Research and developing countries: hopes and hypes

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البحوث في البلدان النامية: بين الآمال الواقعية والكلام المعسول

فرحات معظَّم

الخلاصة: تتطرَّق هذه الورقة إلى المشكلة العالمية المتمثِّلة في ضمان مراعاة المعايير الأخلاقية في البحوث التي تُجرَى على البشر، وتركِّز على الصعوبات النوعية التي تواجهها البلدان النامية في هذا الصدد، ولاسيَّما باكستان. وتناقش الورقة كذلك تأثير المعايير الاجتماعية التقليدية والتَّراتُبيَّة للعلاقة بين الطبيب والمريض في إبراز هذه المشكلات. وتتناول الورقة بالوصف قضيَّتَيْن مُستَجدَّتَيْن في باكستان، لهما أهمية خاصة، ألا وهما: التزايُد المتصاعد في عدد التجارب السريرية التي تجريها جهات متعدِّدة الجنسيات على الأدوية، والعروض التي تقدِّمها شركات تجارية بادعاء علاج جميع الأمراض عن طريق زرع الخلايا الجذعية، ادِّعاءً غيرَ مُسْنَد بالبيِّنات. وتُبرز الورقة أخيراً أهمية مراعاة الممارسات الأخلاقية في البحوث، في إطار الواقع الثقافي والاجتماعي والاقتصادي للمجتمعات.

SUMMARY The paper outlines the universal problem of ensuring ethical practices in human subject research, and focuses on specific difficulties faced in the developing world with particular reference to Pakistan. It discusses the influence of traditional and hierarchical social norms of physician–patient relationships in heightening these problems. Two emerging issues of specific concern in Pakistan are described: an exponential rise in multinational clinical drug trials, and commercial ventures offering unproven stem cell "therapy" for all kinds of diseases. The importance of introducing ethical practices in research within the context of local cultural and socioeconomic realities is highlighted.

Recherche et pays en développement : espoirs et boniments

RÉSUMÉ Le présent article décrit le problème universel qui consiste à garantir des pratiques éthiques dans la recherche sur les sujets humains et s'intéresse aux difficultés spécifiques rencontrées dans le monde en développement, et plus particulièrement au Pakistan. Il examine l'influence qu'ont les normes sociales traditionnelles et hiérarchiques dans la relation médecin-patient pour intensifier ces problèmes. Deux nouvelles questions particulièrement préoccupantes au Pakistan y sont décrites : une augmentation exponentielle des essais pharmaceutiques cliniques multinationaux, et les projets commerciaux offrant des thérapies cellulaires à l'efficacité non prouvée pour tous genres de maladies. L'importance de l'introduction de pratiques éthiques dans la recherche dans le contexte des réalités culturelles et socioéconomiques locales est soulignée.

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Importance of and obstacles to ethical research

The issue of ethical research and the difficulties we face in assuring ethical research in the background of deeply ingrained cultural norms and values that define our interactions both with patients and healthy human subjects are, in my opinion, especially important for us, the healthcare professionals and investigators who live and work in developing countries such as Pakistan.

In the May 2005 issue of *Nature*, Martinson and his co-authors reported that one-third of all United States scientists had engaged in serious research misconduct in the past 3 years [*1*]. Along the same lines, in a recent interview to the *Boston Globe*, an American newspaper, Mr Greg Koski, Director of the US Government Office for Human Research Protection, expressed his concern about medical research involving human subjects in the United States [*2*]. Mr Koski stated that “medical research in the US is in a critical condition”. He compared it to a “nuclear reactor” that was facing meltdown. These concerns about unethical research are being expressed in a country that has played a major role in the development of guidelines for international research ethics, and probably has more institutional review boards and oversight mechanisms in place than any other country in the world.

What is apparent, therefore, is that ensuring that human subject research is conducted in an ethical fashion is no easy matter anywhere in the world. Such comment also suggests that merely establishing ethics review committees, or becoming familiar with international ethical guidelines that have been formulated and revised many times, and will undoubtedly be re-revised, are insufficient *in themselves* as safeguards against unethical research and exploitation of human subjects.

Nonetheless, there is significant international effort at the moment to establish ethics review committees in developing countries, which are increasingly functioning as host countries for multinational, collaborative research. Without ethics review committees in place to approve proposals, it is difficult to embark on such research and impossible to publish the results in indexed journals. However, a committee is only as ethical as the members who constitute its body. Innumerable examples are available in the literature that demonstrate that ethics review committees can end up serving as no more than official tools stamping “approved” on proposals when members are not united by shared values [*3,4*], which include a duty to protect the most vulnerable, but instead are primarily driven by personal gain. We can formulate impressive ethical guidelines, but these are only effective if researchers have a strong sense of moral responsibility, compassion and empathy towards those they recruit as research participants.

The situation in Pakistan

Conducting research in hierarchical, traditional countries such as Pakistan adds yet another dimension to the difficulties in assuring that it is done in an ethical manner; an “indigenous” layer of cultural norms makes it even more of an uphill task, but it is a task that we are morally bound to shoulder. The historical and social construct of the Pakistan culture, the socioeconomic realities (with similarities to other countries in this region) and some of the deeply rooted values and customs pose challenges that are specific to this part of the world. We who live here know them, and only we can address them.

Perhaps the most important factor that places human subjects at risk in this part of the world is the magnification of "power differentials" inherent in hierarchical societies such as Pakistan. This difference is particularly pronounced in the interactions between physicians and scientists and those they take care of or enrol in research projects. In Pakistan, scientists and physicians constitute the "elite" section of society. They are by and large the "English-speaking", affluent, highly educated minority in a society where the majority of those they deal with in their professional lives are "Urdu-speaking", poor, generally illiterate or misinformed and disadvantaged in many other ways.

The authority and respect, made legitimate both culturally and religiously, that physicians and researchers are given in Pakistan is quite extraordinary. In most industrialized countries, professional–public interactions in healthcare and research domains rest on an egalitarian, contractual foundation in which the rights of the individual (human subject or patient) are central pillars. Moreover, legal mechanisms are available and made accessible in these societies as recourse to those who believe that their rights have been violated. Furthermore, the general level of public education and knowledge makes this a mechanism that both patients and research subjects can, and do, tend to use.

In Pakistan, and other countries in this region, we live in a different universe. The general public, whether healthy or ill, regards anyone connected to the medical profession with a reverence that has long been lost in industrialized countries. Laypeople that physicians deal with professionally continue to perceive them, and often refer to them, as their *maa-baap* (mother or father) who knows what lies in their best interest. I have referred to this relationship in my writings as one characterizing a "relational morality", a fiduciary relationship based on trust rather than one that is contractual in nature and rests on the rights of individuals [*5*]. A physician–researcher's authority is further augmented by the position accorded to healers in Islam; they are considered to be the instrument of God's mercy on earth, a statement that can be found in Al-Ruhawi's 9th century treatise, *Adab al-tabib* [*6*]. In a country where patients frequently say that "up there is Allah, and down here is you, doctor sahib", they are unlikely to suspect that a doctor has anything but their best interest at heart when he/she suggests a line of action to them.

Added to this is the other reality in Pakistan – absent, weak or only-on-paper accountability processes both at institutional and governmental levels. The lack of accountability processes and the powerful power differential can serve as a lethal combination for human research subjects and patients alike, making the potential for abuse of both truly phenomenal. Through workshops held in Pakistan, healthcare professionals and scientists are becoming familiar with the Helsinki Declaration, the Council for International Organizations of Medical Sciences (CIOMS) and other research ethics guidelines. But knowledge of such guidelines is one thing; application of this knowledge within the *specificity* and context of existing cultural and professional practices and socioeconomic realities, is quite another. This is a matter we have neither reflected on sufficiently nor kept adequately in sight in developing countries.

Emerging issues in Pakistan

There are 2 emerging developments in Pakistan related to medical research that I consider among the most troubling. These are also issues that are emerging in many other developing countries of this region.

Clinical drug trials

We are beginning to see an exponential increase in clinical drug trials in Pakistan in which multinational pharmaceutical companies are major players. In a majority of collaborative trials, sponsors are from countries of the developed world while co-investigators and research subjects are drawn from African and Asian countries. In the case of drug trials, because it is the physicians who prescribe drugs, they are the ones being approached to serve as investigators using their patients as research subjects. Drug trials now constitute the most common form of research taking place in Pakistan [*7,8*]. Almost two-thirds of research proposals that are reviewed every year by the ethics review committee of one of the teaching institutions in this country involve drug trials (personal communication).

From 1995 to 1999, the proportion of new drugs approved for use in the United States on the basis of trials conducted *outside* America increased from 9% to 27% [*9*]. In a report in the *Washington Post* in May 2005, Mr Yamada of the multinational GlaxoSmithKline is quoted as saying that the company’s “outsourced” clinical trials are expected to rise from 29% to 50% within 2 years [*10*]. This makes obvious economic sense. Countries of the developing world offer many advantages, besides lower overhead costs, for conducting such research when compared to industrialized nations. Many South Asian countries such as Pakistan have large, illiterate populations to draw on as subjects. Many have physicians who are well conversant with English and some of them have had part of their training in the United Kingdom or the United States. Above all, supervision and monitoring mechanisms are either weak, absent or amenable to manipulation.

Conducting clinical drug trials in developing countries is a necessity. We need to investigate, understand and develop effective preventive and curative approaches to diseases that are endemic to this region. But the benefits of such research must accrue to the communities used for research. Well known to many is the “10/90 gap” described in the 2003–2004 Report of the Global Forum for Health Research [*11*]. The report highlights the fact that of the 73 billion US dollars America was investing annually in health research at the turn of the 21st century, less than 10% was being devoted to health problems that account for 90% of the global disease burden.

In clinical drug trials, there are inherent conflicts of interest when physicians serve as investigators. These conflicts, which can lead to coercion and exploitation of patients, are compounded in societies such as Pakistan where physicians have immense authority and are revered as instruments of God’s mercy. In Pakistan, as elsewhere, healthcare institutions and physicians are increasingly succumbing to blatant financial incentives – leased cars, international trips, help with education of children, and even plain cash – to participate in drug trials that would be questionable in other countries [*12,13*]. When our primary professional objectives become personal gain, academic or monetary, we convert research and healthcare into marketable commodities. This is an unconscionable rejection of what the healthcare profession is all about.

The hype of stem cell “therapy”

The second development, which, in my opinion, needs serious attention from principled citizens, professionals and laypeople alike, are the burgeoning of private, commercial enterprises that are beginning to present research that is still in its preliminary stages as proven therapy or treatment for various diseases. Desperate patients and misinformed or unscrupulous physicians are being approached directly by such for-profit business enterprises.

The latest example of the presentation of research that is promising but still in its early stages is related to stem cells. Autologous stem cells that are drawn from patients and then re-infused into the patients following professed "retroversion" to totipotency are being increasingly offered as treatment for all manner of diseases.

A recent news item in *The Dawn* (the leading English newspaper in Pakistan) reported a press conference in which a member of the Sindh government expressed moral outrage at people he described as "fake" spiritual healers and magicians [*14*]. In Urdu he referred to them as unscrupulous "*amil, kamil aur jadoogar* (magicians)". He complained that not only poor patients but even educated people were being duped by their fake promises. The government official then promised that "wide action" would be taken against them soon, and the "wall chalkings" that they use as advertisements for their fictitious cures would be removed. The irony of this report, in light of the recent inauguration of a private company in Karachi claiming the availability of "therapy with stem cells" for a multitude of diseases, will become clear later.

But first let us return briefly to the status of stem cell research in a recent article by Braude, Minger and Warwick published in the *British medical journal* [*15*]. The authors are a professor of haematology, a professor of obstetrics and gynaecology and the director of a stem cell laboratory in the United Kingdom. They wrote with concern about the "escalating number of clinics offering stem cell cures for all sorts of ills". This, they believe, was leading a promising technology rapidly into the realm of quackery. They said, "Despite inadequate preliminary data on clinical safety or from animal experiments, trials using [stem] cells derived from autologous BM (bone marrow) samples are already being conducted on patients ..." The urgency for treatment of severe diseases is the justification given for this practice. The authors note that urgency can never be used as an excuse for offering unproven therapy and exploiting desperate patients. And they are correct.

And yet, commercial enterprises that offer treatment by using the patient's own stem cells are beginning to spring up for problems as diverse as Parkinson disease, muscular dystrophy and other neurological disorders, thalassaemia, paralysis from strokes, depression and heart disease. These have been reported from Mexico, Brazil, Barbados, China, the Ukraine, Russia and India [*16*]. Now, this commercial enterprise has found its way into Pakistan through a private company, which was asked to stop its unethical practice in India in 2004. They have now found a haven in Pakistan.

In an interview to *Newsline*, a Pakistani magazine, the researcher (and owner) of the private company in Karachi involved in this therapy described what she is able to do with stem cells [*17*]. She said the technique that was being used could "virtually be called the magic touch". To translate this into Urdu, the technique she is offering is a form of *jadoo* (magic); by analogy she is therefore a *jadoogar*, an entity the government official previously mentioned had condemned as unacceptable in Pakistan.

What is the difference then between the *jadoogar* that the honourable member of the Sindh government was so upset about and the treatment, the "magic touch", being offered openly through use of stem cells in Pakistan? The difference is that whereas the *jadoogar* and spiritual healers generally hail from the poorer sections of society and advertise on city walls, physicians and scientists who promise stem cell treatment belong to the elite of the country, are patronized by the rich and the influential and advertise in the leading newspapers of the country.

Conclusion

Biomedical research has led to tremendous benefits for the human race, and it offers great hope for the future. However, it is being high-jacked by private, commercial enterprises that are willing to by-pass meticulous scientific methodology and ethical standards. Yet, the hyped up promises for therapy of all manner of diseases that they make can be extraordinarily seductive to those with serious diseases.

Much of this appeal is due to the fact that we are in an era in which science wears a mantle woven with power, authority and credibility. Because of this, it takes courage to make a stand against it when it is abused for personal gain at the cost of the unwary, the uninformed and the disadvantaged in our societies. But a stand against unethical use of research must be made, whether this occurs through multinational drug trials or when untested research is touted as therapy. It is our moral responsibility as healthcare professionals and researchers to do so.

To conclude, for those who appreciate the beauty of Urdu poetry, here is what Allama Iqbal has to say about our obligation to move beyond the ease of acquiring rhetorical expertise in words to the struggle involved in achieving the heroism of a virtuous person who acts in moral ways.

Guftaar kaa yey ghazi to bana
Kirdar kaa ghazi bun na saka

(Master was he when it came to smooth talk
But as man of virtuous action? A naught).

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8th World Congress of Bioethics. A Just and Healthy Society

The Chinese Medical Association, the Chinese Society of Medical Ethics, and the International Association of Bioethics are holding the 8th World Congress of Bioethics from 6 to 9 August 2006 in Beijing, in conjunction with other important bioethics events. This Congress will offer a comprehensive examination of the full range of issues in bioethics, many generated by the latest developments in biotechnology and health systems and by the age-old dilemmas of medical practice and research. Further information can be found at the Congress website: www.chinamed.com.cn/IAB2006