

Summer 2002

THE EFGCP NEWS

The Newsletter of the **European Forum for Good Clinical Practice****'A Place to Meet'**

Focus on Africa
and Asia:
Ethics and Clinical
Research in Africa

The 2001 Joseph J Hoet
Lecture

Ethics and Medical Care
in Africa

EC Malaria Control
Programme



Africa, and the pity of Africa

World aid agencies predict that the food situation in a swathe of Africa from Malawi to Botswana will become even more desperate as a period of extreme climatic fluctuation threatens famine. This adds to the already desperate situation created by HIV/AIDS described so eloquently by Professor Hoosen Coovadia, Paediatrics and Child Health, University of Natal, South Africa, at this year's EFGCP Annual conference.

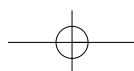


"Professor Hoosen Coovadia giving his keynote address on the second day of the Year 2002 Annual EFGCP Conference."

Prof Coovadia gave the keynote speech on the second day of the conference and left his audience numb and silent. Our own concerns about the ethics of clinical research in Europe were suddenly overwhelmed by his picture of the stark clinical options in Africa. Yet, as Dr. Cor Oosterwijk (Chairman, Patient and Parent Organisations in the Netherlands) put it, "At the level of individual suffering it makes little difference if you are one of a small or large population". Professor Hoosen Coovadia has wide clinical and research experience in vaccines and clinical trials in the field of AIDS (the full text of his talk can be found on page 6).

This issue of EFGCP News contains other important contributions about Africa. Sickness in Africa denotes an 'opportunity' to the unscrupulous, but the Continent's health leaders are now preparing an ethics defensive. Two years ago (January 2001), the Pan-African Bioethics Initiative (PABIN) was established in Lusaka, at a 'Seminar on Ethical Review Committees in Africa', organised by the WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR), the Council for International Organisations of Medical Science (CIOMS), the European

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CHAIRMAN'S MESSAGE**'Informed Consent', 'Informed Assent'
perhaps, even 'Informed Request'
What's in a name?**

The EFGCP has been hosting a lot of discussions around the idea of "Better Medicines for Children" this year. It has been the theme for our Annual Meeting in January 2002, for the European Commission's "proposed regulatory actions on paediatric medicinal products" published February 28th, and for the EFGCP Forum Discussions on those proposals held on 17

April, together with our expert colleagues in the Confederation of European Specialists in Paediatrics (CESP). We submitted our commentary to the European Commission on the last possible day, end of April 2002, "just in time"!

Placing our usual emphasis we put patients issues firmly in the middle of all these debates, so talk inevitably turned to ethics. Working with underage subjects in clinical research brings its additional challenges. So Informed Consent as required by modern codes of conduct like GCP must come from the parents or legal guardians.

Not yet universally agreed is a growing appreciation that this is not sufficient though. Child subjects of almost any age can grasp what

it will mean to them to participate, so long as it is explained to them in appropriate words and ways. While not easy for most people to actually achieve, this process can really lead to "Informed Assent" in the best case, and surely this is now what we all should strive for.

This theme deserves much deeper investigation, what are the skills needed to achieve "Informed Assent", how are they acquired and passed on and how can we judge if we have enough of them to approve the studies proposed? Here's work for parents, children, paediatricians, communicators and bioethicists galore.

And what is this "Informed Request" then, when it's at home? It is just a word change I like to play with, but it conveys to me something essentially desirable, a potential research subject sitting forward and asking to be included after having had a study properly explained to them. More dynamic and appropriate for this day and age than the alternative, worn-down potential subject mutely nodding his or her consent, don't you think? Whatever age they are perhaps.

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**Clinical Research in Africa
Ethics, Culture and the Law**

Dr Ames Dhai

Africa's need for health research

Most people in Africa live in abject poverty. Also, because so many of them suffer from diseases there can be no meaningful fight against poverty. Populations plagued with malaria, intestinal worms, tuberculosis, HIV/AIDS and other devastating diseases cannot contribute effectively to national wealth and their own well being. Africa has a desperate need for health research, but has little capacity to set up large scale programs. For this reason, collaboration between researchers and research institutions within and outside Africa is an option that cannot be ignored. Therefore major biomedical research in Africa is mostly initiated by scientists from the developed world who often suggest the areas of research collaboration.¹

Setting the research agenda

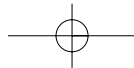
While global considerations are important, research must be area specific. Research priorities need to be directed at the needs and interests of the host nation, region and district.¹ If this does not happen the findings may not be locally or nationally applicable; they may not even be in line with the cultural, social, political, economic, ecological, environmental, and technical realities of the area. To avoid this, identification of the research problem and the entire theme for research should be shared between the funding source and people of the recipient country.

In general, health research projects are financed by non-governmental organizations (WHO, UNAIDS, etc) or pharmaceutical companies. The scope for negotiation varies

considerably. All too often prospective partners from the pharmaceutical industry arrive in developing countries with research proposals and protocols already fully developed. The impoverished partner is hastily asked to sign on the dotted line. 'Beating the deadline' is often the reason furnished for this haste. The poor partner rushes to sign and seize this opportunity. Scientists from both the 'North' and 'South' need to ask if such an approach is ethical. It is important that decisions on the research agenda are made together by all partners.

Dubious motives

Though most biomedical research in the developing world is undoubtedly conducted with good intentions, we need to look carefully at the research agendas of studies



funded from outside the developing world. It is much to be regretted that dubious motives do exist for such studies (see table). We need to be conscious of them when we are approached by sponsors who would conduct research in our countries.²

- Low costs
- Low risk of litigation
- Less stringent ethical review
- Populations prepared to co-operate with almost any study that appears curative
- Possible under-reporting of side effects because of low awareness
- Lack of truly informed consent because of poor understanding
- Populations unfamiliar with elements of individual consent
- Researcher ambition
- Sponsor's desire to create new markets

Collaborative research

The most critical component of a successful collaboration is mutual trust between the parties concerned, based upon transparency. It is essential to begin this process before launching a collaborative project, by ensuring that the partners are fully knowledgeable about the planned research and that a commitment is made towards sharing responsibilities. The conception, development and execution of a research project should also involve the communities concerned - the intended beneficiaries. Studies should not satisfy solely the quests of scientists. This is the only way that research can be relevant to the participating communities. Through such involvement these important stakeholders are likely to appreciate the results and how they can be used to solve their own health problems.

Shared benefits

The benefits of collaborative research should accrue not only to the sponsor, but also to the host country's research personnel and patient population.

Research personnel

It is often the case that publications from collaborative research projects list only the funding partners (who may claim also patents or copyrights, or gain financially), without mentioning their southern partners. Research results constitute intellectual property and should be shared amongst the research partners.¹ The results should be presented in a manner that is easily understood by all stakeholders, including policy-makers and

decision-takers. They should be disseminated to end-users beyond readers of scholarly journals.⁴

Furthermore, health research partnerships should strengthen the research capacity and research ethics of both individual researchers and their parent institutions. Research cooperation can then lead to meaningful self-reliance and sustainability, thereby enabling developing countries to deal increasingly with their own major health problems, without always waiting for a northern initiative.

Patient population

It is seldom that participating communities are given even a simple acknowledgement in journal articles. This is a responsibility of the research team. Moreover, study communities have also the right to an early account of the results, described in simple terms, in their own languages. Beyond that, a transition of the results into therapeutic benefit is more complex. Nonetheless, research teams have an obligation to incorporate mechanisms into the study design that will ensure a therapeutic benefit for the participating patients.

Culture and informed consent

The cultural background of research participants must be understood with regard to how informed consent is obtained. Ethical conflict is quite likely to emerge when researchers and participating patients come from different cultures.

In Africa a person does not perceive himself or herself as an individual in his or her own right, but rather as an extension of a family serving as an intermediary between ancestors and future generations. Moreover, authority is located in the leader of a village or community, and the head of a household (usually a man). Because of this perception, an insistence on first person informed consent in group-orientated cultures is viewed as morally unacceptable.²

Today, however, African societies are changing in ways that make informed consent requirements more appropriate rather than less.² There are more than 900 different contemporary, or historical, ethnic and cultural groups described in Africa; and these groups have not been static. African culture and traditions were disrupted by Africa's colonial history. Prolonged civil warfare, urbanization, education, industrialization, and more recently the AIDS epidemic, have caused extensive changes to traditional lifestyles.

Village leaders have declined in number; there are problems in identifying them and

assessing whether or not they can be genuinely trusted.³ They may not speak for all the inhabitants of a village - which may include refugees and immigrants. In some countries party officials and cell leaders have replaced traditional leaders. Other countries have dictators. In others almost all trace of traditional life has been wiped out by civil war. Hence, where consent is obtained from a village leader or government official, it cannot always be assumed that consent was given in the best interests of study participants.

Another change in many African countries is the growing emancipation of women resulting from education, which will drive the movement towards personal informed consent.

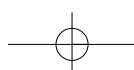
Nonetheless there may be some merit in the tradition of community consent as an effective safeguard against the abuse of vulnerable populations. In this case, community consent should be obtained directly from the community itself; involving perhaps an hierarchical chain of consent - through the government, the chief of a district, the head of a village and ending in village meetings. At the end, however, individual consent must always be sought and should preside over community consent.

The requirement of informed consent should not constitute an insurmountable barrier to obtaining valid consent or refusal. Differences of education, culture and class between researchers and participant subjects are not peculiar to the African continent. With extra effort researchers in developed countries effectively communicate with subjects whose backgrounds are different from their own. The challenge may be greater in Africa and, for a little longer, consent may rely partially on community decisions. Eventually, however, the process will conform to an eventual world standard. In the meantime, just as there is no single African culture, so each research project and cultural setting requires special attention to the way informed consent is obtained.

Ethics and research conduct

It should be remarked that ethics in research means not only a well-designed trial that articulates the sentiments of respect for persons, beneficence, non-maleficence and justice. There remains also the potential to violate the rights of research participants, particularly those from poor and vulnerable communities, while the research is underway. An important aspect of ethics in research is to ensure periodic monitoring and evaluations

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What role do international guidelines play in clinical care?

The year 2001 Joseph J. Hoet lecture: *The Declaration of Helsinki*

Professor Nathan Clumeck

I am very pleased to be here today and honoured to have this chair, to express my point of view on what is happening at the moment concerning ethical problems in clinical trials.

The world of clinical research is now changing in ways that engender new ethical problems that are complex and controversial. Clinical research is now big business, but its activities are not globally distributed. Take AIDS as an example, ninety-five percent of patients are found in Africa, Asia and Latin America whereas ninety-five percent of the money disbursed on AIDS drugs and research is spent in the developed countries, where patients are fewer. This gap has implications and we should all be concerned when injustice comes to fill it.

Ethical controversies about the protection of communities and involvement of children in clinical trials relate to issues that are rather particular in developing countries. The underlying predicament is that, in order to pursue science and improve our knowledge, we are obliged to perform the clinical studies in developing countries, where most patients live. This raises the critical question "Which ethical standards should apply?". Let me first state some of the ethical dilemmas.

Informed consent

Good clinical practice (GCP) guidelines stipulate that subjects shall be given a proper explanation of what will be done; necessarily, this entails that subjects understand the value of informed consent. All published papers state that subjects were informed and gave signed consent.

However, we know from clinical practice how difficult it can be to explain a study design to patients, to explain the real benefits and risks. Moreover, we also know that in poor, under-developed countries between 50%

and 90% of the people are illiterate. So what does 'informed consent' mean in such populations?

Benefit/risk ratio

A discussion of benefit versus risk is particularly pertinent if we look at the AIDS vaccine story. The AIDS virus has many different sub-types (HIV-1 A, B or C). The problem is that the most prevalent sub-types in the United States and Europe are totally different from those in Africa and Asia. Until recently AIDS vaccine research was performed with virus sub-types prevalent in developed countries, whereas the trials were performed in poor countries - where the prevalence of HIV is high. So the risk/benefit ratio was totally unbalanced as the vaccine was not appropriate to the countries where it was tested, in the first phase of evaluating efficacy and tolerance.

Patient selection criteria

In clinical research we select patients according to specified criteria; but what is left of these criteria if patients insist on different forms of compensation, e.g., food, money or some other basic need? We then become drawn into either selecting subjects differently or choosing whom we select. The decision could represent a source of bias.

Comparison treatments

When we perform a clinical trial we have to consider a control treatment. Should that be the best standard treatment, the locally available alternative, or, when no effective treatment exists, a placebo?

Social benefit

In the summer of 2000 there was hot discussion in South Africa because the government had decided clinical research was not its priority - which was poverty. We tried hard to convince the government of the value

to their people of AIDS research; people were dying from the disease. This example illustrates that social priorities can determine the realisation of a clinical trial. Therefore it is relevant to ask "What is the value of a particular research project to a country with inadequate resources?".

Treatment beyond the study

Finally, the provision of continuing treatment to research participants becomes a key issue, when research is limited in time and resources. Consider what happens. Suddenly you have doctors and nurses coming into a village and everything is raised in quality. Treatment is given for a few months. Then the study stops, everything disappears and the village goes back to the eighteenth century. What provision should be made for continuing treatment?

Guidelines for research

Current GCP guidelines cover how research should be conducted in our rich countries. They are founded on a set of ethical principles forged by history. I would remind you of the Nuremberg Court, created after the Second World War, and its judicial decision condemning the atrocities of Nazi physicians. The focus then was on the need for consent and a favourable risk/benefit ratio for patients and society. This was followed by *The Declaration of Helsinki*, and its subsequent amendments, which introduced a fairer risk/benefit ratio, independent review and drew a distinction between 'therapeutic' and 'non-therapeutic' research.

The *Declaration* also stated that in research on man the interest of science and society should never take precedence over considerations relating to the well-being of research subjects. In any clinical study all patients, including those of a control group,



"Professor Nathan Clumeck giving Year 2001 Joseph J. Hoet Lecture."

should be assured of the best proven diagnostic and therapeutic methods.

Unfortunately, reality has distanced us from these principles. In recent years our standards have been challenged by trials related to the AIDS epidemic, performed in developing countries, which have fuelled the ethical debate. Our problem now is how to apply GCP guidelines to poorly resourced countries that do not have specialist care units?

New context for research ethics

The HIV/AIDS epidemic is a new paradigm for the various inter-related and complicated problems, just discussed. Today, without question, if you discuss ethics you also discuss science, but you have to consider, too, ethics in relation to industry and the free market; investors will not put in money if no profit is to be gained. Also, if you talk about a free market, you talk about politics. So we are talking about the relationship between science and politics. In the the worst situation ethics and politics confront each other. When we perform clinical trials potential conflicts arise, because we are concerned with individual benefit; however, individual benefit must now be balanced against the interests of industry, which sponsors the study, and public health interests. Sometimes these interests diverge.

Industry is mostly concerned with fast results and the early registration of a drug. The ultimate strategy of such an objective would be to compare the new therapy with 'nothing'. It follows, therefore, that when no standard treatment exists a placebo is justified as the control. In fact the standard of care in the poorest countries is 'nothing' and the big temptation is to use a placebo.

Public Health authorities are interested in long term cost-effectiveness. In the case of AIDS the cost-effectiveness of new therapies is obvious. Since the discovery of new therapies morbidity and mortality have both decreased, together with the cost of hospitalizations.

If we look at these different interests, we are immediately confronted by an ethics question "Which ethical stance will determine their resolution, a pragmatic and relativistic 'utilitarian ethic', or a 'universal ethic'?" That is the core of the debate today.

Utilitarian ethics

The way that clinical trials in pregnant women with AIDS were undertaken, initially in developed countries then in poor countries, illustrates the debate.

In 1985 a research protocol was developed in the United States to address the problem of pregnant women with AIDS. This protocol provided for HIV-testing and counselling, together with lengthy oral azidothymidine

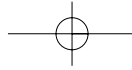
(AZT) therapy enhanced by intravenous administration at delivery. Women were asked not to breast-feed and newborn babies were treated for six weeks. The estimated cost of this heavy protocol was approximately \$800. The control was a placebo, because there was no other therapy, and this was totally ethical. The study demonstrated that maternal transmission decreased from 30% to less than 10%. So AZT became standard therapy for pregnant women in the United States and Europe.

It should be noted that when this treatment was discussed for pregnant women in under-developed countries some American authorities said, bizarrely, that even though the protocol was effective in some countries it was unlikely that it could be exported successfully to many others. These authorities therefore advocated more placebo controlled trials in such countries:

"The most compelling reason for using a placebo controlled arm is that no current intervention is standard practice, and placebo controlled studies provide a fast response and definitive answers to questions about safety and value of intervention in the setting in which the study is performed."

This argument may be described as 'ethical relativism', i.e. a pragmatic 'utilitarian ethic'. I shall later contrast this with a 'universal ethic'. The issue was hardly debated in the medical literature.

Ethical standards, therefore, were already breached when industry decided to sponsor a controlled trial of nevirapine (NVP) in pregnant Ugandan women. Out of 14000 African women tested for HIV/AIDS, two thousand (16%) were sero-positive. Approximately 600 of these sero-positive women received randomized treatments after giving 'informed consent'. The trial hypocritically avoided the 'placebo problem' by administering double ineffective doses of AZT orally, just before delivery. In this trial, not only was AZT given at a sub-therapeutic dose, but there was no follow-up and no treatment of the mother after delivery. I would remind you that in the American trial AZT was given orally for months before an intravenous dose at delivery. Of course the Uganda study successfully demonstrated that NVP was superior to AZT. However, as all women had a very high viral load, those treated inadequately with AZT were to die from opportunistic infections within a few months or years. The scientists concerned may have prevented them from delivering sero-positive babies, but they did not prevent



the children becoming orphans. Even more cynically, these babies were not treated in the following months because they were used in research on viral load, immunity, or for HIV culture!

So 'ethical relativism' means that one accepts double standards for research in developing countries. One thereby accepts less effective standards of care; one accepts the abandonment of treatment when a trial ends; and one accepts that the interests of science prevail over those of patients. In my view this is totally unacceptable. Ethical rules should be universal. All humans deserve the best care possible. A stop should be put to utilitarian ethics.

Rather than be fatalistic about this aberration, ultimately risking a single, lower, worldwide standard, we need to strengthen the protection of human subjects everywhere,

including in our own countries. Pressure is being exerted, too, on certain clinical trials here in our developed countries. The pressure is to recruit patients aggressively because of Health Authority requirements, Regulatory Rules, etc.. Such aggressive recruitment leads to an erosion of informed consent and a failure to adhere to the standards of good clinical practice. For example, some centres fail to disqualify subjects who do not meet study criteria or fail to report adverse events; there is also a failure to train research staff adequately.

Universal ethics

Marcia Angel (previous editor-in-chief of the New England Journal of Medicine) took a very high stand against utilitarian ethics. Like her, we should ask: "Is academic medicine for sale?". What makes clinical research ethical? What would constitute a universal ethic?

A universal ethic would require that we reaffirm the social and scientific value of treatment, that our goal is to improve health, well-being and knowledge. We must respect a subject's autonomy and welfare by accepting that the person may withdraw from the study. We must also inform subjects of the risks and benefits of the proposed treatment, and those of the clinical investigations. The informed consent form must explain clearly the purpose of the study, the potential risks and benefits, and the alternatives. We must be fair in our subject selection and not target poor people, stigmatized people, vulnerable individuals etc. We must accept independent review and try to minimise potential conflicts of interest by securing financial independence. Lastly, we must accept the analysed data and produce objective reports. All these rules should be the duty and honour of any scientist.

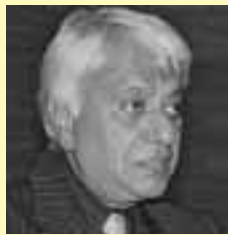
FEATURE

Ethics and Innovation in the Scales of Health

Professor Hoosen M. Coovadia

Different ethical dilemmas

In this talk I shall contrast the major issues of ethics and good clinical practice that determine paediatric services in Europe and the U.S.A., with those that concern Africa and much of the Third World. We are on the brink of a new scientific age and you in highly developed countries have already engaged in ethical deliberations that are quite unprecedented. I anticipate that the sort of issues you will face are those that will result from discovery of the human genome, each one of which has already enormous ethical, social, political and economic implications. The dilemmas you are likely to face are those of identifying heritable diseases, antenatally or at birth, of what to do about the foetus, and of what advice to give parents and society. You may even be able to recognise the capabilities of individuals at birth. What will that imply for society? You may discover and prevent diseases or undesirable traits. What will you do with that information? Of course



"At what point do you say "I am really sorry, but I just cannot treat this child anymore"? We face this every day."

you know the serious, economic conflicts of interest in this research. I have no doubt that these conflicts will increase as the technologies become more commercialised. I have a healthy respect for the scale of the problems you face.

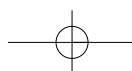
My own experience is entirely different. What we see is the great majority of children in the world. That is the first difference. The scale of issues I am going to talk about are overwhelmingly the issues of huge populations, millions and millions of people.

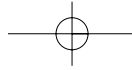
In the global burden of disease the commonest problems amongst adults and children are pneumonia, perinatal conditions,

diarrhoeal diseases, HIV and AIDS. The seriousness of these diseases is largely controlled in the developed world. For us they dominate and impact heavily upon our societies. Infectious diseases are still a leading cause of death if you take the world as a whole. They account for almost half of all deaths in young adults and children. In addition, there are other conditions such as perinatal diseases, nutritional diseases and injuries. They may not be your top priority, but they still determine our workload, the clinical difficulties, and the ethical issues we face in the developing world.

The HIV/AIDS epidemic

The largest of all our problems is undoubtedly the HIV/AIDS epidemic, which now ravages the world. South Africa has the largest prevalence of the globe. Out of all the 40 million cases of HIV/AIDS, worldwide, the horrific figure in sub-Saharan Africa is about 28 million. That is a phenomenal





concentration. In my country we have the largest number, more than 5 million people who are HIV/AIDS infected. So, though we account for 0.6% of the world's population, we have approximately 10% of the world's HIV/AIDS cases and that will not go away. For us and much of Africa, perhaps India soon and China later, this disease outranks everything we have ever experienced. It is difficult to speak about it, here, because it is very hard to imagine the impact of a disease that is worse than smallpox, the black death and even slavery in terms of the number of people who have died, and the suffering it causes. AIDS is the culmination of all those plagues that humanity has ever known. It is all of them, but in a way it is none of them, because it wreaks its own havoc and it sows its own destruction in a way that is almost unimaginable. It engraves its own inscription on our societies and it creates its own myths. So it is very hard to escape from a disease such as that, in talking about ethics and clinical practice.

Ethics, governments and HIV/AIDS

What are the ethics of government, government responsibility, and government denial in the face of an epidemic? What are the moral and ethical responsibilities of institutions like the corporate sector, etc? Since 1984 the spread of HIV/AIDS has been very rapid indeed. It now has enveloped most of Southern Africa and large parts of East and West Africa. The first child I saw with HIV was in 1989-90. Could governments have done anything to prevent, delay or reduce the impact of that spread?

It is very easy to be critical in retrospect, but there is certainly a culpability, involving a whole range of social institutions including governments, for not having done enough. Those who follow the political twists and turns of my own government know its bizarre position. The government was unable to face the scientific reality of HIV as a virus causing AIDS. The problem of government denial exists throughout much of Africa. It has incapacitated an effective, efficient and rapid response to the epidemic and may account for some of its present scale. I must say, however, that in the past few years there has been a dramatic shift in the way government in Africa has approached the problem and there is a new rigour and enthusiasm in trying to address it.

Let us now look at what our governments spend on something as manifestly good as an epidermal powder immunisation vaccine.

Some low income countries finance the total cost, some 25% or more of the cost, but at the bottom of the ladder you find many that finance less than 25%, and some finance nothing at all, even for a routine vaccine.

So, in the face of government inertia what does one do? Is government culpability and inaction something of an ethical issue for us all? I think it is, and if you take a wider view of ethics I would argue that there has been a contest between civil society and governments in many parts of the world, which in some cases has resulted in government action being coerced by social institutions.

Despite our problems, we function democratically in South Africa and our judicial institutions are something to be proud of. Activists have used our Constitution to oblige the government to house poor people expelled from their land. The government was reluctant to provide AIDS treatment, but activist groups took the government to court, to make it provide basic things like anti-retroviral drugs, to prevent mother-to-child transmission. So political issues are being driven by activists and in terms of government ethical responsibilities I think this is important.

Health care crisis

It is difficult, if not impossible, for us to provide good clinical care which you in Europe and the U.S.A. regard as a right. A study from the Africa Centre, funded by the U.K. Wellcome Trust, showed that AIDS accounts for more than 35% of all child deaths in rural areas. In your countries children mostly die from prematurity, pneumonia or birth asphyxia. Children in Africa die largely from HIV/AIDS. Our wards are overwhelmed. About 40%-60% of all paediatric beds are occupied by HIV patients. Our public services are overwhelmed and it is really very difficult, in the absence of some major intervention, to provide good clinical care. How can you teach good clinical medicine if there is no differential diagnosis, because AIDS causes everything? How do you teach, if you cannot teach the ability to analyse critically a case of paralysis, pneumonia, headache, etc.? On that scale, AIDS makes it not only difficult to provide good clinical care, it compromises our ability to adhere to strict ethical rules. Which does not mean that we must not try.

The ethics concern where you draw the line as to whom you treat or do not treat. That is the ethical issue and it is basic to good clinical care. At what point do you say "I am really sorry, but I just cannot treat this child

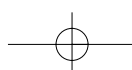
anymore"? We face this every day. I face it in the intensive care unit. Do we admit the child with HIV whose lifespan will be no more than 3 to 4 years? Do I admit him, or her, over and above a child who is not HIV infected? We have had to make some raw decisions. We do not admit children with AIDS into the intensive care unit, though other people do. There is no unanimity on this. There is just individual experience, poorly documented, a bit chaotic and we do what we think is right.

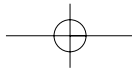
In addition, there are the complications of AIDS. In my hospital, King Edward VIII, tuberculosis is by far the worst complication in adults. South African antenatal clinic figures also show a rise of tuberculosis. Committing yourself to treat tuberculosis is not easy because you get multi-resistant TB. There are cancers, too, for example Kaposi's sarcoma. If you see a lovely young woman totally disfigured by this disease and you simply send her home, it does as much harm to your emotional and intellectual wellbeing as it does to the patient. You really cannot live like that. Therefore what these cases do, the ethical issues they raise, compel many of us to work to the last ounce of our energy to see if there is something we can do, beyond what the government provides or society is willing to spend.

Mother-to-child AIDS transmission is my main field of study and it poses a terrible ethical dilemma. The virus is passed antenatally during delivery and through breast milk. In the developed world women who are HIV infected are rightly told not to breast feed, but you cannot do that in Africa and Asia. One of our studies showed that much depends on the type of breast feeding, whether it is mixed breast feeding, the worst option, or exclusive breast feeding which is much better. The debate continues as to the ethics of recommending breast feeding when there is a danger of transmission versus the use of formula feeding with its risk of death from diarrhoea or pneumonia.

Clinical trial ethics

A landmark study in the U.S.A. and France showed that azidothymidine (AZT) could reduce mother-to-child transmission by about 66%. That was a wonderful study and it gave us the first hint that infection could be prevented in babies. Those of us who live in Africa said "That's wonderful news, but we can't apply it in our situation". The French and American standard of care was too expensive, costing at the time about \$1000. We ourselves were working with UNAIDS and many of us





were performing placebo controlled trials. Our French CNRS colleagues in West Africa said we should drop placebo and adopt the French and American regimen as our control treatment. This led to a huge ethical debate, most of it in the columns of the New England Journal of Medicine. We refused to abandon placebo. All those trials have finished now and there are cheaper alternatives. A recent study by the Africa Centre showed that the cost of drugs for the mother-to-child transmission prevention programme is barely noticeable. So, what are the costs today? Salaries! Salaries for counsellors. The various studies in Africa showed that you can reduce the cost of these drugs. However, the ethical argument remains. Had we heeded earlier admonishments we would not have done the studies that made it possible to reduce drug costs to a fraction. The huge debate is over and I would simply add that we really should argue sensibly about what applies ethically in one situation and what is the standard of care in another.

Ramifying impact of HIV/AIDS

I shall not go through the entire litany of AIDS consequences, but it is not sufficient to consider just health issues. AIDS kills teachers,

weakens the educational system and denies children schooling. If you want good child care you need quality education and education for everyone, especially girls. This now is not possible because in countries like Zambia more teachers die from AIDS than the country produces through its teaching colleges. We have not yet reached that stage in South Africa, but we are seriously compromised. One hundred thousand have no teachers and the situation is getting worse as teachers die. Although my interest is mother-to child transmission, I cannot regard it as the ambit of my work. You have to be involved beyond that and join your advocacy and commitment to things like education and welfare. Men who migrate to a mining area have a higher HIV-status than non-migrants and the reasons are obvious, e.g. migrants live in single sex hostels. Therefore economic factors and marriage can affect the ethical issues around child health and care. Children cannot make ethics decisions for themselves. They depend on adults to decide their participation in trials. In my part of the world the overwhelming majority of women up to age 40, with babies, are not married. What are you going to tell them about family life and parental consent for research? The implications of this are

simply phenomenal and that is not just in South Africa.

World commitment to help

The world has been asked for seven to nine billion dollars to help us fight AIDS, TB and Malaria. The intention is to spend it on care and support, anti-retroviral drugs, orphan drugs, palliative care, prevention, and other needs. It is important to see what will be the commitment of world agencies and the industrialised nations to providing such finance.

I shall conclude by recalling that the past few years have seen a monumental upheaval in the social, political and economic life of the entire world. However, the millions of people whom I have mentioned continue to face problems that are solved in the industrialised world. For them AIDS and TB cause unbearable pain and suffering. These diseases paralyse progress and threaten the fabric of society. It is necessary to ask organisations like yours to do whatever is possible to support our struggle against these calamities. I expect other institutions in Europe and the U.S.A will do what they should and those of us who live in these developing countries shall do what we must.

EEC NEWS

The EC Regional Malaria Control Programme in Cambodia, Laos and Vietnam and its commitment to ethics development for the Asia Pacific

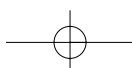
As part of its contribution to supporting development in the Southeast Asian region the European Commission established, in March 1996, a programme titled 'Regional Malaria Control Programme in Cambodia, Laos and Vietnam'. As the title suggests, this Programme aims at addressing the problem of malaria, which is endemic in the three countries due to many factors. The Programme started in mid-1997 and will end on the 31st December 2002.

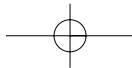
Since the causes of malaria in these three countries are similar, the Programme was structured so that malaria is controlled not only nationally, but also regionally in order to use best the resources provided. Among the approaches adopted, the integration of malaria

control with other disease control is highlighted as a key point, contributing significantly to the sustainability of the Programme. In fact, experience gained from this malaria Programme has served as a reference to help these countries deal with other communicable diseases, using not only the knowledge gained and material provided, but also the model itself. While the three National components in each country work side by side, with the National Malaria Control Programme of the respective countries, to tackle malaria inside the country, the Regional component (also called the 'Regional Project') of the Programme, endeavours to link these national efforts into a broader front through interventions

that, if conducted regionally, would yield better results, such as border malaria, communication, indicators, study, training, co-ordination.

As this Programme is supported by the European Union, the study activities are inevitably mandated to follow European standards, among which ethics is considered a priority. Far from imposing new concepts on the beneficiaries, the introduction of these standards has been met with outstretched arms. On the one hand, this is explained by the growing understanding that development goes hand in hand with quality and standards, and on the other hand, by the commitment of the countries to the current trend of globalisation.





Under the framework of the Regional Project, support for bioethics has been provided, so far, for the following activities:

Regional level:

- Provision of membership fee to members from Cambodia, Laos and Vietnam for the *Forum for Ethical Review Committees in Asia & the Western Pacific* (FERCAP).
- Support for FERCAP members to attend the FERCAP Workshop in Manila, the Philippines (2001).
- Support for participants from Cambodia, Laos and Vietnam to attend the 2nd Asia Pacific Bioethics Conference in Manila (2001).
- Support for health professionals (17 participants) to attend the "International Course on Research Ethics" (2000 and 2001) at Thammasat University, Bangkok, Thailand.
- Support for health professionals (6 participants) to attend the course "Training on Bioethics for research" in Manila, Philippines (2001).

Country level:

- Translation, printing and distribution of the "Operational Guidelines for Ethics Committee that Review Biomedical Research" in the national languages: Khmer, Lao and Vietnamese.

Laos:

- Assessment of ethics practices for biomedical research in Lao PDR.
- National workshop (65 participants) on ethics for biomedical research: introduction of international standards in Lao PDR.
- Proposal for establishment of a National Ethics Committee and a national *Standard Operating Procedures* (SOP) for Lao PDR.

During the last year (2002) of Project implementation, bioethics intervention will intensify as a major issue in all three countries. If the Project plan is successfully fulfilled, by the end of 2002, Cambodia, Lao PDR and Vietnam should have their National Ethics Committee in operation, in conjunction with either the National Institute of Public Health or

another peer institute. Basic documents relating to research ethics, such as *The Helsinki Declaration*, *The Nuremberg Code*, *ICH Guideline on GCP*, *CIOMS Guidelines for Biomedical Research Involving Human Subjects*, *Surveying and Evaluating Ethical Review Practices: A Complementary Guideline to the Operational Guidelines for Reviewing Biomedical Research*, should be available in the national languages; biomedical researchers should be trained by an introductory course on ethics for biomedical research, whereby they will become familiar with the global ethical environment.

As the project is nearing the end, sustainability is an important concern, especially for ethics-related matters. To work out a plan to appropriately sustain the current intervention, the project's plan is to open its door to any organization and donor who is interested in working toward continued success in bioethics, in the Asia-Pacific Region.

*Dr. Frédérick Gay, Regional Co-ordinator
Regional Malaria Control Programme in
Cambodia, Laos and Vietnam*

CONFERENCE ESDP

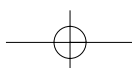
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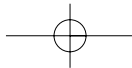
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Africa, and the pity of Africa

Continued from page 1

Forum for Good Clinical Practice (EFGCP), the Medical University of South Africa, and the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER).

One year later, in Cape Town, February 2002, PABIN organised an 'International Symposium on Good Ethical Practices in Health Research in Africa', with the support of CIOOMS, EFGCP and other organisations. The symposium included a 'Workshop on Developing Ethical Review in Africa in Light of Contemporary Issues in the Biomedical

Research Ethics'. The aim of the workshop was to examine the need for human subject protection in the course of biomedical research in Africa. It considered especially how recent guidelines could be implemented in Africa, i.e. the WHO/TDR *Operational Guidelines for Ethics Committees That Review Biomedical Research* (2000) and its companion guideline *Surveying and Evaluating Ethical Review Practices* based upon the EFGCP *European Guidelines for Auditing Independent Ethics Committees* (2001).

Professor Coovadia describes the enormous scale of AIDS in Africa. AIDS "makes it difficult to provide good clinical care and it compromises our ability to adhere to strict ethical rules. Which does not mean that we must not try". This fortitude calls for worldwide support to relieve the suffering of Africa.

Robert Pigache

Clinical Research in Africa – Ethics, Culture and the Law

Continued from page 3

that examine all phases of a project, including its execution and management.

African guidelines for research in Africa

The African Charter on Human and People's Rights article 29(7) states that there is a duty to "... preserve and strengthen **positive** African cultural values...".³ Where first person consent is not recognized this could be viewed as an affront to basic human dignity. An affront to basic human dignity cannot, under any circumstances be perceived as a "positive" value.

With respect to the law and research, most legal frameworks do have legal mechanisms safeguarding human research subjects. In South Africa, besides common law and

statutory protection, the protection of research subjects is affirmed by the supreme law of the country consistent with the rights to equality, human dignity and the freedom and security of persons as affirmed by the Constitution.⁴ A respect for human dignity should guide any researcher in his or her practice of research where human participants are involved. Respecting human dignity underpins an ethos of a good and honourable researcher-participant relationship.

There is now a convincing argument for Africa to establish standards and practices in the arena of research ethics specific to African needs. The time has come for stakeholders from the African continent to articulate and promulgate guidelines – research ethics for Africa by Africa.

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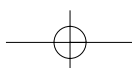
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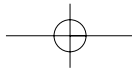
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