the end of the academic year. This was important to ensure that I would be able to contact the students for the interviews before they had left the schools after their graduation.

This first phase of the project was quite time and resources consuming because I had to travel to each school twice in three months. Each of these two trips, comprising a visit to each of the five medical schools, took at least 10 days and entailed some 1150 km (700 miles) of travel.

In fact, I believe that there are three aspects that deserve to be stressed for future researchers in this area. Firstly, that research involving several medical schools in Brazil has to take into account a rather long period of time to achieve the necessary permissions. Secondly, that it is important to have an assistant researcher in each school (if possible), as they could deal with the possible problems more rapidly and efficiently than an isolated researcher. Finally, that in the case of research in medical schools in Brazil, personal contact is much more effective than any other method of communication.

3.8 Purposive sampling method: why was it used in this research?

Choosing a sampling method may seem easy at first sight. After all, there are many books that can help a researcher to select one that is appropriate to her/his research objectives. However, a researcher will have to take into account not only the objectives of his/her research.

In a perfect world, issues related to time and resource constraints and access to the participants would not be a problem. Conversely, in real world research, they are fundamental to the definition of the study design, and to the option of the sampling method that will be employed (Robson, 1993).

In the specific case of this study, I had already envisioned the possible problems that could occur in the main data collection as discussed in Sections 3.5 and 3.7. Furthermore, the intention of this research was to serve as an exploratory survey about the problem of

bias in medical research and its relationships with medical education, rather than an explanatory study about this subject.

To do an exploratory study using a purposive sampling method was not a random option of the researcher in this study. In fact, it was the result of the combination of three factors. Firstly, the research would involve only five Brazilian medical schools that were not randomly chosen (see Section 3.6), and there are more than 100 medical schools in Brazil (see Section 2.3). Secondly, the time and resource limitations involved in this study (see Section 3.6) also restricted the number of possible participants. Finally, this field of study is underdeveloped and it seems important to the future of evidence-based medicine and continuing medical education, as was discussed in Chapters 1 and 2.

Consequently, even at the cost of reducing the external validity or generalisability of the outcomes of this research, the most reasonable approach was to employ a purposive sampling or theoretical sampling method (Robson, 1993; Baker, 1999; Silverman, 2000).

As stated by Baker:

> Non-probability sampling also may be used effectively in the studies that seek to explore ideas that are still undeveloped. In such exploratory studies, the object may be to generate theories or hypotheses that might then be studied using a probability sample (Baker, 1999, p.138).

Therefore, a positive aspect of the proposed research method was the opportunity to obtain meaningful data that can underpin future research on the area.

3.9 Tools used in the main data collection

In this section the structures of the questionnaires for the teachers and students, and the structure and objectives of the interviews, which were used in the main data collection of this study, will be appraised. These questionnaires and interviews are the result of the outcomes of the pilot study, which was discussed in Section 3.5. The final questionnaire

in Portuguese, and their translation to English, is available in Appendix 3, whereas a transcribed and translated interview is presented in Appendix 5.

The questionnaires had two different but complementary objectives. The first was to obtain quantitative data that could permit the first research question of this study (see Section 3.4) to be answered. The second was to collect qualitative data that could underpin the framework of the interviews, which were used to help answer the other two research questions.

In Section 3.9.1 each question of the teacher and student questionnaires is scrutinised with respect to their structure and objectives, while Section 3.9.3 discusses the structure and aims of the interviews.

3.9.1 The teacher and student questionnaires

The first four questions of the teacher questionnaire were:

1 **Your present occupation** (Tick more than one if necessary)
    ☐ **Teaching**
    ☐ **Research**
    ☐ **Extension**
    ☐ **Administration**

2 **Have you published papers in the last 5 years?** (Tick more than one if necessary)
    ☐ **Yes, in Brazil**
    ☐ **Yes, in foreign countries (please cite countries)** ....
    ☐ **No, I have not published papers in the last 5 years**

3 **Which was (were) the language(s) of publication?**(Tick more than one if necessary)
    ☐ **Portuguese**
    ☐ **Spanish**
    ☐ **English**
    ☐ **Other** ....

4 Your academic background is:

☐ Specialist

☐ Masters

☐ Doctoral

☐ Post-doctoral studies

These four questions were designed to gather some personal information about the teachers, their present occupation and their academic background. This information could then be compared with that from previous research (see Sections 2.3 and 3.2). In addition, it would enable the determination of the extent to which the sample in the present study was different from a preceding larger study which involved teachers of Brazilian medical schools, the CINAEM project (CINAEM, 1997), discussed in Section 2.3.

Questions 2 and 3 had the same objectives as in the pilot study: to evaluate whether the teachers who responded to the questionnaire were consumers or producers of medical research. This evaluation would not be complete without the information about their academic background, which was the objective of the fourth question.

In the informal contacts that occurred in the pilot study, one of the main complaints of the teachers was that they were overwhelmed by several different responsibilities in medical schools. At the same time, the students in their final year complained that it was difficult to receive some information about bias, due to the reduced contact they had with their teachers (see Section 3.5.4). Question 1 therefore aimed to determine whether the participants in the present study were involved with other activities besides teaching. Additionally, the sixth question (shown immediately below) was intended to determine how often they had discussed the subject of bias with their students in the previous year.

6 How often did you discuss the problem of methodological deviations (bias) with your students in the last year?

☐ Frequently

☐ Rarely

☐ Never

☐ I do not remember

As discussed in Chapter 1, knowledge about bias entail being aware of several factors that affect the methods employed in medical research, and their effects on the results of isolated studies, meta-analyses and systematic reviews.

It was therefore important to establish how the participants were acquiring their knowledge about bias, and how this knowledge influenced their evaluation about the outcomes of medical research. These were the aims of Questions 5 and 7:

5   **Which was the method that helped you to acquire your present knowledge about systematic deviations (bias) in medical research?** (Tick one or more boxes)

☐ **Books about methodology of research**

☐ **Medical congresses or conferences**

☐ **Medical journals. Please cite one** ………………....…………………………..…………..

☐ **Special courses. Please cite one** ………………....……………………………………

☐ **The Internet**

☐ **Other** (please specify)……..………………………………………………………………

7   **How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias? Please explain.**

Question 5 is a multiple-choice question, and its results will be discussed in Chapter 4, while Question 7 is an open question that encompasses a qualitative approach, and its outcomes will be considered in Chapter 5.

In order to evaluate the level of awareness in the teachers who participated in this study about bias in medical research, the results of Questions 8 and 9 were used. Actually, these questions between them combine seven individual questions. They include four assertions that intend to evaluate the personal feelings of the participants about common doubts concerning the problem of bias, with three assertions that are considered essentially true by authors of the literature discussed in Chapter 1.

Questions 8 and 9 were planned as two pooled questions in order to provide solutions to two potential problems. The first intention was to reduce the apparent number of questions on the questionnaire in an attempt to increase the response rate. The second intention was due to the fact that in the pilot study (where they were individual questions) it was found that the respondents had a tendency to follow what they believed was a logical sequence for the responses.

To circumvent this problem and attempt to ensure that respondents read and considered each statement separately, different kinds of assertions were mixed in the two questions. Three assertions (8c, 9b and 9c) are based in the international literature, and are considered true by most authors. They were used to evaluate quantitatively the level of knowledge about bias in medical research (see Section 4.2.2). Conversely, the remaining assertions of questions 8 and 9 focus on areas that are still under discussion. These assertions are intended to collect qualitative information about what the participant believes about the subject.

8 **In relation to the problem of methodological deviations (bias) in medical research you believe that** (Please tick):

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
It is a problem of scientific methodology, with no relation to undergraduate medical courses					
Courses of scientific methodology are responsible for the transmission of knowledge about bias					
Methodological deviations (bias) in medical research are progressively becoming an ethical issue					
Medical journals are responsible for the evaluation of methodological deviations in papers they publish					

9 **In the statements below choose the alternative that is most compatible with your personal opinion** (Please tick):

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
Systematic reviews and meta-analyses are the best ways to acquire valid knowledge in medicine					
Publication bias is a menace to the quality of systematic reviews and meta-analyses					
Systematic deviations (bias) in randomised clinical trials may exaggerate the results of future meta-analyses					

An important feature of this study's methodology was that it included participants from five different medical schools (see Section 3.6). Medical schools do share many common characteristics as they have the collective objective of, in theory, graduating physicians who should be comparable with reference to their medical skills. However, their methods to achieve this aim, and their degree of success in accomplishing this task, may differ in many aspects as discussed in Sections 2.3 and 3.2.

Consequently, the use of a rigid interview schedule could result in inconsistent outcomes. In order to avoid such a problem, questions 10, 11 and 12 were included in the teachers' questionnaire:

10 **In your opinion, how should the knowledge about bias in research be transferred to the students of a medical school?**

11 **Do you believe that changes in the curriculum of medical schools are necessary in order to achieve a better transference of knowledge about bias in medical research?**

☐Yes

☐ No

12 **If your answer to the previous question was Yes, what should be changed?**

These questions therefore had three objectives. Firstly, to probe the participants' opinions about the matter as a single group of medical teachers. Secondly, to try to unveil differences among participants from the individual medical schools. Thirdly, to underpin the necessary differences in the approaches adopted in the interviews undertaken in each individual school.

Finally, the last two questions, 13 and 14, of the teacher questionnaire were of value for my research because written acceptance of an interview would circumvent the need for another sequence of permissions, as described in Section 3.7.

13 Do you agree with a personal interview, if necessary, to enlighten some aspects of the present questionnaire?

☐ Yes
☐ No

14 If you agree, provided that the anonymity of participants at the presentation of the results of this research is assured, would you permit the interview to be recorded for subsequent analysis?

☐ Yes
☐ No

As discussed in Section 3.5.4, the interviews in the pilot study showed some important discrepancies between the opinions of the teachers and students on the matter of the transmission of knowledge about bias in research to students. Additionally, the student interviews also demonstrated that although most of the teachers had declared in their questionnaire that they were transmitting such knowledge to their students, the students' opinion was that they were not receiving it.

Consequently, the first three questions on the student questionnaire, shown below, were intended to determine their personal evaluation of their level of knowledge about bias, how they obtained such information, and if they were aware of their teachers' efforts to transmit to them knowledge about the matter.

1   How would you rate your present knowledge about bias in medical research?

☐ **High**

☐ **Average**

☐ **Low**

☐ **None** (if none, please go to question 3)

2   **Which was the method that helped you to acquire your present knowledge about systematic deviations (bias) in medical research?** (Tick one or more boxes)

☐ **The curricular courses for graduation**

☐ **Books about methodology of research**

☐ **Medical congresses or conferences**

☐ **Medical journals. Please cite one** ……………………………………………..………..…………

☐ **Special courses. Please cite one** …………………………………………....………..……….

☐ **The Internet**

☐ **Other.** (Please specify) ……………………………..…………....………………………………

3   **How often did your teachers discuss the problem of methodological deviations (bias) with you in the last year?**

☐ **Frequently**

☐ **Rarely**

☐ **Never**

☐ **I do not remember**

Question 4 was the same as Question 7 on the teacher questionnaire; however, it had a slightly different objective. While the first three questions were closed questions and might be answered without much reflection, Question 4 was intended to probe how students were using their knowledge about bias in medical research when evaluating scientific papers, which is an important issue in continuing medical education.

4   **How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias? Please explain.**

The next five questions of the students' questionnaire were the same as Questions 8 to 12 of the teacher questionnaire discussed previously. It was anticipated that the students' answers would allow comparisons to be made between their points of view, as recipients of information about bias in medical research, and their teachers' opinions.

Finally, the last two questions on the student questionnaire, which were the same as those on the teacher questionnaire, functioned as a written acceptance for a future interview.

3.9.2 The interviews

After the pilot study (Section 3.5), it became clear that the interviews in the main data collection phase should fulfil three concurrent objectives. The main objective was undoubtedly to answer the second and third research questions of this study (see Section 3.4). However, the pilot study also showed that in order for this to happen, the interviews had to be organised in a way that circumvented two major constraints. The first was the amount of time the participants would allow these interviews to last and the second was the possibly diametrically opposing opinions of the participants about the importance of the matter for medical education.

In relation to the time needed for the interviews, the pilot study demonstrated that as the participants are busy professionals with very tight agendas, the interviews should be structured so as to obtain most of the relevant data related to the second and third research questions in about 30 minutes. This would entail a difficult compromise between asking direct questions whilst trying to avoid slipping into asking leading questions, which could result in interviewees agreeing out of politeness or simply stopping talking. A simple "yes" or "no" as an answer at the beginning of an interview could jeopardise the interview's development in the allowed (restricted) amount of time it would probably have.

To help to overcome these problems, two different strategies were used during the interviews.

The first strategy was to allow a certain flexibility in the order and wording of the questions. However, the basic form of the interviews, as discussed in Section 3.5.3, was retained. To help to achieve this objective, the information obtained in the open questions of the questionnaires was used. This approach helped to avoid starting the interview with questions that could elicit a very strong reaction from the interviewee.

The second strategy was to try to use something that seemed detrimental to the study on first sight: the low response rate of the questionnaires (which will be discussed in Chapter 4). Accordingly, the interviewees were asked an initial question about their opinion concerning the questionnaires' low response rate. This helped create a sort of 'partnership' between the interviewer and interviewee, and allowed the interviewer subsequently to employ direct questions without causing a defensive response from the interviewee.

In fact, with the exception of some minor methodological modifications discussed in the previous few paragraphs, the structure and aims of the interviews were fundamentally the same as the interviews of the pilot study discussed in Sections 3.5.3 and 3.5.4. The result of such modifications can be better seen in the interview sample available in Appendix 5.

Chapter 4

Quantitative aspects of the questionnaires:
answering the first research question

4.1 Introduction

At the end of May 2003, the necessary permissions from the medical schools that were involved in this research (Section 3.7) were received. The schools also provided the lists of teachers from the selected departments and students in the last year of their courses, which allowed the researcher to define the possible participants in the study. These lists showed that 829 members of the five schools (293 students and 536 teachers) fulfilled the criteria to be a participant in the study. These criteria were: for the teachers to be a member of the Internal Medicine, Paediatrics, Gynaecology and Obstetrics or Surgery Departments, and for students to be in the last year of the medical course, as discussed in Section 3.4.

In June 2003, the questionnaires were delivered, in personalised envelopes, to the Co-ordinator of the Graduation Council of each of the schools. Each of the Co-ordinators was responsible for distributing them to the aforementioned Departments, and to the students. This approach for the questionnaire distribution was decided in the meetings that occurred in the schools that participated in this study, which were required to obtain the permissions to do the research (Section 3.7).

The response rate was low in the case of the teachers (99 questionnaires, 18.5%) and very low in the case of the students (21 questionnaires, 7.2%), in spite of two reminders sent by email to the Co-ordinators in August 2003. This low response rate will be more thoroughly discussed in Chapter 5, as it became one of the main issues explored in the face-to-face interviews.

However, a low response rate was already expected due to the previous experience in the pilot study (Section 3.5.2). In addition, a recently published study carried out in one of the

medical schools involved in the present research showed that the initial response rate may be low in Brazil, even when the subject of the research is important to the respondents (Ferreira Filho *et al.*, 2002). In the case of Ferreira Filho *et al.* study, the research topic was the teachers' opinion about the implementation of a new problem-based learning curriculum in the medical course. Although the researchers were members of the same medical school, and stimulated the teachers to collaborate by providing their opinions about the subject, the initial response rate to a mailed questionnaire was 31.7% (85 spontaneous participants from a total of 268 teachers).

There are two final aspects about the questionnaire responses in the present study that must be stressed at this point, which are important for the evaluation of the results. Firstly, I did not have any previous personal contact with the participants before the present study. Secondly, except in the cases when a participant decided to send me his/her name, address, telephone number and/or email address, there was no way of having a subsequent contact with them, since the envelopes for the questionnaire return were identical.

Tables of the coded results of the questionnaires for teachers and students, as well as the coding method in English, are provided in Appendix 4. Although all the data have been transformed to numerical figures, in many cases the numbers assigned in the tables do not represent an evaluation of the results. They are only codes used to facilitate analysis.

Most of the numerical data was analysed using Excel 97 SR-2 (© Microsoft Corporation), enhanced by statistical features provided by the same company. In some cases the software STATS™ (© Decision Analyst Inc.), and STATISTICA (data analysis software system) v.6 (© StatSoft Inc.), were also used.

4.2 Results and discussion of the teacher questionnaire

This section will be divided in two sub-sections due to the objectives of the present research. In Section 4.2.1, the data relating to the constitution of the teachers' sample in this study will be appraised. Section 4.2.2 will contribute to answering the first research question of this study (see Section 3.4).

4.2.1 What was the constitution of the teachers' sample in this study?

According to their answers to the questionnaire, the teachers that participated in the present study had the following academic backgrounds: 13 (13%) possessed a specialist title, 37 (37%) had a Master degree, 42 (42%) a Doctoral degree, and 7 (7%) had completed their post-doctoral studies. Additionally, 81 (82%) of them had had one or more papers published in the last five years.

These data strongly contrast with those obtained by the CINAEM project discussed in Section 2.3, although the CINAEM data about academic background were cumulative. Comparing the percentage of Doctoral degrees (20%), the highest degree considered in the CINAEM project, with the data obtained in the present study (42%), the difference is statistically significant ($z = 5.46$, $p<0.001$). Furthermore, the percentage of teachers who published papers in the last five years in this study (82%) is much higher than is typical, considering the reality of medical research in Brazil as discussed in Section 3.2.

The sampling method used in the present research (see Section 3.8) can be partially responsible for such differences. It could have entailed a kind of selection of the respondents, which had not occurred in the CINAEM project. This selection might have been caused, for instance, by the subject matter of the research (bias in medical research). Also, there is a possibility that only those teachers that are involved in the research process would be interested in such a subject. Both these possibilities were evaluated in the interviews (see Chapter 5).

One of the concerns when structuring the questionnaires (Section 3.5.1) was the possibility of a potential language barrier, as most of the papers about bias in medical research were published in English. However, the high proportion of participants that have published papers in the last five years shows that, at least in this study sample, this would not be a great problem. Furthermore, 42 of them asserted that they had published their studies in English (42% of the total number of participants, and 52% of those teachers that had published papers). Consequently, their answers to the questions that are important for resolving the first research question will probably not be substantially biased by simple misunderstanding of the terminology employed in the questionnaire.

Another important intention of the questionnaire was to determine how these teachers acquired their present knowledge about bias. Nearly half of the participants (56 teachers, 57%) declared that they used more than one method to obtain information about bias in medical research. According to the participants' answers, and considering both multiple and single responses, the cumulative rank of responses was:

- ♦ 56 (57%): books about methodology of research
- ♦ 53 (54%): information received in medical congress and conferences
- ♦ 27 (27%): special courses (85% of these in their Master or Doctoral degrees)
- ♦ 24 (24%): from papers in medical journals
- ♦ 24 (24%): information obtained from the Internet
- ♦ 14 (14%): other sources of information.

The above distribution shows some interesting aspects of the teachers' methods used to acquire knowledge about bias in medical research. It illustrates that a significant proportion of them rely on books, congresses and conferences to attain information about the subject. However, these methods do not seem to be the best way to receive reliable and updated information about the matter, as will be discussed in the next two paragraphs.

As discussed in Chapter 1, although the study of bias in medical research is not recent, it received greater attention only in the last ten years, when the weaknesses of the randomised-controlled trial became evident. Furthermore, as examined in Section 1.4, many important categories of bias that occur in medical research are not directly related to research methodology. Therefore, it is not a surprise to observe that most of the books about medical research methodology of the 1990s, such as Jekel *et al.* (1996), dedicated only a small amount of space to the discussion about bias. Although recent methodology books, such as Hulley *et al.* (2001), show a tendency to enhance the discussion about the matter, it becomes evident examining the bibliography related to Chapters 1 and 2 of the present study that books of research methodology are not the best way to acquire a significant insight into the subject.

The second preferred method (medical congresses and conferences) presents even more negative aspects than obtaining information about bias from research methodology books. As discussed in Section 2.4.2, there is a profound influence of pharmaceutical industries on continuing medical education and in the presentations at medical congresses, transforming these events into a disguised marketing process. Since these industries are considered as one of the most important direct or indirect causes of bias in medical research, it becomes difficult to see how trustworthy knowledge about bias in medical research can be obtained with such a method.

It was unexpected to observe that only 23 participants (23% of the total) said they had received information about bias in medical research in their Masters or Doctoral courses, considering that 86 of them (87% of the total) possess such academic titles. Although it must be recalled that these courses were not explicitly cited in Question 5, it was expected that more participants would recall having contact with such knowledge in their post-graduate courses. This expectation was based on the fact that most of these courses include a research project. As will be discussed in Chapter 5, one of the reasons might be because bias in medical research is not sufficiently emphasised in the postgraduate courses in the medical area.

Finally, the last two important methods of acquiring information about bias in medical research, according to the participants, were from papers published in medical journals and Internet sources. Incidentally, these were the most important sources of the information used to underpin the discussion about bias in Chapters 1 and 2 of the present study.

However, although these methods (medical journals and Internet sources) were present in 24% of the responses to the questionnaire, only 6 (6%) of the teachers declared that they used both methods to acquire knowledge about bias in medical research. This is to some extent remarkable for two reasons. Firstly, because 95% of the participants sent me their e-mail addresses, which indicates that they have Internet access. Secondly, because public university libraries in Brazil suffer from a chronic shortage of printed resources. These two factors in combination, theoretically, should have compelled these teachers to use both medical journals and the Internet to obtain updated information about bias in medical research.

As mentioned in Section 3.9.1, one of the major complaints of the teachers in the pilot study was that they were overwhelmed by several different responsibilities in medical schools. In fact, during informal contacts they asserted that this was the main cause that prevented them from being updated in any educational field besides their own speciality. If one takes into account only the answers to the first question of the teachers that participated in the main data collection of this study, their complaints seem to be quite plausible. Considering four main areas (teaching, research, extension programmes and administration), the participants declared that they were involved in:

♦ 1 (1%) exclusively on administration
♦ 1 (1%) exclusively on extension programmes
♦ 18 (18%) exclusively on teaching
♦ 42 (43%) on teaching plus one other area
♦ 20 (20%) on teaching plus two other areas
♦ 17 (17%) on all the four areas.

As discussed in Section 2.3, being a teacher in a medical school in Brazil is only part of the daily activities for the majority of the teachers. Therefore, the high percentage (79%) of participation in other areas besides teaching seems excessive, and will certainly result in low levels of opportunities for continuing medical education.

The final subject examined in this section of the questionnaire was related to the teachers' personal evaluation about how often they had discussed the problem of bias in medical research with their students in the last year. The data obtained in this question will be compared with the students' similar evaluation in Section 4.3, and are more thoroughly discussed in Chapter 5. According to the teachers that participated in this study, in the previous year:

♦ 28 (28%) of them had discussed the subject frequently with their students
♦ 47 (48%) of them had seldom discussed the subject with their students
♦ 23 (23%) of them had not discussed the subject with their students
♦ 1 (1%) did not remember.

This distribution shows that most of the teachers (71%) that participated in the present study had either seldom or never discussed the problem of bias in medical research with their students in the previous year.

4.2.2 What is the teachers' level of awareness about bias in medical research?

In order to discuss the level of awareness of the teachers about the problem of bias in medical research it will first be necessary to discuss in more depth the reasons for and the structure of the questions that composed this section of the questionnaires. Section 3.9.1 provides an outline of the structure of Questions 8 and 9 of the teacher questionnaire, which are used in this section to appraise their awareness and personal feelings about the subject.

The third assertion of Question 8 (8c) and the second and third assertions of Question 9 (9b and 9c) were employed to evaluate the teachers' level of knowledge about bias in medical research:

- Methodological deviations (bias) in medical research are progressively becoming an ethical issue.
- Publication bias is a menace to the quality of systematic reviews and meta-analyses
- Systematic deviations (bias) in randomised clinical trials may exaggerate the results of future meta-analyses.

These assertions were chosen for three reasons. Firstly, because they are considered as true by the majority of the authors in this field of knowledge, as discussed in Chapters 1 and 2. Secondly, they can also be found easily in the bibliography about the subject of bias published in the last 5 years as they are strongly related to publication bias, which is probably the best studied topic in this field. Finally, because it could be assumed in the present research that any physician that has an adequate level of knowledge about bias in medical research would not have problems agreeing with these assertions, due to the previous two assumptions of this paragraph.

The final allegation of the previous paragraph is extremely important to the analysis of the responses to Questions 8 and 9 of the questionnaire. As discussed in Section 3.4, this study is an exploratory piece of research precisely because there is no previous one that could show the level of awareness about bias among teachers and students in medical schools in Brazil. Consequently, even if it was possible to collect the quantitative data needed to answer the first research question, there would be no means of comparing the results with some prior study. Therefore, the solution was to possess at least a theoretical quantitative expectation of the outcomes, as in the case that the participants were all entirely aware of the problem of bias in medical research.

Employing the assumptions examined in the previous paragraphs, it was presumed that a group of medical teachers conscious of the problem under study and that have a reasonable academic knowledge about bias in medical research would choose the option "strongly agree" as an answer for the three aforementioned assertions. The final numerical result of such choice would be a mean cumulative response score of 4.0 (strongly agree), considering the assertions 8c, 9b and 9c, in view of the coding used in this research (see Appendix 4).

In fact, the teachers' responses to the questionnaire showed the following statistical outline, considering the mean cumulative response score to the assertions 8c, 9b and 9c:

- ♦ Mean.. 2.84
- ♦ Median....................................... 3.00
- ♦ Standard error.............................. 0.06
- ♦ Standard deviation......................... 1.07
- ♦ Sample Variance........................... 1.14
- ♦ Confidence Level (95%).................... 0.12
- ♦ Confidence Intervals of the Mean (95%) 2.72 to 2.96

These results show that the teachers' sample of this study has a statistically significant (and lower) level of knowledge about bias in medical research than what was expected, as elicited by the values of the confidence intervals of the mean. However, one must consider the limitations and assumptions of the methods employed in this study.

Therefore, a sensible approach to such results is that these teachers do have some knowledge about bias, but probably not to the required level for a comprehensive perception about the subject.

The remaining four assertions of Questions 8 (8a, 8b and 8d) and 9 (9a) have a different connotation when compared with the other three discussed in the previous paragraphs. They represent areas of knowledge about bias in medical research and medical education that are still undeveloped, or that are under debate. They have been used to probe how the teachers that participated in this research react and solve problems related to the practical application of their knowledge about bias. Although a numerical coding system has been used (see Appendix 4), these numbers do not represent scores about their knowledge on the matter, just an instrument to make possible an eventual statistical analysis.

The first assertion (8a) is related to the pilot study outcomes. Something that was evident in the pilot study was that some teachers believed that the problem of bias in medical research was strictly a question of violation of scientific methodology. For that reason it was decided to evaluate the opinion of the participants of the main data collection using the assertion: "It is a problem of scientific methodology, with no relation to undergraduate medical courses". Their opinion about the assertion was:

- ♦ 41 (42%) strongly disagreed
- ♦ 34 (34%) disagreed
- ♦ 16 (16%) agreed
- ♦ 4(4%) strongly agreed
- ♦ 4 (4%) did not have an opinion about the matter.

Even without any further statistical analysis, their answer is very clear. The majority (76%) disagrees that the problem of bias in medical research can be dissociated from medical education. This is a very important finding of the present study, and will subsequently be used in our discussion in Section 4.4.

The answers to Assertion 8b ("Courses of scientific methodology are responsible for the transmission of knowledge about bias") showed that:

- 51 (52%) of the teachers agreed with the assertion
- 20 (20%) strongly agreed
- 20 (20%) disagreed
- 4 (4%) strongly disagreed
- 4 (4%) did not have an opinion about the matter

Considering that among the five medical schools involved in this research two did not have a scientific methodology course, and in the remaining three the available time for such a course is about 1% of the total available hours of the medical course (see Section 3.6), these results were noteworthy. In fact, as it was an isolated question about the subject, the registered answers do not allow one to decide if these teachers were not simply manifesting their desire for the existence (or enhancement) of such a scientific methodology course. Consequently, these results were used in the subsequent face-to-face interviews, which will be discussed in Chapter 5.

One important aspect of the problem of bias in medical research is that there is limited data about the opinion of teachers in relation to the real purpose and utility of the published systematic reviews and meta-analyses as a method for continuing medical education (CME). Assertion 9a intended to evaluate their opinion about this doubtful aspect of CME. The statement "Systematic reviews and meta-analyses are the best ways to acquire valid knowledge in medicine" elicited the following answers from the teachers:

- 47 (48%) agreed with the statement
- 17 (17%) strongly agreed
- 27 (27%) disagreed
- 3 (3%) strongly disagreed
- 5 (5%) did not have an opinion about the matter.

The results indicate that, although there is international concern about the efficacy and trustworthiness of the results of systematic reviews and meta-analyses (see Section 1.5), most of these teachers (65%) still believe that they are the best ways to acquire valid knowledge in medicine.

Finally, in order to complete the analysis of the answers to the statements used in Questions 8 and 9, the responses to assertion 8d must be considered. It states that: "Medical journals are responsible for the evaluation of methodological deviations in papers they publish". The answers to this question were:

♦ 45 teachers (46%) agreed that medical journals were responsible

♦ 24 (24%) strongly agreed

♦ 23 (23%) disagreed

♦ 4 (4%) strongly disagreed

♦ 3 (3%) did not have an opinion about the matter.

Once more, there is no need for further statistical analysis, as 70% of the teachers agreed or strongly agreed with the assertion. In fact, this assertion was introduced in the questionnaire in order to try indirectly to determine if the teachers were using their own critical appraisal to evaluate the papers methodologically, or if they were relying on the peer reviewing of each journal. The answer is clear; they are relying on the journals' competence at unveiling possible methodological flaws in the articles accepted for publication.

The final subject of this discussion of the quantitative aspects of the teachers' questionnaire is related to the answers to Question 11. It was intended to determine whether or not the teachers felt a curriculum change was necessary in order to transmit knowledge about bias in medical research to their students in an appropriate manner. Their answers were:

♦ 68 (69%) Yes

♦ 31 (31%) No.

Evidently, the majority of the teachers that participated in this study (69%) believe that curriculum changes are needed to achieve the objective of transmitting appropriate knowledge about bias in medical research to their students.

Attempts were made to undertake more refined statistical analysis of the questionnaire data by comparing sub-samples of the data and by undertaking cross-tabulation. Unfortunately, the relatively small number of participants in some of the sub-samples precluded statistically significant conclusions. However, the combination of such information with the interviews data (see Chapter 5) allowed for deeper qualitative insights and enabled some conclusions to be drawn at a finer level.

4.3 Results and discussion of the student questionnaire

The student questionnaire in this study had some differences in conception and structure when compared to the teacher questionnaire discussed in Section 4.2. The main objective of both questionnaires was to try to unveil the present level of awareness about bias in medical research in five Brazilian medical schools. In addition, they were intended to probe the teachers' and students' opinions about the possible methods that could improve the transference of such knowledge in the medical course. However, while in the case of the teachers it was important to determine several aspects related to their academic life (Section 4.2.1), this seemed not to be important in the case of the students. Therefore, the examination of the students' responses will be accomplished in one single section of this study.

Before starting the analysis of the data of the student questionnaire, it is necessary to comment on one aspect of the students' sample in this study. Either in their answers to the questionnaire, or in the subsequent interviews, 15 (71%) of them reported to have participated in research projects during their courses. This is a very high percentage of participation considering the reality of medical research in Brazil, as discussed in Section 3.2. As it happened in the case of the teachers (Section 4.2.1), the sampling method and the subject matter of the present research may be partially responsible, as those students who were involved in research would be more inclined to answer the questionnaire.

The first question of the student questionnaire intended to appraise their self-evaluation about their present level of knowledge about bias in medical research. Their responses showed that:

- ♦ 11 (53%) believed that they had a low degree of knowledge about bias
- ♦ 8 (38%) thought that they had an average degree
- ♦ 1 (5%) declared to have a high degree
- ♦ 1 (5%) stated that had no knowledge about the matter

It is evident that the majority of the students (19 out of 21 students) that participated in this study believed that they had an average or low comprehension about bias in medical research.

In relation to the approach these students were using to acquire information about the matter, their responses were (using a cumulative methodology, as they could choose more than one answer in this question):

- ♦ 16 (76%) their curricular courses
- ♦ 9 (43%) medical congresses and conferences
- ♦ 5 (24%) books of scientific methodology
- ♦ 5 (24%) the Internet
- ♦ 4 (19%) other sources
- ♦ 2 (10%) special courses
- ♦ 1 (5%) medical journals.

As might be expected, 76% of them relied on the information provided in their curricular courses. As was the case with their teachers (see Section 4.2.1), the students also used medical congresses and books of scientific methodology to acquire knowledge about bias in medical research. It was worthy of note that none of them used the combination of the Internet and medical journals.

The students' answers to Question 3 (see Appendix 4) show that the subject of bias in research was rarely (62%) or never (33%) a matter of discussion among teachers and students in these medical schools. Only one student (5%) reported that such discussions occurred frequently.

The second part of the students' questionnaire, which was intended to establish their level of awareness about bias in medical research, began with Question 5. Questions 5 and 6 of the students' questionnaire were identical to Questions 8 and 9 of the teachers' questionnaire (see Appendix 4). Following the same statistical interpretation used in the teachers' questionnaire (Section 4.2.2), the statistical analysis of the students' cumulative responses to assertions 5c, 6b and 6c was:

- ♦ Mean 2.67
- ♦ Median 3.00
- ♦ Standard error 0.14
- ♦ Standard deviation 1.12
- ♦ Sample Variance 1.26
- ♦ Confidence level (95%) 0.28
- ♦ Confidence Intervals of the Mean (95%) 2.39 to 2.95

As happened in the teachers' questionnaire analysis, the confidence intervals of the mean (CIM) show that these students do have some knowledge about the subject of bias in medical research. However, considering the expected theoretical mean cumulative response score of 4.0 as discussed in Section 4.2.2, this knowledge is not to the required level for a more meaningful perception about the subject.

One interesting aspect of the statistical analysis of the results is that it displays that the CIM of the teachers (2.72 to 2.96) overlaps the CIM of the students (2.39 to 2.95). The calculated 95% Confidence intervals for the difference between the means was −0.125 to 0.462. As these CIMs are related to the same assertions, it is not possible to conclude that there is a reasonable statistical possibility that they belong to different populations. This hypothetical population (which aggregates teachers and students of the five medical schools under study) would possess a common average knowledge about bias, which would have a numerical value of 2.81 (CIM (95%): 2.70 to 2.92), according to the methodology used in this study.

The remaining assertions of Questions 5 and 6 (5a, 5b, 5d and 6a) are also the same that were used in the teachers' questionnaire (8a, 8b, 8d and 9a), as can be seen in Appendix 4. They also share the same theoretical connotation already discussed in Section 4.2.2. Consequently, they will be analysed in the next few paragraphs by comparing the students' results with the opinions of their teachers.

In relation to the assertion that bias in medical research would be a problem of scientific methodology, with no relation to the medical course (5a), the student opinions were:

- ♦ 15 (71%) of them disagreed
- ♦ 4 (19%) strongly disagreed
- ♦ 2 (10%) did not have an opinion about the matter.

On this issue, the students' point of view reinforces the opinion of the teachers.

The same pattern of concordance can be seen in the case of the possible responsibility of courses on scientific methodology to transmit the necessary knowledge about bias (5b), as the distribution of the students' responses was:

- ♦ 15 (72%) of them agreed with the assertion
- ♦ 4 (19%) disagreed
- ♦ 1 (5%) strongly agreed
- ♦ 1 (5%) did not have an opinion about the matter.

In relation to whether medical journals are responsible for the evaluation of the methodological deviations of the papers they publish (5d), the proportions of concordance and discordance were very similar to the teachers' responses. The results were:

- ♦ 10 (47%) agreed with the assertion
- ♦ 4 (19%) strongly agreed
- ♦ 5 (24%) disagreed
- ♦ 2 (10%) did not have an opinion about the matter.

Finally, the last of the assertions of Questions 5 and 6 stated that systematic reviews and meta-analyses are the best way to acquire valid knowledge in medicine (6a). This was the only assertion that revealed a difference between the teachers and students. The students' responses were:

- ♦ 11 (52%) disagreed with the assertion
- ♦ 5 (24%) agreed
- ♦ 3 (14%) strongly agreed
- ♦ 2 (10%) did not have an opinion about the matter.

While 64% of the teachers agreed or strongly agreed with the assertion, only 38% of the students had the same opinion ($z=2.34$, $p=0.03$). It would be difficult to evaluate such a difference between the students' and teachers' opinions using only the questionnaire data. Consequently, the evaluation of the difference will be done in Chapter 5, with the help of the qualitative data obtained in the questionnaire and face-to-face interviews.

The last question on the students' questionnaire that permitted a numerical approach to its analysis was Question 8. Similarly to Question 11 on the teachers' questionnaire, it intended to evaluate the students' opinion about whether it or not a curriculum change was necessary in order to attain an appropriate transmission of knowledge about bias in medical research. Their answers were:

- ♦ 17 (81%) Yes
- ♦ 04 (19%) No.

Once more, the students' responses revealed the same pattern as their teachers' answers previously discussed in Section 4.2.2.

Hence, the analysis of the second part of the students' questionnaire shows that, with only one exception (Assertion 6a), the results reproduced the same pattern of responses of the teachers' questionnaire.

4.4 Conclusions

Although the results of the quantitative aspects of the questionnaires will be analysed further, in conjunction with the qualitative data obtained in this study and considered in Chapters 5 and 8, they are already sufficiently clear to permit two important conclusions of the present research to be outlined.

The first and main conclusion is related to the first research question of this study, as discussed in Section 3.4:

> What is the level of awareness about bias in medical research among teachers of Internal Medicine, Surgery, Gynaecology and Obstetrics, and Paediatrics, and students of the final year of the course of medicine, in five medical schools in the state of Paraná (Brazil)?

The results of the teachers' and students' responses discussed in this chapter allow me to state that, in relation to the participants in this study, the level of awareness of bias can be considered insufficient and fragmentary. This conclusion can be considered as statistically valid only for the participants of the present research. This is due to the sort of sampling method adopted in this research (see Section 3.8) and the low response rate to the questionnaires.

However, one must consider at least two factors that may expand the external validity of the present study. Firstly, the teacher profiles in this study (Section 4.2.1) show that they have a higher academic background than the average Brazilian medical teacher (see Sections 2.3). Secondly, as discussed in Section 4.3, the level of knowledge about bias of teachers and students in this research suggests that they behaved as members of the same statistical population.

Considering the two aforementioned factors, it does not seem preposterous to assume that even an adequate random sample of teachers and students in these medical schools would not show a much better result, in relation to the level of awareness about bias in medical research.

The second important conclusion is related to the genesis of bias in medical research. As discussed in Chapter 1, the most frequently considered hypothesis for the endemic occurrence of bias in medical research is based in the medical research methodology. However, the responses of our participants to Question 9a (teachers) and 6a (students) show that they reject the idea that the present occurrence of bias in medical research is due mainly to research methodological problems.

Finally, the third conclusion is that the teachers and students seldom discuss the matter of bias in medical research, as can be seen by their answers in Sections 4.2.1 and 4.3. Such a lack of discussion is likely to be a constraint to the transmission of knowledge about bias in medical research and its prevention.

One interesting aspect of the quantitative analysis of the questionnaires was the detection of a similar level of knowledge about bias in medical research among teachers and students of the five Brazilian medical schools that participated in this study. In addition, it was not possible to detect a difference in the level of awareness about bias among these five schools, although they employ different curricular structures in their medical courses. Such an outcome may seem peculiar; however, there are at least three concurrent causes that may have contributed to the statistical similarity of the results.

The first factor that probably contributed to the final results was that the average knowledge of the teachers about the subject was lower than should be expected in accordance with the methodology proposed for this study (see Section 4.2.2). According to such a methodology, a group of physicians with a reasonable academic knowledge about bias in medical research should have an average score in the three assertions of 4 (four), with only a very small variation in the confidence intervals of the mean. In such a case, the statistical analysis of the means of teachers and students would certainly show a statistically significant difference between them.

A second concurrent cause for the statistical similarity of the level of knowledge about the subject between teachers and students in the present study was the composition of the student sample. As discussed in Section 4.3, 71% of the students

that participated in this study had also participated in research projects during their courses. Such a percentage is very high for Brazilian standards and this sample composition may well have artificially overestimated the real level of knowledge about bias in medical research among medical students.

Finally, the lack of difference in the level of knowledge about the problem of bias in medical research among the medical schools that participated in this research may be due to the fact that the discussion about such a problem is not present on their curricula. Although they may have different 'intended' curricula, their 'delivered' and 'hidden' curricula (see Chapter 6) may be very similar, at least with regard to the subject of medical research methodology and the critical appraisal of medical research.

Chapter 5

Qualitative outcomes of the questionnaires and interviews: answering the second and third research questions

5.1 Introduction

While the previous chapter of this study focused on the analysis of the quantitative data obtained using the questionnaires, this chapter has a different, although complementary, objective. It aims to answer the remaining two research questions (see Section 3.4) through a qualitative analysis of the data acquired in the open questions of the questionnaires and the subsequent interviews with teachers and students of the five Brazilian medical schools involved in this study. However, before the analysis itself, some aspects of the participants of the second phase of this research, and of the methodology employed in the analysis of the data, need to be presented and discussed.

5.1.1 Constitution of the teachers' sample in the interview phase of this study

The first aspect that deserves to be appraised is the composition of the sample of teachers and students in this section of the study. As discussed in Section 3.9.1, one of the questions on the questionnaires asked the participants whether they would permit a subsequent interview or not. Of the 99 teachers who participated in the first phase, 50 (51%) of them answered "Yes" to this question, while 11 (52%) of the 21 students that returned the questionnaires also agreed to be interviewed in the second phase of this study.

At the beginning of the interview stage of this research, the intention was to interview all the participants that had agreed to be interviewed, irrespective of the specific number of participants in each medical school. This decision was based on the fact that, as discussed in Chapter 4, the participants of this study behaved as members of the same statistical population, at least in respect to the subject matter of this study. Even though they belong to different schools, with different curriculum structures (see Chapter 6), the quantitative

analysis of the questionnaires showed that they had a very similar attitude in relation to the problem of bias in medical research and its relationships with medical education.

The interviews occurred between the first week of September 2003 and the last week of October 2003. As expected (see Section 3.9.2), most of them (95%) took place during the surgery hours of the participants, and had an average duration of 33 minutes. Unfortunately, the initial aspiration to undertake 61 interviews was not totally fulfilled. From the initial 50 possible interviews with the teachers only 38 actually occurred. This reduction was due to three factors:

- Four of the teachers when contacted by telephone declared that had changed their minds and did not want to be interviewed.
- Three of the teachers did not return any of four or more of the researcher's messages asking for a personal contact.
- Five of the teachers were absent from their medical schools during the period of time when the interviews occurred (two were on vacation, and three doing their post-graduation studies in a different medical school)

In contrast, all of the 11 students that agreed in the first phase of this study were actually interviewed.

Consequently, 49 participants (38 teachers and 11 students) were interviewed in the second phase of this study. From these 49 interviews, 44 were tape-recorded for subsequent transcription and five were reconstructed from the researchers' notes within four hours after they occurred because these participants declared that they would not like to have their interviews tape-recorded. After these five were reconstructed, they were compared with the taped interviews and, as this comparison did not show major inconsistencies concerning their final structure and content, their data were used in the subsequent analysis.

In order to evaluate whether or not these participants significantly differed from the original sample of this study, it was necessary to undertake a statistical evaluation of their level of knowledge about bias in medical research. It was performed employing the same

methodology used in Chapter 4 (see Sections 4.2.2 and 4.3), using as data their previous answers to the questionnaires. The result of such evaluation was:

Interviewed teachers

- ♦ Mean 2.84
- ♦ Median 3.00
- ♦ Standard error 0.09
- ♦ Standard deviation 0.97
- ♦ Sample variance 0.95
- ♦ Confidence level (95%) 0.18
- ♦ Confidence intervals of the mean (95%) .... 2.66 to 3.02

Interviewed students

- ♦ Mean 2.84
- ♦ Median 3.00
- ♦ Standard error 0.17
- ♦ Standard deviation 0.97
- ♦ Sample variance 0.95
- ♦ Confidence level (95%) 0.34
- ♦ Confidence intervals of the mean (95%) .... 2.50 to 3.18

Comparing these data with the previous results discussed in Section 4.2.2 it becomes evident that the average knowledge about bias in medical research of the teachers' sample (mean = 2.84) is equal to the average obtained in the analysis of the questionnaires (mean = 2.84). However, both the confidence intervals of the mean (CIM) and the standard error increased due to the reduction of the number of participants (99 to 38). In the case of the students, there was an apparent increase in average knowledge, which was raised from 2.67 to 2.84. However, the calculated 95% confidence intervals for the difference of the means was −0.64 to 0.28, which indicates that such a difference has no statistical significance.

A final aspect of the sample composition of the participants in this phase of this study was their academic background. In relation to this feature, the distribution of the teachers who participated in the second phase of this study was:

- Six (16%) possessed a specialist title
- Nine (24%) possessed a Masters degree
- 19 (50%) possessed a Doctoral degree
- Four (10%) had completed their post-doctoral studies.

Although there was a certain numeric variation with respect to the distribution of academic background discussed in Section 4.2.1, this difference is not statistically significant. In the case of the students, the only evident difference was a rise from 71% (see Section 4.3) to 85% in the proportion of those who had participated in research projects during their medical courses. However, this difference also lacks statistical significance.

Therefore, considering the data discussed in this section, it is possible to state that the participants in the second phase of this study had a similar level of knowledge about bias in medical research and a not dissimilar academic background as the participants in the first phase (see Chapter 4). However, one must be aware that this statement is based on the methodology employed in this study, as discussed in Section 4.2.2.

5.1.2 Theoretical framework of the interviews' qualitative data analysis

According to Ryan and Bernard (2000):

> Coding is the heart and soul of *whole-text analysis*. Coding forces the researcher to make judgements about the meanings of contiguous blocks of text. The fundamental tasks associated with coding are sampling, identifying themes, building codebooks, marking texts, constructing models (relationships among codes), and testing these models against empirical data. (Ryan and Bernard, 2000, p.780)

The question of the sampling method employed in this study was discussed in previous sections (see Sections 3.8 and 5.1.1). Therefore, according to Ryan and Bernard (2000), it remains to be discussed in the present section how themes were identified in this research, and how the codebooks of these themes were constructed. It will also be noticed that the task of constructing relationships among codes will be achieved during the identification of the themes, due to the theoretical framework employed for such identification.

Identifying themes (or 'thematic units' as they were named by Krippendorf (1980)) and constructing codebooks is, as stated by Ryan and Bernard in a recent review about the matter, 'one of the most fundamental tasks in qualitative research' (Ryan and Bernard, 2003, p.85). These authors also assert that:

> Given the variety for methods available for coding texts, the obvious question is, When are the various techniques most appropriate? Clearly, there is no one right way to find themes, but some techniques are more effective under some conditions than others. (Ryan and Bernard, 2003, p.100)

In most qualitative research, themes are induced from the text itself (interviews, documents, etc.). However, although some themes used in the analysis of the interview data of the present study did arise from the text of the interview transcripts, this was not the case for most of them. In fact, the majority of the themes used in the qualitative analysis of this research evolved from the research questions (Section 3.4), the results of the pilot study (Section 3.5), and the quantitative analysis of the questionnaires responses (Chapter 4). Although qualitative researchers do not very commonly acknowledge the development of themes for qualitative analysis using an *a priori* approach, it is considered valid by accredited researchers, as pointed out by Ryan and Bernard:

> Themes come both from the data (an inductive approach) and from the investigator's prior theoretical understanding of the phenomenon under study (an a priori approach). A priori themes come from the characteristics of the phenomenon being studied; from already agreed on professional definitions found in literature reviews; from local, common-sense constructs; and from

researchers' values, theoretical orientations, and personal experiences ... (Ryan and Bernard, 2003, p.88)

In the case of the present research, the codebook for the qualitative analysis of the interviews in this research was based in four major themes:

1. Case data (which comprises the participants and schools' information)
2. Questionnaire response rates
3. Bias in medical research
4. Possible solutions to the problem.

The title of these themes was chosen as a reminder of their initial origin. For instance, the second theme is related to all the data obtained in the participants' answers to the first question of the interviews, which was structured based in the low response rate of the questionnaires of this research. Conversely, the fourth theme is directly related to the third research question of this study (see Section 3.4), and to the participants' answers in the questionnaires. The third theme congregates the participants' viewpoints about the problem of bias in medical research, in particular their opinion about the possible factors that are influencing their existence and prevalence in medical research.

Several sub-themes where created for each of these four major themes. They were created based on the international literature about the subject of bias in medical research, the participants' responses to the previous questionnaires, and the researcher notes done during the transcription of the interviews. The resulting complete codebook is available in Appendix 5, and was the basis for the list of nodes used in NUD*IST 4 (© Qualitative Solutions & Research Pty Ltd), which was the software used for the coding and initial analysis of the qualitative data of this study.

In fact, the definition of the themes as explained in the previous few paragraphs underpinned the choice of the theoretical framework employed in the analysis of the qualitative data in this research, which will be discussed in the next sections of this chapter. It will become evident during such discussion that the use of 'thematic analysis', as described by Aronson (1994) and Boyatzis (1998), was a natural result of the combination of the kind of data obtained and the fundamental purposes of this research.

5.1.3 Notation system utilised in the presentation of the data

In the researcher raw data files, as well as in the NUD*IST® files, the identification of the participants followed the structure presented in the Interviews' Coding available in Appendix 5. However, in order to preserve the anonymity of the participants, the citations of excerpts of their interviews in this chapter will be identified only by the words 'Teacher' or 'Student' followed by a number. This number was randomly assigned to each participant, and has no relation to the order of the interviews or the participants' medical school. The reason for such a convention is that some teachers and students could eventually know the sequence of the interviews in their schools, and that knowledge would jeopardise the anonymity of the participants.

The excerpts of the interviews will be quoted in English. However, the interviews were originally undertaken, transcribed and analysed in Portuguese. Although care was taken in order to ensure that the English translation could transmit the real meaning of the interviewees' opinions, in some cases it was necessary for the researcher to add brief comments to enlighten the translated transcript. These comments will always be in brackets and in italic (*e.g. comments*) in order to allow the reader to recognise promptly that these are researcher comments. Dots without brackets (...) were used to represent small pauses in the interviewees' discourse. In the case that only part of the interviewees' response was quoted, these quotations include dots in square brackets ([...]) where material has been omitted.

5.2 Qualitative analysis of the interviews

The qualitative analysis of the interviews was conducted according to the major themes of the Interviews' Coding available in Appendix 5. However, some preliminary explanations are required to elucidate some aspects of the structure of this section.

This section will be divided in three subsections:

- Questionnaire response rate

- Bias in medical research
- Possible solutions for the problem.

The first subsection (Questionnaire response rate) is based in the interviewees' responses to a very simple question: 'Why, in your opinion, did I have such a low response rate to my questionnaires in the five medical schools?'. Actually, this question was meant to create a kind of partnership between the researcher and the interviewees (see Section 3.9.2). However, the participants' responses were so rich in information that it became essential to answering the remaining two research questions of this study.

The second subsection (Bias in medical research) contains the participants' viewpoints about the causes for the present incidence of bias in medical research. In addition, it includes their opinions about the possible influence of present medical education, the researchers' behaviour, and other external influences (e.g. the pharmaceutical companies) in the high level of methodological deviations that are occurring in medical research.

Finally, the third subsection (Possible solutions for the problem) analyses the participants' suggestions not only for reducing the extent of bias in medical research, but also for increasing the level of awareness of medical students about the problem. This dual objective of this subsection resulted from the participants' opinions in the second subsection, as most of them considered the medical courses (and post-graduation courses) as one of the most important factors for the present situation of medical research.

In fact, as it can be evaluated in Section 5.1.2, these three subsections reproduce the central themes from which the NUD*IST® nodes where created for the analysis of the interviews' transcripts.

5.2.1 Questionnaire response rates

The first question in all the interviews of this study was:

'Something that really surprised me was the low response rate to my questionnaires in all the five medical schools that are involved in this study. In your opinion, what could be the causes for such a low response rate?'.

Interestingly, 78% of the teachers interviewed used the term 'research culture' in the first or second phrase of their answers. In fact, 95% of them used such term in some part of the interview. As Teacher-41 points out:

"Teacher-41: We do not have a research culture in our schools ... I believe it is very difficult to do this kind of research in Brazil ... I had the same problem in my thesis ... I tried to focus my research on a matter that I believed would be important to all the Departments that are related to my medical area of research ... At that time, there were 102 such Departments in all the medical schools in Brazil ... I contacted all of them by telephone and by mail ... and received only 32 answers! And several of them with incomplete data ... I believe that people do not value this kind of research ... it is not part of our culture to participate in such research. [...]"

Differently, the students' answers were focused on three basic themes: lack of knowledge, lack of time, and lack of interest. They were present in combination in 75% of the students' interviews, and if considered as isolated themes they were present in 100% of the students' interviews. Good examples are provided by the opinions of Student-115 and Student-108:

"Student-115: Well ... in the case of the students' response rate I believe it was lack of interest in the matter ... [...] In fact, the last year of our courses is very hard for all of us ... preoccupations with the residency test ... lack of time to do everything ... and other problems ... that might also have contributed to the low response rate. [...] In fact, the subject matter of your research might also not have helped ... Most of my colleagues never had contact with this subject ... They may have felt uncomfortable to answer about something that they do not know ... or know just a little about ... Our course is essentially technical ... medical research is not a preoccupation for many of my colleagues. [...]"

"Student-108: I believe that the students' low response rate was due to the fact that research methodology is not part of the curricular structure of our course ... The teachers seem not to have an interest in this subject ... [...] If the subject of your research was something technical ... practical ... I believe the students' response rate would be greater ...[...]"

The teachers never mentioned the issue of lack of knowledge about bias in medical research that was so pervasive in the students' interviews when answering the first question. However, when their first answer was followed by the probe question: 'Do you believe that the subject matter of my research had some influence in the low number of responses?', 80% of them agreed that a lack of knowledge could have been a factor that influenced the response rate. This was the case, for example, for Teacher-54:

"Teacher-54: Oh yes! Of course this *(the subject matter of the research)* might have influenced the response rate ... of course ... You see ... there is not a course about research methodology in our school ... In fact, as you know, medical knowledge has grown up a lot in recent decades ... it is becoming almost impossible to transmit all that knowledge in the six years we have to do it... Unfortunately, we are forced to leave some aspects of medical knowledge for the residency course ... or post-graduation courses ... So, many of the students that have not answered your questionnaire might still not have had a deep contact with the subject ... and some teachers too ... [...]"

In 35% of the teachers' interviews, the probe question also elicited responses connecting the low level of knowledge of the students to the medical course itself:

"Teacher-40: [...] I believe that the medical courses are responsible for that ... The student is not receiving enough information about research methods ... In fact ... not even enough to understand the methodology and results of a published paper ... It is basically an educational flaw in most medical schools I know ...[...] And I can say more ... most of the teachers also have a very limited knowledge about scientific methodology ... [...]"

Asked about the possibility that this low level of knowledge could be related to the fact that most papers about bias in medical research are been published in English, and by American and UK journals, the participants' opinion was almost unanimous; 90% of the interviewees (teachers and students) declared that such language barrier do not exist. As Teacher-30 pointed out:

"Teacher-30: I do not believe that this problem of language is important ... As you know, most of the best medical books and journals are in English ... Most of the medical teachers and students have an adequate level of technical English ... This is not a problem ... Of course most of us do not speak fluent English, nor would be able to write a paper in English, but they undoubtedly can understand a paper ... Also, I know that you can have access to the most important journals in all the medical schools of Paraná State ... this is also not a problem ... And you have Internet connection in all these schools ... [...]"

The second most common expressions used by the teachers when answering the first question, or the second probe question, was 'lack of motivation' or 'not feeling motivated' (65% of the teachers' interviews). They were used mainly concerning financial or career issues, as in the following excerpt from Teacher-20's responses:

"Teacher-20: Well ... I believe that the main reason (*for the low response rate*) is a general lack of motivation that is presently prevalent in our medical schools ... It is due to low salaries, bad work conditions, etc ... The teachers are reducing the time they dedicate to the schools or even to teaching matters ... Of course, this also reflects on the students' behaviour ... they perceive this lack of motivation in their teachers. We are having difficulties receiving answers from our own teachers and students about important subjects that are affecting our medical school ... It is not a problem that happened only with your questionnaire ... [...]"

Although Teacher-20 and several other teachers were very categorical in linking the possible lack of motivation of the teachers to a similar process occurring among the students, the students' interviews do not confirm such an association. In fact, the students

showed a remarkable motivation, but focused on one only and specific objective: their residency (i.e. specialisation) test. As Student-97 summarised:

> "Student-97: [...] The real problem is that everyone of us (*students in the last year of the course*) is fundamentally focused on our residency test ... Nothing else matters ... Who says this is not true, is lying ... To be sincere, I have only answered your questionnaire because I am interested in medical research ... However, your envelope remained in my desk for almost a month before I opened it ... As there are just a small number of my colleagues that are interested in research, you could not have a great response rate ... [...] Even our teachers tell us every day that the only thing that matters is to be successful in the residency test and get our specialisation certificate ... Otherwise, you will be a nobody in medicine ... I heard that every single day in the past two years ...[...]"

In fact, although not with such richness of details, the issue of the 'residency test' was present in all but one of the students' interviews. It was generally associated with other expressions such as 'lack of time', 'stress', and 'other priorities', and was used especially to explain why their colleagues did not respond the questionnaires. This insistence in explaining their colleagues' actions is understandable if one remembers that the hierarchical system of a medical school is very rigid. The students were possibly just reproducing their behaviour in relation to their teachers, as the researcher was introduced to them as a 'physician' and 'teacher'. However, it became evident during the interviews that the residency test was indeed the centre of the life of the interviewed students.

Finally, when asked if the researcher should use some other method to try to interview some non-respondents, once again the respondents (teachers and students) were unanimous. They believed that if the person did not answer the questionnaire she/he would not accept to be interviewed. The teachers were especially emphatic in their responses. Most of them stated that participation in the present research was discussed in their Departments; therefore, it would be useless to try to convince a teacher that had not send the questionnaire back to the researcher.

Although the attempt was made to evaluate if the kind of answers of the respondents had differences according to the medical schools to which they belonged, or their academic background, these relationships turned out to be statistically non-significant. These evaluations were done separately for teachers and students, as the answers analysed in this subsection already showed important differences of opinion between teachers and students.

5.2.2 Bias in medical research

The structured questions discussed in Sections 3.5.3 and 3.9.2 were used in order to obtain the participants' opinions about the possible causes of the high level of bias in medical papers. However, unlike the initial part of the interview discussed in the previous subsection, the order in which they were asked depended on the development of the interviews. In addition, some small rephrasing of the questions, as well as different probe questions, were used when the researcher felt it was necessary to obtain the maximum possible amount of relevant data in the restricted time allowed for the interviews.

In fact, during the data analysis it was observed that the sequence and structure of the questions, as described in the aforementioned Sections, was kept unchanged in 45% of the interviews. In the remaining 55% there were some changes due to rephrasing and/or individual probe questions. Therefore, in order to keep the reader informed about whether the text quoted came from a direct question or from a rephrased/individual probe question, we will add the term **probe question** in brackets before the quoting when appropriate.

The second part of the interview usually began with a question related to the interviewee's response to the first assertion of Question 8 (teachers' questionnaire) or 5 (students' questionnaire):

In relation to the problem of methodological deviations (bias) in medical research you believe that :

(Please tick)

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
It is a problem of scientific methodology, with no relation to undergraduate medical courses					

This assertion was chosen because the majority of the participants (teachers and students) showed in their responses that they do believe that there is a relationship between the present structure of medical courses, and the problem of bias in medical research. The researcher usually asked the interviewees to explain in more depth their own answer to the assertion.

The answers to this question were much more direct and focused when the interviewee was a teacher than when she/he was a student, as showed in the answers quoted below:

"Teacher-18: Of course they have a strong relationship with the present structure of medical courses! ... Fundamentally, because the discussion about this problem (*bias in medical research*) is not considered as a priority ... priorities are the technical aspects of medicine ... Eventually a physician will have contact with such knowledge in the post-graduation courses ... eventually ...The medical courses are at least partially responsible for what is happening in medical research ... undoubtedly ...[...]"

"Student-100: Well ... I believe people are making mistakes because they do not know the correct way of doing research ... The medical education I have received did not include such kind of information ... The small knowledge I have today was acquired participating in the scientific initiation programme ... but this is not the basic medical education ... I believe ... If I commit mistakes doing research because I was not taught the correct way of doing it then the medical course is also responsible for this, isn't it? [...]"

Although the opinions quoted above are good examples of a reasonably high proportion of the interviewees (60% of the teachers and 55% of the students), they do not truly represent the opinion of all participants. The remaining teachers and students divided themselves between two main clusters of answers: those who focused on what can or should be taught in a medical course, and those who recognised that the problem exists but did not believe it is possible to correct it within the present duration of a medical course. As exemplified by the answers of Teacher-4 and Student-107:

"Teacher-4: Well ... I must say that when I answered that question of your questionnaire I was thinking that in fact the medical course is partially responsible for the problem (*bias in medical research*) ... However, I do not believe it is responsible for providing in depth information about the matter ... Medical courses are technical courses ... the student is here to learn how to be a physician ... It is already almost a miracle we can do that in six years ... The problem is that a person graduates ... puts a 'Dr' in front of their name and thinks he/she is a teacher and a researcher ... So, what must really be stressed during the course ... and it is generally not stressed ... is that they are here to become a physician ... they should be aware that they should not engage in teaching or research without an adequate post-graduation course ... [...]"

"Student-107: Well ... if this problem is happening (*bias in medical research*) the medical education has its share of responsibility ... Some of my colleagues spend some days collecting data in the medical records and believe that they are researchers ... I think this is wrong ... However, I do not see how something could be done with the present structure of the course ... I barely had time to sleep in this last year ... I think that a solution would be to aggregate the two or three years of the residency programme to the six years of the normal course ... this would eliminate the stress of the residency test and give more time for a decent research training programme ... [...]"

These answers show that, according to the participants, there is undoubtedly a relationship between medical education and the incidence of bias in medical research. However, to which level of medical education the rectification of the present situation should be attributed is still a matter of discussion. In addition, the answers illustrate that

the possible solutions to the problem (which will be discussed in the next section) may encompass several different and concurrent educational measures.

The last part of the second phase of the interviews tried to evaluate the participants' opinions about other factors that, in their opinion, are also important to the problem of bias in medical research. It focused particularly on the researchers' behaviour (e.g. misconduct) and external factors (e.g. pharmaceutical companies), and during the data analysis was the part that showed the greatest structural variability.

In some interviews, just the fact of starting to talk about the relationship between medical education and bias in medical research was enough to ensure a spontaneous continuation of the discourse involving researchers' behaviour and external factors. In these cases, the researcher only needed to nod or say some reassuring words (e.g. 'I see...'). Conversely, in other interviews it was necessary to use small probe questions (e.g. 'and the pharmaceutics companies?') or even more direct and complex questions (e.g. 'And do you believe this is happening principally because of a researcher lack of knowledge or is it caused by researchers' misconduct?'). Consequently, the use of the notation (**probe question**) before the identification of the respondent in the next few paragraphs will be very frequent.

The first aspect investigated in the interviews was the participants' opinions about what was the main cause for the present extent of bias in medical research. Would it be more related to the lack of knowledge of the researchers about the correct methodology or to researcher misconduct and external factors (e.g. pharmaceutical companies)?

The reason for address this aspect was that, as it will be discussed in Section 5.3, there is great concern in the international medical research community about the present relationships between the pharmaceutical industry and physicians, researchers, and medical associations. Several papers where published in the last four years in the main American and British medical journals that suggest that these relationships are affecting not only medical research, but also medical education and physician attitudes. However, the present researcher found no similar concern in Brazilian medical journals.

Most of the teachers and students (90%) said that in their opinion was the most important factor for the existence and prevalence of bias in medical research was researchers' lack of knowledge about the correct research methodology. Interestingly, many of them used a Portuguese expression that almost exactly corresponds to 'I would like to believe that...', or other equivalent expressions. This may imply that what he/she was saying was more a hope than a solid opinion. In either the natural flow of their answers or when the researcher followed up with a probe question, all admitted that they knew about cases involving other causes. However, they stressed that they still believed that lack of knowledge was the most important. As stated by Teacher-92:

"Teacher-92: Well ... I cannot talk about all medical research ... I can talk only what I have seen in my daily work ... I believe that the mistakes (*in research*) are occurring by lack of knowledge ... or naivety ... I do not want to believe that they are intentional ... At least from the colleagues I know ... However, there are many ways that bias may occur in medical research if you are not aware of the correct methodology ... And most medical researchers are not (*aware*) ... [....]"

When the researcher persisted, asking if Teacher-92 really believed that research misconduct was not playing an important role in the number of biased papers, her answer was:

"**(probe question)** Teacher-92: Well ... we all know that much medical research is in fact pointless ... they are done just to enhance the researcher *curriculum vitae* ... Of course, these researches have a rather lax way of sampling and presenting the data ... This could be considered scientific misconduct, isn't it? ... However, I do not know if these researchers are aware about the importance of what they are doing ...[...]"

Conversely, Student-113 answer is a good example of the students' responses:

"Student-113: This is a difficult question... I am not sure if I have enough information to answer your questions ... I do not really believe that people would make so many mistakes intentionally ... I might have not received a good

information about research methodology ... however, I had a very good course on Ethics... all of us (*physicians*) have, isn't it? ... To manipulate a piece of research would be a serious ethical deviation, wouldn't it? ... People talk ... just gossip ... that someone has changed the results in order to publish ... but people never prove that ... [...]"

The analysis of the responses showed that there is a possible problem in the way the interviewees (teachers and students) understand the idea of scientific misconduct in medical research. In several cases researchers who have committed errors in their research were, in a certain sense, 'forgiven'. Their conduct was attributed to the fact that they "need" to publish, or that "there is not enough governmental support for medical research", and that "most researchers are not aware of the correct methodology".

In order to evaluate how the participants perceive the problem of the influence of pharmaceutical companies in medical research it was always necessary to use a probe question to elicit a response. The question usually used was: 'And the pharmaceutical companies, do you believe they have some kind of importance in the problem of bias in medical research?'. It was used in the interviews in which the participant said that there are other possible causes for the present situation of medical research besides the lack of knowledge of the researchers, but did not specify what these causes were. This was the case in 43% of the interviews, in which even when the researcher asked about the possibility of scientific misconduct the participant did not really made explicit what these 'other causes' were.

Surprisingly, despite the importance given to the matter in the international journals, only four interviewees (8% of the total) saw the pharmaceutical industry as a possible cause of bias in medical research. Some (17% of the teachers) even believe that they are important partners, as declared Teacher-31:

> "(**probe question**) Teacher-31: [...] I have no problems with the pharmaceutical industry ... Actually, if I did not have the support of the ***(*pharmaceutical company name omitted by researcher*) I would not have been able to do and publish more than 10 papers in the last five years ... I see no problem in this relationship because they never forced me to do anything that I would not like to

do in my research ... And you know how difficult it is to obtain money from the Brazilian government ... [...]"

Actually, most teachers (67%) in these medical schools agreed that besides the lack of knowledge of research methodology and the lack of motivation, already discussed above, there were three other factors that they considered more deleterious to medical research than the influence of pharmaceutical companies. These factors are: lack of resources, lack of time to do a valid research, and the pressure researchers are under in order to finish the research and publish it in the shortest possible period of time. As Teacher-70 put it:

"**(probe question)** Teacher-70: I do not see the relationships with the pharmaceutical industry as a problem ... Real problems are that when you start to do a piece of research, and need 'X' of resources and time to do it correctly, and you receive only half the resources you need ... and begin to suffer all kinds of pressure to finish it quickly ... These are real problems when doing medical research in Brazil ... Our medical schools and research financing organisations think that all research is equal and should be finished in the same period of time ... [...]"

In the case of the students' opinions about what was discussed in the above few paragraphs, it became clear since the beginning of the interview phase of this study that they did not have a personal opinion on the matter. They always declared that they did not have enough knowledge about the subject to discuss it. When stimulated by the researcher, most of them started their discourse with the phrase 'The teachers say that...' and repeated the same opinions as their teachers.

However, there were four important teachers' interviews that showed some aspects about the problem of the relationships between the pharmaceutics industry and medical research. Although they represent less than 10% of the total number of the interviews, they may shed light on some aspects of these relationships. The first one to be quoted was the answer of Teacher-4 when answering the probe question: 'And the pharmaceutical companies, do you believe they have some kind of importance in the problem of bias in medical research?':

"(**probe question**) Teacher-4: Well ... I do not believe that it is a problem in Brazil ... However, I am aware that this is a problem in the developed countries ... I was thinking only about medical research here ... As everybody knows, our medical research is in its early stages ... probably it is not considered as important by pharmaceutical companies ... See ... I am not saying that we are less permissive than the researchers in other countries ... it is just a question of opportunity ... If they begin to spend in medical research here what they spend, for instance, in the USA ... well ... you will see queues of Brazilian researchers asking for money ... Only then, I believe that we will begin to have problems related to these relationships ... [...]"

This seems to be a rather sensible opinion. This teacher expresses the view that Brazilian medical research is not having problems with relationships between pharmaceutical companies and researchers because, in fact, these relationships do not exist in a detectable quantity. However, three teachers in three different schools reported that they had had problems in these contacts in a very similar way. One of them was Teacher-84, who gave a rather long statement about her experience, which is summarised bellow:

"(**probe question**) Teacher-84: [...] After my Masters, I was interested in (*a special disease*) which treatment is (*a specific drug* ... [...] As it always happens here in Brazil, we were not able to receive a grant to do it ... Then we contacted the pharmaceutical company that produced that drug and they were interested ... after all, we had the patients they need to test their drug ... I thought ... [...] When we started the research, the company already had the sampling protocol ready ... We never even had an opportunity to learn how to do it ... [...] The data was collected and sent to the pharmaceutical company statisticians ... and to another company in order to do the adequate writing, so it could be published in a good journal ... they said at the time ... [...] At the end, we just signed a paper agreeing with the results ... and it was published ... Much research, which is done inside the medical schools, is done exactly like that ... [...] Only after my doctoral studies, which were really good, was it that I realised exactly what happened ... but it was to late to fix things up, isn't it? ...[...]"

The data about this subject collected in the present research are not sufficient to permit the researcher to reach any definitive conclusions. However, it shows that the influence of the pharmaceutical industry in medical research done inside the schools that participated in this study might be greater than the participants might be aware (or wanted to speak) of. Actually, as will be discussed in Section 5.3, this kind of concealed influence from these industries in medical research is being reported with an increased frequency in international journals in the last few years.

Finally, as was the case in Section 5.2.1, attempts to evaluate the possibility of connecting a specific group of responses to different schools, or to the participants' academic backgrounds failed to show statistical significance.

5.2.3 Possible solutions for the problem

In this sub-section the participants' proposals meaningful to the possible educational measures that could help to minimise the problem of bias in medical research will be analysed. No effort will be made in this sub-section to make an in depth comparison with the international opinion about the matter, because such a comparison will be a feature of Chapter 7.

In their questionnaires' responses, teachers and students showed an evident preference for a curriculum change in order to transmit appropriate knowledge about bias in medical research (see Sections 4.2.2 and 4.3). This preference was determined by the number of participants that answered 'yes' to a direct question in their questionnaire responses:

> 'Do you believe that changes in the curriculum of medical schools are necessary
> in order to achieve a better transference of knowledge about bias in medical
> research?'.

However, in the interviews' analysis it become clear that such change could mean different educational interventions for the interviewees, depending on three factors:

- The kind of curriculum their schools were using or implementing at the moment of the interviews.

- Whether the interviewees thought a modification should be done in the normal medical course or in the post-graduation courses (residency, Masters, or Doctoral courses).

- The level of knowledge about scientific methodology and the problem of bias in medical research a medical student should have at the end of her/his course according to the participants' opinion

Consequently, those simple 'yes' or 'no' responses in the questionnaires turned out into a much more rich, although intricate, mosaic of responses in the qualitative data analysis of the interviews in the present research.

Although some few percentages of the answers are provided simply to illustrate their absolute frequency, no attempts were made to evaluate them as a statistical representation of the opinions of the teachers and the students who participated in this research.

Two fundamental reasons underpinned the researchers' decision to present the data in this section in such a way. Firstly, because the main objective of this part of the interviews' analysis was to collect and analyse as many proposals of the participants as possible for a future discussion about their potential efficacy and feasibility in Chapter 7. It was not proposed as an evaluation about the 'correct', 'incorrect', 'more desirable', or 'more frequently chosen' method that should be employed. Secondly, in order to reduce the possibility of the occurrence of what Boyatzis (1998) calls "projection", which he considers one of the three major threats to the correct use of thematic analysis. As stated by this author:

> It is simply "reading into" or "attributing to" another person something that is your own characteristic, emotion, value, attitude, or such. With ambiguous qualitative information, there is more opportunity for and invitation to projection from the researcher than in most types of research. (Boyatzis, 1998, p.13)

In most of the interviews it was necessary to use probe questions in order to obtain the data, and the present researcher is a physician who also has his own defined point of view about the subject. Consequently, analysing the data using the relative proportions of the answers could induce the present researcher, even unconsciously, to disregard important information contained in those answers that only a few participants opted for.

At the beginning of the analysis, it was observed that there was an evident division among the teachers that participated in this research. Those teachers that belonged to schools with 'traditional' (i.e. sequential) curricula (3 schools) had a greater tendency to propose a curricular change in the basic medical course as solution to the lack of knowledge of their students about scientific methodology. Conversely, teachers of the schools that either already had adopted the problem based learning (PBL) structure (1 school), or were in the process of adopting it (1 school), where less prone to propose curricular changes in their basic medical course. As may be observed in the answers of Teacher-75 and Teacher-42:

> "Teacher-75: I do believe that a curriculum modification is necessary ... We must introduce our students to the basic concepts of medical research at the beginning of their courses ... and this initial course of scientific methodology should be followed by seminars every year throughout their medical courses. This is the only way to create and maintain a good level of knowledge in the matter ... [...]"

Conversely, teachers of the schools that either already had adopted the problem based learning (PBL) structure (1 school), or were in the process of adopting it (1 school), were less prone to propose curricular changes in their basic medical course. As may be observed in the answer of Teacher-42:

> "Teacher-42: [...] It is not necessary a curriculum change ... It is just a question of introducing the discussion of scientific methodology problems in the modules we already have ... [...]"

However, when asked how the eventual modifications could be implemented, both teachers recognised that existence of difficulties:

"**(probe question)** Teacher-75: Well … I must recognise that it is more easy to speak about than to do such a change (*of curriculum structure*) … It would involve the modification, and even a reduction, of other courses … and this is not very easy to do in a structure like ours … Also, there is a problem of who will be responsible for such a course … We do not have many skilled researchers, and those we have are already committed to several other activities … It will not be easy … […]"

"**(probe question)** Teacher-42: […] The biggest problem I can see at the moment is our lack of skilled teachers to implement such a modification … It will have to be a progressive and relatively long process … […]"

A reasonable proportion (55%) of the students that participated in this study showed a remarkably similar opinion about the subject when compared with their teachers' interviews. In fact, even the proportion of those students that agreed with the opinions quoted in the previous few paragraphs was similar to teachers' proportion (60%). The only difference was that the students usually started their answers with the phrase: "I am not really sure, but…", or some other equivalent phrase.

The remaining 40% of the teachers, and 45% of the students either believed that research methodology should be a subject for study in the post-graduation courses, or understood that there should be a clear distinction between physicians, researchers and medical teachers in order to reduce the problem of bias in medical research. Good examples of both lines of reasoning are the answers of Teacher-4 (who had already expressed a similar opinion when quoted in Section 5.2.2), and Teacher-7:

"**(probe question)** Teacher-4: […] As I told you before I am really convinced that physicians, medical researchers, and medical teachers should be considered distinct professions, even if they share the same undergraduate courses … They should be prepared to undertake their own separated responsibilities …The real problem I can see is a person who tries to do everything at the same time, which is very common nowadays … The solution (*for the problem of bias in medical research*) is very clear to me … it is just a question of defining the boundaries

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that should separate what is to be a physician, a medical researcher, and a medical teacher ... [...]"

"(probe question) Teacher-7: Many of my colleagues may disagree of my opinion ... However, I cannot see any possibility of introducing such course (*about scientific methodology*) in the medical undergraduate courses ... In fact, I really cannot see a motive to do something like that ... Scientific methodology is, and should remain, a part of the post-graduation courses ... If problems are occurring because the post-graduation courses are not providing adequate information, they are the ones that should be changed ... [...]"

Differently from their teachers, the remaining 55% of the students focused their answers in only one solution. All of them believe that there is no possible way of introducing a new course in the present medical course, and that such knowledge should be provided in their residency. As stated by Student-99:

"(probe question) Student-99: Well ... this is a difficult question ... It is possible that our teachers could find a better solution, but, as a student, I do not see how a new course (*of scientific methodology*) could be feasible ... We already have more courses than it is possible for a person to handle ... And who will be responsible for such a course? ... Anyway, I do believe that it will be possible to have something like that in the residency program ... I think that such kind of knowledge could be more profitable in the residency because then we will be focused in preparing ourselves to be an specialist ... Do you agree? ... [...]"

During the analysis of this last part of the interviews, an interesting pattern of responses emerged. It was not caused by a specific probe question of the present researcher or correlated to any specific answer of the interviewees. Usually, it was an additional comment of the interviewee, and occurred in 20% of the teachers' interviews but not in the students' interviews. As in the case of Teacher-31 when talking about the problem of bias in medical research:

"Teacher-31: […] And really … I believe that this problem (*of bias in medical research*) is been overemphasised by the media … I do not believe that there are so many mistakes occurring (*in medical research*) … […]"

Although it occurred in a relatively low proportion (20%), and only in the teachers' interviews, it is an interesting finding. These teachers seem to be politely expressing something that could be translated as: "Look, this is an important problem to you, because it is the base of your research. However, it does not seem such a big problem to us.". Therefore, future researchers in this area should be aware of the fact that such kind of reasoning, in a more subtle way than an overt opposition, may hinder possible solutions to the problem of bias in medical research.

5.3 Conclusions

As stated at the beginning of this chapter, the main aim of the interviews was to help to answer the second and the third research question of this study. The second research question was:

> In the participants' opinion, are the systematic errors that exist in medical research the result of factors related only to the methodology of research, or are they also a manifestation of habits acquired during medical education and postgraduate courses?

According to the discussion of the existent evidence in Chapters 1 and 2 and the data collected in five Brazilian medical schools (Chapters 4 and 5), it is clear that both these two factors are important. Although the methodology currently employed in medical research may be partially responsible, the lack of knowledge among physicians and researchers about the correct methodological approach to medical problems, which seems to have its roots in the undergraduate medical courses, also have its role in the incidence of bias in medical research.

Evidently, such a statement is valid only for the five medical schools that participated in this research. However, as it will be discussed in Chapter 7, according to several

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international publications, such a statement may be considered as valid not only in these particular medical schools of the Paraná State (Brazil), but also in several other countries.

Furthermore, the data obtained in the present research reveals that the answer to the third research question ("What can be changed in medical education in order to reduce systematic errors in research?") can be a very difficult one. As it can be perceived by the answers of teachers and students of the five Brazilian medical schools, such an answer entails a more reflective evaluation of the curriculum structure, teachers' level of training in research methods, and aims of today's medical teachers and students.

As was the case in the analysis of the questionnaires (see Section 4.4), the analysis of the interviews did not show a substantial difference of opinions among teachers of different schools in respect to the problems of the questionnaire response rates (Section 5.2.1) and of bias in medical research (Section 5.2.2). Such similarity of opinions is probably due to the fact that, although they were teachers in different schools with somewhat different curricula, they perceive the subject matter of this research from the same perspective. It is interesting to notice that, as discussed in Chapter 6, a curricular change in a medical school does not necessarily entail the modification of the beliefs of its' teachers in respect to some subjects.

However, there were noticeable differences in the interviews in relation to the teachers' opinions about the possible educational measures that should be adopted to reduce the problem of bias in medical research and the low level of awareness of students and teachers about this problem (Section 5.2.3). There was an evident choice for a curricular change among the teachers that belong to schools that adopt more traditional curricula, while in those schools that have problem-based structured curricula the teachers did not perceive that a curricular change would be necessary.

The difference of points of view of these two groups of teachers is perfectly understandable. A traditional medical curriculum is strongly based in the 'specialisation' process that occurred in medicine since the end of the 19th century. Such a process in fact created a kind of 'compartmentalisation' of medical knowledge that was the basis of the present 'Departments' inside medical schools (see Chapter 6). Teachers that are accustomed to such a subdivision will naturally see a new area of medical knowledge as

detached from their own department or the other existing departments, a situation that requires for its solution the reaction of a new physical and bureaucratic structure (i.e., a new department). Conversely, the teachers of those schools that have adopted a problem-based learning model probably do not see the eventual introduction of some new aspects of medical knowledge in the modules that compose their curricula as a problem.

In fact, such a difference of perspective of medical teachers, which seems dependent on the curricular structure they are habituated, is more than a curious finding of this study. It is an important aspect to be considered by future researchers in the area, especially if their study involves some kind of 'action research' in these medical schools.

The students that participated in the interviews' phase of this study showed a remarkable similarity in their opinions, irrespective of the kind of intended curriculum to which their schools submitted them. Their fundamental expectation is to be successful as practising physicians, and they can only see an opportunity to be successful if they can do well in their attempts to be a specialist in a particular area of medical knowledge. Although there is some evidence that this kind of behaviour may be acquired inside the medical schools (see Section 5.2.2), the data collected in this study cannot dismiss the possibility that these students already had such an opinion at the moment they made their application to a medical course.

Either as a manifestation of pre-existing aspirations or as an acquired trait, these opinions of the students show that it will be important to take into account these aspects of the students' hidden curriculum (see Chapter 6) before any attempt is made to modify the present structure of medical schools curricula. This might be especially true in respect of the introduction of concepts about medical research methodology and critical appraisal of medical research, topics that these students at the moment do not seem to see as fundamentally important to their future professional life.

Chapter 6

Curriculum structure of medical schools: their possible influence on the solution for the problem of bias in medical research

6.1 Introduction

In the discussion of the results of the questionnaires in Chapter 4 it seemed evident that the participants believed that curriculum change was necessary in order to attain an appropriate transmission of knowledge about bias in medical research. However, the analysis of the interviews in Chapter 5 demonstrated that such a change represented different educational actions for the participants. Furthermore, it also showed that even those participants who believed that such a curricular modification should happen at the undergraduate stage of medical education had doubts about its feasibility.

Consequently, in this chapter I will try to answer three fundamental questions that are important to underpin the discussion of the possible solutions for the problem of bias in medical research in Chapter 7:

1. What is the basic structure of the curricula in modern medical schools?
2. Can we alter the quality of teaching in a medical school by changing the curriculum?
3. Why has the present research shown such a degree of resistance to a change, or doubts about its feasibility, among the participants?

As will be seen in the following sections, the answer to these apparently simple questions is not straightforward. However, the discussion of these matters will undoubtedly unveil interesting and important aspects of present medical education in Brazil, and in other countries.

6.2 What is the basic structure of the curricula in modern medical schools?

A simplistic but somewhat inaccurate answer could be: there are those curricula based in the 'traditional' (i.e. sequential) model, and those based in the 'problem-based learning' (PBL) model.

Although undoubtedly the basic structure of medical courses has many features in common all over the world, the above answer leaves aside important differences caused by financial, political and regional factors. In fact, as Wojtczak and Schwarz assert, 'medical schools worldwide need to have a set of global standards and requirements to guide medical education curricula' (Wojtczak and Schwarz, 2000, p.555). However:

> They (*the global standards*) represent only a portion of requirements since the curriculum of each country and medical school has to address its unique health and social needs. (Wojtczak and Schwarz, 2000, p.555)

These 'unique health and social needs' may sometimes transform similar 'written curricula' into a very different 'applied curricula'. As stated by Prideaux (2004):

> In contemporary medical education it is argued that the curriculum should achieve a "symbiosis" with the health services and communities in which the student will serve. The values that underlie the curriculum should enhance health service provision. (Prideaux, 2003, p.268)

Such 'symbiosis' would, in fact, really transform our initial question of this section in a very difficult one, because it would be difficult to centre our answer only in the written proposals of a specific medical school.

Prideaux (2003) considers that there are three levels of a curriculum:

- The planned curriculum
- The delivered curriculum

- The experienced curriculum.

The planned curriculum would be what the designers initially intended. This initial structure would show the influence of how school administrators organise such ideas, and how teachers understand them, and also how they really transfer such ideas to the students (which would be the delivered curriculum). Finally, the experienced curriculum would be what is in fact learned by the students. Actually, there must also to be considered the behaviours, knowledge and performances that the learners suppose to be important, which Snyder (1991) named as 'the hidden curriculum'.

In a medical school these subsequent modifications of the initial idea of a planned curriculum may in fact miss any attempt to define what is the final structure that could be called a modern medical school curriculum. This is specially true when one remembers that medicine is a profession that is based in professional practice, and that this professional practice is strongly related to the delivered, experienced, and 'hidden' curricula. Consequently, the written proposal of a specific medical school may be misleading to the purpose of answering the question that is the basis of this section.

Additionally, as Burton and McDonald (2001) explain, even the way medical educators understand the term 'curriculum' should be investigated:

> Although the concept of 'curriculum' is complex, a common understanding of the term by those involved in medical education is essential, given the current climate of medical curriculum development and reform. It has not previously been established that such a common frame of reference exists. (Burton and McDonald, 2001, p.187)

Covering 85% of the medical educators and 35% of the third-year medical students at the University of Sheffield Medical School (UK), the conclusions of Burton and McDonald (2001) are important for the present discussion. Their intention was to gather information about what the participants understand by 'curriculum', using an email survey as the instrument of their research.

Burton and McDonald (2001) make clear that they consider that there is a great difference between 'curriculum' and 'syllabus', although the latter may indeed be an element of the former. For them, 'syllabus' is simply "a statement or outline of the subjects covered by a course of teaching …" (Burton and McDonald, 2001, p.189). Prideaux (2003) makes the same point.

One of the conclusions of Burton and McDonald was:

> If our results represent the kind of understanding of 'curriculum' amongst medical educators then they raise the question of whether we are reforming curriculum or syllabus. In order to facilitate debate about curriculum reform, we believe that it is necessary to step back from the proposed models of change and establish a common framework of understanding that will allow us to go beyond a superficial tinkering with issues of syllabus. (Burton and McDonald, 2001, p.190)

I believe that their concern is totally justified because it is very difficult to discuss the matter of what a modern medical curriculum is if all we have generally presented by medical schools are their syllabuses. Furthermore, comparing just the 'statement or outline of the subjects covered by a course of teaching' can be misleading to the purpose of the present study.

A possible solution to our problem could be to investigate how governments and professional medical associations envisage a modern medical undergraduate curriculum as revealed in such publications as:

- *Health Professions Education: a Bridge to Quality*, from the Institute of Medicine of the National Academies (USA) (Greiner and Knebel, 2004),
- *Tomorrow's Doctors*, from the General Medical Council (UK) (General Medical Council, 2002),
- *Diretrizes Curriculares Nacionais do Curso de Graduação em Medicina*, from the Conselho Nacional de Educação (Brazilian National Education Council) (Brazil) (Conselho Nacional de Educação, 2001).

Unfortunately, such an investigation does not provide a definitive answer to our question either. These documents from three different countries share a joint problem. All of them offer very sensible suggestions about what should be the expected outcome of a medical course (i.e. the physician), but only offer general guidelines, and leave to each medical school the task of transforming such guidelines into a real curriculum. Interestingly, all three documents show an evident intention of creating stronger relationships between medical schools and the health services of these three countries.

Some authors have a harsher opinion concerning this kind of approach to the subject:

> The GMC's vision, laid out in *Tomorrow's Doctors* ... has both catalysed and legitimised the key (*curricular*) reforms. The core of the revised *Tomorrow's Doctors* is a poorly structured and rather repetitive list of 96 items that are supposed to define a good doctor. This list is dominated by advice on how doctors should interact with their patients and colleagues ... Bizarrely, only six items describe the unique qualities that distinguish a doctor from other healthcare workers. (Williams and Lau, 2004, p.93)

Actually, such a lack of structured information creates great concern among scholars involved with the establishment of standards in medical education. Discussing the standards in medical education in European Union, Leinster (2003) asserts that:

> The standards relating to the content of basic medical education are laid down in Article 23 of the Directive (*) ... At first sight these appear specific but on closer inspection they are so general as to be meaningless as a standard. Without further definition it is impossible to be sure what is meant by 'adequate', 'sufficient' or 'suitable' and the so-called standards are open to varied interpretations by different regulatory authorities and institutions. (Leinster, 2003, p.508) (* *European Council Directive 93/16*)

We can conclude that the task of defining what a curriculum of a modern medical school should be is really a difficult one. Probably because of this, most researchers prefer to

discuss 'models' of curricula rather than the real structure of a modern curriculum for a medical school.

6.2.1 Curriculum models in modern medical schools

According to Prideaux (2003) there are two main groups of models:

- Prescriptive models
- Descriptive models.

Prescriptive models focus essentially in defining the objectives, or purposes, of a curriculum design in order to structure it. As summarised on Tyler's 'objectives model' (1949):

- What educational purposes should the institution seek to attain?
- What educational experiences are likely to attain the purposes?
- How can these educational experiences be organised effectively?
- How can we determine whether these purposes are being attained?

(Tyler, 1949, p.1)

The use of an 'outcomes-based' curriculum is becoming more popular in medical education. This shift was due to some serious criticism about the possibility that the 'objectives model' restricted the curriculum to a narrow range of student skills and knowledge. As stated by Prideaux:

> The use of outcomes is becoming more popular in medical education, and this has the important effect of focusing curriculum designers on what the students do rather on what the staff do. ... (*However,*) An exclusive concern with specific competencies or precisely defined knowledge and skills to be acquired may result in the exclusion of higher order content that is important in preparing medical professionals. (Prideaux, 2003, p.269)

By 'higher order content' is meant the transmission of the capacity of problem solving and the processes that should be employed in order to allow the student to acquire values that are important in medical practice (Prideaux, 2003). In fact, the 'outcomes-based' curriculum is very similar to Tyler's (1949) 'objectives model' curriculum. The fundamental difference is that the former entails that the curriculum should be based on the expected outcomes to be obtained by students, whereas the latter is based on the curriculum designers' belief about the necessary knowledge a physician should obtain in a medical school.

Most of the medical schools worldwide have prescriptive curricula (or syllabuses) that they have been adapting progressively since the first half of the 20th century, according specially to their internal needs and resources. This has created several 'hybrid' local curricula structures that are in fact only variations on the prescriptive curricula theme. However, as will be discussed in Sections 6.2.2 and 6.3, they are under heavy pressure to evolve into a different curriculum structure. This pressure is due to political and social modifications and needs that occurred in the last quarter of the 20th century.

Conversely, descriptive models centre themselves on the importance of situation and context (i.e. situational analysis) of a particular school, country or region. As explained by Prideaux (2003):

> In this model, curriculum designers thoroughly and systematically analyse the situation in which they work for its effect on what they do in the curriculum. The impact of both external and internal factors is assessed and implications for the curriculum are determined ... What is possible in curriculum design depends heavily on the context in which the process takes place. (Prideaux, 2003, pp.269-270)

The main criticism of descriptive models is that they are very time and resource consuming. In addition, there is no definite evidence that they provide a better result than prescriptive models in medical education.

6.2.2 The present situation in Brazil

As explained in Section 2.3, medical education in Brazil has a history of little less than 200 years. At the start of this period Brazilian medical education was heavily influenced by the European model of medicine, as Brazil was a colony of Portugal. However, a radical shift occurred between 1916 and 1925, when the USA government through the Rockefeller Foundation started a long period of educational and political influence on Brazilian education including, of course, medical education (Lima-Gonçalves, 2002).

USA medical education was suffering the impact of the 'Flexner Report' (Flexner, 1910). The 'Flexner Report', a 364-page report written by Abraham Flexner and officially entitled 'Medical Education in the United States and Canada: A Report to the Carnegie Foundation for the Advancement of Teaching' had direct consequences for Brazilian medical education. Its structure was very well summarised by Hiatt and Stockton (2003):

> (*The*) ... tome arose from research conducted by Flexner, who claimed to have visited and objectively evaluated 156 graduate and twelve postgraduate medical schools in the United States and Canada. He sought data on five points for each of the schools: (1) entrance requirements and adherence to them, (2) the size and training of the faculty, (3) the sum and allocation of endowment and fees to support the institution, (4) the adequacy and quality of the laboratories as well as the training and qualifications of the laboratory instructors, and (5) the relationships between the school and its associated hospitals. (Hiatt and Stockton, 2003, p.38)

Although this report has been considered as 'the most influential publication of all' for medical education (Johnson, 1983), it really represents the natural evolution of a process of medical education evolution:

> It should be noted that Flexner's approach was remarkable, but not entirely novel. It was rooted in the British Victorian social reformers' enthusiasm for collection and enumeration and likely influenced by an article based on school inspections performed by the Council on Medical Education of the American Medical Association in 1906. Flexner walked on paths that others had recently pioneered. (Hiatt and Stockton, 2003, p.38)

The combination of the 'Flexner Report', the new 'prescriptive models' discussed in Section 6.2.1 and a strong North American influence in Brazilian medical education underpin the present medical curricula in Brazil.

In fact, this combination had such an intense impact on the Brazilian medical education that in a recent editorial in a Brazilian medical journal, Perez (2004) declares that:

> Flexner's proposal was: "... *the definition of admission standards and the lengthening of medical education to four years; the introduction of laboratory based teaching, the encouragement of full-time teaching; the creation of a basic cycle and the expansion of clinical education, specially in hospitals, the linking of medical schools to universities, the emphasis on biologic research as a way to overcome an empirical approach in medical education, the linking of research to teaching and the control of professional exercise through the introduction of professional regulation."* These guidelines are still the core of medical education and practice but subject to criticism. (Perez, 2004, p.12)

Although there were (and are) several attempts at modifying Brazilian medical education system, we must accept that most of the present curricula (or syllabuses) of medical schools in Brazil are still based in concepts from the first half of the 20th century. This was caused by the simple fact that in 1950, when the whole process of 'adaptation' to the North American 'style' of medical education was completed, there were just 13 medical schools in Brazil (Lima-Gonçalves, 2002), and those which were created after these initial 13 mirrored their educational structure on these schools.

Due to the intense relationship with the medical education system in the USA, including a large number of Brazilian physicians who had undertaken their post-graduate studies in American medical schools, the Brazilian medical schools also started a huge program of 'residency' (i.e. specialisation). According to Lima-Gonçalves (2002), between 1945 and 1948 the Brazilian 'residency' programs were structured in two medical schools in the States of São Paulo and Rio de Janeiro following the basic configuration of similar programs in the USA. The remaining Brazilian medical schools soon adopted these pioneer programs.

This phase of intense 'specialisation' had its effects in the normal programs of undergraduate medical education, as discussed in Chapter 5. Evidently, each school had to adapt its curriculum (and syllabus) according to the new internal balance of forces caused by the subdivision of the main areas of medicine that occurred.

At the end of the 1980s this delicate balance of forces inside Brazilian medical schools was disrupted. In 1988 the Brazilian Constituent Assembly changed the Brazilian Constitution, and, among other changes, created the Sistema Unificado de Saúde (Unified Health System). Such a system required different physicians from those who had been provided by the intense 'specialisation' process inside Brazilian medical schools. Since the Brazilian Government funds the most important medical schools, these schools came under intense pressure to change their educational processes. The CINAEM project discussed in Section 2.3 was a result of such political pressure.

The final result of these internal and external pressures for change in Brazilian medical schools has yet to be seen. At the moment it is not possible to foresee which will be the curriculum of a modern medical school in Brazil. Some of the reasons for such uncertainty will be discussed in Sections 6.3 and 6.4.

6.3 Can we alter the quality of teaching in a medical school by changing the curriculum?

The question that is the title of this section is part of the title of an elegant speech made by Amanda K. Gilbert at 'The Higher Education Research and Development Society of Australasia' (HERA) Conference in July, 2002 (Gilbert, 2002), in which she reasons that:

> University teachers are coming under increasing pressure to alter the curricula they teach. Often the reasons for this are related to the styles of teaching employed by those teachers and their concepts of learning and teaching in general. For teachers this can be puzzling and stressful. After all, many are highly experienced, well respected by their students and colleagues. Academic developers are in a difficult position as they try to encourage teachers to develop

critical rationales and beliefs about learning and teaching, often in the context of political and organisational agenda. (Gilbert, 2002, p.1)

In Brazil, Perez (2004) also shows a similar concern about the real motives that are involved in the present interest in medical curriculum changes:

> In Brazil in the last two decades medical schools have been accused by civil society of not qualifying professionals to meet the needs of population. Therefore, it is necessary to recover, however timidly, historical moments of medical education, to avoid the generalisation implying that changing curricula, reformulating medical courses would be enough to change medical education. (Perez, 2004, p.13)

At this point one may argue that such a discussion about change is only happening due to the fact that medical schools are old educational structures, based on beliefs from the first half of the 20th century, as discussed in Section 6.2.2. However, evidence from Saudi Arabia does not support such a statement. In Saudi Arabia, the first medical school started in 1969, and the most recent one was inaugurated in 1996. Consequently, we have a medical education history in Saudi Arabia of only 35 years. Nevertheless, Alshehri (2001) states that:

> A reassessment of the objectives of the curricula is needed. This should be based on the country's development plans, social trends, and economical factors. Similarly, the contents of the curricula should be reassessed to avoid overcrowding of the clinical and basic courses. Vocational skills and attitude domains need to be included. (Alshehri, 2001, p.320)

One interesting aspect of Alshehri's paper is that it has a strong statement about why such modifications should happen:

> There has to be a reassessment of the objectives of our curricula and what changes are required. We have to respond to the social issues, the country development plans, as well as available resources. It should be realized that unless the educational system responds from within to these issues, it will be

forced to respond by external forces in the course of time. (Alshehri, 2001, p.321)

Habituated to a long period of almost exclusive internal control over their curricula, how are medical schools responding to the referred 'external forces'? If they are changing, how successful are such changes? Which are the possible changes that are really meaningful to medical education outcomes, i.e. the graduated physician?

These are questions that have been the main preoccupation of medical educators and academic developers in the last 30 years. In order to answer them one must keep in mind that:

A curriculum is the result of human agency. It is underpinned by a set of values and beliefs about what students should know and how they come to know it. The curriculum of any institution is often contested and problematic. Some people may support a set of underlying values that are no longer relevant. (Prideaux, 2003, p.268)

As discussed in Section 6.2, most of the medical schools' curricula are a result of a combination of beliefs from the first quarter of the 20th century and the political balance of forces elicited by the progressive 'specialisation' of medicine. Additionally, in many countries the course is divided in two segments.

In most Brazilian medical schools the first three years of the six-year course have a strong focus on the 'basic sciences' (anatomy, physiology, etc...) while 'professional training' of the students occurs in the final three years. Most of the teachers involved in the first three years are not physicians, whilst most of the teachers of the 'professional training' phase are. Such a division creates an extra impediment to curricular changes, because these two groups of teachers have different academic backgrounds, and different points of view about what a medical student should know. As pointed out by Carraccio *et al.* (2002), engaging faculty in a major curricular change in a medical school is one of the most critical aspects in the success of such a change.

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This situation does not seem to be an isolated problem of Brazilian medical schools. As Whitcomb (2000) states, in a report of the Association of American Medical Colleges about ten stories of curriculum change in America:

> Although some schools have been able to introduce a number of structured small-group learning exercises into the final years of the curriculum, many schools, including some that have planned to do so, have not been successful in accomplishing even this relatively modest change. The lack of innovation ... is almost certainly due to the fact that many members of the clinical faculty do not believe that changes are needed. (Whitcomb, 2000, p.5)

Consequently, just the existence of 'external forces' is not sufficient to entail a successful curricular change in medical schools. This 'faculty resistance' to a change may also be a factor that may explain the existence of so many 'hybrid' models in the present medical schools (Jones *et al.*, 2001).

The history of medical curricula changes and implementation in the last 30 years is a history of some few successes (Davis and Harden, 2003), many partial modifications and several unsuccessful attempts (Gilbert, 2002). There seems to be several reasons for these different outcomes (Davis and Harden, 2003). However, Spencer and Jordan (2001) present an interesting point of view about the possible main obstacle to reforms:

> The ills of healthcare education have long been recognised and it may be argued that the slow progress in its reform is due, not only to the lack of institutional recognition of the importance of educational innovation and change, but also to lack of leadership ... With certain notable exceptions, those who rise to positions of authority and influence are appointed because of their expertise and success in scientific achievement rather than pedagogical proficiency and vision. (Spencer and Jordan, 2001 pp.ii38-ii39)

Discussing the 'competency model', proposed by the UK Department of Health, Talbot (2004) evaluated an important aspect about the 'faculty resistance' to a curriculum change. It is the way curriculum designers' beliefs can be very different from the faculty beliefs:

I am not for a moment suggesting that a doctor, at whatever level of training, should not be competent in undertaking assigned tasks, but that these 'monocultural classifications' of competence cause a person to be '… only understood in terms of sameness and conformity' (*) … Further, competence is not the same as understanding. Understanding brings with it a critical edge and, in this era of evidence-based practice, a critical edge is a priceless tool for the professional. (* *Quoting Garrick, 1998)* (Talbot, 2004, p.591)

It is evident that the 'faculty resistance' to changes is not a position due only to a resistance against an external political pressure for a change, but also a genuine concern that such a change may have deleterious effects on medical education. Discussing a successful curriculum change at the University of Dundee (UK) medical school Davis and Harden (2003) report that one of the lessons learned in their successful attempt was that:

There is a need for the commitment of all staff to the curriculum process. Different levels of educational expertise, however, are required. A critical mass of staff need to have an understanding of the underpinning educational principles and concepts and the educational vocabulary to discuss educational developments and to take part in the decision-making processes. Medical staff with educational expertise are needed for educational facilities such as the clinical skill centre. Professionalism in medical education is needed to support the curriculum, the assessment and the staff in their teaching activities. (Davis and Harden, 2003, p.607)

Therefore, one important aspect that is necessary to keep in mind in order to attain a successful and enduring curricular change in a medical school is to overcome 'faculty resistance'. This can only be accomplished by employing a progressive and time-consuming process of 'persuasion and enlightenment' about the whole procedure. However, such a process of 'persuasion and enlightenment' has to be based in the response to a central question: which are the possible changes that are really meaningful to medical education outcomes, i.e. the graduated physician?

The discussion about the 'possible changes' is as difficult as deciding which is the basic structure of the curricula in modern medical schools (see Section 6.2). Actually, what is really happening in medical education is a polarisation between 'flexnerian prescriptive' models and 'problem-based learning' (PBL) models. The discussion about such a polarisation, which has occurred over the last 30 to 40 years (Colliver, 2000), and the final conclusion about which one of them would be more 'meaningful to medical education outcomes', seems far from an end. As Williams and Lau (2004) state:

> Debate has been lively about whether "new" curriculums will actually produce better doctors than the old curriculums. Predictably, traditionalists complain that medical knowledge is being "dumbed down"; equally predictably, reformers claim that liberating students from the drudgery of learning facts will improve their problem solving skills. The jury must remain out until the two have been adequately compared, although the available evidence indicates that factual knowledge is the essential base for developing the problem solving skills of a good clinician. (Williams and Lau, 2004, p.93)

The concern of Williams and Lau is not an isolated manifestation of a specific medical school in UK. Colliver (2000), in a systematic review of PBL effectiveness for knowledge acquisition and clinical performance, concludes that:

> Despite the claims that the PBL process is based on fundamental educational principles and underlying hypothetical mechanisms in a way that should improve learning, this review of the research on the effectiveness of PBL curricula provides no convincing evidence that PBL improves knowledge base and clinical performance, at least not the magnitude that would be expected given the extensive resources required for the operation of a PBL curriculum. (Colliver, 2000, p.266)

According to Leung (2001), some supporters of the PBL curriculum argue that it would be unreasonable to expect that students would do significantly better in a PBL than a traditional curriculum when submitted to a clinical performance test. The cause for such lack of difference would be that medical students are in a certain way 'selected for success in a traditional curriculum' (Leung, 2001, p.306). In fact, according to Lechner

(2001) examination results cannot measure deep learning and life-long learning, which are important aspects in medical education.

However, Leung (2001) concludes that although there are several theories to explain how the PBL process works as an educational instrument there has been little qualitative research about the subject to allow a definitive conclusion about its effectiveness. Furthermore, the 'planned curriculum' of a specific medical school can differ from the 'delivered curriculum' (see Section 6.2), bringing difficulties to the evaluation of which was the cause of the 'successful' or 'unsuccessful' outcomes measured at that particular school. These differences between the planned and delivered curricula can be very subtle or very evident, as exemplified in Jones *et al.*:

> At the University of Washington, for example, "curricular drift" developed 5 years after a major curricular reform, with both basic scientists and clinicians showing regression to the mean in terms of reintroducing teaching topics, and expanding teaching time, partly in response to financial pressures. At the University of Trondheim, Norway, the introduction of a problem-based medical curriculum, implemented in 1993, was also compromised by what is described as a high degree of autonomy of the individual faculty members and resistance to radical change, resulting in a hybrid model of learning methods. (Jones *et al.*, 2001, p.701)

Such a behavior of faculty is not an orchestrated phenomenon. It is caused not only because they have doubts about the effectiveness of changes, but also because these medical educators are foreseeing serious problems to healthcare programs. As William and Lau (2004) assert:

> Some medical schools have now largely abandoned formal teaching of basic medical sciences, leaving students to explore these crucial areas alone or through the poorly suited approach of PBL. No evidence exists that this approach will produce better doctors; indeed, new doctors will now risk not knowing enough to practise effectively and safely. (Williams and Lau, 2004, p.92)

In summary, it seems that 'external forces' by themselves are not sufficient to provoke meaningful changes in the present medical curricula. Also, at the moment, it is very difficult to evaluate how successful are the changes that are occurring, and if they will really mean an advance in medical education.

Consequently, the answer to the question that is the title of the present section of this study (Can we alter the quality of teaching in a medical school by changing the curriculum?) is not a straightforward one. Changes in medical curricula are needed due to the social and political modifications that are occurring all over the world. However, which are the needed changes and how beneficial they will be to medical education is still a matter of discussion.

6.4 Why has the present research shown such a degree of resistance to a change, or doubts about its feasibility, among the participants?

The five medical schools that participated in the present study are from Paraná State (Brazil). One of them has adopted the problem-based learning (PBL) model in the last seven years, while a second one is in a process of adopting a hybrid model using a PBL approach in the 'professional training' period of its course. The remaining three are under heavy governmental and internal pressure for a change due to the CINAEM report (see Section 2.3) and the new Brazilian Unified Health System (see Section 6.2.2).

The teachers in these schools had suffered or are suffering the traumatic process of changing their teaching methods, or have in some cases sincere doubts about the whole process of change. The traumatic process of change was well described by Kamien (2003), when he narrates the experience of the first nine professors of 'community practice' in the Australian medical schools:

> Four of the professors commented on departmental instability due to personalities "adept at the art of white-anting" (i.e., undermining). Also, three hybrid departments had structural difficulties that led to disagreement about aims and resources. One professor described his experience as "cruelly caught

between the sociologists on the left and the GPs on the right". (Kamien, 2003, p.12)

Furthermore, several of the teachers in these five Brazilian schools are now facing the difficult question of which are the possible changes that are really meaningful to medical education (see Section 6.3). For some of them the answer might not be compatible with the present intended or performed changes, leading them to an automatic rejection of any proposed change, as explained by Bowe *et al.*:

> However ... sincere intent to change may be short-lived and followed by a discouraging return to old behaviors. Failure to sustain the initial resolve to change can be misinterpreted as a lack of commitment to one's original goals and eventually lead to greater effort expended in rationalizing the *status quo* rather than changing it. (Bowe *et al.*, 2003, p.715)

Considering what was discussed in this section, the findings reported in Chapter 5 (Section 5.3.3) make sense. Even those teachers that believed that curricular change was needed in order to achieve a better transference of knowledge about bias in medical research have many plausible reasons to have doubts about the feasibility of such a change.

In the case of the students that participated in the present study, the most reasonable cause for their answers about possible curricular changes in their interviews (Section 5.2.3) is an effect of the 'hidden curriculum' (see Section 6.2). At the moment, although their schools are in a process of changing, the students themselves are focused on one specific objective: their specialisation programs. Anything that is not concerned with this specific goal will be considered as less important for many of them. This aspect of the 'hidden curriculum' will probably survive many years after the 'successful' or 'unsuccessful' changes in the 'planned curriculum' of their schools.

The hidden curriculum and the delivered curriculum (Prideaux, 2003) are really important in medical schools, and need to be remembered in any attempt to change a specific school curriculum. As revealed by Delva *et al.* (2000) several forces beyond the instructional methods of a particular medical school influence medical students learning strategies.

According to these authors, the content overload of most medical curricula forces the medical students to find efficient but not necessarily better methods to learn. Delva *et al.* also assert that:

> A second force to be considered is students' perceptions of what is "important". Student perceptions of what has value have greater influence on what they do than does the instructional context ... The assessment system is a strong indicator of what will be valued and thereby has a powerful effect on student learning behavior ... (Delva *et al.*, 2000, p.174)

Consequently, it seems realistic to admit that proposed changes to medical schools curricula may face the overt or veiled opposition of teachers and students. In the case of the teachers because they might not be really convinced that change is necessary, and in the case of the students because of their beliefs about what will be important for their lives as physicians or, more prosaically, what is examined.

As there is an intense exchange of information between teachers and students inside medical schools it is likely that such a combination of interests will be extremely resistant to change. Perhaps, the only effective measure to break down such a 'vicious circle' would be a long and progressive process of persuasion, rather than a governmental or 'top to down' decision about what should be the 'ideal' profile of future physicians.

6.5 Conclusions

The question of what should be the basic structure of the curricula in modern medical schools is still a matter of discussion. Most of the present medical school curricula are adaptations of a basic model developed in the first half of the 20th century. In addition, a great debate is occurring at the moment in relation to the possible changes of such curricula that can be meaningful for the evolution of medical education. Such debate involves political, cultural and internal pressures for a change. The final result (i.e. the 'modern medical curriculum') is yet to be seen.

However, it is clear that any attempt to propose curricular change in order to minimise the lack of knowledge about bias in medical research in medical schools will require a very careful approach. Any proposal will have to take into account the characteristics of each particular medical school. Such characteristics include not only the physical structure and resources of each individual school, but also beliefs and aspirations of faculty and students. Any attempt to implement curricular change without a careful evaluation of the aforementioned individual school characteristics is prone to a less than successful outcome.

Chapter 7

The problem of bias in medical research as a reflection of a 'vicious circle'

7.1 Introduction

The problem of the high incidence of bias in medical research has been considered for a long period of time as a methodological problem, as discussed in Chapter 1. From such a perspective, besides the evident problem to medical research itself caused by the frequency of biased papers, it would also be a potential cause of disruption of modern medical education processes such as evidence-based medicine and evidence-based learning. Such reasoning about the problem entailed the creation of the most important methods of detection and correction of bias, and also provoked the strong reaction of the main medical journals against the existence of these alleged 'methodological deviations' (see Sections 1.4 and 1.5). Unfortunately, intense efforts over the last 25 years to detect and eliminate this problem have been less than successful.

This chapter intends to discuss a different approach to the subject of the present prevalence of bias in medical research. Such an approach is fundamentally based on the possible existence of a 'vicious circle' which would be responsible for the maintenance of high levels of bias despite the present measures adopted for their eradication from medical research. The expression 'vicious circle' will be used in this study to represent, according to the Oxford Dictionary, 'a sequence of reciprocal cause and effect in which two or more elements intensify and aggravate each other, leading inexorably to a worsening of the situation' (Pearsall, 2001).

Sections 7.2, 7.3, 7.4 and 7.5 discuss the main elements of such a 'vicious circle' and their relationships, and Section 7.6 will focus on possible methods to overcome such a situation.

7.2 Main components of the proposed 'vicious circle'

In the first three chapters of the present study several reasons for the existence of bias in medical research were discussed. However, as it is common in the existent bibliography, most of the time they were discussed as isolated motives for the existence and prevalence of bias in medical research. In this section these causes will be examined as elements of the 'vicious circle' proposed in Section 7.1.They will be discussed as three interrelated subsets of causes for the present prevalence of bias in medical research:

1- The present structure of modern medical education
2- The influence of health care related industries in medical education and research
3- The misuse of medical research methodology.

This sequence is based on my own perception about the problem, based on a bibliographic review (Chapters 1, 2 and 3), the results of my research in five Brazilian medical schools (Chapters 4 and 5) and the evaluation of the present curriculum structure of medical schools discussed in Chapter 6. It should not be regarded as an immutable and predetermined sequence, since the relative importance of each element of the 'vicious circle' may differ in different countries and depends on the precise configuration of medical research and the kind of sponsorship. However, as will be discussed in the next three sections, all three aforementioned subsets of causes are jointly connected to the high incidence of bias in medical research, and also to the possible solutions for this problem.

7.3 The present structure of modern medical education

The discussion of the results of the present research in Chapters 4 and 5, and the evaluation of the curriculum structure of modern medical schools in Chapter 6 showed two important aspects of medical education in Brazil and at least some other countries. Firstly, it is centred on 'specialisation', despite government efforts aimed to modify such a focus. Secondly, that such 'specialisation' has not been associated with a better understanding of the issues related to medical research methodological structure and problems.

Recognising the deficiency of knowledge by physicians of research methodological issues, the American Institute of Medicine established in 1991 the Committee on Addressing Career Paths for Clinical Research (Whitcomb and Walter, 2000). This committee was intended to consider ways of enhancing the quality of training of clinical investigators. In its 1994 report (Kelley and Randolph, 1994), the committee recognised that few American specialisation programs adequately prepared physicians to undertake research involving human subjects.

In a subsequent evaluation of the problem, Whitcomb and Walter (2000) suggest that from the 1400 internal medicine specialisation programs in the USA evaluated in the period of 1997-1998 only 170 would be prepared to follow the American Board of Internal Medicine recommendations about research training of specialists. It is the opinion of these authors that training program directors would face formidable challenges to re-structure their programs in order to provide opportunities for students interested in careers as medical researchers.

Although there are no Brazilian data available about the problem discussed in the previous two paragraphs, it seems likely that such lack of training about research is also happening in the Brazilian specialisation programs. As discussed in Section 6.2.2, the educational structure of Brazilian medical schools was adopted as an adaptation of the North American model.

However, it must be remembered that these courses are structured to provide physicians with technical clinical training in a specific medical area, and not to prepare them for medical research. In fact, these programs may indeed improve the formation of technically skilled specialists in several areas of medicine, although they were not designed for the formation of the 'physician-scientist', or even the 'physician-researcher'. This point is well made by Rosenberg (2000):

> Because residency training in internal medicine, either general or subspecialty, is designed to train clinicians, it should come as no surprise that it does just that. In the past, many programs added training in research to the principal experience of preparing expert clinicians, and that, too, was good—as long as the research training was rigorous and extensive enough to prepare internists for lengthy

careers as physician-scientists. As information in the life sciences relevant to health and disease has exploded, however, obtaining the requisite research training within a medical subspecialty or even a department has become increasingly problematic. (Rosenberg, 2000, pp.831-832)

The term 'physician-scientist' that I will use in the present discussion was defined by Zemlo *et al.* (2000) as follows:

… we define physician-scientists as those individuals holding an M.D. or M.D./Ph.D. degree who perform biomedical research of any type as their primary professional activity. We include physician-scientists who are conducting basic research (fundamental investigations that do not focus directly on patients or their diseases), disease-oriented research (investigations that involve the causes and treatments of disease, but do not involve direct contact with patients), or patient-oriented research (clinically oriented studies that involve physical contact with patients). (Zemlo *et al.*, 2000, p.221)

Therefore, a 'physician-scientist', according to Zemlo *et al.* (2000), is a physician whose *primary* professional activity is biomedical research. The term 'physician-researcher' will be used here to represent those physicians for whom research is *part* of their professional activity.

According to the data obtained in five Brazilian schools (Chapters 4 and 5), and the conclusions of the CINAEM report (Section 2.3), it is clear that most of the physicians involved in research in Brazil can be classified as 'physician-researchers' rather than 'physician-scientists'. Most of these Brazilian 'physician-researchers' are probably involved in medical research despite the fact that they did not receive much formal training in medical research methods either in their undergraduate or in their specialisation courses. Indeed, the CINAEM report revealed that most of these teachers did not possess post-graduation titles (see Section 2.3).

One of the factors for this involvement by Brazilian 'physician-researchers' in research projects despite the lack of formal training to perform them might be pressure from their own medical schools. According to the CINAEM report, most Brazilian medical schools

reported that the number of published papers and participation in research projects were taken into account in the teachers' assessment (see Section 2.3).

Such a situation may lead, according to Bangdiwala and Muñoz (2001), to poorly planned, poorly conducted, poorly analysed and poorly presented medical research, which situation would be as unethical as recommending an inadequate medication for a patient, and does not seem to be an isolated Brazilian problem.

Discussing the problem of training clinical researchers in biostatistics worldwide in order to collaborate as co-investigators in epidemiological studies, Bangdiwala and Muñoz (2001) offer an interesting overview of the problem. According to these authors, several problems happen in these collaborations due to the lack of knowledge about statistical methods among physicians and other health professionals:

> Physicians and other health professionals are increasingly aware of their need for biostatistical knowledge, not only if directly involved in research activities, but also if, as a clinical practitioner, one wishes to keep abreast of advances in the field. One alternative for the clinical researcher is to completely rely on a trained biostatistician and to blindly accept the answers obtained from such collaboration. For the clinicians reading the latest scientific journals in their field, this is equivalent to ignoring the methods section of the research articles. This is evidently not a healthy approach, for the obvious reason that an uneducated researcher is not in a position to critically appraise the literature or to effectively collaborate in a research team. (Bangdiwala and Munõz, (2001, p.265)

At the same time that changes in medical education in Brazil and some other countries in recent decades seem to be reducing the capacity of 'physician-researchers' to perform valid clinical research, or even critically to appraise the medical literature, there is evidence of a decline in the number of 'physician-scientists'. In fact, studies about this subject in the USA (Rosenberg, 1999; Zemlo *et al*., 2000) and Canada (Honer and Linseman, 2004) show a remarkably similar pattern of reduction, indicating that fewer young MDs are interested in a career as 'physician-scientist'.

Although these authors focus on the financial disincentives of a career as 'physician-scientist', at least Rosenberg (1999, 2000) admits that one of the factors for such a decline may be that fewer MDs are being prepared by their training to be capable of becoming 'physician-scientists'. As Wilkinson and Oddone (2002) state:

> The absence of adequate funding has almost certainly been a major factor, but so, too has the virtual absence of programs designed to prepare clinicians for clinical research careers. As clinical research has become more complex and specialized, formal training is now almost a necessity for those wishing to acquire the quantitative and methodological skills necessary to pursue a career in clinical research. (Wilkinson and Oddone, 2002, p.99)

It is interesting to remember at this point one of the conclusions of the qualitative analysis of the data of the present study (Section 5.3). It was concluded that the lack of knowledge among Brazilian physicians and researchers about the correct methodological approach to medical problems apparently had its roots in undergraduate medical courses. The discussion in this section of the international situation concerning the issue seems to validate that conclusion.

In summary, the modifications of medical education in recent decades in a number of countries have triggered a 'drift' towards a more 'technically-based' professional structure for the production of clinicians, which is transforming the graduate physician into a somewhat uncritical consumer of medical research. Further, such modifications have entailed a progressive reduction in the number and influence of the 'physician-scientists' and their replacement by the 'physician-researchers', a less than ideal substitution at a time of progressive sophistication of medical research methodology.

Such modifications, although possibly enhancing the technical skills of physicians, also reduced their capacity for clinical judgement and decision-making (Coulehan and Williams, 2003). According to Coulehan and Williams:

> … many physicians are neither aware of the "best evidence", nor how to access it, nor how to use it; nor do they utilize basic concepts of probability, utility, risk, and benefit in everyday practice. In other words, the popular assumption

that modern medical practice must be scientific is questionable, because "scientific" implies the use of high-quality data and a logical decision process that are often absent. (Coulehan and Williams, 2003, p.8)

As will be discussed in the next section, such characteristics of today's physicians and 'physician-researchers' facilitated the present influence of the pharmaceutical industry on medical education and research.

7.4 The influence of the pharmaceutical industry on medical education and research

In Section 2.4 the problem of the relationships of the pharmaceutical industry with medical research and continuing medical education was discussed as one of the factors that influence the existence of bias in medical research. Although pharmaceutical companies are participants in a global set of health care related industries they are undoubtedly a most important influence on medical education and research. It will be shown in this section how the influence of such industries contributes to the proposed 'vicious circle' responsible for the unacceptable incidence of bias in medical research.

It must be stressed that I fully recognise, as most physicians do, the importance of pharmaceutical industries in the development of many life-saving and life-enhancing therapies, especially in the second half of the 20th century. However, as usually happens with the powerful medications these industries produce, such a success was accompanied by many deleterious 'side-effects', especially upon medical education and medical research. As stated by Antonuccio *et al.* (2003):

> The pharmaceutical industry has contributed to many life-saving innovations in medicine and has become one of the most successful industries in the world. As a result, pharmaceutical industry financial and marketing influences extend to federal regulatory agencies, professional organizations, medical journals, continuing medical education, scientific researchers, media experts, and consumer advocacy organizations. These extensive influences have created

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conflicts of interest that have undermined the credibility of medical research and education. (Antonuccio *et al.*, 2003, p.1028)

The financial and political power of the pharmaceutical industry is undeniable. According to Abraham (2002) their sales are estimated in US$130 billion in the USA and UK£7 billion in the UK. Worldwide, these industries generate an annual revenue of more than US$400 billion and spent, just in the USA, more than US$19 billion in advertising in 2001 and US$200 million in lobbying and political campaign contributions over the two years 1999 and 2000 (Antonuccio *et al.*, 2003). The effect of such a financial and political power upon medical research have been so intense that DeAngelis *et al.* (2001) estimate that 70% of all clinical drug trials in the USA are directly or indirectly financed by pharmaceutical industries.

Pharmaceutical companies are commercial corporations that depend on their revenues and profits to survive and grow. It should not be a surprise that they are using their profits to do exactly that. In a perfect world their interests would converge with medical education and medical research to meet the needs of public health. Unfortunately, as will be discussed further below, the interests of pharmaceutical companies, medical education and medical research seem to be progressively diverging from the this ideal objective.

To explain such a divergence, the influence of the pharmaceutical industry upon the individual physician and the present structure of medical education and research must be evaluated.

7.4.1 Physician-industry relations

The relationships between pharmaceutical companies and practising physicians are notorious even for those who are not directly involved in medical practice. As discussed in Section 2.4.2, doctors and the pharmaceutical industry are entangled in a ubiquitous and controversial web of interactions (Moynihan, 2003).

As could be expected, this kind of 'partnership' seems to be heavily in favour of the stronger 'partner':

The medical profession has largely abdicated its responsibility to educate medical students and doctors in the use of prescription drugs. Drug companies now support most continuing medical education, medical conferences and meetings of professional associations. (Angell, 2004, p.1452)

Angell (2004) also asserts that physicians pretend to believe that drug companies can provide objective information about their own products. She believes that it would be a self-evident absurdity to consider that medical professionals perceive investor-owned companies as producers of impartial and critical evaluations about their products. In fact, she states that the answer is that these companies are 'paying' these physicians with continuing medical education credits, perks and free lunches.

However, is such a judgement consistent with the evidence discussed in the present study? Would it be really 'a self-evident absurdity' that these physicians are behaving like that? My answer to both questions is 'no'. The fundamental reason might be that many of these physicians have been transformed into uncritical consumers of the results of medical research by the present structure of medical education, as discussed in Section 7.3.

Although physicians themselves believe that marketing strategies of the pharmaceutical industry do not affect them, there is evidence that such strategies do have an influence on physician objectivity and behaviour (Coyle, 2002; Breen, 2004). The importance of the combination of such a lack of awareness of physicians about the problem and the present influence of the pharmaceutical companies is well summarised by Breen (2004):

It is a significant ethical failing to aspire to such independence (*professional independence*) and to the respect and trust that underpin an effective doctor-patient relationship while wilfully or ignorantly denying the evidence that the pharmaceutical industry does affect our prescribing behaviour ... Most doctors seem to genuinely perceive they are immune to such influences, seeing themselves as acting only on the best available evidence in the interests of their patients ... These issues are not new, but their significance has increased in parallel with the growth of the size, power and influence of the pharmaceutical industry. (Breen, 2004, p.410)

Obviously, this situation becomes even worse when it involves marketing production presented as 'scientific evidence', which these physicians are not equipped to correctly appraise (Wazana, 2000) (See also Sections 4.4 and 5.3).

The issue of the structure of present continuing medical education (CME) seems to be even more relevant for our discussion. As discussed in Section 2.4.2 the influence of pharmaceutical companies upon CME is evident. Whether such an influence is a positive or negative one to practising physicians is still a matter of discussion, although much of the evidence supports the idea of a negative influence. An example of such debate can be better visualised by the opposing opinions published in an important medical journal (the *Journal of the American Medical Association*):

> The pharmaceutical industry has gone too far. It is assuming a role in continuing medical education (CME) that is inappropriate for an industry with a vested interest in selling prescription drugs ... As a result, CME is now so closely linked with the marketing of pharmaceuticals that its integrity and credibility are being questioned. The problem is not new, but it has recently grown to alarming proportions. (Relman, 2001, p.2009)

> Industry-supported conferences, seminars, and symposia are helping physicians to provide the best, most appropriate, and most up-to-date health care of their patients ... Patients are the ultimate beneficiaries of industry-supported CME, and patients ultimately experience the consequences if physicians are not fully informed about the latest medical advances. (Holmer, 2001, p.2012)

The quoted opinion of Holmer (2001) seems at first sight really sensible. Considering that pharmaceutical companies are directly or indirectly involved in most present medical research (as will be discussed in Section 7.4.2), these industries seem to be 'the best, most appropriate, and must up-to date' source of reliable medical information. However, evidence shows that this might not be exactly true.

In the last two decades pharmaceutical companies have been focusing on the development of the so called 'me-too' drugs. 'Me-too' drugs are minor variations of the existing drugs

that are highly profitable to pharmaceutical companies (Angel, 2004). These profits are due to the fact that small variations in the structure of an existing drug allow these companies to continue to have exclusive rights over these medications after their rights on the older drug have expired. In order to make profits on such drugs it is required that physicians prescribe them.

The most important problem with the aforementioned drugs is that:

> There is generally no good reason to believe that one me-too drug is better than another, since they are seldom compared head-to-head at equivalent doses in clinical trials. Instead, they are tested against placebo, and so all we know is that they are better than nothing. In fact, it's conceivable that, within me-too families, each successive drug is actually *worse* than the one before. Without suitable comparative testing, we'll never know. (Angell, 2004, p.1451)

According to the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (2004), from 1998 through 2003, 487 drugs were approved by the FDA. Of these 487 drugs, only 67 (14%) were considered as being new or improved compounds. The remaining 420 (86%) were classified as having therapeutic qualities similar to currently marketed drugs, or were new formulations (or combinations) of old ones.

Consequently, it seems feasible to conclude that the 'latest medical advances' cited by Holmer (2001) are not so outstanding. In fact, the pharmaceutical industry is apparently using its financial power to dominate CME in order to do a disguised marketing of their 'me-too' drugs (Angell, 2004). This kind of approach would be extremely profitable to pharmaceutical companies, as the cost of the development of a 'me-too' drug is considerably less than the development of a really new product.

Actually, it seems that the described interdependence between physicians and the pharmaceutical industry constitutes the first 'loop' of the proposed 'vicious circle' (Section 7.1). Physicians believe that they are receiving the 'best evidence' and the pharmaceutical industry is providing such 'best evidence' which physicians are not able to appraise critically. As these companies are 'rewarded' with greater profits they enhance their influence.

A sensible question at this point would be: 'Physicians are intelligent professionals, is it possible that they are not aware of such a situation?'. Shaughnessy and Slawson (1999) have an interesting opinion about this issue:

> Educators faced with adult learners who are overwhelmed with information yet underskilled in learning are caught in a paradox. On the one hand, adults are self directed and make their own decisions, from what to eat to what to learn. This is the psychological characteristic that differentiates them from children. Yet when these adults are placed in a learning environment, they immediately revert back to the role into which they were conditioned by the pedagogical model – that of passive dependency of the teacher. (Shaughnessy and Slawson, 1999, p.1280)

It seems that the pharmaceutical companies are not only aware of such characteristics but are efficiently using them for their benefit.

Of course, the proposed 'loop' would eventually vanish if pharmaceutical companies could not control the 'evidence' they use in their contacts with physicians and in their CME programs. This will be the subject matter of Section 7.4.2.

7.4.2 Physician-industry relations associated with the 'physician-researcher'

In Section 2.4.1 the influence of pharmaceutical industry on the production and dissemination of medical research outcomes was briefly discussed. Such a discussion focused mainly on one specific problem: the possible influence of the pharmaceutical industry in the present incidence of publication bias in medical research. It was also suggested in Section 2.4.1 that such a problem might be caused by the direct influence of the pharmaceutical industry upon medical researchers, as was illustrated by the quotation of Garland (2004) about her problems with a particular pharmaceutical industry sponsorship.

The aim of this section is to deepen such a discussion. It will focus on how (and how much) these relationships between the pharmaceutical industry and the 'physician-researchers' might be related to the growing number of cases of overt and veiled scientific

misconduct in medical research. Furthermore, this discussion intends to show the importance of the pharmaceutical companies interference on present medical research, aimed at the production of 'evidence' used for the marketing processes of their products.

When discussing medical research problems people usually remember cases of outright fraud. However, although such cases are important, and have more impact on the media, they are probably nearly always, particularly if they pertain to important matters, sooner or later unveiled in a 'healthy' and 'peer-reviewed' research structure, not only in medicine but also in other fields of knowledge. In fact, in the long run the most important and damaging aspects of scientific misconduct are generally those which do not configure an overt fraud, but remain unveiled causing long-lasting effects upon scientific knowledge, undermining the reliability and credibility of science in a specific area.

Unfortunately, as will be discussed in this section, medical research seems to have been plagued by both overt fraud and such broader instance of scientific misconduct in recent decades, probably to an extend never before seen. This situation can be fatal to an area of science that is based essentially on trust. Trust is the basis of the physician/patient relationship and also of the physician/medical research relationship.

Horton (2001), in discussing a 1998 international medical statisticians' survey, presents an appalling glimpse of such a situation:

> A survey of 442 medical statisticians, completed in 1998, obtained a 37% response rate. Despite this poor return, half of all respondents knew of at least one fraudulent project done in the previous 10 years. Forty-three (26%) statisticians reported fabrication and falsification; 32 (20%) described deceptive reporting of data; 31 (19%) knew of data suppression; and 16 (10%) were aware of instances of deceptive design and analysis. Worse still, 30% of this sample had engaged in a fraudulent project. (Horton, 2001, p.594)

Most medical statisticians are not physicians. They have become indispensable in many projects within the present medical research structure essentially due to the progressive sophistication of research methods and the (already discussed) lack of knowledge about research methodology of the 'physician-researcher' (Section 7.3).

One could argue that 'physician-researchers' involved in the aforementioned disturbing proportion of scientific misconduct may have been driven to produce such studies in order to obtain academic or professional prestige. However, this is not the case for the statisticians who are often not mentioned as authors in medical studies. What could be the forces that are impelling these professionals to collaborate in such projects?

The answer to such a question may not be as straightforward as most people might believe. Such behaviour of medical statisticians and 'physician-researchers' seems to be connected with a less discussed aspect of present medical research that Rettig (2000) called 'the industrialisation of medical research'. Rettig (2000) used this expression to describe the effect in the last 25 years on medical research of companies specialising in the design of medical trials, recruitment of physicians and patients, analysis of data and reporting of results that are connected to the pharmaceutical industry. In this discussion I will show that such 'industrialisation' is becoming more pervasive, and that the boundaries between these companies and academic research seems presently rather blurred.

These 'contract research organisations' (CROs) (Rettig, 2000, p.134) were initially important to pharmaceutical companies in the USA essentially to provide the pharmaceutical industry with the 'evidence' needed for the U.S. Food and Drug Administration approval of their drugs. However, they became increasingly more influential and internationalised. In 1999 there were at least 550 American and foreign-based CROs according to Rettig (2000). As stated by Rettig they are now involved in:

> Clinical trial management services for all phases (*which*) include project management, study and protocol design, case report form development, clinical database design, data entry and verification, data management, statistical analysis and reporting, investigator and site selection, healthy volunteer and special population recruitment, investigator meetings, clinical monitoring, centralized clinical trial laboratory, bioanalytical and clinical chemistry laboratory services, pharmacokinetics and pharmacodynamics, expert report writing, and regulatory applications. (Rettig, 2000, p.137)

An example of the 'efficiency' of the present work of these 'contract research organisations' can be evaluated in the quotation of Teacher-84 in Section 5.2.2 (page 122). Equally, the influence of such organisations upon medical research is indicated by the disclosure that one of them (Quintiles Transnational Corporation) reported a net revenue of US$1.19 billion in 1998 (Rettig, 2000).

There are many possible ways to appraise this problem. However, I would like to focus on four aspects of the above quotation: 'study and protocol design', 'investigator and site selection', 'statistical analysis and reporting' and 'expert report writing'. It will be shown that the purposive manipulation of the four mentioned components of medical research may entail the production of 'tailored' evidence. Such 'evidence' may be used for a range of outcomes, from 'proving' the efficacy of a treatment to providing the 'best evidence' to a continuing medical education guideline.

It is necessary to stress that the proposed manipulation suggested in the preceding paragraphs may vary from an overt control over the four mentioned aspects (which is probably a rare occurrence) to a more subtle and insidious influence. For instance, one can choose an 'investigator and site' that may be more prone to allow some adaptations of the 'study and protocol design', and selectively sponsor such research. Subsequently, this investigator may accept some help in the 'statistical analysis and reporting' of her/his data and the help of some 'expert report writing' in order to adequate his/her paper to the publication in a prominent medical journal.

Although such a kind of reasoning may seem a personal opinion, it is underpinned by the existing international evidence about the subject and by the data of the present study (see Section 5.2.2).

Some characteristics of the present physician and 'physician-researcher' are important to the present discussion. In Section 3.3 some evidence about the possible connection between the unethical behaviour of researchers and the existence of bias in medical research was discussed. One of the points discussed was that some authors believed that medical students were considering unethical behaviour as a morally acceptable conduct. In fact, according to Coulehan *et al.* (2003):

We have argued elsewhere ... that the failure of medical education to focus on producing good doctors, rather than simply on producing good technicians, is an ethical failure ... Medical students, house officers, and practising physicians report that they receive little, if any, explicit training in professionalism, and many believe that they become less humanistic and more cynical as their education progress ... (Coulehan *et al.* 2003, p.22)

Coulehan *et al.* (2003) believe that there is an even more important ethical deficiency. According to them, medical students and physicians have an imperfect development of the notion of moral responsibility towards the community in which they live caused by the non-reflective professionalism engendered by the present medical education. This means that these students and physicians would not be able to consider that they have a social responsibility that goes beyond good patient care. Considering that the present 'physician-researcher' is fundamentally a specialist for whom the act of doing research is only *part* of his/her daily activities (see Section 7.3), this lack of social responsibility is particularly worrisome.

Good science is essentially based on the social responsibility of scientists. If some of these 'physician-scientists' lack the moral basis that underpins social responsibility, they would be prone to accept uncritically 'modifications' in their research, if such 'modifications' could entail personal or professional advantages. They would become the perfect selection for the aforementioned 'contract research organisations'.

Consequently, such subversion of the 'physician-researcher' moral reasoning towards his/her research project and aims is an important and essential step towards the production of 'tailored' medical evidence. The successive steps entailing the manipulation of the 'statistical analysis and reporting' and the effect of the 'expert report writing' ('ghostwriting') will be discussed in the next few paragraphs.

Most, although not all, of the problems of 'tailored' medical research occur in clinical trials. It is important to remember that Section 1.3 showed that most biased data analyses in such studies are due to lack of statistical knowledge or to intentional manipulation of data or results (Mills, 1993). Considering that current medical education in many medical schools is not providing students with the necessary skills to deal with the statistical data

analysis required in today's medical research (see Chapters 4 and 5), and that the 'contract research organisations' all too often exist to 'prove' pre-determined assumptions, it is not difficult to understand why so many studies show biased results.

The problems of research structure and data analysis of present medical research are so important to the future of medical science that they will be discussed in more detail in Section 7.5.

Finally, there is the problem of 'ghostwriting', euphemistically described as 'expert report writing'. The conclusion of a 1996 survey among 809 authors (69% response rate) of papers published in three peer-reviewed large-circulation and three peer-reviewed smaller-circulation American journals carried out by Flanagin *et al.* was:

> In conclusion, our study demonstrates that a substantial proportion of articles in peer-reviewed medical journals have honorary authors and ghost authors. The findings also show that the ICMJE (*International Committee of Medical Journal Editors*) authorship guidelines may not be well understood by all authors …
> (Flanagin, *et al.*, 1998, p.224)

Despite these conclusions, and the effort of medical journals worldwide, this question of authorship seems still unsolved.

A good summary of what has been discussed in the previous few paragraphs is the opinion of 13 medical journal editors about the matter:

> As CROs (*contract research organisations*) and academic medical centres compete head to head for the opportunity to enrol patients in clinical trials, corporate sponsors have been able to dictate the terms of participation in the trial, terms that are not always in the best interest of academic investigators, the study participants or the advancement of science generally. Investigators may have little or no input into trial design … and limited participation in data interpretation … These terms are draconian for self-respecting scientists, but many have accepted them because they know that if they not, the sponsor will find someone else who will … There have been a number of recent public

examples of such problems, and we suspect that many more go unreported. (Davidoff *et al.*, 2001, p.786)

In fact, medical journals and their editors, according at least to the participants of the present study (see Section 4.3), would be the last possible avenue for deterring this 'flood' of manipulated medical information which is been caused by the so-called 'conflicts of interests' pervasive in present medical research. However, according to Richard Smith, editor for 25 years of the *British Medical Journal*, this is not happening:

> Journals didn't begin to think about conflict of interest until the 1980s, and even the most "advanced" journals didn't actually implement policies until after the millennium. Most journals still don't have policies. Yet substantial evidence has accumulated on the powerful influence of conflicts of interest, and it is at least arguable that medical journals are more an extension of the marketing arm of pharmaceutical companies than independent scientific forums. (Smith, 2004, p.243)

At this point I believe that the evidence presented shows the existence of a second 'loop' of the 'vicious circle' proposed in Section 7.1, involving the relationships between medical education and bias in medical research. Such a 'loop' was created and is being maintained by the deficiencies of medical education and the powerful influence of pharmaceutical industries upon medical research and the 'physician-researcher'.

7.5 The problems of the misuse of medical research methodology

The strengths and weakness of randomised controlled trials (RCTs), along with some of their intrinsic methodological problems, were discussed in the Sections 1.3, 1.4 and 2.2. However, such a discussion focused essentially on the technical aspects of their use in present medical research.

This section will present the approaches that are used by some researchers and contract research organisations (CROs) to exploit such weaknesses and intrinsic methodological problems of RCTs in order to produce and publish biased 'evidence'. It will also examine

how such biased 'evidence' is being used to maintain and reinforce the 'vicious circle' proposed in Section 7.1.

As discussed in Section 1.4, probably the most studied form of bias in medical research is publication bias and its various ways of influencing medical knowledge. The real effect of such bias has been difficult to evaluate precisely due to the fact that it was problematical to unearth the unpublished or duplicated papers about a specific medical procedure or treatment.

However, an elegant and recent paper by Melander *et al.* (2003) may shed some light not only upon the problem of publication bias but also upon the incidence and importance of the manipulation of data in medical research and the problem of authorship. These authors had the rare opportunity of following up the destiny of 42 short-term placebo controlled clinical trials that were submitted by pharmaceutical companies to the Swedish drug regulatory authority as a basis for marketing approval for treating depression.

These 42 clinical trials were related to five selective serotonin reuptake inhibitors approved in Sweden between 1989 and 1994. Melander *et al.* (2003) were not only able to track down how they were subsequently published in medical journals, but also to compare the results of these papers published between 1983 and 1999.

According to Melander *et al.* (2003):

> In a cohort of studies ... we found evidence of duplicate publication, selective publication, and selective reporting. There was a high frequency of duplication due to the inclusion of different subsets of studies in several pooled publications ... Although both intention to treat analyses and per protocol analyses were available in the submission to the regulatory agency, only 24% of the stand alone publications reported the usually less favourable intention to treat results. In our material this selective reporting was the major cause for bias in overall estimates based on published data. (Melander *et al.*, 2003, p.1173)

This kind of manipulation of data presentation is much more subtle and difficult to uncover than the simple statistical manipulation of data discussed in Section 1.3. It would

be extremely difficult for a medical journal editor to figure out that the paper submitted for his/her approval was based on a 'selected' data analysis. This is especially true when, as declared by Smith (2004), the number of paper submissions to the *British Medical Journal* reaches the fantastic number of 8000 a year, a figure that is probably not that different to that for other major medical journals.

There are several reasons for such kinds of behaviour of the 'physician-scientists', as discussed in Section 7.4.2. However, Melander *et al.* (2003) propose one particularly interesting and disturbing explanation:

> All the studies in our investigation were initiated by the sponsor, and the investigators were usually clinical practitioners for whom academic research was not the primary interest. Hence, the decision of how and whether a study should be published was probably left entirely to the sponsor. (Melander *et al.*, 2003, p.1174)

These authors consider that to rely only on published data to choose a specific drug for depression may be difficult due to the biased evidence that presently exists in the field. They also suggest that a choice of a specific selective serotonin reuptake inhibitor based on a pooled analysis of publicly available data is not likely to be supported by an analysis considering the total body of evidence.

The process of the manipulation of results and the publishing methods of research described above has the clear aim of creating a body of biased evidence strongly favouring the use of these drugs in medical practice. According to the data presented by Melander *et al.* (2003), the authors of these papers are behaving as 'ghost-authors' used mainly to create an aura of respectability which will permit the use of such papers in overt marketing of the drugs to the practising physician, or as part of the pharmaceutical industry's CME programs.

As independent researchers focus on the subject there will possibly be a progressive shift of the evidence towards the real effects, including side effects, of the drugs in question. However, since these researchers work with more restricted resources and do not have the

technical support of the CROs, it may take years (if it ever happens) before the real effects of such drugs are unveiled.

Although lacking the strong connection between the incidence of selective reporting bias and the pharmaceutical industry which is evident in Melander *et al.*'s (2003) paper, Chan *et al.* (2004a, 2004b) report similar problem in their studies in Canada and Denmark. According to Chan *et al.* (2004b):

> The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles, as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention. (Chan *et al.*, 2004b, p.2457)

A second, although no less important, problem is caused by the use of the results of clinical trials as an expression of the real effects of drugs or procedures in a population. As discussed in Section 2.2, the external validity of isolated trials has been severely criticised (Gross *et al.*, 2002), especially due to the fact that the inclusion or exclusion criteria of participants in these studies may impede the generalisation of trial results to 'real life' (Kennedy *et al.*, 2003).

Actually, Dieppe *et al.* (2004), discussing the problem of the use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) based only on the 'evidence' presented by published clinical trials, declare in their summary that even high quality scientific evidence from drug trials may not be generalised to the whole population. This situation would be caused, according to these authors, due to the fact that:

> Minority groups and older people are often excluded from the trials.
> Drugs tend to be used for a wider range of indications than those for which they were trialed.
> People at risk of adverse events are often deliberately excluded from the trials.
> Benefits and harms of drugs are not measured on comparable scales. (Dieppe *et al.*, 2004, p.31)

In fact, the large-scale adoption of new NSAIDs by Australian general practitioners described by Kerr *et al.* (2003) is a good example of a hasty and uncritical therapeutic 'shift'. According to these authors, in this particular case such a 'shift' was probably based on the 'evidence' provided by the pharmaceutical companies:

> A number of lessons can be gleaned from the Australian experience of large-scale early adoption of celecoxib and rofecoxib by GPs. Intense drug promotion can create perceptions about medications that strongly influence patterns of prescribing and use, yet may not be in line with best available evidence. Further, such rapid uptake can place patients at risk of adverse drug reactions and serious drug interactions through coprescribing. (Kerr *et al.*, 2003, p.407)

According to Kerr *et al.* (2003) the increase in the number of prescriptions of these drugs in Australia coincided with two marketing campaigns of the pharmaceutical companies. One of these campaigns focused on the medical profession, promoting the message that these new drugs were 'safer' than the traditional NSAIDs, despite the fact that the studies available did not show that the adverse events profile of these drugs was much different from the traditional ones. The second marketing campaign focused on the consumers through television and newspaper promotion of celecoxib.

In fact, the studies of Kerr *et al.* (2003) and Dieppe *et al.* (2004) are directly related to the findings of Melander *et al.* (2003). They ultimately illustrate how the misuse of the medical research methodology may be used to create and promote biased 'evidence', and to disseminate such biased 'evidence' to physicians and patients. Furthermore, this biased information may, intentionally or unintentionally, act as a 'contaminant' of the continuing medical education programs, reinforcing the two 'loops' of the proposed 'vicious circle' connecting medical education and the present incidence of bias in medical research as discussed in Section 7.4.

The issue of how (and how much) such marketing approaches of pharmaceutical industry are affecting medical students is still a matter of discussion. According to Rogers *et al.* (2004):

There is no published research comparing the attitudes and prescribing habits of students exposed to pharmaceutical representatives during medical schools with those protected from such influences. However, there is evidence that limiting pharmaceutical industry contacts during postgraduate training produces specialists who perceive drug company information as less useful ... (Rogers *et al.*, 2004, p.412)

Research on this specific topic would probably be extremely useful to underpin future discussions on the possible solutions for the problem of bias in medical research and its relationships with medical education.

7.6 Possible solutions for the problem of bias in medical research

As illustrated in Sections 7.2, 7.3, 7.4 and 7.5, the acceptance of the hypothesis about the existence of a 'vicious circle' (Section 7.1) connecting medical education, medical practice, medical research and the pharmaceutical industry makes it easier to perceive how these elements are related to the present incidence of bias in medical research. Such acceptance also facilitates the discussion of possible solutions to the problem, irrespective of the differences that exist among countries and medical educational methodologies.

However, to accept that such a 'vicious circle' really exists also entails the recognition that no isolated action focused on only one subsidiary element of its structure will be really successful. 'Vicious circles' have the characteristic of restructuring themselves using alternative pathways when submitted to isolated corrective actions that do not focus on its core structural element. In fact they may even become stronger and more difficult to eliminate, as these alternative pathways may be more sophisticated and intricate than the initial ones.

A possible example of such a problem is the opinion of Douglas Altman (Altman, 2002) about the modifications that occurred in medical research since his editorial in the *British Medical Journal* in 1994 (Altman, 1994), which was discussed in Section 2.1. In his 2002 paper he declared that he suspected that many basic errors of medical research were less common in 2002 than in 1994; however, he also stated that he believed that there was

evidence of frequent misapplication of the newer advanced statistical techniques in medical research. This is exactly what one should expect from a 'vicious circle' as suggested in the previous paragraph. The adoption by the major medical journals of the CONSORT statement (see Section 2.1) elicited a sophistication in the structure of medical research methodology and reporting but did not eliminate the existence of bias in medical research.

However, if the basic cause of the present disarray in medical research is not based on the research methodology employed in medical studies, what could be the main element of the proposed 'vicious circle' that should be blamed for such a situation?

Based on the discussion of the three main subsets of causes for the prevalence of bias in medical research (Sections 7.3, 7.4 and 7.5) and the results of my research in five Brazilian medical schools (Chapters 4 and 5), I believe that it is possible to put much of the blame for the current level of bias in medical research on the present medical education structure. In the next few paragraphs I will suggest how the present structure of medical education, based on a progressive 'specialisation', combined with a low level of ethical development of medical students and physicians can be considered as the core element of the proposed 'vicious circle'.

As a physician and teacher I would prefer to blame, as many do, the evident influence of the pharmaceutical industry on the behaviour of individual physicians, 'physician-researchers' and 'physician-scientists' and on the structures of continuing medical education programmes and evidence-based medicine. However, although such interference is undoubtedly present and important it cannot explain why so many physicians, medical researchers, medical educators and medical policy makers accept such interference without questioning its ethical basis.

Pharmaceutical companies are legal producers and sellers of drugs worldwide. Consequently, as with other legal industries, they are entitled to promote and sell their products, and seek for profit in such endeavour. However, it is not feasible to equate commercial ethics and medical ethics. The ethical principles employed by the physician are (or should be) based on the suppression of self-interest (Allman, 2003), and such

suppression would evidently be suicidal to a profit-based industry. According to Allman (2003):

> Suppression of self-interest is an essential activity for the physician ... It is a central element of the act of profession described by Pellegrino and Thomasma, wherein the physician offers to help the patient, promises to be competent, to act in the patient's interest, to restrain his self-interest, and not to violate the patient's trust. (Allman, 2003, pp.156-157)

Consequently, in this discussion no further efforts will be made to compare such different ethical principles or to justify such fundamental ethical differences. They are simply different and will remain like that so long as pharmaceutical companies continue to be profit-based organisations and physicians continue to be members of a profession that abdicates self-interest. As will be discussed in the next few paragraphs, the complete disentanglement of medical practice, research and education from the present influence of the pharmaceutical industry is one of the basic steps towards the solution of the problem of bias in medical research.

At first glance, the proposition of such disentanglement may seem preposterous and too radical. However, one must remember that medicine has endured with success similar educational and ethical challenges in its history, as was the case in respect of antisepsis and vaccination in the 19th century.

In order to discuss the feasibility and ethical basis of the proposed disentanglement, I will divide this discussion in three main areas:

1. The medical student and the practising physician
2. The present problems of medical research
3. The challenges to continuing medical education.

7.6.1 The medical student and the practising physician

The relationships between pharmaceutical companies and practising physicians were discussed in Section 7.4.1. This section will discuss the ethical problems involved in such

relationships, which are the real motive that underpin the proposal for a complete cessation of these relations between physicians and pharmaceutical representatives. Although there has been, according to Rogers *et al.* (2004), little debate about the ethics of the pharmaceutical industry's relationships with medical students, I shall demonstrate that the reasoning behind arguing that such contacts inside medical schools need to be eliminated is based on the same principles that apply to the pharmaceutical industry's relationships with practising physicians.

The basic problems of relationships between physicians and the pharmaceutical industry were discussed in Section 7.4.1 where it was argued that these contacts are not occurring for the benefit of the physicians' medical skills, but due to the pharmaceutical industry's marketing strategies. Consequently, these contacts are not only unnecessary but also deleterious, and should be disapproved of and terminated.

However, there is an even more important aspect to the relationship between physicians and pharmaceutical representatives. This is the question of the common habit of physicians to expect pharmaceutical representatives to provide trinkets, perks, free lunches, trips, continuing medical education credits, etc. Allman (2003) states that:

> Ostensibly cheap favours are given by friendly representatives, usually with a pitch for the product *du jour* ... Acceptance of these modest gifts seem inconsequential; experience suggests otherwise ... How much they really cost is unclear; that they are given at such expense to the pharmaceutical manufacturer suggest that they alter physician behaviour. (Allman, 2003, p.157)

One may argue that there is no problem here. All legal industries worldwide make some direct advertisement to their consumers using such strategies. The real problem behind such strategies of pharmaceutical companies is that they are being used not to convince the ultimate consumers (the patients) but the physicians. Such a kind of marketing transforms the physician into a disguised remunerated promoter of drugs, which is ethically unacceptable. In fact, the final consumers (the patients) are those who are subsidising such expenditures. According to Allman (2003):

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> The receipt of such emoluments serves only the physician's interest and may be counter to that of the patient, and thus violates the act of profession. Justification for such behaviour rests on an unstated, inescapable, but fragile assumption that being a physician confers entitlement ... This occurs at that time when the patient most trusts the doctor, during the writing of the prescription, an act that promises "Here is how I will help you." If the prescribed product is that which is best for the patient, influences brought to bear have been paid for by the patient who had no knowledge that he or she would subsidize such expenditures. More disturbing, the product marketed by the physician's benefactor may not be that which is the best for the patient. (Allman, 2003, p.158)

Consequently, whether prescribing the best treatment for the patient or, worse than that, not the best one, the physician who receives some benefit from pharmaceutical companies is at ethical fault. He or she is receiving indirectly (and secretly) from the patient, who is the final consumer of the drugs. In this case the physician is receiving more than he/she has previously agreed with this patient would be charged for his/her act as a physician. This reasoning is also valid in relation to those countries in which the National Health Service provides the necessary drugs to the patients (e.g. the UK), as the patients as taxpayers are ultimately paying for these medications. Such behaviour conflicts directly with the concept of 'suppressing self-interest' which is one of the basic ethical principles of medical practice. As Allman (2003) clearly points out:

> The physician is not the drug manufacturer's "customer" and, therefore, has no entitlement to privileges rooted in the client-provider relationship ... The doctor's obligation is to prescribe the safest, most efficacious, least expensive drug, based on scientifically sound, unbiased judgement. Any motive on the part of the physician other than the patient's good is indefensible and is the ethical descendent of the properly discredited practices of kickbacks and fee splitting for referrals. (Allman, 2003, p.159)

It seems pointless to discuss here what should be the precise monetary value of such 'gifts' from pharmaceutical companies to physicians in order for them to be considered ethically 'acceptable'. After all, what is fundamentally unethical is the *act* of receiving such 'gifts', not the amount of money involved.

In many medical schools there is a lack of discussion about these ethical problems. Furthermore, many of these schools permit their students to have direct and uncontrolled contact with pharmaceutical representatives. Consequently, these schools are at least partially responsible for the extension of the problem of the present entanglement between physicians and the pharmaceutical industry. Although medical students do not prescribe, such relationships create in the medical student the incorrect impression that they are acceptable and harmless, a notion that she/he will maintain in professional practice.

However, it must be stressed that the simple fact of prohibiting contacts with pharmaceutical representatives, and introducing in students' ethics courses the discussion of the concepts briefly outlined in the previous few paragraphs, will not be sufficient. As discussed in Chapter 6, due to its own characteristics, medical education is strongly based in the hidden curriculum and in role models. Consequently, such measures will only be efficacious if they are understood, accepted and supported by the majority of faculty members of these medical schools. Otherwise, the proposed measures will be at risk of becoming just a part of the written curricula of the medical schools and never be effectively implemented.

A simple example may illustrate the fact that physicians for several reasons may eventually not adopt a confirmed method aimed at the improvement of medical practice even if such a method is formally required. One of these methods is the simple act of handwashing before and after patient contact, which is considered one of the most important measures for preventing and controlling hospital transmitted infections (Tibballs, 1996).

The benefits of handwashing have been repeatedly demonstrated over the past 150 years (Buchan, 2003), and the requirement for handwashing is based on a fundamental principle of medical practice ('First do no harm') (Rea and Upshur, 2001). However, Tibballs' study (1996) in an Australian hospital shows that the observed rate of physician's handwashing was only 8.6% before and 10.8% after patient contact, although these physicians self-estimated their handwashing rates to be much higher. Evidently, there are

many possible causes for such a low rate of handwashing among physicians. However, the Handwashing Liaison Group (1999) believes that:

> Role models are important in hospital practice. Junior doctors washed their hands more often when consultants set an example ... Unfortunately, poor practice can also be learnt at the bedside. Junior staff and students taught to wash their hands abandoned the habit when others, especially more senior ward staff, did not bother. Senior staff should take the lead to achieve lasting behavioural change. (Handwashing Liaison Group, 1999, p.686)

It seems reasonable to suppose that such 'role model' influence will also be extremely important for the success of the proposed measures that aim to terminate the present relationships between physicians and pharmaceutical representatives.

Additionally, the medical professional associations should state clearly in their ethical guidelines that these associations consider the discussed relationships between physicians and the pharmaceutical companies as definitively unethical, rather than merely 'undesirable' or 'questionable'. Such a change of perspective about the problem would reinforce and legitimise the educational measures proposed above.

I recognise that the educational measures proposed would not be unproblematic in their implementation and may not be easily accepted by the members of some medical schools and by some practising physicians. However, the alternative of implementing some other more palliative measures will not eliminate one of the loops of the proposed 'vicious circle' (see Sections 7.1 and 7.4.1). In fact, palliative measures may entail a kind of acceptance, even justification, of the practice, and would only strengthen such a loop.

7.6.2 The present problem of medical research

In his editorial at the British Medical Journal in 1994 Douglas G. Altman stated that much poor medical research was due to the fact that researchers were carrying out research that they were ill equipped to perform (Altman, 1994) (see Section 2.1). More than twenty years after his editorial, I must sadly agree with him and comment that many physicians

nowadays are also ill equipped even to correctly and critically evaluate the results of present medical research.

There are several possible concurrent causes for this lack of knowledge of physicians and medical researchers about the methodology of research and the interpretation of research results, which were discussed in Chapters 1, 2 and 3. However, considering the data collected in five Brazilian medical schools (see Chapters 4 and 5) and the international evidence available, it is patent that the present structure of medical education in many medical schools should be considered a major cause for this situation.

Many medical schools seem to have abdicated their responsibility to instruct their students about the correct ethical and methodological aspects of medical research while favouring the development of a more 'technical' approach to medicine. Such a change created a bizarre situation. Their technically well-prepared students will have to acquire outside of academia, and mostly after their graduation, the necessary skills to correctly appraise the research evidence that will be necessary to keep them abreast with advances in their profession. In fact, few will be able to acquire such skills, while most of them will become uncritical consumers of 'contaminated' continuing medical education programs as will be discussed in Section 7.6.3.

It should not be a surprise that very few of these physicians become 'physician-scientists' as discussed in Section 7.3. Worse than that, some of them will become 'physician-researchers' without being well equipped for the task, as pointed out by Altman (1994).

The results of the interviews of my research in five Brazilian medical schools (Chapter 5) show that it will not be an easy task to convince the medical teachers of the need for a curricular change. Such curricular change is absolutely necessary to introduce in these schools' curricula the discussion of the ethical and methodological basis of medical research in its multiple aspects. Furthermore, this kind of teaching should not be considered as supplementary knowledge to the technical skills of their students, but as an important tool for the future development of their students as practising physicians or medical researchers.

More positively, my personal contacts with the teachers that participated in this research convinced me that most of them would be likely to accept such curricular modifications if they were certain that such modifications would lead to the improvement of medical education.

A fundamental question that remains to be answered about the lack of knowledge among many of today's medical researchers concerning research methodology and ethical principles is: 'How and why are these physicians being permitted to do medical research if they do not have the necessary skills?'.

The answer to this question is quite straightforward. The medical associations and most medical schools are very stringent in the matter of not allowing their members to perform medical acts that they are not competent to do. Paradoxically, most of these associations and schools do not have formal ethical and procedural guidelines that clearly state the necessary skills a physician should have in order to engage efficiently in the area of medical research. In fact, most of the existing guidelines only focus on ethical aspects of the relationships between the researcher and the patients involved in the research.

This lack of a clear research policy creates a strange situation. The simple fact of being a physician seems to be the necessary entitlement to do medical research, despite the well-known fact that few physicians are being well prepared for such an enterprise. Worse than that, many medical schools in some countries use participation in research projects as part of the assessment of their teachers (see Section 2.3). Such an assessment policy disregards the fact that a well-trained and technically efficient teacher may be ill equipped for medical research.

The situation described in the previous few paragraphs can only be solved by adopting for medical research the same stringency employed for the professional acts of physicians. More rigorous ethical and procedural guidelines are needed for medical research, and these guidelines should be based in the moral principle of the social responsibility of science.

Such improved guidelines will allow local research ethical boards in medical schools to evaluate and control much more than the present ethical problems of the relationships

between medical researchers and patients. These boards will be able to consider and evaluate the methods of a proposed piece of research, the skilfulness of the researcher to perform it and the adequacy of the funding that will be employed. Medical schools policy makers will also have to accept the fact that undertaking medical research is not something that every medical teacher will or should do in his/her professional life.

These corrective measures will certainly entail a reduction of the medical scientific production. However, it is definitely better to have fewer research projects than biased ones, as correctly asserted by Altman (1994).

The second, although no less important, aspect of the pharmaceutical industry's current involvement in medical research is the problem of its funding of such research and the consequent conflicts of interest that arise from this. This problem is probably the most discussed and controversial issue in medical research at the moment.

Once the ethical reasoning discussed in Section 7.6.1 is accepted, it does not seem to me that the problem of the so-called 'conflicts of interest' is too difficult to solve. It is surely obvious that if direct contacts with pharmaceutical representatives are ethically not acceptable due to the fundamental ethical differences between academia and the pharmaceutical industry, the same reasoning must be applied to the funding of medical research by this industry.

It would be, at the very least, odd to accept that a faculty member who advocates the existence of a 'firewall' between his/her students and the pharmaceutical companies could accept such funding for her/his research. In fact, as discussed in Section 7.6.1, it would not be a question of discussing *how* or *how much,* but a question of *why* this specific teacher accepted such a 'partnership'. Such a kind of rationalisation of the facts would transform the difficult task of qualifying and quantifying the so-called 'conflicts of interest' into a simple punishable offence of ethical misconduct.

While the proposed measures can help to revitalise academic medical research, they do not prohibit pharmaceutical companies from carrying out and publishing their own research about their products. The only difference is that the authors of such research would have to clearly state their relationships with a specified company in order to inhibit

the present incidence of 'ghost-writing' and 'ghost-authorship' in medical research. Any attempt to evade such disclosure should not be considered only as a minor unethical act of the authors, as usually happens nowadays, but as a serious and punishable instance of misconduct on the grounds of industrial marketing. In fact, I do believe that pharmaceutical companies are perfectly capable of contributing to medical advancement without the present entanglement with academic medical research.

Evidently, the proposed measures will not solve all the present problems of medical research. However, such a change of perspective will allow medical schools in different countries to concentrate their research resources on the investigation of particular aspects of medical knowledge and therapeutics that are important to their population's health care. These studies would be focused on the topics that are relevant to the well-being of these populations and not on the areas of medical knowledge that are particularly important to the pharmaceutical industry.

7.6.3 The challenges to continuing medical education

The structures of continuing medical education (CME) and life-long learning procedures in medicine are worldwide fundamental aspects in the life of physicians. There is no doubt about their importance not only in medicine but also in other professions that are based on the progressive growing and reshaping of knowledge throughout time. The concept that a physician must update her/his knowledge is a belief that all medical students, teachers and practising physicians recognise as true.

In some countries, such as the USA, attendance on CME programs has a 'mandatory' connotation, due to the fact that the 'credits' obtained on CME courses are required for maintaining the accreditation of physicians by the professional organisations. In other countries, such as Brazil, they are 'recommended' and 'sponsored' by the professional organisations, although they do not have a 'mandatory' connotation, as physicians are not usually re-evaluated by their professional organisations after their initial certification.

Such a difference among countries is reflected in the way CME programs are evaluated in respect of their quality and academic credibility. For instance, in the USA the Accreditation Council for Continuing Medical Education (ACCME) must endorse these

programs while in Brazil they are, as previously stated, 'recommended' and 'sponsored' by a specific professional organisation related to their educational content. In both cases the central idea would be that these courses are receiving a kind of 'certification' that they have a good scientific level and are free from commercial bias.

At first glance, the USA model of 'certification' of CME programmes seems much more stringent than the Brazilian with respect to the evaluation of the quality and academic soundness of such courses. However, according to Elliot (2004) this does not seem to be exactly true, as he states that:

> Here's how the business works. The pharmaceutical industry puts up the money, usually in the form of an "unrestricted educational grant". The grant goes for a for-profit medical education and/or communications company (MECC) which, in consultation with its pharma sponsor, puts together an "educational programme". The company and the MECC recruit academic physicians to deliver the program in return for a small cut of the grant. If the MECC is accredited by the Accreditation Council for Continuing Medical Education, it can offer the educational program on its own. (Elliot, 2004, pp.18-19)

As Elliot (2004) discloses, in those cases when the MECC is not accredited by the ACCME, such companies uses the continuing medical education office of a medical school which certifies that the program is free from commercial bias. The final result is that continuing medical education programs in both countries become 'contaminated' by commercial bias in either an overt or a veiled way.

However, one may ask what the problem is, given that practising physicians, academic physicians, medical schools, professional organisations, MECC companies and, of course, pharmaceutical companies seem all to be profiting from such behaviour? According to Allman (2003) the ethical problem is:

> By ceding the financing of continuing medical education to the drug industry, the profession and (*academic*) hospitals endorse a view that education is no longer their own responsibility, but instead the responsibility of business ... Converting medical education into a hybrid educational and promotional activity

is inconsistent with a proper ethic of medicine and the duty of competence. Departments are absolved of their didactic responsibilities and then transfer that responsibility to those whose intent is something additional to the dissemination of scientifically rigorous information. (Allman, 2003, p.162)

As Elliot (2004) correctly points out, the final result is that pharmaceutical companies are able to make their advertisements to physicians keeping a false appearance of objectivity.

One may reason that some advertisement is compensated by the fact that pharmaceutical companies are directly financing medical schools, practising physicians and academic physicians in doing something that they could not afford to do by themselves. However, such reasoning encloses a fundamental ethical imperfection. The imperfection is that this kind of reasoning leaves aside the opinion of those who actually finance these programmes: the patients

There is no possible moral reasoning that may exonerate academic physicians, medical schools and professional associations of the ethical misdemeanour of such entanglement with pharmaceutical companies. As previously discussed in Section 7.6.1, the moral concept of suppressing self-interest is a universal and fundamental basis of medical practice. Even if some physicians may sometimes forget this moral concept, there are no excuses for academics, medical schools and professional associations doing so too.

Consequently, the evident solution for the aforementioned problems of continuing medical education is the formal and definitive avoidance of relationships with the pharmaceutical companies.

In summary, although both pharmaceutical companies and physicians should undoubtedly share a common objective, which would be the improvement of the health conditions of the population, there are fundamental and irreconcilable differences concerning the ethical principles of the medical profession and the commercial perspectives of pharmaceutical companies. Therefore, I propose the total termination of their present communal activities in respect of health care, medical education and medical research. In my opinion, such disentanglement will be advantageous specifically to those who should always be the main beneficiaries of heath care: the patients.

In addition, several other educational measures are proposed in this chapter which should also be implemented in order to achieve the definitive rupture of the proposed existent 'vicious circle' connecting medical education and the prevalence of bias in medical research.

Chapter 8

Discussion and Conclusions

8.1 Introduction

The discussion of the current literature about the problem of bias in medical research in Chapters 1 and 2 shows that the present incidence of biased studies is a matter of growing concern among medical researchers, educators and medical journal editors. Since 1979 when Sackett presented one of the first studies about the issue (Sackett, 1979), several other researchers have contributed to the objective of detecting and/or avoiding the existence of these inaccuracies in medical studies (see Section 1.3). In addition, the most important medical journals have adopted several measures over the last decade in order to ensure the quality of the studies they are publishing (Begg *et al.*, 1996; Moher *et al.* 2001).

However, such efforts to eliminate the problem of bias in medical research have been based in 'linear' reasoning about the issue, according to which the known causes of the problem would act as concurrent reasons for the present incidence of bias in medical research. If such reasoning is correct, each of the possible causes could be regarded as an isolated factor, and the possible corrective measures would also be cumulatively effective as isolated processes.

The evaluation of the relevant literature about the problem and the results of the research conducted in five Brazilian medical schools lead me to propose that the present incidence of bias in medical research is, in fact, principally the result of a vicious circle. Such a vicious circle encompasses in its genesis and maintenance the present structure of medical research, medical education and the influence of the pharmaceutical industry.

Although it is not possible to discard the possibility that the various causes for the current level of bias in medical research were initially isolated factors, I propose that they are nowadays entangled in a self-maintained and well structured arrangement, configuring the proposed vicious circle (see Chapter 7).

In order to expose and explain the most important components of the proposed vicious circle it will be necessary to review the main concepts about the origins of bias in medical research discussed in Chapters 1 and 2 and also the research results examined in Chapters 4 and 5.

It will be shown that, once the known factors for the existence and prevalence of bias in medical research are seen as participants in a complex self-maintained structure of a vicious circle, it becomes easier not only to see why the present measures against this problem are not fully effective, but also how to implement new and more effective measures.

Furthermore, this chapter will discuss how simple, and apparently less harmful, components of the vicious circle interconnecting medical research and medical education may actually be the possible key to the solution of the problems that afflict modern medical research.

8.2 The industrialisation of current medical research

In order to clarify what is meant by the term 'medical research' it is necessary to explain that research in medicine is presently divided in two main areas: laboratory-oriented research and patient-oriented research (clinical research). As Rettig (2000) explains:

> Clinical research is understood today as being the bridge between laboratory science and clinical practice. A distinction now is made between laboratory-oriented research and patient-oriented research, the latter requiring direct physician-to-patient interaction. Some patient-oriented research is translational, a deliberate effort to apply laboratory research results to a small number of patients in a clinical setting. Much of it consists of clinical trials in humans of

new diagnostic or therapeutic products (drugs, biologics, medical devices) …
(Rettig, 2000, p.131)

In the discussion about the structure and aims of medical research in this section I will use the terms 'medical research' and 'clinical research' as synonymous. On the rare occasions that I will have to make a comment about laboratory-oriented research I will use the term 'laboratory research'.

Another important concept that will be used in the present discussion is that of the 'industrialisation of clinical research'. Such a concept is well explained by Rettig (2000):

> Industrialization of clinical research fundamentally constitutes the emergence of clinical research – and especially clinical trials – as a large, rapid growing "line of business". Although this is occurring mainly in drug development, it appears also in biotechnology and medical device development. Industrialization also reflects an intensified search for efficiency throughout the product development cycle, especially in the organization and conduct of drug clinical trials. (Rettig, 2000, p.140)

Rettig (2000) also points out that such 'industrialisation' is poorly understood by many both in academia and government research agencies. He asserts that it is leading to a modification of medical research, which is quite different today in relation to what it has been in the recent past.

In his editorial in the *British Medical Journal* in 1994, discussed in Section 2.1, Altman stated that 'we need less research, better research, and research done for the right reasons' (Altman, 1994, p.283). Although his editorial focused mainly on the problems caused by the medical researchers' habits, aims and lack of scientific research methodology knowledge, I believe that his statement may in fact be extended to many other aspects of current medical research.

However, an initial doubt may arise when one reads such a statement. Is it possible that an area of scientific knowledge that seems to be in a continuous and escalating discovery

of new treatments for several diseases needs 'less research'? The surprising answer, which will be explained in the next few paragraphs, is: yes, it is possible!

The first aspect that must be discussed to explain this is what the main focus of current medical research is, at least considering the number of published papers in medical journals. In fact, the majority of papers published would be classified as 'clinical research' outcomes according to Rettig's definition (Rettig, 2000). Laboratory research in medicine is rare, extremely time consuming and financially very expensive.

Much such published clinical research, as discussed in Section 7.4.2, is actually the product of the action of the contract research organisations (CROs). Such companies have the central aim of producing as much 'evidence' as possible in order to underpin the marketing of pharmaceutical products. In order to achieve this aim, CROs have to accomplish two modifications on the studies they produce. The first is to transform these studies in something academically acceptable introducing as authors physicians and medical teachers that can not be readily connected with the CROs or to the pharmaceutical companies. The second modification is to create as many papers as possible from the same study in order to enhance artificially the 'evidence' produced.

Such a behaviour was clearly unveiled by Melander *et al.* (2003) in their study about the fate of 42 placebo-controlled studies submitted to the Swedish drug regulatory authority as the basis for marketing approval for a class of drugs:

> ... 21 studies contributed to at least two publications each, and three studies contributed to five publications ... (Melander *et al.*, 2003, p.1171)

> ... eight studies resulted in three pooled publications based on different combinations of studies. The pooled analyses ... appeared simultaneously ... with one author in common but without cross reference ... There was no author name in common in the pooled and stand alone publications. (Melander *et al*, 2003, p.1172)

It is necessary to stress that such a number of publications was achieved based on studies that compared the drugs and the placebo. From the point of view of drug efficacy such

studies, even if correctly implemented and analysed, only show that these drugs are better than using absolutely nothing. However, they had undoubtedly fulfilled the central aim of producing a great volume of 'evidence' that can be used for marketing purposes.

One perverse side effect of such publications is to enhance the 'noise' and artificially reduce the relative quantity of real 'information' that can be obtained in medical journals. Although they may be well written by ghost-writers and well analysed by efficient statisticians (see Section 7.4.2), these papers do not entail an enhancement of medical knowledge but they certainly do represent a substantial profit for CROs and pharmaceutical companies.

The possibility that this kind of problem can be solved by the current editorial measures adopted by the major medical journals is remote. Although the majority of the participants of my research in five Brazilian medical schools believe that medical journals are responsible for the evaluation of possible bias in the papers they publish (Sections 4.2.2 and 4.3), even the editors of such journals are sceptical about the efficiency of current editorial measures. As Smith (2004) stated:

> Peer review is still in the dark age with most journals, and the *BMJ* has not progressed far. After centuries of being unexamined, the sacred process of peer review has been shown through research to be slow, ineffective, a lottery, biased, incapable of detecting fraud, and prone to abuse ... Authorship is another issue with which we've seen little progress. It long ago became clear that many studies included authors who had done little or nothing and excluded people who had done a great deal of work. (Smith, 2004, p.243)

It must also be remembered that most medical journals are also dependent on the pharmaceutical companies (and several are in fact an extension of the marketing branch of such companies). Those journals that are not an extension of the marketing branch of pharmaceutical companies have to ensure the existence of profits in their budgets in order to survive economically. To attain such profits many of them rely on the earnings obtained from advertisements of pharmaceutical companies and sales of reprints of selected papers used by these companies in their marketing programs.

Consequently, it seems reasonable to admit that Altman (1994) was correct and that we may possibly need 'less research' as he stated. The problem that remains to be solved is how such a reduction should happen.

Actually, the previous few paragraphs show a frightening monolithic and well-structured situation. It does not seem to have apparent flaws that could be used to break such a powerful loop of economical interests entailed by the current industrialisation of medical research. However, as will be discussed in the final paragraphs of this section it is possible that the solution should involve a less discussed aspect implicated in such a loop. This would be, as mentioned by Rettig (2000), the poor understanding of academia and government research agencies about the real structure of the industrialisation of medical research.

Altman's statement also includes the need for 'better research'. How could one possibly judge what could be considered as 'better research' in medicine? What could be the standards that could be used to classify a clinical research as 'better' or 'worse'?

In fact, such standards not only exist but were discussed in Sections 1.2, 1.3, 1.4 and 2.2 of the present study and are available in the references that underpinned the discussion in these sections. These standards are fundamentally based on the correct and conscious choice of the best research method(s) that should be employed to answer the research questions and also on an adequate knowledge of the strengths and weaknesses of the chosen research method(s).

According to such standards, as an example, the studies reported by Melander *et al.* (2003) and discussed in the previous paragraphs should not even have been performed and certainly did not deserve publication. There is no scientific justification for performing and publishing a clinical research comparing a new drug with placebo when there is already an available treatment for a specific illness. As Sackett and Oxman (2003) correctly pointed out in a rather ironic paper about the problem:

> With our protocol strategies … as long as your "me too" drug isn't a lot worse
> than a sip of triple distilled water, we can guarantee you a positive trial. (Sackett
> and Oxman, 2003, p.1442)

These authors are correct in their ironic evaluation of how easy is to bias such studies. The central problem is well known in medical research, and was properly explained by James Mills in his paper 'Data torturing' (Mills, 1993):

> There are two major types of data torturing. In the first, which I term "opportunistic" data torturing, the perpetrator simply pores over the data until a "significant" association is found between variables and then devises a biologically plausible hypothesis to fit the association. The second, or "Procrustean", type of data torturing is performed by deciding on the hypothesis to be proved and making the data fit the hypothesis ... (Mills, 1993, p.1196).

I suspect that most studies using placebos are very prone to having their data 'tortured' in a 'opportunistic' or 'Procrustean' way, transforming their conclusions into something that is incompatible with scientific correctness and objectivity. As the researcher in this kind of study is fundamentally comparing the effects of a drug against absolutely nothing, he/she can easily, consciously or unconsciously, use an 'opportunistic' or 'Procrustean' approach to his/her data analysis and research conclusions. In fact, as explained by Mills (1993), the final result of expert 'data torturing' will not be perceived as biased by most skilled readers.

If this is the case, why such kind of studies are still being performed and published? There are several reasons. Some of these are related to the physician-researcher's aims and expectations in relation to his/her real motive when doing a piece of research. Others are connected to the loop of economic interests described in the previous few paragraphs and to the current policy for approval of drugs for marketing of such governmental drug control agencies as the American Food and Drug Administration Agency (FDA).

The governmental drug control agencies in most countries still accept for the initial approval of the marketing of a new drug the drug/placebo controlled trials as a 'proof' of their 'efficacy' and 'safety'. According to Rettig (2000), since 1997 the FDA has markedly reduced its review time for the approval of new drugs. This reduction is consistent with a change in the philosophy of drug evaluation. Such a change entailed the substitution of a policy of avoiding the premature release of new drugs until safety has

been decisively proved by a policy of facilitating rapid access to the possible benefits of new therapeutics. As the question of the availability of new drugs for people is a worldwide governmental policy matter, many countries are, to a greater or lesser extent, adopting the same guidelines.

Obviously, a policy of faster drug approval does not fit well with the use of a research methodology that involves comparing the real effects (and side effects) of a new drug with those of one or more drugs that are already used for the same condition or illness. These kind of trials are extremely time and resource consuming, and not infrequently lead to inconclusive results, requiring new comparisons to be made until the relative efficacy and safety of the new drug is established with some confidence.

Although these more in-depth and time consuming studies are not 'shielded' against any possibility of bias, the iterative characteristic that is inherent to their methodology is a partial guarantee against the 'data torturing' so common in the drug *versus* placebo studies. However, who would care to sponsor such studies once the drug is already approved by the governmental drug evaluation agencies?

The answer may sound cynical and frightening. These drugs will in fact be tested in a whole population of users of the therapy. This kind of 'testing' will continue until the real effects are fully known or, worse than that, until the volume of harmful side effects will eventually force the pharmaceutical companies to stop their production, a feature that is becoming common in the drug market (see Section 8.3).

For the pharmaceutical companies such a kind of 'rapid approval' is welcome as it reduces their costs, and the existent CROs are perfectly equipped to produce the necessary studies they need for a drug's approval. The studies used nowadays for the approval of drugs by governmental agencies (drug versus placebo) also permit CROs to create what may seem for someone unskilled in medical research methodology 'solid evidence' for the quality and safety of new drugs.

Such a strategy is clearly seen in the findings of the study by Melander *et al.* (2003) that showed the proliferation of published papers based on a relatively small number of initial studies. This 'evidence' can be subsequently used in the pharmaceutical companies' overt

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or disguised marketing campaigns focussed on the general public or practising physicians. The efficacy of such a marketing strategy is evident in the study of Kerr *et al.* (2003) about the early large-scale adoption of new anti-inflammatory drugs by Australian general practitioners discussed in Section 7.5.

For many physician-researchers, using a twisted moral reasoning that 'what is not forbidden is permitted', the adoption of the drug/placebo research methodology is also a piece of good fortune. With a simple and reproducible research method they can generate a great number of studies with 'positive' results which are easier to publish as discussed in Section 1.4. Of course, with the support of the CROs, as described in Section 7.5, the burden of such a task can also be greatly reduced.

Consequently, the finding discussed in Section 5.2.2 that teachers and students in a certain way 'forgive' the eventual research errors of physicians-researchers should not be a surprise. After all, even the research rules for drug approvals of the governmental drug agencies can be considered a little bit lax with respect to medical research methodology.

As was the case in the discussion of the question of whether 'less research' is needed, evaluation of Altman's assertion that 'better research' is needed in medicine (Altman, 1994) shows that the current industrialisation of medical research constitutes the same monolithic and well-structured situation. However, such an evaluation also reinforces the feeling that a disturbing kind of ethical lassitude seems to be pervasively present in academia and governmental drug regulatory agencies.

The 'normalisation' of the relationships between academic science and the pharmaceutical companies' interests in the industrialisation of medical research might be one of the causes of this ethical lassitude. As Sismondo (2004) points out:

> At the beginning of the century (*20th century*), academic scientists clearly perceived that association with pharmaceutical companies was a problem, at least for their reputations, if not for substantial ethical reasons. By the 1940s the situation had changed considerably, and academic-industrial collaborations had become somewhat normalized … (Sismondo, 2004, p.150).

Such a kind of amalgamation of interests between academics, government and the pharmaceutical companies, which can be presumed to have rather different ethical perspectives (see Section 7.6), may be one of the key features for understanding the present situation of medical research.

Finally, the last part of Altman's assertion is that medicine needs 'research done for the right reasons' (Altman, 1994). Interestingly, this aspect of medical research has been less considered in the discussion about the current incidence of bias in medical research. Probably this is happening because when one uses a 'linear' approach to the problem it becomes difficult to perceive that there are at least three groups of 'right reasons' for a particular piece of medical research to be performed. These groups are related to the improvement of medical knowledge and medical care, the economic interests of the pharmaceutical industry and some physician-researchers, and the policies of the government's drug control agencies.

In a perfect world, these three groups of 'right reasons' would have at least one important common point of convergence: the improvement of the well-being of the population as a result of the outcomes of medical research. Unfortunately, as will be demonstrated in the next few paragraphs, the convergence point has progressively changed in recent decades as a result of the industrialisation of medical research. The central 'right reason' of much medical research nowadays is essentially personal or industrial profit; and the well being of the population has gradually become a secondary aim of such research.

It would be preposterous to believe that before the industrialisation of medical research physician-scientists did not expect to receive the merits and profits due to an important piece of research. Also, it is understandable that pharmaceutical companies seek for profits and that governmental drug agencies have to cope with political and economical constraints and the population requirements for better health care. However, what will be argued here is that the boundaries among their aims and aspirations became rather blurred in recent decades, entailing an unwelcome shift in the objectives of physician-researchers and the governmental regulatory agencies towards the interests of the pharmaceutical companies.

Consequently, the real problem is that the 'right reasons' to do research nowadays seems rather dependent on the pharmaceutical companies' needs and objectives. From such a perspective the previously discussed study of Melander et al. (2003) only shows that much medical research is frequently being done for one reason: to authenticate the desires and aspirations of pharmaceutical companies.

However, is it possible that such relationships between physician-researchers and pharmaceutical companies have in fact changed in recent decades? According to Drews (2003), the answer to this question is that these relationships have indeed changed. He states that:

> The closeness of the industry to medical biological science and their willingness to submit to the rigor and discipline of good science is being replaced by a marketing dogma in which R&D (*Research and Development*) is degraded to a tool for generating medicines that qualify as blockbusters ... Finally, the ethics of successful business have replaced those of medicine. The supreme loyalty of today's companies is not primarily directed at patients and their physicians but at shareholders. Consequently, the most influential figures in today's pharmaceutical companies are no longer the heads of R&D but the heads of marketing and finance. (Drews, 2003, p.411)

Drews (2003) identifies as 'blockbusters' those medicines that can each generate annual revenues to a pharmaceutical company of or in excess of one billion US dollars. Everything necessary to achieve this goal is now considered as the main responsibility of its marketing department.

Also according to Drews (2003), for most of the 20th century the pharmaceutical industry was characterized by the following properties:

- Great individuality.
- Firm commitment to science and the ways in which science unfolds.
- Cultural and ethical standards that often seemed to be derived from those of medicine itself. (Drews, 2003, p.411)

However, it seems that these qualities are being progressively lost (Abraham, 2002, Antonuccio *et al.*, 2003). According to Drews (2003), one of the reasons is the on-going process of mergers between pharmaceutical companies and general consolidation in the industry. Today, there are fewer large pharmaceutical companies and also fewer differences between the remaining companies in relation to the aforementioned 'marketing dogma'.

As the objectives of the most economically powerful 'partner' in the medical research enterprise changed there was also a progressive modification not only in the structure but also in the aims of much medical research. The rise in the importance of the marketing and financial departments of pharmaceutical companies and the consequent relative loss of importance of the R&D departments entailed a much more aggressive approach of these companies towards the 'tailoring' of a new concept of medical research that suited their interests.

Surprisingly, the change in the industry's reasons for doing clinical research did not provoke the expected rejection from academia and governmental agencies in relation to such an alteration of objectives. In fact, the contamination of these two social structures by the new conceptual structure of clinical research of the pharmaceutical companies caused a drift of their research aims towards the industry model (Abraham, 2002).

However, why has such a change been occurring inside pharmaceutical companies? And why do most of the professional associations, academia and governmental agencies worldwide seem to be so lenient to the change in the focus of clinical research?

The answer to the first question is that the productivity of pharmaceutical companies in relation to truly new products has been falling short of their own expectations since at least 1993, according to the number of submissions made to the European Medicines Evaluation Agency (EMEA) and the American Food and Drug Administration agency (FDA) (Drews, 2003). In order to maintain their level of profit these companies are progressively more dependent not only on the creation of new 'markets' (see Section 8.3) but also in the increase of the use of their existing drugs (and 'me-too' drugs, see Section 7.4.1).

Such an increase in the use of existing drugs or ones very similar to them is exactly the intention of pharmaceutical companies when using their marketing department and the CROs to convince physicians to prescribe and physician-researchers to collaborate in dubious research as described in Chapter 7. Consequently, the data presented in Section 7.4 which showed that the pharmaceutical industry's marketing departments spent in 2001, just in the USA, more than US$19 billion (Antonuccio *et al.*, 2003) are not surprising. It is not a question of creating new drugs; it is a question of selling the existing ones. As Drews (2003) points out:

> Most big pharma companies have embarked on strategies that aim primarily at profitability. The tool that is most prominently employed to implement this strategy is marketing ... The medical needs of patients and scientific opportunities as they emerge from an open process of scientific enquiry have become secondary considerations. This attitude not only represents a reversal of the process of scientific innovation but also marks a significant deviation from the way in which pharma companies operated two or three decades ago. (Drews, 2003, p.416)

One may argue, and I would have to agree, that pharmaceutical companies are as entitled to seek for profit as any other commercial enterprise. However, the real point is that when such companies consider the pursuit of the solutions of medical needs of patients, and the support of medical research aimed at really providing such solutions to be secondary they cannot be considered as partners of true medical research and medical education.

In this case, the most important common point of convergence of the 'right reasons' to perform a piece of medical research that previously characterized the relationships between academia and the pharmaceutical industry clearly disappears. This simple fact seems to be easily forgotten by academics, professional associations, physician-researchers, policy makers and governmental agencies when discussing the problems of current medical research and health care.

Maintaining the image of a 'partner' of medical research while in fact transforming the enterprise so that it accepts their methods and aims is a major marketing achievement of pharmaceutical companies. Such a success can be seen from several answers of the

participants of my study discussed in Section 5.2.2. It seems reasonable to suppose that the same is also happening in other medical schools, professional associations and governmental agencies.

In fact, what this discussion about 'research done for the right reasons' (Altman, 1994) seems to reveal so far is that the conclusions drawn from the discussions about 'less research' and 'better research' are also applicable here. We continue to have a central and most powerful force – the pharmaceutical industry – dominating and controlling what seems to be the weaker side – academia, medical-researchers and government drug control agencies – to such an extent that it might seem that there is little that can be done to save medical research and medical education.

If this was the case, my reasoning about the problem should finish here with the sad conclusion that medicine is doomed to become a technical profession dominated by the pharmaceutical industry, which would dictate the rules of present and future medical education and research. However, I do not think that such a conclusion is correct, and I shall explain the reasons for my disbelief in the next few paragraphs.

For a long period of time academia, practising physicians and the pharmaceutical industry had established more or less friendly relationships, although at the beginning of the 20th century academic researchers saw the association with pharmaceutical companies as a problem (Sismondo, 2004). However, according to Moynihan (2003a), nowadays 'finding senior medical researchers or clinicians without financial ties to pharmaceutical companies has become exceedingly difficult' at least in the USA (Moynihan, 2003a, p.1189). According to Moynihan (2003a):

> Those regarded as 'thought leaders' routinely work as paid members of drug companies' advisory boards despite the evidences that the practice is part of industry's promotional machinery. (Moynihan, 2003a, p.1189)

Furthermore, Moynihan (2003a) discloses that pharmaceutical companies are heavily sponsoring professional societies and their guidelines writing panels, whilst accredited events in continuing medical education seem to be just an occasion for speakers paid by these companies to speak about their drugs.

Although it is easy to 'demonize' the pharmaceutical industry, it is necessary at this point of the present discussion to evaluate clearly which are the possible real causes of the present situation of medical research. As discussed in the previous paragraphs it is clear that there has been a profound change in the pharmaceutical industry's objectives and marketing strategies since the second half of the 20th century. However, it also seems obvious that a major change occurred in academia, transforming those previously cautious and more or less friendly relationships described by Sismondo (2004) into an overt domination. Such domination, in fact, does not seem only to be economical but also comprises the modification of the aims and objectives of medical research and medical education, as discussed by Moynihan (2003a).

When discussing the present problems of medical research in Section 7.6.2 it was pointed out that many medical schools seemed to have abdicated their responsibility for instructing their students about the correct ethical and methodological aspects of medical research. Also, as was shown in Section 6.2, governments and professional medical associations offer only general guidelines about what should be the expected of the outcomes of a medical course. Furthermore, as Moynihan (2003a) states, many of the professional medical associations are too connected to the pharmaceutical industry (a subject that will be discussed in more detail in Section 8.3).

These three aspects related to the problem of bias in medical research and its relationships with medical education are in my opinion the points that are more prone to be identified as the possible targets for modifications that may entail a correction of the problems of current medical research. As will be discussed in Sections 8.3 and 8.4 such modifications can not only solve the present problems but also prevent the existence of future ones.

However, at least one conclusion may be drawn from the discussion in this section. The current approach of establishing a group of 'norms of conduct' aiming at the maintenance and 'improvement' of the current relationships between academic medical research and the pharmaceutical industry is inconsistent with reality. As discussed in this section, the central objectives of the pharmaceutical industry's current approach to medical research are incompatible with authentic medical science and its ethical foundations.

8.3 'Medicalisation' in health-care

The concept of 'medicalisation' has been proposed in order to identify, analyze and criticize the social processes in which human daily life aspects are being transformed into medical issues (Verweij, 1999). However, according to Peyser (2004):

> The question of what is pathology and what is normal is not pure science. It has profound sociocultural, legal, political, and philosophical implications, all a matter of practical human interest. It is too important to be left solely to experts. (Peyser, 2004, p.7)

Peyser (2004) was able to condense in these two small phrases much of the problem related to correctly defining the term 'medicalisation'. For the sake of simplicity, I will use in this study the opinion of Conrad (1992) that 'medicalisation' is to transform an aspect of human life in a medical problem by:

> ... using medical language to describe a problem, adopting a medical framework to understand a problem, or using a medical intervention to "treat" it. This is a sociocultural process that may or may not involve the medical profession, lead to medical social control or medical treatment, or be the result of intentional expansion by the medical profession. (Conrad, 1992, p.211)

As pointed out Purdy (2001), such a definition is value neutral and may in fact permit the use of the term in a positive way. Indeed, the term 'medicalisation' will be employed in the current discussion precisely because of this way of reading the term. To make use of a more incisive definition reinforcing the negative aspects of 'medicalisation' as Purdy (2001) proposes would be deleterious to the aims of the present discussion, even though I agree that the term is usually employed negatively to refer to the phenomenon of reducing complex personal and social issues to 'treatable' medical problems.

As will be demonstrated in this section, the issue of medicalisation involves many of the aspects already discussed in Section 8.2. As is the case for the industrialisation of current medical research, the problem of medicalisation is highly connected with the economic

domination of medical practice, with ethical issues and with the lack of knowledge about medical research aims and methods. However, even though medicalisation of health-care is tightly connected with the problems that afflict current medical research, it has some characteristics that transform it in an especial problem in medicine.

Some of these characteristics of medicalisation that will be discussed include the influence of lay media and the empowerment of specialists and professional medical associations. In addition, while in the case of medical research patients are mostly passive actors in the process, with respect to medicalisation they and patient associations have an important and active role.

Furthermore, the discussion in Section 8.2 focused on the influence of the pharmaceutical industry on current medical research due to the fact that such influence is well studied and has an evident connection with the marketing strategies of the pharmaceutical companies. However, the producers of medical diagnostic devices and screening tests seem to be using the same marketing methods in order to increase their profits. Their influence upon current medical research is not as obvious as that of the pharmaceutical industry's but their influence on the behaviour of practising physicians and health-care management as a whole may be rather important.

The central problem about evaluating medicalisation is that such a term means, when used in a positive way, that there is strong epidemiological evidence that one aspect of human life that is not necessarily harmful in itself needs to be avoided or 'treated' to prevent future medical problems. However, as Johansson (1996) states:

> If research produces knowledge about health, and knowledge is essential for improving health, then health research improves health, particularly through policy. Health transition research is exceptionally important to the production of useful knowledge ... because it deals with the causes of improved health over time. While the logic is sound health research is not. It is a contentious field currently producing more confusion than enlightenment, in which continuing uncertainty means that it is difficult to identify and apply genuinely useful knowledge. (Johansson, 1996, p.371)

There are several examples in which the medicalisation of human habits was in fact a positive achievement for health. This was the case of with John Snow's observations about the cholera outbreak in London in 1849 (Cartwright and Biddiss, 1972). Although Snow did not know what the real cause of cholera was, his evaluation of the water-drinking habits of 69 people who lived close to a water-pump in Broad Street (London) was a masterpiece of logical thinking. According to Cartwright and Biddiss (1972):

> Snow did not discover the true cause of cholera, the micro-organism, but he came very close to the truth. He proved beyond question that cholera is a water-borne disease and his evidence started a train of events that, in the end, controlled the great epidemics of cholera, dysentery and typhoid. (Cartwright and Biddiss, 1972, p.162)

However, why Snow was successful is seldom discussed. Fundamentally, he was successful for three reasons:

- He was dealing with a one-cause/one-effect problem,
- Although simple, his research methodology was unbiased and appropriate to investigate the problem,
- According to the historical records, he had no problems in relation to 'conflicts of interest'.

These three reasons for the success of the Snow's approach to the problem of cholera are not particular to this situation. They are firmly embedded in the solution to several problems that affected human life until the end of the 19th century (Osler, 1921). In fact, at the beginning of the 20th century Osler (1921) already connected the idea of 'sanitation' to what he called 'the rise of preventive medicine'.

Another aspect that is seldom discussed about these medical interventions in human life and habits is the question of the 'cost/benefit ratio' they entail. In the case of cholera, as an example, some people may have had political, religious, personal and economic reasons not to accept (and even to deplore) the subsequent results of the application of Snow's recommendations for solving the problem. However, for the vast majority of

people there was undoubtedly an improvement in the quality of life. Such a cost/benefit ratio fulfills the necessary social responsibility that is expected from the interference of medicine in the population's life and habits.

More than 70 years after Osler (1921) predicted the rise of preventive medicine Johansson (1996) saw health research from a quite different perspective:

> Health research, including health transition research, is distributed over a number of fields which in themselves comprise separate academically-based disciplines and subdisciplines ... In the present research environment it is generally true that most health research is done to advance the welfare of a field and the experts in it. The competition between fields means that the overarching goal of all social science research — the improvement of human welfare — is easily lost in the struggle for disciplinary hegemony. (Johansson, 1996, p.371)

Johansson (1996) focused his study on the current complexity of the correct definition of health and also looked at the 'competition' among different 'populations of experts' about the matter. However, as will be shown, the few lines of his work quoted above are rather emblematic in relation to the issue of medicalisation in health-care.

Such a kind of change in health research is part of the problem that Moynihan *et al.* (2002) called 'disease mongering', which is a complete subversion of the initial principles of medicalisation discussed in the case of the cholera control. As Moynihan *et al.* (2002) argue:

> Within many disease categories informal alliances have emerged, comprising drug company staff, doctors, and consumer groups. Ostensibly engaged in raising public awareness about underdiagnosed and undertreated problems, these alliances tend to promote a view of their particular condition as widespread, serious and treatable. Because these "disease awareness" campaigns are commonly linked to companies' marketing strategies, they operate to expand markets for new pharmaceutical products. (Moynihan *et al.*, 2002, p.886)

According to these authors, such approach also causes the perverse situation of playing-down or ignoring the fact that many such conditions are self-limiting, have a relatively benign natural history or can be controlled by alternative strategies.

In order to clarify these negative aspects of medicalisation and explain why this issue is important to the present discussion I will use as an example the medicalisation of women's health (and, more specifically, of the menopause). I have chosen this aspect of human health medicalisation due to the fact that it presents all the negative aspects of medicalisation and also because it has been extensively studied and discussed since the beginning of the second half of the 20th century.

There were three phases in the medicalisation of the menopause. The first was to use medical language to describe the 'problem' which was followed by the adoption of a medical framework to 'understand and explain' it. Finally, based on the existing 'evidence' medical interventions were introduced to 'treat' such a problem. This final phase of medicalisation of the menopause comprised not only the drug treatment but also diagnostic procedures.

The transformation of the normal process of the menopause, which occurs in all midlife women due to a modification of their hormonal profile, was initiated by calling this natural modification a 'hormone deficiency'. As a 'deficiency' it should be treated with a 'hormone therapy replacement'. This configures a classic case of using medical language in order to create the process of medicalisation. However, it would be difficult to convince women to initiate a long and expensive treatment, not to mention the side effects of such a treatment, just using as a reason the common symptoms of menopause. For most midlife women they are mild and transitory as can be depicted by the evaluation of the rates of core symptom reporting in Japan, Canada and the USA (Avis et al., 1993).

However, one way of convincing these women was to link 'hormone deficiency' with some real and life-threatening medical condition. As Meyer (2001) states:

> The three major diseases that are being linked with the lower estrogen levels of midlife and older women are heart disease, osteoporosis and, most recently, Alzheimer's disease. Primary prevention of these diseases is the rationale used

for urging healthy midlife and older women to take long term hormone. Although there have been many challenges to these links and warnings against the widespread use of hormones, these challenges and warnings have either been ignored or trivialized. (Meyer, 2001, pp.769-770)

These three main diseases that have been connected to menopause share one common feature: many factors are involved not only in their onset but also in their development in a specific person. Such a characteristic makes their control and treatment rather different than in the case of cholera that is a one-cause/one-effect disease. Consequently, common sense should be enough to recognise that 'hormone deficiency' could be considered only as a possible risk factor, not a direct cause in most cases.

To transform this possible risk factor into a definitive cause was a major feat of 'evidence' creation, marketing and distortion of health research. It involved not only all the features of the industrialisation of medical research discussed in Section 8.2 but also the involvement of the lay media, consumer groups, medical professional associations, governmental drug control agencies, practising physicians and academia.

The involvement of lay media and consumer groups is understandable as it entails the use of common marketing procedures. As Moynihan *et al.* (2002) state:

> A key strategy … is to target the news media with stories designed to create fears about the condition or disease and draw attention to the latest treatment. Company sponsored advisory boards supply the "independent experts" for these stories, consumer groups provide the "victims", and public relations companies provide media outlets with the positive spin about the latest "breakthrough" medications. (Moynihan *et al.*, 2002, p.886)

So, it is easy to understand how the lay media, consumer groups and possible 'patients' can get involved. However, how and why are medical professional associations, governmental drug control agencies, practising physicians and academia engaged in such schemes? Whatever the answer the final result was impressive. According to Hersh *et al.* (2004) in 1999 there were 90 million hormone therapy replacement prescriptions in the

USA alone. Such a level of prescriptions probably also entailed a high (but unknown) number of bone mineral density scans and laboratory screening tests for hormonal levels.

Unfortunately, the answer to the question of the previous paragraph - how and why are medical professional associations, governmental drug control agencies, practising physicians and academia engaged in such schemes? - is deleterious to the image of these groups. As discussed in Chapter 7 and Section 8.2 all these participants in this particular case of medicalisation are, willingly or not, profoundly entangled with the pharmaceutical industry's interests and aims.

In July 2002 the Working Group for the Women's Health Initiative Investigators (WGWHI) published in the *Journal of the American Medical Association* the results of a randomised controlled primary prevention trial in which 161,809 post-menopausal American women were enrolled between 1993 and 1998. The conclusion of this study, based on the results obtained from a sample of 16,608 women was:

> Overall health risks exceeded benefits from the use of combined estrogen plus progestin for an average 5.2-year follow up among healthy postmenopausal US women. All cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases ... (Working Group for the Women's Health Initiative Investigators, 2002, p.321).

After the publication of this study, the American Food and Drug Administration Agency withdraw its previous certification for the use of such hormonal combination for the 'treatment' of healthy post-menopausal women. It seemed that this was a good end to a bad medical story, except of course for those women who had problems connected to their menopause hormonal 'treatment'.

However, Hersh *et al.* (2004) show that, although there was a reduction, the number of prescriptions of hormone therapy for post-menopausal women in the USA one year after the WGWHI publication was still high (53 million/year). Apparently, the central idea that menopausal women should be 'treated' is still considered as true by many physicians. Bad habits seem really difficult to be eradicated.

In fact, the problem of the medicalisation of the menopause may be related to the last part of the definition used in this discussion. According to this definition, the persistence in the medicalisation of menopausal women could be due to the fact that it leads to 'intentional expansion by the medical profession' (Conrad, 1992, p.211).

It is not only pharmaceutical companies, mineral bone density scan device producers and screening test producers that are profiting from the medicalisation of menopause. Considering that around 12% of the world's population is composed of women who are over 45 years old (Kaufert, 1996), one can imagine how many potential 'patients' were created simply by the implementation of this kind of medicalisation.

It should not therefore be surprising to find that women are still being 'treated', and that medical professional organisations may be involved in less than ethical attitudes, as Brühl (2003) reveals:

> Several thousand German gynaecologists have been the target of a campaign promoting postmenopausal hormone replacement therapy (HRT) which claimed that the negative findings of a major US study (*Conclusion quoted above*) were of "highly limited relevance" to the German population. The message was, in part, disguised as the official statements of a large professional organisation for gynaecologists, the Berufsverband der Frauenärzte. (Brühl, K.K., 2003, 1161)

According to Brühl's account of the problem it is difficult to separate the real involvement of the hormone commission of the professional organisation and the influence of two German companies that sell hormone treatments.

Although the end of the 'medicalisation' of women's menopause cannot yet be foreseen, its evaluation can show that once more we are facing an ethical dilemma. Considering our discussion in the previous paragraphs of this section and in Chapter 7, medical professional associations, governmental drug control agencies, practising physicians and academia have poorly understood this ethical dilemma.

A central issue in the case of the medicalisation of the menopause was what Moynihan *et al.* (2002 called the 'marketing of fear'. This kind of 'marketing' is especially evident in the case of the link created between low hormonal levels and osteoporosis. According to these authors:

> The construction of the WHO (*World Health Organisation*) diagnostic criteria is such that large numbers of healthy women at menopause will automatically be diagnosed as having this "disease" (*osteoporosis*) because their bones are being compared with those of much younger women. Against a background of controversy over disease definition, poor predictive value of bone density measurement, and heavily advertised expensive therapies ... corporate backed promotional activities are attempting to persuade millions of healthy women worldwide that they are sick. (Moynihan *et al.*, 2002, p.889)

The case of the connection between osteoporosis and bone fracture is illustrative in relation to the issue of the 'marketing of fear' process, and three aspects of the connection can be stressed. Firstly, bone densitometry is not a good predictor of future hip fracture (Wilkin, 2001) which is the most disabling kind of fracture in elderly people. Secondly, hip fracture is rare before the age of 65 and osteoporosis is one of the risk factors involved in its occurrence in older women, not a disease that causes hip fracture (Pearce, 2001). Thirdly, fractures in older women (and also older men) result from falls, most of them occurring during normal daily activities (Campbell, 2002). These falls are caused by several factors including visual impairment, drugs that act on the central nervous system or that lower blood pressure, impaired cognition, etc. (Swift, 2001).

Consequently, to focus on one risk factor (osteoporosis) and to transform it in a 'disease' which midlife women should 'treat' for decades with potentially harmful drugs is misleading. Actually, if preventive measures are needed in order to prevent fractures they should be implemented by the reduction of all the known risk factors involved in the occurrence of fractures in the whole population (not only women) aged over 65 (Day, 2002).

The practice of the 'marketing of fear' conflicts directly with one of the fundamentals of medical ethics: 'do no harm'. What could be more harmful to a healthy person than

deceptively convincing her/him that she/he is sick and needs 'treatment' for the rest of her/his life, and will never be 'cured'? Also, what can be done in order to reverse such an expectation of being a 'sick' person when, eventually, it is demonstrated that the proposed 'sickness' and 'treatment' are essentially a marketing creation?

These questions lead to the discussion of a significant matter: the moral problem of medicalisation in preventive health-care. Such a moral problem has its roots in a simple fact which was described by Verweij (1999):

> For many forms of prevention to be effective, the co-operation or involvement of individual persons is necessary. But, as the target groups mostly consist of healthy people, it is far from self-evident that these persons will take the initiative and request to participation in prevention and health promotion programmes. Often prevention programmes have to be brought under the attention of members of target groups. (Verweij, 1999, p.89)

As discussed by Sackett (2002), such characteristics of preventive measures in health care entail a different approach and responsibility than those of 'curative' medicine. In 'curative' medicine someone who needs help with an established disease seeks an individual physician. This individual physician can only promise to this particular patient to do the best to treat him/her; never to guarantee that his/her medical intervention will make the patient better.

However, the fundamental promise that is implicitly or explicitly made to individuals when they are exhorted to accept a preventive intervention is exactly that most of them will be better for it, or at least that such interventions will not be harmful to them. If there are doubts that such preventive medical procedures or treatments can fulfil this promise it should not be implemented, or, in the case that it has already been implemented, it should immediately be terminated. As Verweij (1999) correctly points out:

> The main conclusion may be that it is not self-evidently a good thing that preventive care is offered wherever possible, even if autonomous choices of people are respected and harm is ruled out ... preventive care to healthy people

is only accepted if the expected health benefits are large and certain: the burden of proof is with the proponent of the intervention. (Verweij, 1999, p.107)

According to Sackett (2002), in the case of the medicalisation of the menopause there was a subversion of the basic principle for implementing a medical preventive intervention outlined in the previous paragraph. In 1997 a systematic review of 23 trials (Hemminki and McPherson, 1997) showed a substantial increase of the risk of cardiovascular disease related to post-menopausal hormone therapy. The WGWHI (2002) study only confirmed this risk:

Absolute excess risks per 10000 person-years attributable to estrogen plus progestin were 7 more CHD (*coronary heart disease*) events, 8 more strokes, 8 more PEs (*pulmonary embolisms*), and 8 more invasive breast cancers, while the absolute risk reductions per 10000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10000 person-years. (Working Group for the Women's Health Initiative Investigators, 2002, p.321)

There was therefore enough evidence to stop this medical intervention five years before it has actually occurred. One may argue that practising physicians were at that time (1997) the subjects of a heavy marketing effort of the pharmaceutical industry, and also were being compelled to prescribe by their patients (who were convinced of the need of such 'replacement' by marketing in the lay media). However, what is the excuse for the lack of action of the professional medical associations, governmental drug control agencies and academia?

Professional medical associations do not exist just to defend the interests of physicians. The core objective of their existence should be to ensure that their members are strictly following the ethical and scientific principles of the medical profession on behalf of patient wellbeing. Drug control agencies should be exactly what their name presupposes, and act accordingly. Finally, academia should be the moral and scientific reservoir where professional medical associations and drug control agencies would find not only their members but also the ethical and scientific support required to fulfil their social responsibilities.

Conversely, pharmaceutical companies, medical device producers and screening test producers are, as discussed in Chapter 7, commercial corporations that depend on their revenues and profits to survive and grow. They are undoubtedly important participants in the vicious circle that has led to the problems outlined in this section. However, to focus only on the control of the objectives and behaviour of these commercial corporations would be a misguided interpretation of the problem. This would be to ignore the innermost and more modifiable contributors to the vicious circle, namely academia and medical education.

Distinct from the discussion of the industrialisation of current medical research, the example of the medicalisation of the menopause shows a much clearer instance of the vicious circle in which the pharmaceutical industry, drug control agencies, professional medical associations and academia are all entangled. Such an example demonstrates that, at least in this particular case, less frequently discussed components of such a vicious circle played an important role not only in the creation of the phenomenon of the medicalisation of the menopause but also in the maintenance of the erroneous concepts that entailed its conception, even when there was enough evidence against this kind of medical intervention.

It is not conceivable that the pharmaceutical industry, medical device manufacturers and screening test manufacturers could have created the worldwide conditions needed for such a kind of medicalisation without the participation, conscious or otherwise, of the other members of the vicious circle. In fact, the same kind of structure seems to be involved in several other cases of medicalisation (Moynihan *et al.* 2002), one of them being the 'partial androgen deficiency of the ageing man' (PADAM) (Gladh *et al.*, 2005).

The case of PADAM is particularly interesting because it embodies several aspects that are similar to the issue of the medicalisation of the menopause. Based on the average decline of active testosterone, and symptoms such as 'increased abdominal circumference', 'decreased libido', 'less strong erection' and 'lack of energy', Gladh *et al.* (2005) propose the existence of a 'clinically relevant deficit' they called 'partial androgen deficiency of the ageing man'. These authors are members of a Swedish medical school and their study was partially funded by the pharmaceutical company

Organon ®. Based on such group of 'symptoms' and considering that a fall in testosterone levels is a physiological fact of ageing in man, one can only imagine how many millions of men will be 'diagnosed' as having such a 'clinically relevant deficit'.

As was demonstrated in this section, the original simple and efficient method used in the solution of the cholera problem in London by Snow (Cartwright and Biddiss, 1972) evolved into a rather intermingled structure based on economic profit, personal interests and the empowerment of professional associations. All such modifications of the ethical and structural processes of preventive medicine took place with, at least, the complacent acceptance of such deviations by academia. It is therefore necessary for the purposes of the present study to discuss the responsibility of academia and medical education.

8.4 The responsibility of academia and medical education

It might sound strange to use the term 'responsibility' when discussing the factors related to academia and medical education that are important for the present study. According to the discussion in Chapter 7 and Sections 8.2 and 8.3, it may seem that these structures are victims, or at most helpless collaborators, of a powerful corporate structure that is presently dominating medical research, medical education and medical practice.

However, once they are considered as elements of a vicious circle they in fact become 'participants' in such a circle. Their influence and responsibility in the maintenance of the vicious circle cannot be evaluated by their apparent fragility, but by the role they play in the continuation and reinforcement of such a structure. In fact, academia and medical education may seem to have different levels of participation and responsibility depending on the medical school and country that one is evaluating. However, as will be shown, they are always active participants.

Such a perspective is important not only to describe the known participants of the vicious circle in which are entangled the pharmaceutical industry, medical research and medical education. It may also give important clues in relation to possible ways of breaking such a circle and also about the feasibility of such interventions.

In order to correctly evaluate the responsibility of academia and medical education it is necessary to delimit which are (or should be) the main duties of both structures. The first one should undoubtedly be to produce good doctors. The real problem is to define validly what a 'good doctor' is. According to Macnaughton (2000):

> ... doctors need to understand their patients through a scientific knowledge ... and to appreciate how scientific research can help them to make decisions about the best treatment for their patients. But this scientific approach needs to be modified in the clinical situation when dealing with the individual patient. A "humane" doctor is required, with the understanding, assisted by interpretative ability and insight, and governed by ethical sensitivity, to apply this scientific evidence and skills to the individual patient. (Macnaughton, 2000, p.23)

The above quoted definition is a rather sensible way of describing how a 'good doctor' should be and behave. In fact, a less complex definition which also encompasses the necessary qualities of a 'good doctor' and the responsibility of present medical education is the one proposed by Hurwitz and Vass (2002):

> The varieties of good, poor, and bad doctors are diverse and may sometimes coexist in the same individual. This does not make becoming a good doctor an unattainable ideal. Medical education today should be aiming to marry the skills and sensitivities of the applied scientist to the reflective capabilities of the medical humanist. (Hurwitz and Vass, 2002, p.668)

Discussing the reasons why current medical education is successful or not in meeting these standards is probably the best way of evaluating the share of responsibility that medical education has in relation to the present situation. Macnaughton concedes that 'this (*producing such kind of doctors*) is a tall order for medical education to take on' (Macnaughton, 2000, p.23). This difficulty is due to the fact that in the 20th century the focus of medical education was largely on giving medical students only the scientific knowledge and skills required of a doctor.

In fact, the problem in this specific matter is to decide whether medical students are being 'trained' or 'educated' to be doctors. In the present discussion I will use the term 'trained'

to represent the view that they should receive in medical schools only the scientific knowledge and skills required of a doctor. Conversely, the term 'educated' will represent the notion that their medical schools should fulfil all the requisites of the definition of Macnaughton (2000) quoted above.

In Chapter 6 it was argued that medicine is a profession that is based in professional practice, and that such practice is clearly related to the delivered and hidden curricula. The data obtained in my research, and discussed in Chapters 4 and 5, demonstrate that the delivered and hidden curricula of the five medical schools that participated in this study, and also the curricula of several other countries, seem to be focused expressly in the specialisation of medical practice and learning. Such specialisation usually precludes the correct transmission of the ethical and methodological principles of medical research (see Chapter 5). However, many Brazilian teachers and students have exposed in their answers that they believe that specialisation is not only necessary, but in fact the cornerstone of their success as practising physicians (see Chapter 5).

Therefore, at least in these schools, a medical student would receive only the necessary scientific knowledge and skills required of a 'specialised' doctor, and that would not be sufficient to fulfil all the requisites of the expected structure of an 'educated' doctor. In fact, as discussed in Section 7.6.2, many medical schools seem to have abdicated their responsibility to instruct their students about ethical and methodological aspects of medical research while favouring the development of a more 'technical' approach to medicine.

Such abdication would constitute an educational flaw, even if one accepted the view that these students should only receive 'the necessary scientific knowledge and skills' in order to become good doctors. This is true, for example, when one considers that to acquire the necessary scientific knowledge entails a critical appraisal of such knowledge, particularly in a time of intense industrialisation of medical research (Section 8.2) and medicalisation of health-care (Section 8.3). Students who have not received sufficient education about the ethical and methodological basis of medical research would be expected to behave, whether as practising physicians or as physician-researchers, as uncritical participants in the vicious circle that afflicts medical education and medical research.

In order to produce good doctors, medical education should not only focus on specialisation but also, at least, in giving to medical students the necessary scientific knowledge and skills which are required nowadays – and this includes knowledge about what is necessary to become a good doctor, in the broader sense. Furthermore, medical education must provide the students with the ethical basis that is necessary to underpin the development of their social responsibility in respect to science, as discussed in Section 7.4.2. According to Coulehan *et al.* (2003):

> ... the failure of medical education to focus on producing good doctors, rather than simply on producing good technicians, is an ethical failure. Moreover, the introduction and development of biomedical ethics teaching in medical schools over the last 30 years has not ameliorated this. (Coulehan *et al.*, 2003, p.21)

It is understandable that such a situation is happening as the teaching of biomedical ethics conflicts with the information medical students are receiving in the medical schools due to the delivered, experienced and hidden curricula (see Chapter 6). The 'role models' for these students, as a result of the failure of academia to provide them with better ones, are the 'specialised' and 'successful' physicians, who may not always be the ethical ones as discussed in Sections 7.4.2, 7.5 and 7.6.2.

Additionally, the teaching of medical ethics in many schools is nearly always concerned with things like informed consent, beneficence, non-maleficence and justice. However, it fails to consider subjects like whether doctors are being drawn to treat certain conditions as diseases when they are not and also pays scant attention to the economic and political forces that affect medical research and medical education.

According to such reasoning, a simple course of scientific methodology, which was the proposal of several teachers and students that participated in this study (see Section 5.2.3) may not accomplish a great deal. As its objectives would be to correct the present low level of knowledge about medical research methodology and bias in medical research, the students (and teachers) might see it as a mere accessory to the written curriculum if such matters do not become a real preoccupation for academia.

This discussion also unveils an interesting aspect that is seldom discussed. When academia abdicated from its duty to provide a broader scientific knowledge (which entails a critical appraisal of such knowledge) a kind of 'vacant' area in medical education and medical research was created. Such vacant area was then occupied by the pharmaceutical industry.

If this is the case, one cannot describe the present situation of medical research and medical education as a result of an 'invasion' or the 'domination' of the pharmaceutical industry in these areas. At most, it would be a 'consensual appropriation'. For many members of academia, also including many in medical schools, this consensual appropriation was welcomed since it resulted in a substantial increase in power and resources for those who understood and accepted such appropriation. In fact, such a kind of acceptance is evident in the answers of some of the participants of my study (see Section 5.2.2).

However, such a partnership had deleterious side effects for medical research and medical education (see Section 2.2 and Chapter 7). Actually, it may have contributed to the aggravation of an important problem of current undergraduate medical education, exposed by Coulehan *et al.* (2003):

> The socialization process that occurs during medical training conflicts with, and tends to diminish, many of the attributes and values usually associated with good doctoring ... Although these characteristics are often reinforced by the explicit curriculum in medical schools, the tacit learning that trainees receive in the hospital and institutional setting promotes other, and often conflicting, personal attributes – such as detachment, entitlement, wariness, cynicism, an ethic of technique, and a moral myopia about the needs of patients beyond one's immediate field of vision. (Coulehan *et al.*, 2003, p.21)

Additionally, the pharmaceutical industry's 'appropriation' of a substantial part of medical research and continuing medical education (CME) significantly reduced the possibility that this educational flaw within undergraduate medical education could be corrected in post-graduation courses and CME programs (see Section 7.6.3).

Consequently, the opinion manifested in the answers of 40% of the teachers and 45% of the students that participated in my research (Section 5.2.3) that medical research methodology should be a subject for study in post-graduation courses would not be realistic. This is especially true when one remembers that at least part of the current problem of the incidence of bias in medical research has its roots in the moral and scientific formation of 'physician-researchers' (see Section 7.4.2), and that such formation should in fact be structured in their undergraduate courses.

The appropriation of medical research by the pharmaceutical industry is not happening without some traumatic experiences for a number of members of academia, who are feeling that their academic freedom and ethical principles are being jeopardised by such appropriation. One salient example of such a traumatic experience is the case involving Dr. Nancy Olivieri, the Hospital for Sick Children (Toronto), the University of Toronto and Apotex, a Canadian pharmaceutical company (Thompson *et al.*, 2001).

In this particular case Apotex sued Dr Olivieri due to the disclosure and publication of her research results about deferiprone (a bivalent ion chelator) which showed a low level of efficacy and the occurrence of an increase of hepatic fibrosis in patients with thalassemia who used the drug. Dr Olivieri had signed a confidentiality agreement in a previous short-term, uncontrolled clinical trial with the same drug, which was sponsored by a grant from Apotex to the Hospital for Sick Children (Toronto). However, she had not signed a similar agreement when she started the second trial.

Although the complete discussion of this traumatic episode falls outside the scope of the present discussion, there are some aspects of it that are emblematic in relation to the possible known and unknown problems of the present entanglement between academia and pharmaceutical industry. As Nathan and Weatherall (2002) point out, the central issue in this case was the failure of academia to defend two essential foundations of science, namely academic freedom and the right to publish.

Analysing the Olivieri case, Nathan and Weatherall (2002) conclude that:

> Although the Olivieri debacle is complicated by personal animosity, poor administrative judgment, and bad behaviour among academic colleagues, the

case report raises a number of fundamental questions about the research interface among teaching hospitals, academic clinical departments of universities, and industry. As the authors of the CAU (*Canadian Association of University Teachers*) report state in their summary (*Thompson et al., 2001*), these are issues that affect the entire biologic-research community. (Nathan and Weatherall, 2002, p.1369).

Nathan and Weatherall (2002) also assert that although the Olivieri case was unusual, it was not unique, and that there are other examples of serious failure of institutional support in similar circumstances. This failure is mostly related to cases in which the industry threatens researchers due to conflicts of interests with regard to whether or not to publish research results that may be contrary to industry interests.

The real problem in this particular case, as can be depicted from the discussion of Nathan and Weatherall about the position of the University of Toronto, is that it shows that academia is sometimes entitling itself to discuss the limits of academic freedom of researchers when it affects academia financial or power arrangements. What results is therefore a rather bizarre situation. Whilst, among other problems, academia is being rather lenient in the subject matters of the industrialisation of medical research and medicalisation in health-care (Sections 8.3 and 8.4), it can accept the position of judging the limits and correctness of two universally established principles of science, namely academic freedom and the right to publish.

Consequently, academia and medical education are failing to accomplish two of their central responsibilities: the formation of good doctors and the defence of the central ethical principles of good science. Furthermore, these failures are fundamentally due to the abdication of academia and medical education of their responsibility to provide a broader scientific knowledge and introduce solid ethical principles to medical students. Such a failure, combined with an indiscriminate entanglement with the pharmaceutical industry is responsible for many of the present problems of medical education and medical research.

At this point it is necessary to conclude that, although it might seem to many a somewhat naïve proposition, the absolute disentanglement of the communal activities of academia

and the pharmaceutical industry (see Section 7.6.3) is not only desirable but in fact necessary in respect to health-care, medical education and medical research.

8.5 Conclusions

Neither the discussion about bias in research nor its prevention and correction is novel in science. The existence of systematic distortions of statistical results, or inaccurate processes that may occur at any stage of any piece of research which may interfere with its results, are well-studied problems in many fields of science. This is also the case in medical research as discussed in Chapter 1.

However, differently from several other areas of science, the increasing knowledge about the problem of bias, its detection and correction (see Chapter 1 and Section 2.2) is not resulting in a significant limitation of its level of occurrence in the case of medical research. The investigation and discussion of the possible causes for such a puzzling situation, and specially the relationship between the problem of bias in medical research and the structure of current medical education, which could be one such cause, underpinned the formulation of the present study.

In fact, this study has its roots in an editorial by Douglas G. Altman in which he stated that much poor medical research 'arises because researchers feel compelled for career reasons to carry out research that they are ill equipped to perform, and nobody stops them' (Altman, 1994, p.283). As a physician and a teacher such a statement seemed astonishing to me. I could understand that some medical researchers were feeling compelled to publish for career reasons. However, it seemed to me hard to believe that the high incidence of bias in medical research was due to such a cause. More startling yet was his affirmation that they were 'ill equipped' and that 'nobody stops them'.

Was it possible that medical researchers are 'ill equipped' to do research when the basis of good medical research is readily available, and when the predominant focus of current undergraduate medical education and continuing medical education is exactly on 'evidence-based medicine'? How could it be possible that 'nobody stops them' if academia and the professional medical associations have a significant influence upon

academic researchers and physicians in respect to counselling and determining the correct ethical and methodological aspects of medical research and medical practice?

In order to at least partially answer these questions I have conducted a research in five Brazilian medical schools (see Chapter 3) in order to evaluate three aspects of present medical education that could answer the first question in the previous paragraph. The first aspect was to appraise the level of awareness of teachers and students about the problem of bias in medical research. The second was to gather their opinions about whether these systematic errors are being caused only by methodological problems within research or whether they are also a manifestation of habits acquired during the process of medical education. The final aspect was to identify their points of view about what could be changed in medical education in order to reduce the present incidence of bias in medical research.

The results of this research (Chapters 4 and 5) demonstrate that:

- In relation to the participants of this research the level of awareness about bias in medical research can be considered insufficient and fragmentary. Further, there were no efficient formal methods of introducing medical students to such a problem in medical research in these schools.
- The participants rejected the hypothesis that the present incidence of bias in medical research is due mainly to methodological problems. They were aware that current medical education could be one of the causes of the problem.
- Medical education in the medical schools that participated in my research, irrespective of the apparently different curricula, is focused on an intense 'specialisation' of medical knowledge and medical practice.

It also became evident that undergraduate medical students do not have real opportunities to evaluate and discuss the structure and problems of medical research. In a 'specialised' medical world, it seems that there is neither place nor time for the discussion of such problems with undergraduate students.

Such a strong focus on 'specialisation' led me to investigate the real structure of a modern medical school curriculum (Chapter 6). This investigation revealed that the 'specialisation' process that is happening in the schools that participated in my study is also present in several medical schools of many countries. More than that, it showed that there still is a lively debate about what a modern medical curriculum should consist of, and especially of how to implement it.

However, it also became evident that no prescribed model will survive within a medical school without the agreement of faculty members and medical students. Unfortunately, it seems that the present accepted process of 'specialisation' is neither enhancing the present low level of awareness of student and faculty members about the problem of bias in medical research nor contributing to a discussion of alternative models of medical education.

Therefore, I have, sadly, to agree with Altman (1994). The current medical education in many medical schools of several countries does not well equip their students to become medical researchers. In fact, these schools are not even preparing their students to face the challenges of a medical practice based on research evidence.

However, it may still be argued that this is a minor problem. In any case, the argument might continue, these 'researchers-to-be' and practising physicians can always count on post-graduation programmes and continuing medical education courses to acquire such knowledge. Unfortunately, the evaluation of the current structure of formation of medical researchers and the aims of today's continuing medical education demonstrates that they cannot fulfil such expectations (Section 2.4, Chapter 7).

At this point of my research it became clear that there is in fact a relationship between the problems of current medical research and medical education. However, such a relationship does not have a direct 'cause/effect' kind of association. Actually, medical research and medical education are participants in a vicious circle in which they are entangled together with the pharmaceutical industry, academia, professional medical associations and medical journals (Chapter 7).

It is rather difficult to define when such a worldwide encompassing vicious circle was established; however, there is sufficient evidence about the reasons why and how it is being maintained and reinforced in the last decades. These reasons will be given in the next few paragraphs, but no attempt will be made to classify them in an order of importance, as such an order may well depend on the specific medical school and country at issue. However, an attempt will be made to reveal the possible best approaches to break out of this vicious circle.

An important participant of the vicious circle is undoubtedly the pharmaceutical industry. From a relatively less important position in respect to medical education and academic medical research at the beginning of the 20th century, the pharmaceutical industry is presently, directly or indirectly, involved in a significant proportion of academic medical research and continuing medical education (CME) (Sections 2.4, 8.2 and 8.3). The central problem of such involvement is the subversion of the moral principles that should underpin academic medical research and CME. These have been progressively substituted by a moral structure that is more compatible with a profit based organisation than with real academic science and education (Chapter 7).

Such a modification of academic medical research and educational objectives, combined with an intense and well orchestrated marketing effort, entailed the industrialisation of current medical research (Section 8.2), and a substantial part of the phenomenon of medicalisation in health care (Section 8.3). Both of these events have been, in recent decades, extremely profitable to pharmaceutical industry, but deleterious for medical education and academic medical research.

However, I do not see these problems as being caused solely by the interference from pharmaceutical industry in medical education and academic medical research, nor as a 'domination' of the industry on academia nor as an irremediable effect of any such domination (Section 8.4).

In fact, this apparent domination has only occurred because academia abdicated its duties to produce 'good doctors' in order to produce 'good technicians', and also renounced to its role in conducting and being responsible for continuing medical education (Sections 2.4.2 and 8.4). Furthermore, and most importantly, academia abdicated its position as the

moral and scientific reservoir of the medical profession in exchange for profit and power for some of its members (Chapter 7, Section 8.4). In its misdemeanour academia dragged many medical professional associations and medical journals to the same short-sighted and self-interested way of behaving, to the detriment of medical education and medical research. Consequently, Altman (1994) was possibly right when he stated that 'nobody stops them'.

The final conclusion of my thesis is that there is indeed a relationship between the problem of bias in medical research and current medical education. However, such relationship is dependent, and is being maintained, by a vicious circle.

Such a vicious circle, in my opinion, will only be disrupted when academia reclaims the control and care of academic medical research and continuing medical education, and simultaneously decides to produce 'good doctors' (Section 8.4). However, this will only happen when academia, which is entitled to do so, votes for a complete disentanglement with the pharmaceutical industry (Chapter 7). Less decisive, and apparently more palliative, solutions in this matter may only cause further reinforcement of the present vicious circle.

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Appendix 1

Nome*...

Endereço*..

....Cidade/Estado*...

CEP*...................Telefone*........................Email*...

Departamento..

(*) = Opcional

1 Sua ocupação atual (assinalar quantas forem necessárias):
   ☐ Ensino
   ☐ Pesquisa
   ☐ Extensão
   ☐ Administrativa

2 Possui trabalhos publicados (assinalar quantas forem necessárias):
   ☐ No Brasil
   ☐ No exterior (citar países) ....
   ☐ Não tem trabalhos publicados

3 Idioma em que os trabalhos foram publicados (assinalar quantas forem necessárias):
   ☐ Português
   ☐ Espanhol
   ☐ Inglês
   ☐ Outros..

4 Formação acadêmica:
   ☐ Especialização
   ☐ Mestrado
   ☐ Doutorado
   ☐ Pós-doutorado

5 Como você tem adquirido informação sobre tendenciosidades (viés) em pesquisa
  médica? (assinale mais de uma opção, se necessário)
   ☐ Através de livros sobre metodologia científica.
   ☐ Em congressos médicos ou conferências.
   ☐ Através de revistas médicas. Favor citar um exemplo:...
   ☐ Através de cursos especiais. Favor citar um exemplo:...
   ☐ Pela Internet

6 No último ano quantas vezes discutiu o problema de tendenciosidades (viés) em pesquisa médica com seus alunos?
- ☐ Freqüentemente
- ☐ Algumas vezes
- ☐ Nenhuma vez
- ☐ Não me recordo

7 De que forma a aquisição de conhecimento sobre tendenciosidades em pesquisas médicas modificou sua maneira de avaliar trabalhos científicos publicados em revistas médicas?

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8 Em relação ao problema de tendenciosidades (viés) em pesquisa médica com quais afirmações abaixo você concordaria? (assinale mais de uma se necessário)
- ☐ É exclusivamente um problema de metodologia científica, sem relação com o ensino médico básico.
- ☐ É responsabilidade do curso de Metodologia Científica de cada escola médica prover o conhecimento sobre estes desvios aos alunos de graduação.
- ☐ Não é algo que deva ser abordado no ensino médico básico, devendo ser motivo de estudo apenas na pós-graduação.
- ☐ As tendenciosidades (viés) em pesquisa médica tem se transformado progressivamente em um problema ético.
- ☐ É responsabilidade das revistas médicas avaliar quais trabalhos apresentam tendenciosidades.
- ☐ Não concordo com nenhuma afirmativa acima.

9 Nas afirmativas abaixo escolha uma alternativa que mais se aproxime de sua opinião pessoal:

a) "Atualmente, revisões sistemáticas e meta-análises são os melhores meios de adquirir novos conhecimentos em Medicina".
- ☐ Concordo plenamente
- ☐ Discordo parcialmente
- ☐ Discordo totalmente
- ☐ Não tenho opinião formada sobre o assunto

b) "Viés de publicação é uma ameaça à qualidade de revisões sistemáticas e meta-análises".
   ☐ Concordo plenamente
   ☐ Discordo parcialmente
   ☐ Discordo totalmente
   ☐ Não tenho opinião formada sobre o assunto

c) "Tendenciosidades metodológicas em ensaios clínicos randomizados podem exagerar de forma significativa os resultados obtidos em meta-análises futuras".
   ☐ Concordo plenamente
   ☐ Discordo parcialmente
   ☐ Discordo totalmente
   ☐ Não tenho opinião formada sobre o assunto

10 Em sua opinião, como o conhecimento sobre viés em pesquisa poderia ser transmitido aos alunos de um curso de Medicina?

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11 Você acredita que sejam necessárias mudanças curriculares nos cursos de Medicina atuais para que a questão de tendenciosidades (viés) em pesquisa médica seja melhor transmitida aos alunos? Quais seriam estas mudanças?

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....
....

12 Concordaria com uma entrevista pessoal, caso seja necessário, para aprofundar aspectos do presente questionário?

☐ Sim

☐ Não

13 Caso concorde, com a garantia de que em nenhum momento será rompido o compromisso de anonimidade dos participantes durante a apresentação dos resultados desta pesquisa, permitiria que ela fosse gravada para análise posterior?

☐ Sim

☐ Não

Name*..

Address*...

.... City / State* ....

ZIP* .... Telephone * .... Email* ....

Department..

(*) = Optional

1   Your present occupation (tick more than one if necessary):
    ☐ Teaching
    ☐ Research
    ☐ Extension
    ☐ Administration

2   I have published papers (tick more than one if necessary):
    ☐ In Brazil
    ☐ In foreign countries (cite countries) ....
    ☐ I have no published papers.

3   Which was (were) the language(s) of publication? (tick more than one if necessary)
    ☐ Portuguese
    ☐ Spanish
    ☐ English
    ☐ Other...

4   Your academic background is:
    ☐ Specialist
    ☐ Master
    ☐ Doctor
    ☐ Post-doctoral studies

5   Which was the method that helped you to acquire your present knowledge about
    systematic deviations (bias) in medical research? (tick one or more boxes)
    ☐ Books about methodology of research
    ☐ Medical congress or conferences
    ☐ Medical journals. Please cite one...
    ☐ Special courses. Please cite one ....
    ☐ The Internet

6   How often did you discuss the problem of methodological deviations (bias) with your students in the last year?
☐ Frequently
☐ Rarely
☐ Never
☐ I do not remember

7   How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias? Please explain.

....

....

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....

....

....

8   In relation to the problem of methodological deviations (bias) in medical research, with which statements below would you agree? (tick more than one if necessary):
☐ It is a problem of scientific methodology, with no relation with the medical graduation course.
☐ The course of Scientific Methodology of each medical school should be responsible to provide the knowledge about these deviations to the students.
☐ It is a subject that should be discussed at the post-graduation level, and not in the graduation course.
☐ The methodological deviations (bias) in medical research are progressively becoming an ethical issue.
☐ Medical journals are responsible for the evaluation of methodological deviations in papers they publish.
☐ I do no agree with any of the above statements.

9   In the statements below choose the alternative that is more compatible with your personal opinion:

a) "Systematic reviews and meta-analyses are presently the best way to acquire knowledge in Medicine"
☐ I totally agree
☐ I partially disagree
☐ I totally disagree
☐ I do not have an opinion about the subject

b) "Publication bias is a menace to the quality of systematic reviews and meta-analyses"
- ☐ I totally agree
- ☐ I partially disagree
- ☐ I totally disagree
- ☐ I do not have an opinion about the subject

c) "Systematic deviations (bias) in randomised clinical trials may significantly exaggerate the results of future meta-analyses"
- ☐ I totally agree
- ☐ I partially disagree
- ☐ I totally disagree
- ☐ I do not have an opinion about the subject

10 In your opinion, how the knowledge about bias in research should be transferred to the students of a medical school?

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11 Do you believe that changes in the curriculum of medical schools are necessary in order to achieve a better transference of knowledge about bias in medical research? What should be changed?

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12 Do you agree with a personal interview, if necessary, to enlighten some aspects of the present questionnaire?

☐ Yes

☐ No

13 If you agree, provided that it is assured the anonymity of participants at the presentation of the results of this research, would you permit the interview to be recorded for posterior analyses?

☐ Yes

☐ No

Nome*..

Endereço*..

....Cidade/Estado*..

CEP*.........................Telefone*.............................Email*...

(*) = Opcional

1 Durante seu curso de Medicina, você colaborou em alguma pesquisa na área médica?
   ☐ Sim
   ☐ Não

2 Estas pesquisas em que colaborou:
   ☐ Foram publicadas no Brasil
   ☐ Foram publicadas no exterior (citar países) ....
   ☐ Não foram publicadas
   ☐ Não sabe se foram publicadas

3 Caso tenham sido publicadas, qual foi o idioma de publicação?
   ☐ Português
   ☐ Espanhol
   ☐ Inglês
   ☐ Outras...

4 Como você tem adquirido informação sobre tendenciosidades (viés) em pesquisa médica? (Assinale mais de uma opção, se necessário)
   ☐ Em meus cursos normais de graduação
   ☐ Através de livros sobre metodologia científica.
   ☐ Em congressos médicos ou conferências.
   ☐ Através de revistas médicas. Favor citar um exemplo: ....
   ☐ Através de cursos especiais. Favor citar um exemplo: ....
   ☐ Pela Internet
   ☐ Não tenho recebido informações sobre o assunto de nenhuma fonte

5 No último ano quantas vezes seus professores discutiram o problema de tendenciosidades (viés) em pesquisa médica com você?
   ☐ Freqüentemente
   ☐ Algumas vezes
   ☐ Nenhuma vez
   ☐ Não recordo quantas vezes

6   De que forma a aquisição de conhecimento sobre tendenciosidades em pesquisa médica modificou sua maneira de avaliar trabalhos científicos publicados em revistas médicas?

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7   Em relação ao problema de tendenciosidades (viés) em pesquisa médica com quais afirmações abaixo você concordaria? (assinale mais de uma se necessário)
   ☐ É exclusivamente um problema de metodologia científica, sem relação com o ensino médico básico.
   ☐ É responsabilidade do curso de Metodologia Científica de cada escola médica prover o conhecimento sobre estes desvios aos alunos de graduação.
   ☐ Não é algo que deva ser abordado no ensino médico básico, devendo ser motivo de estudo apenas na pós-graduação.
   ☐ As tendenciosidades (viés) em pesquisa médica tem se transformado progressivamente em um problema ético.
   ☐ É responsabilidade das revistas médicas avaliar quais trabalhos apresentam tendenciosidades.
   ☐ Não concordo com nenhuma afirmativa acima.

8   Nas afirmativas abaixo escolha uma alternativa que mais se aproxime de sua opinião pessoal

a) "Atualmente, revisões sistemáticas e meta-análises são os melhores meios de adquirir novos conhecimentos em Medicina".
   ☐ Concordo plenamente
   ☐ Discordo parcialmente
   ☐ Discordo totalmente
   ☐ Não tenho opinião formada sobre o assunto

b) "Viés de publicação é uma ameaça à qualidade de revisões sistemáticas e meta-análises".
   ☐ Concordo plenamente
   ☐ Discordo parcialmente
   ☐ Discordo totalmente
   ☐ Não tenho opinião formada sobre o assunto

c) "Tendenciosidades metodológicas em ensaios clínicos randomizados podem exagerar de forma significativa os resultados obtidos em meta-análises futuras".
☐ Concordo plenamente
☐ Discordo parcialmente
☐ Discordo totalmente
☐ Não tenho opinião formada sobre o assunto

9 Em sua opinião, como o conhecimento sobre viés em pesquisa poderia ser transmitido aos alunos de um curso de Medicina?

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10 Você acredita que sejam necessárias mudanças curriculares nos cursos de Medicina atuais para que a questão de tendenciosidades (viés) em pesquisa médica seja melhor transmitida aos alunos? Quais seriam estas mudanças?

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11 Concordaria com uma entrevista pessoal, caso seja necessário, para aprofundar aspectos do presente questionário?
☐ Sim
☐ Não

12 Caso concorde, com a garantia de que em nenhum momento será rompido o compromisso de anonimidade dos participantes durante a apresentação dos resultados desta pesquisa, permitiria que ela fosse gravada para análise posterior?
☐ Sim
☐ Não

Name* ....

Address*...

.... City / State* ....

ZIP* .... Telephone* .... Email* ....

(*) = Optional

1   Have you collaborated with research projects as a medical student?
    ☐ Yes
    ☐ No

2   The research project you participated in:
    ☐ Was published in Brazil
    ☐ Was published in foreign countries (cite countries) ....
    ☐ Was not published
    ☐ I do not know if it was published

3   If the research was published, which was the language of publication?
    ☐ Portuguese
    ☐ Spanish
    ☐ English
    ☐ Other...

4   Which was the method that helped you to acquire your present knowledge about systematic deviations (bias) in medical research? (tick one or more boxes)
    ☐ The curricular courses for graduation
    ☐ Books about methodology of research
    ☐ Medical congress or conferences
    ☐ Medical journals. Please cite one...
    ☐ Special courses. Please cite one... ....
    ☐ The Internet
    ☐ I have not received any information about systematic deviations in medical research from the sources cited aboves

5   How often did your teachers discuss the problem of methodological deviations (bias) with you in the last year?
    ☐ Frequently
    ☐ Rarely
    ☐ Never
    ☐ I do not remember

6   How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias? Please explain.

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7   In relation to the problem of methodological deviations (bias) in medical research, with which statements below would you agree? (tick more than one if necessary)
   ☐   It is a problem of scientific methodology, with no relation with the medical graduation course.
   ☐   The course of Scientific Methodology of each medical school should be responsible to provide the knowledge about these deviations to the students.
   ☐   It is a subject that should be discussed at the post-graduation level, and not in the graduation course.
   ☐   The methodological deviations (bias) in medical research are progressively becoming an ethical issue.
   ☐   Medical journals are responsible for the evaluation of methodological deviations in papers they publish.
   ☐   I do no agree with any of the above statements.

8   In the statements below choose the alternative that is more compatible with your personal opinion:

a)   "Systematic reviews and meta-analyses are presently the best way to acquire knowledge in Medicine"
   ☐ I totally agree
   ☐ I partially disagree
   ☐ I totally disagree
   ☐ I do not have an opinion about the subject

b)   "Publication bias is a menace to the quality of systematic reviews and meta-analyses"
   ☐ I totally agree
   ☐ I partially disagree
   ☐ I totally disagree
   ☐ I do not have an opinion about the subject

c) "Systematic deviations (bias) in randomised clinical trials may significantly exaggerate the results of future meta-analyses"
☐ I totally agree
☐ I partially disagree
☐ I totally disagree
☐ I do not have an opinion about the subject

9 In your opinion, how the knowledge about bias in research should be transferred to the students of a medical school?

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10 Do you believe that changes in the curriculum of medical schools are necessary in order to achieve a better transference of knowledge about bias in medical research? What should be changed?

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11 Do you agree with a personal interview, if necessary, to enlighten some aspects of the present questionnaire?
☐ Yes
☐ No

12 If you agree, provided that it is assured the anonymity of participants at the presentation of the results of this research, would you permit the interview to be recorded for posterior analyses?
☐ Yes
☐ No

Appendix 2

Ponta Grossa,

Caro

Meu nome é Marco Antonio Gimenes Basso e sou médico formado pela Faculdade de Medicina de Botucatu (UNESP).

Atualmente sou Professor Adjunto de Fisiologia e Fisiopatologia Médica na Universidade Estadual de Ponta Grossa - PR (UEPG), e desde agosto de 2001 participo do programa de PhD em Educação no Instituto de Educação da Universidade de Londres.

Um dos objetivos da minha tese é avaliar como são vistos atualmente os desvios metodológicos (viés, *bias*) em pesquisa médica, pelos integrantes das escolas de Medicina do Estado do Paraná. Ao mesmo tempo, gostaria de saber, dos internos e docentes, quais seriam as medidas que poderiam ser adotadas para minimizar o problema.

Anexo a esta carta encontra-se um pequeno questionário onde poderá externar suas opiniões sobre o assunto. Espero que a devolução do questionário seja fácil para você, e por isso estou incluindo um envelope já selado e endereçado a mim, para o retorno do mesmo. Gostaria que retornasse o questionário mesmo que não possa responder a algumas das questões ou tenha dificuldades de qualquer natureza. Sua opinião é muito importante para podermos conhecer melhor o tema, e suas propostas eventualmente poderão trazer avanços na área da Educação Médica.

As informações pessoais como nome e endereço são opcionais, porém se declaradas facilitariam futuros contatos, se forem necessários. Asseguro que estas informações não serão usadas na publicação da tese, nem em futuras publicações em revistas científicas. Considero a anonimidade dos participantes desta pesquisa um princípio ético que será rigorosamente cumprido.

Caso queira qualquer informação adicional, por favor, entre em contato comigo. Estarei à sua disposição para esclarecer qualquer aspecto do projeto.

Desde já, agradeço por sua atenção e participação na pesquisa.

Prof. Marco Antonio Gimenes Basso
Disciplina de Fisiopatologia Médica – UEPG
Rua Heitor Ditzel 135
84050-410 Ponta Grossa – PR
Telefone: (42) 3223-7409
Email : marcoagbasso@uol.com.br

Ponta Grossa,

Dear

My name is Marco Antonio Gimenes Basso and I am a physician graduated by the Faculdade de Medicina de Botucatu (UNESP).

Currently, I am an Associate Professor of Physiology and Pathophysiology at the Universidade Estadual de Ponta Grossa (Paraná). Since August of 2001, I am a participant of the PhD program at the Institute of Education of the University of London.

The main aim of my thesis project is to evaluate how the members of medical schools, in Brazil, perceive the problem of methodological deviations (bias) in medical research. Furthermore, I would like to know the opinion of teachers and interns about the possible educational measures that could be used to reduce this problem.

Annexed to this letter you are receiving a small questionnaire. In order to facilitate the return of the questionnaire, I am including a pre-stamped and addressed envelope. I would ask you to return the questionnaire even if you can not, or would like not, to respond to some questions. Your opinion is very important, and your proposals will eventually contribute to the improvement of medical education.

Your personal information, as name and address, are optional. However, this information would facilitate future contacts. I can ensure you that your personal information will not be used in my thesis or in future publications. In addition, I guarantee that the anonymity of the participants is one of the ethical principles of my research.

If you wish to receive additional information about this project, please contact me by mail, telephone, or email.

Yours truly,

Prof. Marco Antonio Gimenes Basso
Rua Heitor Ditzel – 135
84050-410 Ponta Grossa PR
Telephone: (42) 3223-7409
Email: marcoagbasso@uol.com.br

Appendix 3

1. Teacher Questionnaire in Portuguese

Relações entre a Educação Médica
e os Desvios Sistemáticos (viés, *bias*) em Pesquisa Médica

1 **Sua ocupação atual** (assinalar quantas alternativas forem necessárias):
   - ☐ Ensino
   - ☐ Pesquisa
   - ☐ Extensão
   - ☐ Administrativa

2 **Possui trabalhos publicados nos últimos 5 anos** (assinalar quantas alternativas forem necessárias):
   - ☐ No Brasil
   - ☐ No exterior (citar quais países) ....
   - ☐ Não tem trabalhos publicados

3 **Idioma em que os trabalhos foram publicados** (assinalar quantas alternativas forem necessárias):
   - ☐ Português
   - ☐ Espanhol
   - ☐ Inglês
   - ☐ Outros ....

4 **Formação acadêmica:**
   - ☐ Especialização
   - ☐ Mestrado
   - ☐ Doutorado
   - ☐ Pós-doutorado

5 **Como você tem adquirido informação sobre tendenciosidades** (viés, *bias*) **em pesquisa médica?**
   (assinale mais de uma opção, se necessário)
   - ☐ Através de livros sobre metodologia científica.
   - ☐ Em congressos médicos ou conferências.
   - ☐ Através de revistas médicas. Citar um exemplo: ....
   - ☐ Através de cursos especiais. Citar um exemplo: ....
   - ☐ Pela Internet.
   - ☐ Outros meios. Especificar: ....

6 **No último ano quantas vezes discutiu o problema de tendenciosidades** (viés, *bias*) **em pesquisa médica com seus alunos?**
   - ☐ Frequentemente
   - ☐ Algumas vezes
   - ☐ Nenhuma vez
   - ☐ Não me recordo

7 De que forma a aquisição de conhecimento sobre tendenciosidades (viés, *bias*) em pesquisa médica modificou sua maneira de avaliar trabalhos científicos publicados em revistas médicas?

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8 Em relação ao problema de tendenciosidades (viés, *bias*) em pesquisa médica você acredita que:

	Concordo plenamente	Concordo	Discordo parcialmente	Discordo totalmente	Não tenho opinião sobre o assunto
É um problema de metodologia científica, sem relação com o curso de graduação					
O curso de Metodologia Científica é responsável pela transmissão deste tipo de conhecimento					
As tendenciosidades em pesquisa médica estão se tornando progressivamente um problema ético					
As publicações médicas são responsáveis pela avaliação das tendenciosidades nos artigos que publicam					

9 Nas afirmativas abaixo escolha uma alternativa que mais se aproxime de sua opinião pessoal:

	Concordo plenamente	Concordo	Discordo parcialmente	Discordo totalmente	Não tenho opinião sobre o assunto
Revisões sistemáticas e meta-análises são o melhor meio de obter conhecimento atualizado em Medicina					
Viés (*bias*) de publicação é uma ameaça à qualidade de revisões sistemáticas e meta-análises					
As tendenciosidades em ensaios clínicos randomizados podem causar alterações nas futuras meta-análises					

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10 Em sua opinião, como o conhecimento sobre viés em pesquisa poderia ser transmitido aos alunos de um curso de Medicina?

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11 Você acredita que sejam necessárias mudanças curriculares nos cursos de Medicina atuais para que a questão de tendenciosidades (viés, *bias*) em pesquisa médica seja transmitida aos alunos?

☐ Sim
☐ Não

12 Caso sua resposta à questão anterior seja *Sim*, quais seriam estas mudanças?

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13 Concordaria com uma entrevista pessoal, *caso seja necessário*, para aprofundar aspectos do presente questionário?
☐ Sim
☐ Não

14 **Caso concorde,** *com a garantia de que em nenhum momento será rompido o compromisso de anonimidade dos participantes durante a apresentação dos resultados desta pesquisa,* **permitiria que ela fosse gravada para análise posterior?**
☐ Sim
☐ Não

Nome * ....

Endereço * ....

Cidade/Estado * ....**CEP *** ....

Telefone * .... **E-mail** * ....

Departamento ....
(*) = Opcional

2. Teacher Questionnaire translated

Research on the relationship between medical education and bias in medical research

1   Your present occupation : (tick more than one if necessary)
- ☐ Teaching
- ☐ Research
- ☐ Extension
- ☐ Administration

2   Have you published papers in the last 5 years? : (Tick more than one if necessary)
- ☐ Yes, in Brazil
- ☐ Yes, in foreign countries (please cite countries) ....
- ☐ No, I have not published papers in the last 5 years

3   Which was (were) the language (s) of publication? (Tick more than one if necessary)
- ☐ Portuguese
- ☐ Spanish
- ☐ English
- ☐ Other ....

4   Your academic background is:
- ☐ Specialist
- ☐ Masters
- ☐ Doctoral
- ☐ Post-doctoral studies

5   Which was the method that helped you to acquire your present knowledge about systematic deviations (bias) in medical research?   (Tick one or more boxes)
- ☐ Books about methodology of research
- ☐ Medical congresses or conferences
- ☐ Medical journals. Please cite one ....
- ☐ Special courses. Please cite one ....
- ☐ The Internet
- ☐ Other (please specify) ....

6   How often did you discuss the problem of methodological deviations (bias) with your students in the last year?
- ☐ Frequently
- ☐ Rarely
- ☐ Never
- ☐ I do not remember

7 How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias? Please explain.

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8 In relation to the problem of methodological deviations (bias) in medical research you believe that :
(Please tick)

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
It is a problem of scientific methodology, with no relation to undergraduate medical courses					
Courses of scientific methodology are responsible for the transmission of knowledge about bias					
Methodological deviations (bias) in medical research are progressively becoming an ethical issue					
Medical journals are responsible for the evaluation of methodological deviations in papers they publish					

9 In the statements below choose the alternative that is most compatible with your personal opinion :
(Please tick)

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
Systematic reviews and meta-analyses are the best ways to acquire valid knowledge in medicine					
Publication bias is a menace to the quality of systematic reviews and meta-analyses					
Systematic deviations (bias) in randomised clinical trials may exaggerate the results of future meta-analyses					

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10 In your opinion, how should the knowledge about bias in research be transferred to the students of a medical school?

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11 Do you believe that changes in the curricula of medical schools are necessary in order to achieve a better transference of knowledge about bias in medical research?
☐ Yes
☐ No

12 If your answer to the previous question was *Yes*, what should be changed?

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13 Do you agree with a personal interview, *if necessary*, to enlighten some aspects of the present questionnaire?
☐ Yes
☐ No

14 If you agree, *provided that it the anonymity of participants at the presentation of the results of this research is assured*, would you permit the interview to be recorded for subsequent analysis?
☐ Yes
☐ No

Name * ....

Address * ....

City/State * ....Code * ....

Telephone * ....Email * ....

Department * ....
(*) = Optional

3. Student Questionnaire in Portuguese

Relações entre a Educação Médica
e os Desvios Sistemáticos (viés, *bias*) em Pesquisa Médica

1   Como você classificaria seu conhecimento atual sobre tendenciosidades (viés, *bias*) em pesquisa médica?
- ☐ Alto
- ☐ Médio
- ☐ Baixo
- ☐ Nenhum (Caso sua resposta seja esta, por favor continue na pergunta 3)

2   Como você tem adquirido informação sobre tendenciosidades (viés, *bias*) em pesquisa médica?
(Assinale mais de uma opção, se necessário)

- ☐ Em meus cursos normais de graduação
- ☐ Através de livros sobre metodologia científica.
- ☐ Em congressos médicos ou conferências.
- ☐ Através de revistas médicas. Citar um exemplo: ....
- ☐ Através de cursos especiais. Citar um exemplo: ....
- ☐ Pela Internet
- ☐ Outros meios. Especificar: ....

3   No último ano, quantas vezes seus professores discutiram o problema de tendenciosidades (viés, *bias*) em pesquisa médica com você?
- ☐ Frequentemente
- ☐ Algumas vezes
- ☐ Nenhuma vez
- ☐ Não recordo quantas vezes

4   De que forma a aquisição de conhecimento sobre tendenciosidades em pesquisa médica modificou sua maneira de avaliar trabalhos científicos publicados em revistas médicas?

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5   Em relação ao problema de tendenciosidades (viés, *bias*) em pesquisa médica, você acredita que:

	Concordo plenamente	Concordo	Discordo parcialmente	Discordo totalmente	Não tenho opinião sobre o assunto
É um problema de metodologia científica, sem relação com o curso de graduação					
O curso de Metodologia Científica é responsável pela transmissão deste tipo de conhecimento					
As tendenciosidades em pesquisa médica estão se tornando progressivamente um problema ético					
As publicações médicas são responsáveis pela avaliação das tendenciosidades nos artigos que publicam					

6   Nas afirmativas abaixo escolha uma alternativa que mais se aproxime de sua opinião pessoal:

	Concordo plenamente	Concordo	Discordo parcialmente	Discordo totalmente	Não tenho opinião sobre o assunto
Revisões sistemáticas e meta-análises são o melhor meio de obter conhecimento atualizado em Medicina					
Viés (*bias*) de publicação é uma ameaça à qualidade de revisões sistemáticas e meta-análises					
As tendenciosidades em ensaios clínicos randomizados podem causar alterações nas futuras meta-análises					

7   Em sua opinião, como o conhecimento sobre viés em pesquisa poderia ser transmitido aos alunos de um curso de Medicina?

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8 Você acredita que sejam necessárias mudanças curriculares nos cursos de Medicina atuais para que a questão das tendenciosidades (viés, *bias*) em pesquisa médica seja transmitida aos alunos?

☐ Sim
☐ Não

9 Caso tenha respondido *Sim*, quais seriam essas mudanças?

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10 Concordaria com uma entrevista pessoal, *caso seja necessário*, para aprofundar aspectos do presente questionário?

☐ Sim
☐ Não

11 **Caso concorde,** *com a garantia de que em nenhum momento será rompido o compromisso de anonimidade dos participantes durante a apresentação dos resultados desta pesquisa,* **permitiria que ela fosse gravada para análise posterior?**

☐ Sim
☐ Não

Nome * ....

Endereço * ....

Cidade/Estado * ....CEP * ....

Telefone *...**E-mail *** ....

Departamento ....
(*) = Opcional

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4. Student Questionnaire translated

Research on the relationship between medical education and bias in medical research

1 How would you rate your present knowledge about bias in medical research?
   ☐ High
   ☐ Average
   ☐ Low
   ☐ None (if none, please go to question 3)

2 Which was the method that helped you to acquire your present knowledge about systematic deviations (bias) in medical research?   (Tick one or more boxes)

   ☐ The curricular courses for graduation
   ☐ Books about methodology of research
   ☐ Medical congresses or conferences
   ☐ Medical journals. Please cite one..
   ☐ Special courses. Please cite one ....
   ☐ The Internet
   ☐ Other. Please specify..

3 How often did your teachers discuss the problem of methodological deviations (bias) with you in the last year?
   ☐ Frequently
   ☐ Rarely
   ☐ Never
   ☐ I do not remember

4 How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias? Please explain.

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   ....

5   In relation to the problem of methodological deviations (bias) in medical research you believe that:
    (Please tick)

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
It is a problem of scientific methodology, with no relation to undergraduate medical courses					
Courses of scientific methodology are responsible for the transmission of knowledge about bias					
Methodological deviations (bias) in medical research are progressively becoming an ethical issue					
Medical journals are responsible for the evaluation of methodological deviations in papers they publish					

6   In the statements below choose the alternative that is more compatible with your personal opinion :
    (Please tick)

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
Systematic reviews and meta-analyses are the best ways to acquire valid knowledge in medicine					
Publication bias is a menace to the quality of systematic reviews and meta-analyses					
Systematic deviations (bias) in randomised clinical trials may exaggerate the results of future meta-analyses					

7   In your opinion, how should the knowledge about bias in research be transferred to the students
    of a medical school?

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8   Do you believe that changes in the curricula of medical schools are necessary in order to achieve
    a better transference of knowledge about bias in medical research?

    ☐ Yes
    ☐ No

9   If your answer to the previous question was *Yes*, what should be changed?

    ....

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    ....

10 Do you agree with a personal interview, *if necessary*, to enlighten some aspects of the present
    questionnaire?

    ☐ Yes
    ☐ No

11 If you agree, *provided that the anonymity of participants at the presentation of the results of this research is assured,* would
    you permit the interview to be recorded for posterior analysis?

    ☐ Yes
    ☐ No

Name * ....

Address * ....

City/State * ....Code * ....

Telephone * ....Email * ....
(*) = Optional

Appendix 4

[Teacher questionnaire]

Research on the relationship between medical education and bias in medical research

1 Your present occupation: (tick more than one if necessary)

- ☐ Teaching   **1**
- ☐ Research   **2**
- ☐ Extension   **3**
- ☐ Administration   **4**

2 Have you published papers in the last 5 years? (tick more than one if necessary)

- ☐ Yes, in Brazil   **1**
- ☐ Yes, in foreign countries (please cite countries)   **2**
- ☐ No, I have not published papers in the last 5 years   **3**

3 Which was (were) the language(s) of publication? (tick more than one if necessary)

- ☐ Portuguese   **1**
- ☐ Spanish   **2**
- ☐ English   **3**
- ☐ Other   **4**
-    **None**   **0**

4 Your academic background is:

- ☐ Specialist   **1**
- ☐ Masters   **2**
- ☐ Doctoral   **3**
- ☐ Post-doctoral studies   **4**

5 Which was the method that helped you to acquire your present knowledge about systematic deviations (bias) in medical research? (tick one or more boxes)

- ☐ Books about methodology of research   **1**
- ☐ Medical congresses or conferences   **2**
- ☐ Medical journals. Please cite one   **3**
- ☐ Special courses. Please cite one   **4**
- ☐ The Internet   **5**
- ☐ Other (please specify)   **6**

6 How often did you discuss the problem of methodological deviations (bias) with your students in the last year?

☐ Frequently   1
☐ Rarely   2
☐ Never   3
☐ I do not remember   4

7 How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias? Please explain.

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8 In relation to the problem of methodological deviations (bias) in medical research you believe that: (please tick)

	Strongly agree	Agree	Disagree	Strongly desagree	Do not have an opinion
It is a problem of scientific methodology, with no relation to undergraduate medical courses	1	2	3	4	0
Courses of scientific methodology are responsible for the transmission of knowledge about bias	1	2	4	3	0
The methodological deviations (bias) in medical research are progressively becoming an ethical issue	4	3	2	1	0
Medical journals are responsible for the evaluation of methodological deviations in papers they publish	4	3	2	1	0

9 In the statements below choose the alternative that is most compatible with your personal opinion ? (please tick)

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
Systematic reviews and meta-analyses are the best ways to acquire valid knowledge in medicine	3	4	2	1	0
Publication bias is a menace to the quality of systematic reviews and meta-analyses	4	3	2	1	0
Systematic deviations (bias) in randomised clinical trials may exaggerate the results of future meta-analyses	4	3	2	1	0

10 In your opinion, how should the knowledge about bias in research be transferred to the students of a medical school?

....
....
....
....
....
....

11 Do you believe that changes in the curricula of medical schools are necessary in order to achieve a better transference of knowledge about bias in medical research?

☐ Yes
☐ No

12 If your answer to the previous question was **Yes**, what should be changed?

....
....
....
....
....
....

13 Do you agree with a personal interview, if necessary, to enlighten some aspects of the present questionnaire?

☐ Yes
☐ No

14 If you agree, provided that it is assured the anonymity of participants at the presentation of the results of this research, would you permit the interview to be recorded for posterior analyses?

☐ Yes
☐ No

Name*...

Address*..

.... City / State* ....

ZIP*.................... Telephone*........................... Email*...

(*) = Optional

[Student questionnaire]

Research on the relationship between medical education and bias in medical research

1   How would you rate your present knowledge about bias in medical research?

   ☐ High   **4**
   ☐ Average   **3**
   ☐ Low   **2**
   ☐ None (if none, please go to question 3)   **1**

2   Which was the method that helped you to acquire your present knowledge about systematic deviations (bias) in medical research?   (tick one or more boxes)

   ☐ The curricular courses for graduation   **1**
   ☐ Books about methodology of research   **2**
   ☐ Medical congresses or conferences   **3**
   ☐ Medical journals. Please cite one   **4**
   ☐ Special courses. Please cite one   **5**
   ☐ The Internet   **6**
   ☐ Other. Please specify   **7**

3   How often did your teachers discuss the problem of methodological deviations (bias) with you in the last year?

   ☐ Frequently   **1**
   ☐ Rarely   **2**
   ☐ Never   **3**
   ☐ I do not remember   **4**

4   How much did your evaluation of papers published in medical journals change with the acquisition of knowledge about bias?   Please explain.

   ....

   ....

   ....

   ....

   ....

   ....

5　In relation to the problem of methodological deviations (bias) in medical research you believe that: (please tick)

	Strongly agree	Agree	Disagree	Strongly disagree	Do not habe an opinion
It is a problem of scientific methodology, with no relation to undergraduate medical courses	1	2	3	4	0
Courses of scientific methodology are responsible for the transmission of knowledge about bias	1	2	4	3	0
The methodological deviations (bias) in medical research are progressively becoming an ethical issue	4	3	2	1	0
Medical journals are responsible for the evaluation of methodological deviations in papers they publish	4	3	2	1	0

6　In the statements below choose the alternative that is more compatible with your personal opinion: (please tick)

	Strongly agree	Agree	Disagree	Strongly disagree	Do not have an opinion
Systematic reviews and meta-analyses are the best way to acquire valid knowledge in medicine	3	4	2	1	0
Publication bias is a menace to the quality of systematic reviews and meta-analyses	4	3	2	1	0
Systematic deviations (bias) in randomised clinical trials may exaggerate the results of future meta-analyses	4	3	2	1	0

7　In your opinion, how should the knowledge about bias in research be transferred to the students of a medical school?

....

....

....

....

....

....

8 Do you believe that changes in the curricula of medical schools are necessary in order to achieve a better transference of knowledge about bias in medical research?

☐ Yes
☐ No

9 If your answer to the previous question was **Yes**, what should be changed?

....
....
....
....
....
....

10 Do you agree with a personal interview, if necessary, to enlighten some aspects of the present questionnaire?

☐ Yes
☐ No

11 If you agree, provided that it is assured the anonymity of participants at the presentation of the results of this research, would you permit the interview to be recorded for posterior analyses?

☐ Yes
☐ No

Name* ....

Address*..

.... City / State* ....

ZIP*.........................Telephone* .... Email* ....

(*) = Optional

Q1	Q2	Q3	Q4	Q5	Q6	Q8a	Q8b	Q8c	Q8d	Q9a	Q9b	Q9c	Q11
1	1	1	2	1 and 4	2	2	4	3	3	4	3	3	Yes
1	1	1	1	4	3	1	1	4	4	3	4	4	Yes
1 and 4	1 and 2	1 and 3	3	1,2 and 5	2	2	4	4	3	2	3	3	Yes
1 and 2	1	1	3	1 and 4	1	2	2	3	4	3	3	3	Yes
1 and 2	3	0	2	6	4	4	2	1	2	4	1	1	Yes
1 and 4	3	0	1	1 and 6	2	?	2	4	3	4	3	3	Yes
1,3 and 4	3	0	2	1	2	3	2	3	3	4	3	2	Yes
1	1	1	1	5	3	2	0	3	2	4	1	3	No
1	3	0	1	2 and 4	2	3	1	3	2	4	2	3	Yes
1 and 3	1	1	1	1 and 3	3	3	2	3	2	4	3	3	Yes
1	1 and 2	1 and 3	3	1	3	4	2	3	3	4	0	3	No
1	3	0	1	6	3	2	3	4	1	3	0	0	Yes
1 and 2	3	0	1	1	3	4	2	2	3	4	4	3	Yes
1,2,3 and 4	1	3	2	1,2,3,5 and 6	1	4	2	4	3	3	3	4	Yes
1 and 2	1 and 2	1,2 and 3	3	1 and 4	2	3	4	3	3	4	3	3	Yes
1 and 2	1	1 and 3	2	1,3 and 6	1	4	4	4	2	4	3	3	No
1 and 4	1	1	3	3 and 4	2	4	1	4	4	3	2	2	No
1 and 3	1	1	3	2	2	3	1	3	3	2	3	3	No
1 and 2	1 and 2	1 and 3	3	1 and 2	1	4	1	3	3	4	3	2	No
1,2 and 3	1	1	3	1 and 4	1	4	2	0	3	4	3	4	Yes
1 and 2	1	1	2	1 and 6	1	4	2	2	2	3	3	4	Yes
1,2,3 and 4	1	1	2	3	3	2	3	3	2	4	4	2	Yes
1	3	0	1	1 and 2	2	3	3	3	3	1	3	3	No
1,2 and 3	1	1	3	1,2 and 5	1	4	1	1	3	4	3	3	No
1	3	0	1	2	3	3	0	3	3	0	0	0	Yes
1	1	1	2	4	1	2	2	3	4	4	2	3	Yes
1,2 and 4	1 and 2	3	4	1 and 4	2	3	2	3	2	2	3	3	No
1,2 and 3	1 and 2	1 and 3	4	6	1	4	2	2	0	2	3	3	Yes
1,2,3 and 4	1 and 2	3	4	1,2 and 5	1	3	2	3	2	2	3	3	Yes
1,2 and 3	1	1	2	6	2	3	2	3	3	4	4	3	Yes
1	1	1	3	2	3	0	2	0	0	4	0	0	No
1 and 2	1 and 2	1 and 3	3	1,2,3,4 and 5	1	2	1	4	4	3	3	4	Yes
1 and 2	1	1	3	1,2 and 5	2	3	1	4	2	2	3	3	No
1,2,3 and 4	1	1 and 3	2	1,2 and 4	2	4	2	3	2	3	3	3	Yes
1,2,3 and 4	1 and 2	1 and 3	4	1 and 2	3	4	4	3	1	3	3	3	Yes
1 and 2	1 and 2	1 and 3	2	4	2	4	2	3	2	4	3	3	Yes
1,2 and 3	1 and 2	1 and 3	3	1 and 3	1	4	2	3	3	2	4	3	No
1,2,3 and 4	1	1	3	1,2 and 5	1	4	2	4	2	2	1	3	Yes
1 and 2	1 and 2	1 and 3	3	1 and 5	1	2	1	4	3	4	3	3	Yes
1,2,3 and 4	1 and 2	1 and 3	3	1,2 and 3	1	4	2	1	4	2	1	3	Yes
1,2 and 4	1 and 2	1 and 2	3	5	2	3	1	4	1	4	3	3	No
1,2 and 4	1	1	3	1	1	3	1	3	4	2	3	4	Yes
1,2 and 4	1	1	3	2	3	4	1	3	3	4	4	4	Yes
1 and 2	1	1 and 3	2	1	2	4	2	2	3	4	2	3	Yes
1,2 and 4	1	1	2	2,3 and 6	1	3	2	3	3	4	1	3	No
1,2 and 3	1	1	3	1,2 and 5	2	3	4	4	2	4	3	4	No
1 and 2	1	1	2	1	2	4	4	3	4	3	2	2	Yes
1,2 and 3	1 and 2	1 and 3	3	1,2,3 and 4	2	2	2	2	3	3	2	3	Yes
1 and 4	1 and 2	1 and 3	3	1,2 and 5	2	4	2	4	4	3	4	4	Yes
1,2 and 4	1 and 2	1 and 3	3	6	2	2	4	3	3	1	3	3	Yes

Teacher Questionnaire Responses
(continued)

Q1	Q2	Q3	Q4	Q5	Q6	Q8a	Q8b	Q8c	Q8d	Q9a	Q9b	Q9c	Q11
1	3	0	2	1 and 2	2	3	2	3	3	0	0	0	Yes
1 and 2	3	0	1	1,2 and 5	2	2	2	3	4	4	3	3	No
1 and 2	1 and 2	3	3	1	2	4	1	4	3	4	4	4	Yes
1 and 2	1	1	2	1	2	4	2	3	4	2	3	3	No
1 and 2	1 and 2	3	3	2,3 and 5	1	2	2	4	3	1	4	3	Yes
1	3	0	2	2 and 6	2	4	2	4	4	4	3	4	Yes
1 and 2	1 and 2	1 and 3	2	1	1	4	3	4	4	4	4	4	Yes
1 and 2	1 and 2	1 and 3	2	3	1	4	2	4	4	2	4	4	No
1,2,3 and 4	3	0	3	2 and 3	2	3	2	4	4	0	0	4	Yes
1 and 3	1	1	2	0	3	0	2	0	3	2	0	3	No
1,2,3 and 4	1 and 2	1 and 3	3	2 and 5	2	3	2	3	3	4	3	2	Yes
4	1	1	2	2 and 3	3	3	4	3	3	3	3	4	Yes
1,2,3 and 4	1	1	3	1,2,3,4,5 and 6	3	4	2	4	1	4	3	3	Yes
1	3	0	3	4	3	3	2	2	4	2	3	3	Yes
1 and 2	1 and 2	1 and 3	4	2,3 and 5	2	1	1	2	3	0	0	0	No
1 and 4	3	0	2	6	3	4	4	3	2	4	3	3	Yes
1	1	1	2	1 and 3	2	4	2	3	3	2	3	0	No
1,2,3 and 4	1	1 and 3	2	2 and 5	2	4	4	3	2	3	2	3	Yes
1,3 and 4	1	1	2	2 and 3	3	3	1	2	3	4	3	3	Yes
1	1 and 2	1 and 3	4	1	3	3	1	3	3	4	3	3	No
1 and 3	3	0	1	2,3,4 and 5	2	0	0	3	3	0	0	0	Yes
1 and 4	2	2	1	2	2	3	2	3	3	2	3	3	Yes
1,3 and 4	1	1	2	4	3	4	4	3	2	2	2	3	Yes
1 and 2	1 and 2	1 and 3	3	1 and 4	2	3	4	3	3	4	2	3	No
1,2 and 3	1 and 2	1 and 3	4	1,2 and 3	2	4	2	3	2	2	3	3	Yes
1,2 and 3	1	1	2	1,2 and 4	2	3	4	3	2	4	3	3	Yes
1,2,3 and 4	1 and 2	1 and 3	1	1,2,3 and 4	1	4	4	3	3	2	2	3	Yes
1 and 3	3	0	2	4	3	3	2	4	3	2	4	3	No
1 and 2	1 and 2	1,2 and 3	3	1,2 and 5	2	4	2	3	3	4	4	4	Yes
1 and 3	1	1	2	1	1	4	2	3	2	4	3	2	No
3	1 and 2	3	3	2	2	3	4	3	3	4	2	2	Yes
1	3	0	2	2	3	0	0	4	0	4	0	0	Yes
1,2 and 4	1 and 2	1 and 3	3	1 and 2	1	1	4	4	4	4	4	4	No
1 and 2	2	3	3	4	1	4	4	3	3	2	3	3	No
1 and 2	1 and 2	1 and 3	3	5	2	2	4	4	4	4	3	4	Yes
1,2 and 3	1	1	2	1,2,3 and 4	1	3	2	4	4	2	0	3	Yes
1 and 4	3	0	2	1 and 4	2	3	2	3	3	2	3	3	No
1 and 2	1 and 2	1 and 3	3	2	2	1	1	3	4	3	4	4	Yes
1,2,3 and 4	1 and 2	1,2 and 3	3	2	2	2	2	2	3	4	3	3	Yes
1 and 2	1	1	2	3 and 4	2	4	2	2	2	2	1	3	Yes
1,2,3 and 4	1 and 2	1 and 3	2	5	2	3	2	4	4	2	4	3	Yes
1,2,3 and 4	1 and 2	1,2 and 3	2	3 and 4	2	3	1	3	4	4	3	4	No
1 and 2	1 and 2	3	3	2	3	3	2	3	4	2	3	4	Yes
1,2,3 and 4	1	1	2	1,2,4 and 5	1	4	1	4	4	3	4	4	No
1,2,3 and 4	1	1 and 3	3	1 and 2	2	3	2	2	2	3	3	4	Yes
1	1	1	3	2	3	3	1	2	3	2	1	2	Yes
1	1	1	3	2	1	4	4	4	3	4	3	3	No
1 and 2	1	1	2	1,2 and 6	2	4	2	3	2	4	3	3	Yes
1 and 2	1	1	3	1,2 and 6	1	4	2	3	3	4	4	4	Yes

Student Questionnaire Responses

Q1	Q2	Q3	Q5a	Q5b	Q5c	Q5d	Q6a	Q6b	Q6c	Q8
2	3	3	4	2	3	4	2	3	4	Yes
3	1	3	3	1	3	2	4	4	4	No
2	1	2	3	2	3	2	4	4	3	Yes
2	1	2	4	2	2	3	4	2	3	No
2	3	2	3	2	2	2	4	3	3	Yes
2	2	3	3	2	4	3	3	0	0	Yes
2	1	2	3	2	3	3	4	2	3	No
1	7	3	0	0	0	0	0	0	0	Yes
2	1 and 3	2	0	4	3	0	2	3	4	Yes
3	1 and 7	2	3	2	1	4	2	3	4	No
2	1, 2 and 3	3	4	2	3	2	2	3	3	Yes
4	2 and 4	3	3	4	2	3	2	3	3	Yes
3	1 and 3	3	3	2	3	3	2	3	3	Yes
2	1, 2 and 3	2	3	2	3	3	4	3	3	Yes
2	1	2	3	4	3	2	0	0	0	Yes
3	1,2,5 and 6	2	3	2	3	3	2	3	3	Yes
2	1 and 5	2	3	2	4	3	3	3	3	Yes
3	1,3 and 6	2	4	4	3	3	2	3	3	Yes
3	1,3,6 and 7	2	3	2	3	4	3	3	3	Yes
3	1,3,6 and 7	1	3	2	4	4	2	4	3	Yes
3	1 and 6	2	3	2	2	3	2	2	2	Yes

Appendix 5

INTERVIEWS' CODING
(NODES FOR NUD*IST®, USING THEMATIC ANALYSIS)

1. CASEDATA
    1.1 Participant
    1.2 Title
        1.2.1 Student
        1.2.2 Specialist
        1.2.3 Master
        1.2.4 Doctor
    1.3 School
        1.3.1 PUC
        1.3.2 UEL
        1.3.3 UEM
        1.3.4 UFPR
        1.3.5 UNIOESTE
    1.4 Gender
        1.4.1 female
        1.4.2 male
    1.5 Coded?
        1.5.1 Yes
        1.5.2 No
    1.6 Date of Coding:
    1.7 Department:
    1.8 Average:

2. QUESTIONNAIRES' RESPONSE RATE
    2.1 reasons
        2.1.1 language of publications
        2.1.2 lack of interest
        2.1.3 lack of knowledge
        2.1.4 lack of time
        2.1.5 other priorities
            2.1.5.1 work
            2.1.5.2 residency
    2.2 contact with non-respondents
        2.2.1 possible
        2.2.2 impossible

3. BIAS IN MEDICAL RESEARCH
    3.1 responsibility for their existence
        3.1.1 medical education
            3.1.1.1 graduation
            3.1.1.2 post-graduation
        3.1.2 researcher behaviour
            3.1.2.1 misconduct
            3.1.2.2 lack of knowledge
            3.1.2.3 other
        3.1.3 external influences
            3.1.3.1 pharmaceutical companies

3.1.3.2 career demands
3.1.3.3 other

4. POSSIBLE SOLUTIONS FOR THE PROBLEM
4.1 methodological
4.2 educational
    4.2.1 curriculum modification?
        4.2.1.1 Yes
            4.2.1.1.1 participant proposal
        4.2.1.2 No
    4.2.2 scientific methodology course
        4.2.2.1 necessary
            4.2.2.1.1 participant proposal
        4.2.2.2 unnecessary
4.3 other solutions

5. QUESTIONAIRE RESPONSES

SAMPLE OF THE INTERVIEWS

(TRANSCRIBED AND TRANSLATED)

(#) = Omitted in order to maintain anonymity of the participant

* Teacher (#)

* School: (#)

* Title: (#)

Participant: (#)

Title: (#)

School: (#)

Gender: (#)

Coded?

Date of Coding:

Department: (#)

Researcher: First of all, I would like to thank you for participating in this research. I would also like to reinforce, as already expressed in the questionnaires, that I will keep the anonymity of the participants in all the phases of the research.

Teacher: I understand...

* Q1 Researcher: Well ... despite all my efforts, the number of teachers and students that answered the questionnaires was lower than the what can be found in international publications. In your opinion, which could be the possible causes of this low response rate?

Teacher: Well ... there is a lack of motivation ... it really reveals a reality ... Most of the times that we need an answer, the health professional does not cooperate ... this is not related only to your research ... When asked why, they allege lack of time, that it is only

one more paper to fill in ... they do not understand what they can profit from that ... Another possibility is that this kind of matter, of problem, does not affect them...

* Q2 Researcher: You said that this kind of problem does not affect them ... Do you mean that they do not see this subject as a problem?

Teacher: Yes... this is not a priority ... do you understand? Maybe they can not see what you are researching as a problem ... Also, many teachers are not very familiar with scientific methodology, and probably would not like to disclose such a lack of knowledge about the matter ... In the case of the students ... well ... I believe that most of them do not have at the moment enough knowledge about medical research to answer your questionnaire ... Also, there is something that I call the 'residency paranoia' ... which in fact is being a problem in the last years ... You said that you have not been a teacher in a medical school in the last 25 years ... Well ... A lot of things changed in the medical schools in the last 20 years ... People that dedicate themselves only to teaching and researching inside the medical schools are becoming very rare these days ... Most of the new teachers are in the schools just because of the status that comes with the title of teacher, or for financial reasons ... They have a different mentality, which they are, in a certain way, transmitting to the students ... You may not believe, but I have received in my office students that have just entered the medical school asking what they have to do in order to secure a place in our residency program! ... My God! ... This is something that should be a problem for them almost six years ahead! ... The normal undergraduate program that should entitle them to be a physician is becoming just a kind of 'ritual passage' to their specialisation programmes ...

*Q3 Researcher: Well ... You said that there is a lack of knowledge about the subject of bias in medical research among the students ... However, in the questionnaire you declared that you do not think that a curricular change would be necessary in order to transmit such a knowledge ... Could you please give me your opinion about how and when such knowledge should be available to the students?

Teacher: I must confess that I am not very fond of curricular changes ... Most of the time such changes cause a lot of problems to be done, and the results are far less effective than expected ... You will face several difficulties in order to introduce a new field of

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knowledge in the present curriculum structure ... I believe that the introduction to the basic knowledge about medical research and scientific methodology could be something that every one of the several existent Departments could implement in their normal courses ... Of course, this would entail some changes in the way people think and act that might not be so simple to achieve ... In fact, I also think that such a subject is so important that it should be left to the post-graduation courses ... After all, people need to prepare themselves to be a medical researcher, isn't it? ... The undergraduate medical courses are not exactly the best place to discuss such kind of information ... the student should focus on learning how to be a good physician ... If then, after graduating, he/she decides that wants to do medical research ... well ... he/she should do a good post-graduation training ... Too much research nowadays is being done like baking a cake ... you follow a recipe ... put all the ingredients ... shake well ... and then say that you have done a research ... This is not correct, I believe ... It is only the best way to perpetrate serious mistakes ...

*Q4 Researcher: Yes, serious mistakes can occur if you do a research like that ... And in your opinion these mistakes are occurring more due to lack of knowledge about the correct methodology or due to scientific misconduct of the researchers?

Teacher: Definitively due to lack of knowledge! ... Definitively ... Many post-graduation courses are not really preparing people to be good researchers ... They are only machines to print Masters and Doctoral diplomas ... and make money ... of course ... There are some cases of overt scientific misconduct, but I believe that these are, hopefully, occurring in a small number of researches. In fact, if you want to reduce the number of bias in medical research, you will have to focus on the post-graduation courses ... It is there, not in the undergraduate medical courses, that the problem has its roots ... Also, there is the problem that much research is being done inside the medical schools for the wrong reasons ... because people need to publish ... just because of their status inside the medical schools ... However, these are generally repetitions or adaptations of previous researches that will be published in some secondary journal and disappear ... I do not see them as necessarily harmful to medical knowledge ... just dispensable ... time and resources consuming ... just that ... The real problem is that the medical students may see such a behaviour as normal ... This is a real problem ... because they are going to repeat and amplify the same mistake ... unfortunately ...

*Q5 Researcher: And the influence of the pharmaceutical companies on medical research? Do you believe that it may be an important cause of bias?

Teacher: Well... I do not believe that it is a problem in Brazil ... However, I am aware that this is a problem in the developed countries ... I was thinking only about medical research here ... As everybody knows, our medical research is in its early stages ... probably it is not considered as important by pharmaceutical companies ... See ... I am not saying that we are less permissive than the researchers in other countries ... it is just a question of opportunity ... If they begin to spend in medical research what they spend, for instance, in the USA ... well ... you will see queues of Brazilian researchers asking for money ... Only then, I believe that we will begin to have problems related to these relationships ... In fact ... just as an example ... I can say to you that I believe that the low level of resources to do a good research project, and the unrealistically small period of time that we are allowed to dedicate to do a research, are probably much more important causes of bias than the pharmaceutical industries influence ... at the moment ... for sure ... This way of seeing medical research is causing much more harm ... You see people trying to evaluate a drug or a medical procedure in half the time, and with half of the resources needed ... and what can you get as a result? ... Obviously, nothing! ...

*Q6 Researcher: If you permit me, I would like to return to the problem of lack of knowledge about research methodology and the problem of bias in medical research. As these subjects are being published essentially in American and UK journals, do you believe that people are not reading them due to a language barrier?

Teacher: Absolutely not! ... People can give you hundreds of excuses for not knowing about the subject, ranging from lack of time to lack of interest ... but not that! ... Modern medicine is essentially based in books and journals in English in Brazil ... even our best journals are publishing now papers in English ... That is certainly not a good excuse for the present lack of knowledge about these matters ... Ten or twenty years ago this could be a good excuse ... not because of the language, but because of the access to these information ... but certainly not now ...

*Q7 Researcher: Well … Although at the beginning of our conversation you have already stated some of your beliefs about what should be done, could you please give more details about what could be done in medical education in order to reduce the problem of bias in medical research?

Teacher: Well … when we started this conversation I had a very clear idea about what should be done … However, … and this is point … and this is the interesting thing of having such conversations … I believe that something really has to change in the undergraduate medical courses … The problem is that I have been a teacher for a long time … I do not believe in magic changes in a medical school anymore … In fact, I believe that at the end of your research you will probably have collected many opinions, an then I would like to read your work … and think about another possible solution … However, I still insist that the main changes that must be done are in the post-graduation courses … for sure … Also, we must reinforce the critical evaluation of the researches that are done inside the medical schools … This would reduce the possibility of people that are not prepared to do biased research protocols and results, and also reduce what could be called an "educational bias" in the minds of our students, who graduate thinking that medical research can be done in such a way … Finally, I strongly defend the position that we should have a clear separation between teaching and research … this would reduce a lot the number of researches that are unimportant or even deliberately biased … I am not saying that most of these researches are being intentionally biased … just that most of them are definitively unimportant …

*Researcher: Do not worry … At the end of this research you and all the participants who sent me their addresses or email will certainly receive the final conclusions of my work .

Teacher: That will be very helpful … It can help us to see the problem from a different perspective …

*Q9 Researcher: I know that the time you gently allowed me to do this interview is almost ending, but I would like to ask you an advice … Do you believe I could convince some of the non-respondents to the questionnaires to be interviewed?

Teacher: I am sorry to say that I do not believe you will be able to do that ... I believe that those teachers who wanted to collaborate to your research are the ones that sent you their questionnaires ... In relation to the students ... well ... in our telephone contact you said that you would do (*number of interviews omitted by the researcher*) students' interviews ... I believe that it is more or less the number of students that are involved in our scientific initiation programmes at the moment ... Sorry, but I do not believe you will be able to convince the others ... they do not have much to tell you about the subject matter of your research ...
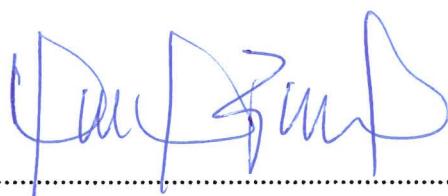
*Researcher: Thank you for the advice ...

END OF RECORDING

Declaration

I, Marco Antonio Gimenes Basso, here declare that the written information of the previous 292 pages of this thesis is the result of my personal intellectual creation, for which I assume total responsibility. Also, that the research data presented on it is a comprehensive compilation of all the data obtained in my study in five Brazilian medical schools, only having been omitted the information that could jeopardise the anonymity of the participants.

I also confirm that the word length of:

1) the thesis is ....72154 words
2) the bibliography is .... 4520 words
3) the appendices is .... 10248 words

..../ ....
     Marco Antonio Gimenes Basso   Date

14/07/2005