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Conflicts of interest in medical practice

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Abstract

It has become more and more apparent that some aspects of current medical practice can no longer be kept solely within the private preserve of the profession. Medical error is now treated in an open fashion because it is clear that frank debate over its incidence, causes and mechanisms are crucial to effective prevention. This has always been one of our worst kept secrets. Equally conflicts of interest [1] assume particular relevance in an occupation whose foundation values demand a robust ethical identity. This is the topic of this essay.

Keywords: Ethics; conflicts of interest, medical professionalism.

The ethical paradox

Medical professionalism has some unique characteristics, which need to be preserved. In simple terms, it means the protection by competent people, specially qualified professionals, of vulnerable people and/or values, which, in our case, are our patients and the delivery of health care in all our areas of intervention [2–4]. This is our social contract, which implies professional autonomy and the correlative right and duty of self-regulation. This requires that we place the interests of the ones we care for above our own and, furthermore, to define and maintain patterns, of competence and integrity and play the role of social partners, with an independent voice based on knowledge and experience. All this has to be anchored in the absolute confidence on a peculiar fiduciary relationship between doctor and patient.

Although it is always claimed that doctors should place the interest of patients above all others, the truth is that this value is often jeopardized by the social, economical and cultural realities of our time and, as noted by Bloche [5], by the ubiquity of clinical work which serves mainly non-clinical goals. In fact, doctors have gotten increasingly involved in a complex web of relationships with other partners, and certainly a neurosurgeon working for an insurance company or a sports club, or acting as an expert in a judicial dispute, is playing a role quite distinct from the traditional medical act. The unequivocal one to one relationship between a doctor and his patient is nowadays just one of the multiple facets of medicine, albeit the noblest and of the longest tradition. But it is pure hypocrisy to claim that it dominates all of the other professional duties of a physician.

In this regard, it is no longer possible to ignore the deep moral paradox that has afflicted us since the time of our father Hippocrates, as noted by Jonsen [6]. This paradox emerges from the perpetual conflict between two basic moral principles: altruism and self-interest, which in its more extreme form is just plain egoism. As pointed out by Jonsen, many social and economic questions in healthcare delivery stem from this same paradox, and the fair balance between these two opposing values constitutes one of the most pungent challenges to our profession. On one side, self-interest promotes values that guarantee self-satisfaction, progression in the academic or professional career, public recognition, financial comfort, in sum, happiness or its illusion . . . . On the other hand, altruism demands the promotion of these same values, but in favour of others and, if needed, with sacrifice of our own. It is certainly naïve to believe that it is possible to create a health care system without taking into account this reality.

In simple terms, it may be said that doctors have their types of self-interests. The first one is easy to quantify and readily appreciated by lay people, and is the financial interest. The second may be called "academic" and includes the contributions to scientific progress, the recognition by peers, competition for

the financing of research, the broadening of the referral basis of patients, attention by the media and, why not saying it simply, the wish to become famous.

The third type is more difficult to define, but its goal is to keep a certain comfort, by not taking on the difficult or risky cases, that could perhaps threaten professional or social reputation.

The sensibility of the public has always been particularly touched by news that doctors are given all sorts of gifts (money, luxury trips) in exchange for prescribing drugs or using certain tools, marketed by the companies that reward them so magnanimously. One should be reminded that in fact the primary aim of such gifts is to engrave in the mind of the receiver the identity of the donor and to create openly or subliminally, the obligation to reattribute [7]. The sociologists also point out that, in our case, gifts create the expectancy of reciprocity which may increase the health costs, affect the objectivity of the clinical decision, and bite the moral core of the profession, inevitably creating the appearance of a conflict of interest. It is important then, to deal openly with this issue.

The conflicts of interest

A conflict of interest arises whenever an individual or an institution has a primary duty and simultaneously a secondary one, that may overwhelm the other, or is sufficiently tempting to create the possibility or the appearance that this may occur [8]. In other words, a conflict of interest may occur in situations in which a primary duty (such as the patients well being or the validity of a research project) is unduly influenced by a secondary interest (such as a financial gain). It is important to emphasise that a conflict of interest is an occurrence, not a kind of systematic behaviour [9].

On the other hand, it is not necessarily a manifestation of wrong doing from a clinical or scientific perspective, as it remains, quite often, just an unjustified suspicion.

It is of interest to note that most of the literature on this topic is being published in the USA and the United Kingdom, but more and more countries are increasingly aware of its relevance, and its socioeconomic repercussions that go well beyond the medical profession. What Relman [10] aptly called the medical-industrial complex is one of most striking realities of our modern economics, and the industry is playing an increasing role industry in the financing and sponsorship of academic research. But perhaps the most decisive factor is that we are now living in an open society, and lawyers, economists, politicians, consumer-advocate groups, and all sorts of lay people are anxious to get into the game and to play a role in areas that were, until now, the province of a tremendously powerful corporation: the doctors.

Financial conflicts

Financial conflicts of interest are certainly the ones that have deserved a closer scrutiny. Besides the fees received for their medical acts, doctors are now being paid by the industry for lectures presenting new drugs or products, or as legal or workman's compensation experts. In these circumstances, conflicts of interest may occur.

It is also clear that physicians are increasingly investing in companies that sell products or drugs in whose investigation or trial, they are involved. As an example, in a paper [11] comparing the effectiveness of different coronary stents, seven of the twelve authors had received consulting or speaking fees from the manufacturers, and three of them owned stock of the company. Although in this case there was a clear disclosure, it is possible that, as noticed by Katz [12], doctors may somehow lose some of their moral authority to speak on health matters as the result of their financial interests.

It should be said, that this is not a question that regards exclusively the medical profession [13, 14]. The journal "Science and Engineering Ethics" of April 2001 reported that only 0.5% of 61134 papers published in 1997 in 181 peer-reviewed journals, contained a disclosure of conflict of interest of the authors.

Perhaps the most ancient economic conflict relates to professional fees. George Bernard Shaw whom, it is well known, was not particularly fond of doctors, wrote in the famous preface of "Doctor's Dilemma": "it is simply unscientific to allege or believe that doctors do not under existing circumstances, perform unnecessary operations and manufacture and prolong illnesses." This accusation is vague and difficult to substantiate, but there is evidence in the North American literature that the system of "fee for service" increases the number of unnecessary procedures. Moreover, in the "managed-care" systems in which doctors receive incentives to reduce the number of procedures or consultations with other specialities, incentives constitute forms of pressure that may affect the quality of the services rendered [15, 16].

Another delicate situation is the so called "self-referral" in which the patients are requested to obtain tests or therapeutic services in facilities owned by the referring physician. An American study demonstrates that the owners of these techniques ordered 54% more MRI, and 28% CTI scans [17]. Equally problematic is the situation that has risen in systems of "managed care" in which the patients are obligated to use contractualized services which may not have an acceptable quality level.

It is increasingly clear, that the technological and scientific growth of modern medicine has made it a very attractive business inviting doctors to take advantage of potential investment opportunities.

Intellectual conflicts

Intellectual conflicts of interest constitute a fascinating question. As noted by Marshall [18] scientists are human beings, thus subject to whims and passions, and tend to surround their own research with a mystic aura. The case of Symon LeVay, a homosexual neurobiologist who published a much publicized paper on gender differences in the size of one of the hypothamic nuclei between the brain of homosexuals (similar to the female brain) and heterosexuals, is often quoted as exemplary. This observation, which was not confirmed by other researchers, might have been tainted by the strong wish to find a biological support for homosexuality.

A strong adversary stance against the risks of tobacco, alcohol or certain drugs may likewise determine the design of the research methodology or the way the results are reported. An ideological bias enforced by repressive political systems was responsible for the infamous research by Nazi doctors which led to death penalties imposed to seven physicians during the Nuremberg trials. The imposition of the absurd genetic theories of Lyssenko or the abject use of psychiatry to eliminate the foes of the regime, in the former Soviet Union, also illustrate the perversity of these types of conflicts. Recently, it is being questioned the complicity of researchers associated with the prestigious "Kaiser Wilhelm Institute" in Germany, who were involved in studies on racial differences, using material collected from victims of concentration camps [19].

Other forms of intellectual conflict were pointed out by Horrobin [8]. For instance, an ideological stance against capitalism or the pharmaceutical industry may oppose any form of financing by it. A philosophical bias may again determine scientific agendas and policies. For some, nutritional factors or a medicine of life-styles is crucial for health maintenance, while others deny the importance of their role.

Finally, Horrobin cites as the most important cause of intellectual conflict the passionate defence of a certain theoretical model and imagines a scientist writing as a conclusion of a paper: "I am delighted by these results since they justify the 25 years I have spent following this line of research".

Conflicts in surgery

There are two types of conflict that are peculiar to surgical specialities. One is related to the surgeon–inventor of instruments, devices or prosthesis [20]. In this situation, the author is both interested not only in demonstrating the safety and efficacy of its product, but also in its promotion, from which he expects to receive dividends. It should be noted that, in this situation, neither efficacy nor safety can usually be demonstrated by randomized controlled trials. Furthermore, in the evaluation of new products, the surgeon may tend to exclude patients whose condition and hence prospect of unsatisfactory results

may affect the reputation of the product under scrutiny. It is also likely that the surgeon-inventor will try his product in his/her own patients which may cause a certain psychological coercion. Equally, if he/she does not test the device on his/her own patients, other surgeons would ask why not.

The second type of surgical conflict is more subtle and relates to what Foster [7] calls "funkionslust", a concept based on the behaviourist theories of Konrad Lorenz, which describes the pleasure and pride in performing certain functions well, which may be the reward for many years perfecting a certain technique. But in surgery this may bring conflicts: the preference for a more complex procedure when a simpler one would do the job, reluctance to send the patient to another specialist, or the resistance to learn a new technique. The primary interest of the patient may be relegated in favour of more personal, albeit understandable human foibles.

We believe that a point of major concern relates to the increasing role neurosurgeons play in promoting industry driven medical devices. This is particularly blatant in the field of spine surgery, with the use of prosthetic material which has not been subjected to a rigorous critical evaluation not only of its therapeutic usefulness, but also in a cost-efficacy perspective. The conflict of interest in these areas are now being subjected to increased scrutiny by health authorities, particularly in the USA". I think this addresses all the points raised.

It is unquestionable that much of the progress in our field is due to innovation and technological developments and contributions from physicians in these areas are invaluable. It is therefore an undeniable professional duty, with correlative ethical implications, for surgeons to participate in the critical evaluation of new technologies and this includes, by necessity, cost-benefit analysis. We shouldn't forget that we are our patients' best advocates and should strive for putting the new technologies at their service. However, the tremendous increase in health care costs demands from us to be concerned with our patients, the patients of our colleagues and even the future patients, and therefore, we should play a decisive role as independent partners in the definition of health care policies. It should be reminded that recent concerns about the threats to medical professionalism demand that we should fight to maintain its foundational values such as altruism, compassion, integrity, truth and competence, and these should not collide with management goals.

Conflicts in academic duties

The academic physician often faces the challenging dilemma of how to balance equitably the time spent in academic, clinical, teaching and managerial activities. Each one of them seeks to claim precedence, their relevance and relative weight varies according to the circumstances, and each one being subject to different and increasingly demanding forms of evaluation. At present, more and more

time is asked of clinical and academic leaders to spend on administrative duties, in part due to increasing scrutiny on the use of finite resources and legal constraints.

As educators, doctors have to deal with the inevitable tension between the duty to care for their patients and the training of future specialists. Foster [7] has rehearsed the question of how and when to decide that a resident is ready to operate on his or her first patient and how is he or she chosen. Are we aware of this conflict of interest when we delegate this responsibility to our junior colleagues? There is, however, clear evidence of the high quality of the services rendered by teaching hospitals and that, with adequate supervision, there is no difference between the results obtained by the trainees or their tutors. But it is crucial that the patient himself understands that he is fulfilling an important social duty, as he constitutes, a vital teaching tool, provided that the quality of care is guaranteed. Bernstein [21] has emphasized that open recognition of the potential ethical tension inherent in the teaching of surgical technique is the first and most important step in solving the intrinsic conflict generated.

The relationship with industry

Most of the literature on conflicts of interest in clinical practice pertains to relationships with industry particularly with the pharmaceutical industry [22–26].

In countries like the USA and the United Kingdom, the funding of biomedical research by industry has grown remarkably. In the USA the industry paid 32% in 1980, and 62% in 2000, of the expenses of clinical trials. The influence of the industry goes well beyond this aspect. Shamasunder and Bero [27] have called attention to the relationships between the pharmaceutical industry and the tobacco companies and how the latter have tried to soften up the marketing of programs for giving up smoking.

In biomedicine, it is the private sector and not academic medicine that develops most of the diagnostic techniques and products used in the treatment and prevention of illnesses, and is also responsible for their marketing. In the most industrialized countries, the universities are deeply involved in investing in "start-up" companies and support research by their members. Many neurosurgeons involved in the research and development of products, have financial ties with the companies that promote them.

Two factors have contributed to the recent interest in the topic of conflicts of interest in these areas. Firstly, was the news of the death of a patient who was participating as a volunteer in a phase I gene therapy trial in which the researcher and the hospital had financial interests [28].

Secondly there has been the suspicion of bias in the reporting of the results of therapeutical trials when the authors have financial ties with the manufacturing companies. The study of Stelfox *et al.* [29] on calcium antagonists is

frequently cited and purportedly demonstrates a positive bias when the authors were associated with the manufacturer. Davidson [30] showed that the report of positive results with new drugs increases if the study is financed by the producer. Finally, and there are many more examples, Friedberg *et al.* [31] showed that studies of the pharmo-economics of oncological drugs supported by the industry reported 5% of unfavourable results in contrast to 38% by non financed studies.

This is certainly a complex and confused issue. Some have pointed out that the methodology of these sort of trials may be designed to favour positive results. This may be achieved by selecting patient groups with a lower rate of co morbidities, or less severe forms of disease [32] called the attention to the fact that in efficacy studies of anti-inflammatory non-steroidal drugs, only 21% of the target population were younger than 65 years of age [33]. It should be noticed, however, that for a drug to reach a phase III, trial it has to go through a strict process of evaluation, and therefore the industry anticipates a probability of success that justifies the investment made. On the other hand, some have suggested that the new drugs are tested against sub optimal doses of other medications already approved and, some studies may include multiple surrogate endpoints, but only the ones which shed a more favourable light on the "new" drug are published.

Montagner *et al.* [34] quote a study that demonstrates that there is no qualitative difference in the methodology of studies funded by the industry and the ones which are not so funded, but others found the first type more reliable. It is possible that the preponderance of positive results in funded trials is due to a tighter pre-selection of the drugs that are pursued to further advanced stages of clinical evaluation.

It is useful to consider the different interests that come into play in biomedical research. From the standpoint of the public, what really matters is that research that is paid for indirectly by the consumer is geared towards the search to independent truth. It matters that those discoveries with potential therapeutic benefit be transferred as soon as possible, after careful, well designed studies, to clinical practice. Finally, it is essential that participation in clinical trials be safe, supported by informed consent, with rapid access to the results, and with an adequate follow-up. The patients or volunteers should also be informed about all possible side-effects that may influence their decision to participate.

This is an area that has deserved a lot of attention because of the death of some volunteers [28, 35]. These cases have raised a number of very important issues concerning both the researchers individually, and the institutional review boards, such as the excessive haste in obtaining results, the incomplete search for possible toxicity of the products tried, the potential vulnerability of employees or medical students to the pressure to serve as volunteers, and the influence of payments received [34]. The need to change the rules of functioning of the

review boards and the use of external boards, have been advocated particularly for multicentre studies.

Finally, it has to be guaranteed that the researcher is not subjected to any kind of external pressure that may affect the selection of the subjects or the publication of results. As mentioned by Bodenheimer [25] many research contracts submitted by the industry have unacceptable publication clauses that have to be renegotiated.

The primary interest of researcher is simply stated the publication in first rate journals of the result of their work. Clearly, this sort of recognition is indisputably a professional asset and may contribute to progression up the academic ladder and strengthens the ties with the industry, with increasing participation in new projects and consequent financial reward.

The interests of the industry are equally simple to enunciate and are the approval and commercialization of new products. Publication of results without peer review is not worth much but publication of results in a first rate journal is very important for the marketing of a new product [25].

It is understandable that there is an inevitable tension between health care delivery and the investigation of new drugs or techniques. The clinician involved in this kind of research is interested in gathering patients for the study, the speedy conclusion of the project and the publication of results. But he has to safeguard the medical component of his task, in a context that may create what has been called "therapeutic misunderstanding" [36]. In fact, "patient-volunteers" may believe that the experimental procedures or drug in trial are prescribed for an anticipated real benefit, even when this is explicitly denied in the consent form. In fact, although the possibility of benefit may be implicit in any therapeutic trial, this is not usually its primary goal. Freedman [37] has indicated the attention that some phase I studies of oncological drugs called studies of efficacy and safety, are designed objectively to determine the maximum tolerated dose, and to call them efficacy studies is misleading.

It is, however, important to consider that an inappropriate "clinical bias" may undermine the scientific validity of the study, by bypassing the randomization process or the "blind" evaluation of the results. Miller at al. [26] have suggested monitoring by a non-participating physician, who may act as a patient's advocate and verify the ethical competence of the researchers.

The relationships between industry and the universities have been raised in numerous debates [38–43], particularly in the American literature, and some have even asked rhetorically if academic medicine is "not for sale". As pointed out by Marciall Angell [44], the ties between clinical researchers and industry assume multiple forms such as grants, consulting fees, dividends, the agreement to borrow the name for articles written by request, the promotion of products in seminars and congresses, etc. The generosity of the industry, in Angell's critical view, knows no limits, has nefarious consequences, and may create in

the young physician the mistaken impression that for every problem there is a pill and somebody from the company to push it.

There is a remarkable variety of policies in dealing with the conflicts of interest in various medical schools and research institutes [35] and, given the diversity of the regulations of different journals and financing agencies, the present rules may no longer be adequate to preserve scientific integrity.

It is not my purpose to discuss this matter in further detail, and although this may seem primarily an "American" problem, the truth is that globalization of medical research makes this a question that should be dealt with openly in any country involved in this type of research. It is known that nowadays about 60% of trials of new drugs in the USA are conducted by private organizations, the "Contract Research Organizations", that contract directly the physicians involved, many of them without hospital affiliations [25, 40, 45]. Since some hospitals or clinics are not particularly suitable or used to this kind of work the so-called "Site Management Organizations", which are independent business enterprises, may help to do the job. Furthermore, there are now private ethical review committees, which also may raise puzzling ethical questions, as it is reasonable to assume that committees with more benevolent criteria may be preferred to the ones with more stringent criteria.

Another concern is mentioned in the literature and relates to the academic output of doctors that are subsidized by industry. A study by Blumenthal *et al.* [46] indicates that there is no difference between them and the non-paid doctors. There are, however, two differences. The "industry physicians" are more productive from the commercial standpoint, and more reserved in communicating their results to their own colleagues. There is therefore, a legitimate fear that the emphasis on commercially rewarding research may have negative repercussions on basic science which is without immediate foreseeable applications.

Conflicts over communication

Publication of the results of industrially financed research is now a matter of grave concern, particularly since it has become apparent that there is a strong resistance to the publication of negative results, by delaying the reporting of unfavourable outcomes. Furthermore, there is evidence that the access of the researchers to the results may be restricted, and there is an occasional practice of hiring "ghost-writers", who did not participate in the investigation to write of the manuscript. On the other hand, historically there has not always been a well defined policy of disclosure of conflict of interest of the authors, the reviewers of the manuscripts, and even of the authors of review articles [47]. However this situation is rapidly changing. The editors of some of the most prestigious international medical journals [48] (such as Lancet, JAMA,

New England Journal of Medicine) have proposed new guidelines to correct a situation that was challenging the credibility of scientific communication in clinical medicine. In fact, an interesting study by Chaudhry *et al.* [49] analyzing whether the disclosure of conflict of interest affected the evaluation by the readers of the reliability of the results, seems to confirm that trust was a diminished when the authors were financed by the industry, in the case of this article, a fictious company.

The journals that have approved such guidelines now demand a clear statement on the personal and financial ties with industry. Moreover, they call the attention for the need for research contracts to guarantee that there should be no limitation of access to the data, and no interference with their analysis, and with the preparation and publication of the manuscript.

It is therefore necessary to describe in detail the role of the sponsor in the collection, analysis, interpretation and publication of the data. It is the role of the editors to assure that there is no conflict of interest involving the reviewers and the editors themselves should abstain from participating in decisions in which they may have a vested interest, personally, professionally or financially.

In such a complex area, the academy must play a leading role, starting with the safety and well being of the participants in clinical trials [50]. It should be the guardian of such fundamental values as the freedom to publish, the objectivity and integrity of the data, and the regulation of economic incentives, which should contemplate both senior and junior scientists. This is underscored in the recommendations of the Task Force of the American Association of Medical Colleges in 2003 [51, 52], that emphasize the importance of distinguishing the strictly scientific aspects of any research project from investment and technological transfer policies.

Conclusions

As I pointed out at the beginning, one of the fundamental aspects that characterize professionalism is the duty to self-regulate. This is carried on by legal and ethical codes, as well as by the intervention of a number of professional regulatory bodies. Ethical codes have to preserve the basic foundation of professional values but the changes in social, economic, political and cultural conditions, as well as the new ethical challenges that the scientific and technological progress are continuously raising, demand the clarification of some rules and even the definition of new ones.

This occurred, for instance, in regard to such questions as medical advertising, relationships with industry and, sooner or later, to complex maters such as "enhancement" technologies, (like searching for better memory, more intelligence, longer life span or engineering desired traits, thus creating the so called "design-babies") therapeutic cloning or even euthanasia.

Professional regulation has extended also to domains such as certification and recertification of competence, accreditation of services and hospitals in matters of teaching and training. Societal scrutiny of medical activity is increasingly vigilant. This is performed informally by the "media" for which the "bad deeds" of doctors are always news and formally by various organizations public or private, including insurance companies and other third party payers.

They are particularly attentive to areas such as professional competence, which were, until quite recently, the exclusive domain of physicians' organizations, but also to the management of resources and the overview of potential conflicts of interest.

The mechanisms of regulation of professionalism have become more demanding and sophisticated, with proliferation of statutes, regulations and guidelines. The statements of the editors of medical journals mentioned before, or the recommendation of the task-force of the Association of American Medical Colleges to regulate the financial conflicts of interest of researchers and institutions clearly illustrate this point [51, 52]. Even research institutions such as the Howard Hughes Medical Institute [53] have found it necessary to define their own code which, in the latter case, limits to 5% the amount of stock owned by scientists in the companies with which they collaborate. They are also concerned about preserving the scientific autonomy including the right to publish their results, and establishing a maximum limit of 90 days to obtain a patent, if required.

The American College of Physicians and the American Society of Internal Medicine have also drafted guidelines concerning the ethical aspects of the relationships between industry and the clinical practice [54]. The fact that they felt it necessary to address such questions as the new modalities of "e-commerce" illustrates the tremendous revolution in this field.

Many of the control mechanisms should be supported by prophylactic rules that have to be included in ethical codes. The disclosure of conflicts of interest should be open and this is certainly better to the profession that the persistent suspicion of illegitimate gains [54, 55] that undermines its credibility and prestige. It is also important to accept the fact that ethical scrutiny is no longer the exclusive duty of the physician, and he should favour a plural and multidisciplinary intervention. This may contribute to finding the right equilibrium between the role to guarantee the safety and protection of patients and volunteers and the aim to pursuing the scientific inquiry whilst abiding by the rules of methodological rigor. The review boards should therefore include scientists, informed lay people, and patients' representatives, who may actually not be totally immune to pressures or dangerous liaisons [56]. This is the only way to achieve what Hannah Arendt called the art of representative thinking. In any circumstance, as Henry Beecher [57] wrote in a celebrated article published in 1966 on the ethics of clinical investigation,

"the most reliable safeguard (is) provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator".

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