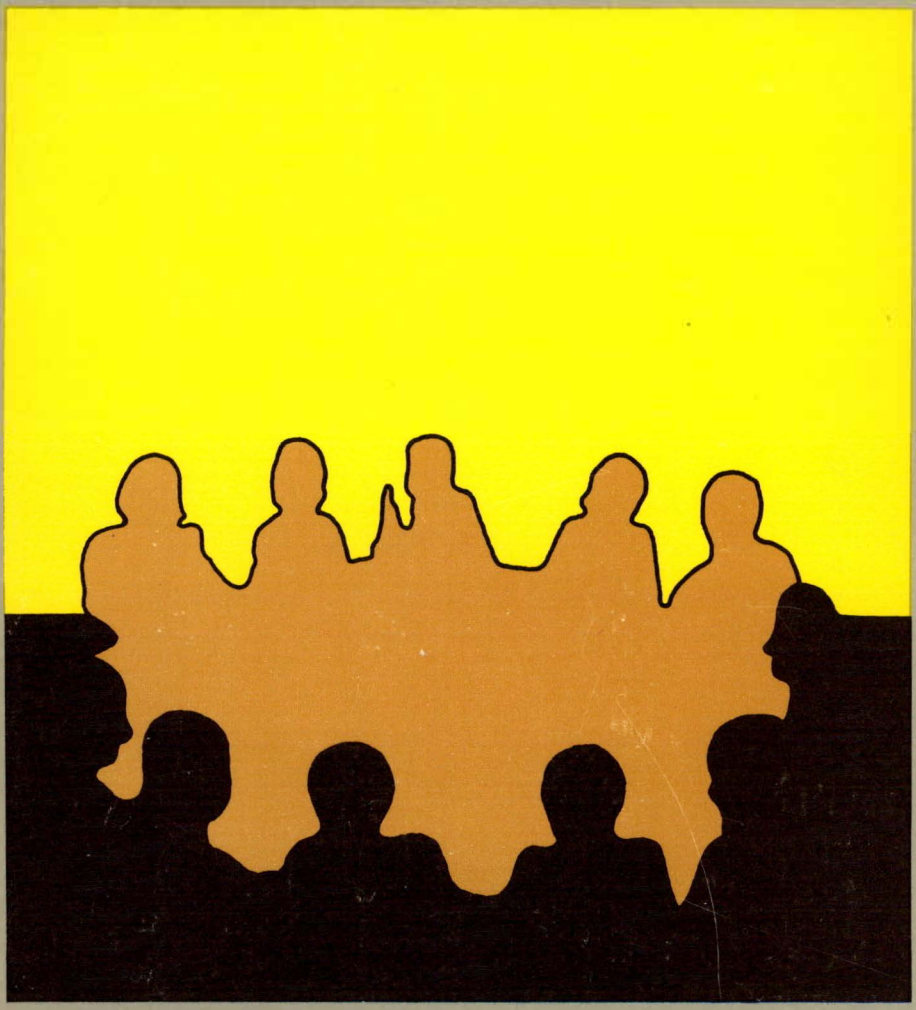
MEDICAL EXPERIMENTATION AND THE PROTECTION OF HUMAN RIGHTS

XIIth CIOMS Round Table Conference

Editors: N. Howard-Jones and Z. Bankowski



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MEDICAL EXPERIMENTATION AND THE PROTECTION OF HUMAN RIGHTS

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Edited by : Dr. Norman Howard-Jones and
Dr. Zbigniew Bankowski

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Council for International Organizations of Medical Sciences (CIOMS)
c/o World Health Organization
Avenue Appia
1211 Geneva 27

The Council for International Organizations of Medical Sciences is an international non-governmental scientific organization established jointly by Unesco and WHO in 1949. It is essentially a federation of non-governmental international societies or unions representing specialized branches of medical sciences and practice. CIOMS has also national members, usually national medical or scientific academies or research councils, and associate members which include international, regional or national associations or societies representing various branches of biomedicine. In 1978 there were fourty-three international members, twenty-four national members and twenty-two associate members, making a total of eighty-nine member organizations.

Sandoz Institute for Health and Socio-Economic Studies
5, route de Florissant
1206 Geneva

The Sandoz Institute, opened in 1974, has five main objectives : to improve the pharmaceutical industry's understanding of its present and future social, economic and political environment; to catalyze practical health care research; to promote communication between the many parties involved in health care; to encourage creative and original approaches to health problems; to collaborate with individuals and organizations in different countries in both doing research and applying its findings. The Institute's activities are interdisciplinary and international, and include a wide range of health services research; organization of meetings of various kinds; publication of its research findings; and participation in practical implementation of proposals.

This conference was sponsored by the World Health Organization and organized with the collaboration and assistance of International Congress and Convention Association and the Ministry of Tourism of Portugal. Preparation of the proceedings for publication was made possible by the financial contribution of the Zlinkoff Fund for Medical Research and Education, New York.

Cover by Adrian Griffiths

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INTRODUCTION

Over the past decade, the Council for International Organizations of Medical Sciences (CIOMS) has organized several round table conferences aimed to stimulate free and informed exchange of opinion on the social, moral, ethical, administrative and legal implications of new developments in biology and medicine. In focusing the latest conference on "Medical Experimentation and the Protection of Human Rights", CIOMS has provided a forum for participants representing many disciplines and drawn from a wide range of countries to discuss how the welfare of subjects taking part in medical research may best be protected and to assess the impact of statutory regulations and ethical review mechanisms in this context.

The prevailing trend to fund medical research either directly from governmental sources or on the recommendation of a central representative professional committee not only provides an effective determinant of national research policy, it also provides some assurance that the services of research subjects are directed toward valid community interests. Moreover, the establishment of national research committees and national drug regulatory authorities, has provided a mechanism for informed, independent supervision of the safety of many proposed investigations.

In most instances, these bodies do not have a specific charge to address ethical issues, nor are they necessarily ideally constituted to do so. Much research remains outside their ambit, and they tend to be remote from the centres at which the work is undertaken. Nonetheless, it is one of the basic principles of the 1975 revision of the Declaration of Helsinki that "the design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance".

To address this principle effectively, ethical assessment has already been formally organized on a local or institutional basis in a number of countries. However, medical research is now undertaken in virtually every region of the world and within communities in which cultural attitudes, socio-economic circumstances and ambient disease patterns vary within wide limits. One of the basic objectives of this meeting, therefore, was to draw from the body of experience now available some ideas as to how the concept of ethical review might most usefully be extended in its coverage.

The account of the conference that follows is an edited one, from which all procedural matter has been eliminated. In a few cases it has not been possible to reproduce more than a partial version of a speaker's remarks because of technical faults that developed in the electronic recording equipment.

FIRST SESSION

HISTORICAL PERSPECTIVES AND ADMINISTRATIVE OPTIONS

Moderator: Alfred Gellhorn

OPENING ADDRESS

T.A. Lambo

Within the province of medicine virtually every decision and every action has its ethical implications, and conflicts of interest inevitably arise when research is grafted to clinical practice. Biomedical research has become more and more necessary in the interest of the community, but recognition of human dignity demands that the rights and interests of all subjects are adequately protected whenever medical experimentation is entertained. Respect for the individual on the one hand, and the increasing necessity for medical research in the interest of the community on the other, determine the very ethos of medicine, and WHO is privileged to join with CIOMS, as it has done in regard to other important problems, in offering this forum to consider how we might best ensure that research on human subjects is conducted in accordance with sound ethical principles.

It is, therefore, a particular pleasure for me to express, on behalf of the Director-General of WHO, and of myself as the Chairman of its Secretariat Committee on Research Involving Human Subjects, sincere gratitude to the Government of Portugal for so generously providing facilities and financial support to make this international conference possible.

By coincidence the International Bill of Human Rights has recently been publisned by the United Nations. The covenants embodied in this bill are intended to depict the fundamental principles of civilization; nonetheless almost thirty years was required before agreement on the formulation of rights acceptable to all the diverse peoples, religions, cultures and ideologies represented within the Member States was achieved.

To define ethical standards in relation to research conducted on man also poses intractable problems. The broad principles enshrined in the Declaration of Helsinki and the more recent Tokyo amendment are, of course, unimpeachable, but any attempt to define standards of practice through adoption of generic provisions ultimately founders because research projects are, in the last analysis, undertaken or rejected on the basis of value judgements. Specific risks to the individual must be considered, and the work must be justified in terms of benefits that may accrue to the community.

We have to accept, however, that the risks cannot always be reliably anticipated, or when anticipated they cannot be reliably assessed, and that judgements on the propriety of a study are intrinsically vulnerable to bias. The individual investigator, insofar as he entertains private ambitions relating to his research and his career, clearly disqualifies himself as an impartial assessor. For some, this difficulty is neatly resolved by projecting responsibility for the decision on to the prospective subjects through the mechanism of informed consent. But how substantial is the protection that the subject derives from this procedure? Everything hangs on the quality of the consent. It would be naïve to assume, for instance, that agreements concluded between doctor and patient, teacher and student, or employer and employee are necessarily immune from subtle, if unintentional, influences, or that all subjects possess adequate knowledge and insight to understand the implications of the information they are given. These problems are compounded when one is dealing with populations of most of the developing countries - populations which have been, and continue to be, victims of many unethical practices and abuses of therapeutic trials, etc.

These considerations force the conclusion that research on man cannot be left exclusively in the hands of the researchers. Much as we may react emotively at the prospect of further incursions upon the traditional academic freedom of the medical profession, statutory controls and mandatory third-party assessments have already become an accepted corollary to research activity in many countries. Suitably adapted to meet local needs, these measures have relevance wherever such studies are conducted and should be enforced.

No one could reasonably question that an opinion on whether a research project bears usefully on prevailing health problems, and whether it has been planned with due regard to social and cultural considerations, is most appropriately formulated by individuals closely identified with the local community. Consequently, during this meeting, much of our attention will be directed to the contribution - both positive and negative - that relevant administrative machinery can offer in countries at various stages of development to safeguard the interest of subjects.

There is a broader issue, however, which we will also have an opportunity to discuss. A cardinal principle of ethics as they apply to research on man - which is established in the various international codes, and has been implicit in much that I have said so far - is that, regardless of any question of risk or inconvenience, the services of human subjects should always be justified in terms of total potential community benefits.

To an increasing extent, research funds are allocated and apportioned by administrators acting on behalf of governments, private foundations or the pharmaceutical industry. Their decisions, although taken at more than one remove from the subjects, have clear ethical implications, since they are a powerful determinant of general trends and objectives in research activity. Obviously society at large has a legitimate interest to know how these policies and priorities are established, to what extent they are responsive to community needs, whether proposed research is subjected to independent assessment, and what liabilities and responsibilities the sponsors accept in the event of injury to subjects.

We are most fortunate in having many representatives of government and industry with us today who are qualified to give authoritative statements on these vital questions. Although no basic differences are likely to emerge between us over broad issues of principle, discussion of professional ethics can always be relied upon to arouse emotions. We can look forward to a lively debate and, I am confident, to a useful exchange of opinion on philosophical considerations and practical objectives.

MEDICAL ETHICS IN THE MODERN WORLD

Alfred Gellhorn

For more than 3000 years a basic code of medical ethics appeared to meet the needs of society in prescribing the acceptable behaviour of physicians. But now in less than forty years, two new types of ethical codes for health professionals have been found necessary and one of these, the ethics of human experimentation, is to be the subject of this international meeting. To set the stage, it is useful to review briefly the historical background of medical ethics.

When human activity became diversified beyond the roles of child nurture-caring and hunter-warrior, the priest-body healer was among the first new jobs established to meet perceived needs, and almost as soon as the doctor appeared, codes were written prescribing his moral and ethical behaviour and obligations. Among the first written records is the Oath of the Hindu Physician prepared about 1500 B.C. The main theme is " ..... do the sick no harm. Once with his patient, the physician must in work and thought attend to nothing but his patient's care and what concerns it." One millenium later the Hippocratic Oath, which many of us took upon graduation from medical school, echoed this pre-emptive concern for the patient: "I will follow that system of regimen which, according to my ability and judgement, I consider for the benefit of my patients and abstain from whatever is deleterious and mischievous". The physician's single-minded concern for his patient together with the other cardinal principle "per primum no nocere", first and foremost do no harm, have been the guiding ethics for doctors for close to 3500 years. And the fact that physicians have, in the main, followed this principle has been a major factor in the confidence and trust in which the medical profession is held.

The high public esteem for the medical profession has had its ups and downs throughout the ages, but from the mid-nineteenth to the mid-twentieth century it was considered pre-eminent among all human activities. This latter century was marked by the flowering of the great research discoveries of Pasteur and Koch, defining the infectious causes of disease, by the initiation of diagnostic technology through the findings of Roentgen, the understanding of the natural history of many diseases and their accurate description by pathologists such as Virchow and clinicians such as Addison, Charcot, Billroth and, in the USA, Osler. Even these exciting advances in knowledge which provided the basis for rational diagnosis of disease were overshadowed by the therapeutic developments in the twenty year period from 1930 to 1950. In 1935, Domagk reported on the effectiveness of an azo dye, Prontosil, in the cure of streptococcal infections, a dramatic discovery for which he was awarded the Nobel Prize in 1938. Soon thereafter, Bovet of France

showed that the active component of Prontosil was sulfanilamide, and the age of synthetic chemotherapeutic agents was off and running. During World War II the development of Alexander Fleming's earlier discovery of the antibiotic effect of penicillin made an even more dramatic therapeutic agent available to the medical profession. Almost weekly the lay, scientific and medical publications announced new developments in the chemotherapy of infectious diseases, including malaria; in salvage of life on the battlefronts by the effective treatment of shock with blood, plasma and blood substitutes; in new anesthetic agents which were extending beyond belief the extent and complexity of surgical procedures; in the use of radioactive isotopes for treatment and for fundamental biochemical research.

By the end of the war, there was a widespread belief, in America and elsewhere that medical research could conquer death and that all that was needed was sufficient money to purchase immortality. Through their elected representatives the public made an almost limitless amount of money available for biomedical research, and knowledge began to be created at an ever more rapid rate, such that by the mid 1950 s research publications were appearing at the rate of one every thirty seconds.

Along with the enormous output of new scientific knowledge and technological innovations there were developments in medical practice which led to changes in the attitudes toward physicians. Specialization became the new trend of medical training and practice with fragmentation of the care of the individual patient and often loss of the close doctor-patient relationship. The advances in knowledge and technology made it possible to prolong the critical physiological functions but without those qualities of life which make living worthwhile. There were concerns regarding the uneven distribution of health care among groups of people, too often determined by economic status. And to add to the difficulty of applying the old medical code of ethics to solve the dilemmas mentioned, the evolution of scientific medical research led to a tremendous increase in experiments using human subjects. To give some quantitative insight into why another ethical code has been found essential, it has been reported that approximately 250 000 research projects involving human subjects have been carried out in the United States since 1947, and this is probably a conservative figure. The need for ethical review of this large clinical research venture can be well understood when at one campus of the University of California 10 000 to 20 000 human subjects participated in experiments during a single year.

Thus, throughout the world there has been an increase in clinical research. More human subjects are at risk, and from a utilitarian viewpoint there is the need to balance risk against benefits, to assure adequate protection against unnecessary risks, and to assure that certain groups of human subjects of experimentation are not put at greater risk than others.

Of equal importance to this utilitarian view is the new social concern with medical experimentation which is strongly related to recent social changes. Those who consider themselves underprivileged or discriminated against or exploited are demanding better protection and more equal rights. This applies to under-developed countries as against developed countries, Blacks as against Whites, women as against men, young as against old, patients as against doctors and subjects as against investigators.

The necessity, then, to safeguard the basic rights and welfare of human subjects had to be met and the ethical codes and physicians' oaths in existence did not specifically speak of human experimentation, so others have been created as we shall learn in detail during this conference. The background to these rested on a judicial decision.

The Nuremberg Code was formulated as a part of the judgement against a group of doctors who performed experiments on prisoners in concentration camps. It was an expression of existing ethical principles which should govern experiments on human beings. This Code is limited in its application to research on healthy subjects who are prisoners. Despite the absence of explicit reference to clinical research, many of the 10 principles which were enunciated have been carried on in later ethical codes. The first and most important principle speaks forcefully to the necessity of obtaining the voluntary and informed consent of the subject.

Another principle relates to the right of the subject to withdraw from the experiment at any time. In other rules, prior experimentation on animals, proper training of qualified scientists and avoidance of unnecessary suffering are explicitly stated, and a major expression is the necessity for justification of the experiments in their anticipated benefit for society.

Since the Nuremberg Code, a number of national codes were adopted by medical research councils, academies of medicine and medical associations, which were derivatives of the Nuremberg principles but more expressly concerned with the protection of the rights of the human subject in clinical research. In 1964 the World Medical Association adopted the Declaration of Helsinki at its 8th General Assembly. The Declaration of Helsinki, which was revised in 1975, made the important distinction between human experimentation which potentially could benefit the subject, as for example the trial of a new anti-tuberculous drug in patients with tuberculosis, and clinical research of potential benefit to mankind, as for example biopsies of normal liver at the time of laparotomy for another reason in order to study liver cell function.

In the case of research combined with patient care, two essential rules were formulated: the doctor must obtain the informed consent of

the patient, and the research must be justified by its potential therapeutic value to the patient.

Non-therapeutic research is governed in the Declaration of Helsinki by four cardinal rules:

1) Protection of the life and health of the subject
2) The subject must be informed of the potential risks
3) The subject must give his free informed consent
4) The subject must be free to withdraw from the experiment at any time

It is apparent how closely this follows the Nuremberg code, but ethical guidelines for a number of important areas of contemporary clinical research, such as behavioural research and research involving whole populations as in the investigation of poliomyelitis vaccine, were not considered.

The various declarations and codes defining ethical aspects of research on human subjects were really no more than pious hopes that doctors would behave ethically. This was not enough for a public which had a growing concern for human rights and in particular, for the rights of underprivileged and more vulnerable persons such as children, prisoners, pregnant women, the mentally deficient and even medical students. To address this concern, ethical review committees were established in the United Kingdom, Sweden and the United States shortly after the beginning of the post-war medical research boom. We will hear more about these from other speakers.

Now there is one additional medical ethical code which has distressingly been found necessary to formulate in recent years because of the involvement of health professionals in torture and other cruel, inhuman and degrading treatment or punishment. You are all aware of featured stories in the public press, telling of specific cases of torture in one country or another and for a few days, you, we, the world have been horrified by the brutality which one group of human beings, under the protection of the state, has inflicted on another. What now must be recognized is that torture has become a world-wide action, and that the torturing of citizens, regardless of sex, age or state of health, is a practice in an ever growing number of countries. Amnesty International has aptly described this as a social cancer. Perhaps you are thinking that doctors, nurses, dentists and other health professionals eradicate cancer - they don't cause it. But, unfortunately, there is ample documentation of the participation of some health professionals in torture.

In 1974, the United Nations General Assembly requested WHO to develop the principles of medical ethics which would be applicable to the

protection of persons subjected to torture. WHO requested advice from a number of non-governmental international organizations, including the World Medical Association and CIOMS.

In 1975 the World Medical Association took the lead in the Declaration of Tokyo which specifically spelled out the prohibitions of physicians in any aspect of torture or other forms of cruel, inhuman or degrading treatment of prisoners or political detainees. At the request of WHO, CIOMS addressed the difficult issues of medical ethics related to prisoners in general. Here CIOMS proposes: that the physician's medical relationship with prisoners or detainees must only be for the purpose of protection or improvement of their health and would be accepted as such outside the prison environment.

It follows from this that it is a contravention of medical ethics to apply knowledge and skills in order to certify prisoners or detainees as fit for any form of punishment that may adversely affect physical or mental health; it is not in conformity with medical ethics to participate in any procedure for restraining prisoners unless it is determined to be necessary for the health of the individual and/or his fellow prisoners or guardians.

Since CIOMS also recognizes the realities of forms of coercion which may be brought to bear on physicians themselves to exact their participation in unethical procedures, CIOMS states that if the physician is forced to disobey the letter of the foregoing principles, his actions should be animated by the will to protect the prisoner or detainee and to minimize the harmful effects to health that he may be powerless to prevent.

So much for a very brief historical perspective.

This conference has an important task to perform, one which is of universal concern. Advances in biomedical knowledge, gained by experimentation on the ultimately necessary animal, man, are necessary for all peoples of the world but these cannot be at the expense of the respect and the preservation of human rights. Through exchange of information, the definition of unresolved issues among the countries here represented, and the establishment of communication mechanisms for international action, this conference can make an important contribution to medicine and to human rights.

EVOLUTION OF FORMAL MECHANISMS FOR ETHICAL REVIEW OF CLINICAL RESEARCH

William J. Curran

Ethical Standards for Human Experimentation

There are generally two opposing views of the applicability of ethical standards to any field of human conduct: one view sees these standards as universal, as moral principals based upon rational thinking by all men. The other view sees ethical standards as parochial, as highly conditioned responses to the local cultural and social experience of the group laying down the ethical rules. When I was in college studying philosophy, I was convinced that moral principles were universal and that all good men could and would abide by the rule of reason. The rigours of moral reasoning seemed to me then to be clear and irrefutable.

Then I went on to law school, I received further training in argumentation and reasoning from the point of view of the adversary system of Anglo-American justice. I found that it was quite possible to argue two (and sometimes three or more) viewpoints arriving at different results - and yet consider each of the views reasonable and even moral. I also discovered the importance of morally neutral positions wherein ethical principles were no real guide at all to decision-making.

Also, in law school, I discovered how many of our seemingly moral principles were quite parochial. Unlike science, law is a parochial subject. Most lawyers today study the law of their own countries and know very little about the law applicable in other nations. There are systems of law such as the Roman Law and the Common Law, but the differences in law between countries, even those professing to follow similar traditions, are still very great.

In the field of ethical standards of human experimentation, we find this classical difference of viewpoint well characterized. The Nuremberg Code, produced for the War Crimes Trials (Crimes Against Humanity) in 1948, was expressive of the first view. The effort was to set forth a decalogue of universal principles adhered to by all good (ethical) investigators throughout the world. This set of ten guidelines was used successfully to prosecute the medical defendants at Nuremberg. It was thought at the time, and for some years afterwards, that the Code covered all types of human experimentation, but especially medical experimentation, since the defendants at Nuremberg were predominently medical in their orientation and training. It was realized later, however, that the Nuremberg principles dealt with experimentation of any kind, not strictly medical, but they dealt with investigations on healthy subjects, not sick people, and that their greatest relevancy was to subjects who are in a situation of limited freedom and physical confinement. The latter situations were

most apt to be found in prisons, mental hospitals, schools and working places.

The next major effort at developing universal standards came in 1964 when the Declaration of Helsinki was adopted by the World Medical Association. The intent was clearly to adopt guidelines applicable on a world-wide basis. Much greater specificity was obtained in these guidelines which for the first time recognized a distinction between clinical research (on medical patients) and non-clinical experimentation (on healthy subjects). The Declaration also acknowledged that legal regulation in the investigator's country would impose additional specific requirements.

Problems of Application

These two sets of principles, as amended, still constitute the basis of universality in the field of ethical-moral standards in human experimentation and clinical investigation. There is a certain commonality in the principles. Stress is placed on obtaining freely informed consent, on balancing risks and benefits, on prior animal research and on the integrity and judgment of the medical investigator.

As the two Codes have been applied, however, it has become apparent that the very general language of most of the provisions makes it difficult to answer specific questions about specific projects merely by examining the ethical pronouncements. Also, various countries have added their own principles, or at least their own interpretation, the universal guidelines. I would cite three examples of fairly widespread problems of application:

(1) Use of prisoners and other classes of subjects in medical research. The Nuremberg Code, as we have noted, is a set of principles especially applicable to controlling but also to authorizing ethical research on prisoners. Nevertheless, the tradition in Europe since World War II has been to avoid all medical research on prisoners. This strong position has been a reaction to the Nazi atrocities. Also, it is generally believed that prisoners cannot be expected to give a free consent to experimental projects. This position is contrary to the whole purpose of the Nuremberg Code. Up to recent years, the USA was in clear disagreement with the European position. Prisoners were used in widespread fashion all over the USA in therapeutic drug trials and other medical and behaviouran experiments. Now, however, there has been a rapid turnabout due to law suits and adverse publicity engendered by civil rights activist groups. Approximately two-thirds of the American states now ban research on prisoners and the ban has been extended to federal penitentiaries. The recommendations of the National Commission on Protection of Human Subjects would virtually end all research in the United States using prison inmates.

In a number of countries, similar total or nearly total prohibitions of use of other classes of subjects have developed, despite the absence of such total bans in any of the universal codes. These other classes have included mental hospital patients, inmates of schools and homes for the retarded, children below the age of adolescence, pregnant women and the developing human fetus.

(2) Different practices on informed consent. All of the countries I have studied adhere to the principle that the informed consent of the subject should be obtained. Yet, when actual practices in the countries are examined, substantial differences are found. In most countries of Europe, the concentration of attention is upon the freedom of the patient or subject to consent or not to consent and not upon the "informing" part of the requirement. Thus, various classes of subjects are excluded even from the opportunity to participate in research, largely because it is thought they cannot freely consent. If the subject is also a patient and has a reasonable potential to benefit from the research, the stress is on protecting the subject-patient from harm or exploitation. It is commonly realized that the average patient will not fully understand the experimental design or the therapeutic innovation. As most physicians I interviewed said, the patient either trusts the doctors and the clinical investigators or he does not. Most do not understand the projects anyway.

Another aspect of the consent issue in which substantial difference of practice can be found is the obtaining of the consent in writing by a signature of the patient or subject, and handing the patient some written description of the project. Many investigators in Europe do not require, in fact they strongly oppose, seeking subjects' signatures to consent forms, even though the Declaration of Helsinki recommends this procedure. I saw little evidence in any European country of the use of written, signed consent forms with the possible exception of the Republic of Ireland for projects supported by the Medical Research Council. Some countries, such as Denmark, utilize a written statement of the project which is given to subject-patients on clinical investigation. The patients can read the statement at their leisure and later another person, not the investigator, returns to the bedside to answer any further questions and to obtain the consent or refusal of the patient orally. The precautions taken here are particularly to avoid any feelings of coercion on the part of the patient and to allow time for reflection about participation. The objective of the practice in Denmark is not only to provide adequate information for an informed consent, but to make the consent as voluntary as possible.

(3) Importance of self-participation and participation by family and loved ones of the investigator. One of the most commonly expressed means of protecting research subjects from involvement in unduely dangerous experiments has been the so-called "Golden Rule" of human experimentation. The rule pre-dates the Nuremberg Code. It states that the investigator should never subject subjects to risks he himself would not take, or to involvement in projects when he would not include himself,

members of his immediate family or other loved ones as subjects. This principle is, of course, a variation of Christ's admonition, "Do unto others as you would have them do unto you.

The Nuremberg Code does adopt a version of this Golden Rule in Principle 5:

> "No experiment shall be conducted where there is a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

This principle has been subjected to a great deal of criticism by ethicists. It is perhaps the least supported principle in the Nuremberg Code, especially in the United States. Nevertheless, this Golden Rule does have a good deal of support among investigators, but not in the same language as that of Principle 5. The Rule is more apt to be applied where there is some doubt about the safety of a project and where the participation of the investigator and/or his family and loved ones provides practical assurance that the investigator does have confidence that the risk is not too great.

Application of this Rule in any particular country depends greatly on the degree of general trust in clinical investigation and medical practitioners by the people of the community. The more the trust, the more this type of personal participation will be a reassurance to patient-subjects. I am afraid, however, that the climate in the USA currently is highly distrustful of investigators and doctors and so the Golden Rule tends to have little support. However, the distrust is much more in educated circles and among civil-rights-conscious people than among a large part of the population who become patients and who want to trust their doctors and who often display a willingness to engage in research for the benefit of others. It must be said that many of the ethicists who write or comment on human experimentation tend to be in the former category rather than the latter. They have read of abuses of subjects by clinical investigators and they are wary of a Rule which seems to allow dangerous practices upon subjects. The Declaration of Helsinki does not contain such a Rule.

My point in each of these examples is that the universal principles do not always have universal support and that they are often applied differently in various countries because of local conditions and traditions. Some of the "differences" are very radical, as I have pointed out above, amounting to the application of different moral judgments about the principles themselves.

The Movement to Ethical Committees

The problems pointed out above have created a demand for additional means of answering specific ethical and legal questions about individual research projects. In the early 1960 s the USA and the UK, and shortly afterwards Sweden, moved to install local ethical review committees which could conduct individual evaluations of proposed biomedical research involving human subjects, health volunteers or sick patients, as well as control subjects. The UK and Sweden were influenced by the requirements of the NIH in Washington regarding the establishment of local ethical review, but it seems clear that both countries were tending in that direction anyway and would probably have set up such a mechanism on their own initiative within a few years.

The systems adopted in these three countries were the forerunners of the establishment of such committees in other countries in more recent years. The objectives of the ethical review committees are similar in each of the three countries. I would list the following:

(1) They provide a mechanism for specific application of general ethical principles to proposed research projects.

(2) They provide an opportunity to add culturally and socially accepted (parochial) national principles to the more international or universal ethical standards found in the Nuremberg and Helsinki guidelines.

(3) They install a mechanism of review which is most acceptable to the researchers and the medical community generally, since the committees are local rather than national and are privately formed or voluntarily formed rather than governmentally selected and imposed. Also, most of the members of the committees are drawn from the research facility, or hospital, or medical school faculty itself where the researchers are situated, thus providing "peer review" by one's own colleagues, rather than regulation by outside "bureaucrats" or "outsiders".

(4) They operate to review projects before they begin rather than after some problem arises and some complaint is made. This practice provides protection of a preventive nature for the benefit of the subjects, rather than a merely punitive measure against investigators after the fact of injury or abuse to a subject.

Experience has shown in the past 15 years that the ethical review mechanism can be made to work for the protection of subjects; that it is an inexpensive and effective procedure; and that it has the support of the research community in every country where it has been installed.

Endorsement in Ethical Codes

The installation of ethical review committees during the 1960 s and early 1970 s and their apparent success and acceptance in the research and medical communities led in 1975 to the inclusion of a new principle supporting this movement in the Amendments of Tokyo to the Declaration of Helsinki of the World Medical Association. The parochial mechanism of peer review, a form of self-regulation by the research community, has thus been endorsed as a universal ethical standard.

Basic Principle 2 is very carefully worded. It is a compromise position among those who strongly supported review committees with considerable power of approval and disapproval of submitted projects, and those who felt that the committees should be advisory only and should reflect the idea of self-regulation.

The final draft adopted at Tokyo is as follows:

> "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance .

It should be noted that the WMA placed its stress on the independence of the committee rather than upon its scope of review or its powers. It was felt that the committee should not be controlled by the administration of the research facility or medical school but should be free to make its own judgments. The scope of review was left completely open; the word "ethics" is not used. Apparently, the committee could comment on the entire project and its overall design and performance. It might even be involved in advising on funding of the project, though this seems doubtful from later comments by the WMA in which the ethical nature of the committee mechanism has been stressed.

It is clear that the WMA saw these committees as advisory, not as binding in their advice. The terms used are "consideration, comment, and guidance". It should be observed that the provision does not indicate who is to submit the protocol to the review committee and who the committee is to advise. In each case, it may seem logical that the investigator was to submit his or her own protocol to the committee for review and that the comment and guidance would be given in return to the same party, the investigator who initiated the review by presenting the protocol, presumably before any activity involving subjects had begun. Nevertheless, these points were not made clear. I do not think that they were an oversight. This vagueness of language allows for different interpretations, intentially I believe, in different countries. The protocol could be given to the committee by the facility or the school or by the Medical Research Council or by a therapeutic drug company sponsor, and the advice of the

committee could be given to any of these or to a funding agency or a government regulatory agency in the drug field. All of these alternatives are possible.

The review mechanism now being installed in Denmark is taking advantage of these flexibilities in Helsinki II to set up procedures different from the earlier prototypes in other countries. This pilot programme of a review system is voluntary in character. The investigator may first make a declaration or statement accompanying his protocol concerning ethical standards. He or she is then free to submit the protocol for local review or it can be submitted by others. Review is not required for all projects. When the committee receives the protocol, it has one month in which to review and comment. If no action is taken, the project is considered reviewed favorably at the end of that time. Also, the investigator can proceed to initiate his or her project before the review is completed. Each of these features of the Danish programme stresses the advisory and voluntary nature of that system.

Another of the principles of Helsinki II should also be considered, however, before the viewpoint is accepted that the review mechanism is as voluntary and advisory as it may seem when only Basic Principle 2 is read. Basic Principle 8 should also be observed. It is as follows:

> "In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication."

This provision is intended to "put teeth" in the rest of the Declaration. It reinforces Basic Principle 2 most importantly because the only objective way an editor can be sure that the investigator has adhered to the principles is by having the project approved by a local review committee. Otherwise, the only other form of compliance is the personal declaration of the investigator as in the Danish system. Certainly in doubtful situations where an editor or a referee of a paper asks questions about ethical justification, the investigator will be helped if he or she is able to indicate that an independent committee has reviewed and approved the procedures in question.

The combination of Basic Principles 2 and 8 place considerable strength behind the establishment of ethical review mechanisms in those countries which have not as yet installed such mechanisms.

Binding Effect for Ethical Review

Based upon the experience to date, I would predict that the pressure of both professional and legal authority will be toward making the decisions of local ethical review committees essentially binding upon the investigator.

The very fact of the widespread support by the research community for these committees and the fact that they are called "ethical committees" militates against ignoring their recommendations.

I would say that this situation makes compliance more likely than it would from a merely legal or regulatory mechanism installed by a national government. The research community in most countries is very closely knit. The investigators usually share similar social backgrounds and similar training. They value their reputations greatly. Advance in their careers is usually highly dependent upon their maintaining a good reputation among their peers in research and academic circles. Very few researchers can afford to ignore the ethical guidelines and the review system accepted by the great bulk of their colleagues. The fact that these committees are made up in large part of these same colleagues makes opposition to the system virtually untenable. The system may continue to be called advisory. In fact, that term and that appearance make the system that much more palatable. Nevertheless, the effect may well be that compliance is virtually universal.

If the above were not enough, experience shows that other more strictly legal measures will be used to encourage and assure compliance with ethical committee recommendations. Funding agencies, including national Medical Research Councils and the National Institutes of Health in the USA, look to these local ethical review committees to approve research proposals. Some of the MRCs may also add their own central ethical review committees to examine all projects or doubtful ones. INSERM in France has established a central ethical committee which seems to function for review of doubtful procedures when questions are raised by local research units or medical schools or other research facilities.

The strongest legal control in most countries may come from the drug regulatory agencies which may require drug company sponsors or clinical investigators to obtain ethical committee approval for all clinical drug trials which are to be used in licensing procedures for the marketing of a new drug.

The last step in legal recognition of ethical review committees and of the binding effect of their recommendations could come if a country adopts a statute or a Ministry directive to that effect. There has been a reluctance in most countries, if not in all countries, to go this far. The continued appearance of self-regulation and voluntary compliance is highly valued, as pointed out above. In the USA, however, the National Commission on Protection of Human Subjects has recently recommended that the Federal Congress enact a statute requiring ethical review of a binding nature.

Further Issues in Ethical Review

At the present time, I feel that the movement toward the establishment of ethical review mechanisms is firmly implanted. I believe other nations in the industrial world and in the developing world will in the near future adopt such mechanisms. They may not be the same as the systems now in place. I hope that each country will determine the best mechanism for its own conditions and traditions.

The two outstanding issues for countries which already have review committees are, it seems to me, the following: (1) the need to analyze the effectiveness of the committees by some type of field evaluation; and (2) the need to examine whether a system of on-going monitoring of projects should be installed along with the current practice of prior review of projects.

Sweden and the USA have initiated evaluation studies of their ethical review mechanisms. The Swedish MRC has commissioned a study by Professor Gustav Gietz which has now been published. This is the most sophisticated (scientifically of all of the evaluations to date. In the USA, a highly useful early study was done by sociologist Bernard Barber and associates and published in 1973(1). A few other studies were done, largely of one review committee. Most important, however, was a national survey conducted in the mid-1970 s by the University of Michigan under contract from the National Commission on Protection of Human Subjects. A summary of the results of that study has very recently been published (2) by the Commission as a part of its report and recommendations on "institutional review boards", the American official title for local ethical review committees.

All of these evaluations are too recent to have had any great impact on ethical review procedures. In general, these latest reports in Sweden and the United States find that the systems are operating reasonably well. Radical changes are not recommended. However, some changes will probably result from these studies.

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1. Barber, B. Research on Human Subjects: Problems of Control in Medical Experimentation, New York, Russell Sage Foundation, 1973.

2. National Commission on Protection of Subjects of Biomedical and Behavioral Research. Report and Recommendations on Institutional Review Boards, Washington, DHEW Pub. No. (05) 78-0008, 1978.

On a more international basis, CIOMS is currently conducting a review and analysis of committee procedures and practices. This study, as it continues, should be very highly valuable as an evaluation of the systems and as a means of exchange of information among nations of the world.

The other issue, monitoring, is quite difficult and sensitive. All of the review committees are interested in obtaining information about compliance by investigators with committee recommendations. Yet, the committees are greatly reluctant to become "policemen" of projects. The ideal of self-regulation by responsible clinical investigators is valued. As the systems become more legal in orientation and more visible to the public (and the press and other mass media) pressure will increase for some type of on-going monitoring. A few scandals will be enough to produce newspaper clamour for such observation.

At present, there is very little formal monitoring in any country I have visited or corresponded with in recent years. It is generally said that local committees composed of colleague-investigators will "know about" problems, deviations or abuses in approved projects. The trouble with this view, of course, is that it is not provable. Some form of monitoring seems virtually inevitable in the course of things, abhorrent as it may be to the committee members and investigators alike.

We might suggest some avenues of approach to monitoring which committees might consider:

(1) A system of self-reporting could be set up under which investigators are encouraged or required to file summary statements annually or otherwise, about their progress. Immediate reports might be required for very serious injuries to subjects similar to those required for adverse effects in drug trials. Also, investigators could be required to seek approval for any important changes in procedures which affect subjects.

(2) A system of subject complaints to the committee could be established as a monitoring device.

(3) The committee could sample a small number of projects for a field investigation to provide some impression of general compliance on informed consent, use of certain subjects, use of drugs, keeping of records, etc.

These three methods are in increasing intensity of surveillance. I have observed each of the three in use in one or another of the Harvard University teaching hospitals. I have not seen any evaluation of their effectiveness.

Lastly, I am hopeful that the international survey by CIOMS will contribute to helping all countries to deal with these matters of evaluation and monitoring in a manner which will retain the support of the biomedical community for this important effort.

STATUTORY REGULATIONS AND ETHICAL CONDUCT

R. Norman Williams

Introduction

In the past few decades the scope and funding of research in all areas of medicine has expanded enormously, and so inevitably has research involving human subjects. In the field of new medicines this has brought tremendous benefits with the development of new life-saving drugs from penicillin to beta-blockers, but this expansion has caused many problems and led to widespread reflection both on the general controls that should be applied to the development of new medicines and on the ethical aspects of human trials in research work.

Another development in this same period of time has been the growing voice of consumer interests, with expectations that any product released onto the market will be well tested and fit for human use. This is a natural expectation in the wake of the thalidomide tragedy, but it has meant that increasingly more attention had to be paid to pre-marketing trials, which include clinical trials on humans.

In clinical trials there are two distinct groups whose needs must be considered - the general public who may eventually be prescribed the product and the individuals participating in the trials. To protect the former, full and thorough pre-marketing trials must be conducted; but to protect the latter these trials must themselves be carefully controlled. The range of products involved means that a considerable number of people become involved in trials covering a wide spectrum of drug treatment.

The balance of interest between the patient involved in the clinical trial and the general public good may at times be extremely delicate.

The risk/benefit balance may be clear in trials say of a new cancer drug on a seriously ill patient, but where trials are on a drug for a minor condition being used on a relatively healthy patient it may not be so clear and to that extent the decision whether the trial should go ahead is rendered the more difficult. Guidelines such as the Nuremburg Code, (1) which was drafted as a result of revulsion over Nazi practices, have been valuable in clarifying some of the ethical issues, but they are of limited application and they are not free of ambiguities.

Because the decision of doctors to engage in particular clinical trials is largely based on knowledge that is not available to the general public and that cannot easily be assessed by those not possessing the relevant qualifications their conduct must to a considerable degree be

self regulated; but because of the risks involved, and also of the temptation of those conducting the trial to take undue advantage of their position, there may also be demands for significant public control. Thus in many countries it is through the countervailing influence of "public" pressure (exercised through regulatory authorities), the demands imposed by the medical profession itself and the commercial pressures of pharmaceutical companies that a successful code of ethics for the control of clinical research must be maintained.

The legal requirements set by different countries not unnaturally reflect widely differing approaches. This ranges from the Swiss situation where until recently the IKS (the regulatory authority) has refrained from setting up an investigational new drug procedure, to Canada where qualified investigators must apply for permission to conduct clinical pharmacology trials (usually in normal healthy volunteers) to indicate the general non-toxic dose range of the drug even before they file a pre-clinical new drug submission with the Drug Advisory Bureau, seeking approval to conduct normal clinical trials.

In addition to, or instead of, requirements imposed by regulatory authorities there are ethical controls of various sorts. In New Zealand current controls are concerned with the credentials of the person investigating the drug, rather than with the drug itself and the nature of the investigation. In Switzerland "The increasing tendency to establish 'Committees for medical ethics' (peer review) in hospitals and the action of the Swiss Academy of Medicine in establishing guidelines for clinical investigation appear to offer a valid alternative to a central agency" (2).

The Position in the United Kingdom

The situation in the UK is somewhere between the two extremes of strict control (whether legal or ethical) and the attitude of leaving it all to the professionals. The Licensing Authority does place a considerable degree of trust in the doctors conducting trials, for example relying on the doctor's word that the results recorded are as observed, which contrasts with the American situation where the Food and Drug Administration expects to see the patient's medical case papers. However, there is also a formal legal set of controls which must be observed when any clinical trial is to be conducted.

Under the 1968 Medicines Act(3) of the UK, proposals for clinical trials must be submitted for approval by the Licensing Authority, although certain trials conducted on a doctor's own initiative on his own named patients fall outside these requirements. There is also a category where exemption from the need to hold a Clinical Trial Certificate may be granted, for example, where a doctor wishes to use a drug that is already licensed, but for some indication other than that given in the licence. Brief details of the proposed trial are submitted to the Licensing Authority, which may grant or refuse an exemption: in the latter case the doctor

must apply for a full Clinical Trial Certificate if he wishes to pursue his proposal, although in fact this rarely happens. In 1977, where the trial had been initiated by the doctor and a quantity of the material was to be supplied by a pharmaceutical company but the trial was not to be under arrangements made by the supplier, 243 applications for exemption were received, 210 were granted, 14 were rejected and there was no further action by the applicant in the other 19 cases when queries were made by officials, presumably because on reconsideration they decided that their proposed trials were not justified.

In reaching a decision on whether to grant a full Clinical Trial Certificate, the Licensing Authority is usually advised by the Committee on Safety of Medicines, which in turn is advised by its sub-committee on Toxicity and Clinical Trials. Such advice is always sought where the trial relates to a new drug or it involves a major new clinical use. The independent experts serving on these bodies give their advice on the basis of pre-clinical data and animal trials. Of 70 cases on which the committee advised in 1977, refusal was advised in 2 cases and the application was withdrawn in 11 cases.

While the committees pay some regard to the ethics of a clinical trial, for example, in considering whether the possible benefits to be gained justify the risk involved, they are not in a position to take account of all the detailed ethical considerations of each proposed study because such information is not required for the purpose of advising the Licensing Authority on the application. Patient selection and monitoring procedures are examples of issues which concern the committees only in broad terms, although they are clearly matters of direct interest to ethical committees.

Advice on the medical ethics of clinical trials is given in a small number of advisory documents, but there are no statutes governing this area and suggestions that they might be introduced have been firmly rejected by the profession. This has been on the grounds that statutory control is unnecessary and likely, if it were to be effective, to be unduly restrictive on clinical practice because of the difficulty of devising a definition of clinical research which is at the same time comprehensive and specific.

In 1975, the UK Department of Health issued a circular(4) which advised that all proposed clinical research investigations should be referred to an ethical committee. The Royal College of Physicians has advised that these committees, whose object is "to safeguard patients, healthy volunteers and the reputation of the profession and its institutions in matters of clinical research investigation"(5) should be composed of medical members experienced in clinical investigation and that in addition there should be a lay member. This system of "peer review" is in line with international codes, including the revised Helsinki Declaration of

1975 which asserts in its Basic Principle Number 2 that "the design and performance of each experimental procedure involving human subjects, should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment, and guidance" (6).

The UK system is now well established, with the majority of ethical committees having lay members. They consider and adjudicate on research proposals in their areas of responsibility, although there is considerable diversity of approach between committees. For example, some meet on a regular (usually monthly) basis to discuss all research proposals, while others conduct most of their business on paper or over the telephone, meeting only 2 or 3 times a year to discuss particularly difficult cases and to review earlier decisions. There are also informal coordination meetings of the chairmen of ethical committees held periodically and organised by the Royal College of Physicians to discuss problems.

It needs to be emphasized that the fact that a medicinal product has been granted a clinical trial certificate or a product licence by the licensing authority in no way absolves the ethical committee from investigating the ethical aspects of that trial. One area that has particularly taxed ethical committees, and indeed all those involved in research, is that of the giving of "informed consent" by those participating in the trials. The Royal College of Physicians advised in its 1973 report that:

> "Except for trivial procedures .... an explanation should be given by a responsible person in the presence of a witness and the agreement of the subject or patient should be recorded with the signature of the person who gave the explanation and of the witness " (7).

But this is not always followed in practice, partly because the researcher may feel that a full explanation could upset the doctor/patient relationship e.g., in a situation where placebos may be used.

Another problem area is the use of children in trials, because it is generally considered that it would be unduly restrictive to forbid all research on children - in the case of medicines it is necessary for example to be aware of the problems of different dose levels for children - and thus ethical committees have an important role to play advising on the merits of each case. The legal position is that no valid consent can be given by any parent or legal guardian to any experimental investigations on children, and that such a purpose for an investigation would afford no defence to a criminal charge of assault. Investigations can be carried out on a child only where it can be shown to have been intended for the individual's direct benefit. This does not preclude the obtaining of information incidentally when this does not require any alteration in the nature of the

normal procedure. While no arbitrary age is fixed in law below which a child is regarded as incapable of giving informed consent, it is generally assumed that the Courts would not accept that a child under the age of 12 years has the capacity to give such consent.

While ethical committees in the UK cover work in the hospital sector they do not as yet cover the work of general practitioners, although there has been some pressure for such an extension. Although, general practitioners, with their long tradition of independence, may resent any controls, such controls would probably be valuable in what is a very complicated area.

Most general practitioners conducting clinical trials do so as a result of being recruited for the task by a pharmaceutical company. A problem in this relationship between doctor and industry is the question of payment. Some would argue that to reimburse the investigator risks potential bias, although generally it is accepted that if a doctor is to put in time and effort as part of a study he is entitled to some sort of reward. However, there is a difficult borderline area where companies mount so-called clinical trials which seem to be thinly-veiled promotional exercises, and payments to a doctor who puts a patient onto a drug regime, which may continue for many years after the "trial" has ended, have provoked some concern. An examination of the proposed trial by an ethical committee, to ensure that it is properly designed and administered could have considerable benefit.

In addition certain studies are carried out within pharmaceutical companies on members of their staff, where there is no coverage by ethical committees. In such circumstances the Association of the British Pharmaceutical Industry's guidelines suggested that "It would be prudent however for studies to be approved by a registered medical practitioner not involved with the investigation" (8). It may be regarded as of some interest that while there are controls on clinical trials with medicinal products, in the UK there are no controls of other kinds of clinical trials. The answer appears to be that we do not seek to control the activities of doctors but the supply and distribution of medicinal products.

The Broad Picture

In other countries practice varies considerably, with some having fairly strict regulations while others impose few or no controls. However, there is a growing trend towards uniformity as countries exchange ideas and information on problems of mutual concern. Thus, in Denmark controls on clinical trials were first introduced by the 1975 Medicines Act. It is now necessary for any doctor carrying out a trial and the manufacturer of the specialty involved to notify the National Health Service that a trial is to be conducted, and on completion they must submit all results to the National Health Service. The NHS may specify conditions to be

applied to the clinical trial and may at any time demand that it be stopped or modified. In other countries though there are no government controls, as until recently in West Germany where "the regulations do not require an independent review committee to be involved in decisions as to what constitutes adequate preclinical data or in decisions on the first administration to man" (9). Section 40 of the German Medicines Act which came into force on 1 January 1978 contains fairly detailed rules as to patient's consent, the qualifications of the physician and the depositing of the documentation with the licensing authority.

Conscious efforts are being made at an international level to bring about some form of unified approach. The Council of Europe's Public Health Committee established a Working Group in 1973 to examine the problems of clinical trials. This group drew up guidelines on such areas as preclinical requirements and the degree of supervision required from regulatory authorities as well as stressing such matters as the need for prior informed consent by subjects. Most European countries now have a system of notification of clinical trials.

In many third-world countries such controls have not yet been introduced. This may be because of the low level of pharmaceutical manufacturing and research in these countries, but it is a potential area of concern because with the imposition of more stringent controls in countries such as the UK and USA some pharmaceutical companies are diverting their research effort to countries where less rigid standards are set. This may be because the companies genuinely feel that they have a potentially beneficial drug whose introduction is being hampered by over-demanding regulatory authorities, but it may be a deliberate attempt to evade controls imposed for the safety of participants in such trials.

Trials on new contraceptive drugs are often conducted in third-world countries. There may be valid reasons for this, as countries with rapidly growing populations may be more eager to try new methods than developed countries where fertility does not pose a problem; but there are also doubts over the use of Asian women as trial subjects for contraceptives which companies will not use on Western women. A similar problem exists in developed countries where ethnic minorities and poorer, less educated groups may be regarded as an easily available pool of subjects for clinical trials; being less well educated than average they may be unable to exercise true informed consent over participation. However, to allow the exploitation of such groups is a dangerous breach of medical ethics which could be a first step on the road towards the perversions of medicine carried out by Nazi doctors.

Another area where there is concern about the subjects used in clinical trials is where long-term patients or prisoners are involved. This is because there may be doubt as to whether they have really given

free consent to their participation. Institutionalized patients may feel dependent on the institutions' administrators and doctors and may be unwilling to refuse to participate in trials for fear of upsetting them. In the case of prisoners it may be felt that they are not in a position to give genuine free consent by virtue of their being in an implicitly coercive situation. Because of such doubts, prisoners are not used as trial subjects in any country in Western or Eastern Europe, although in the USA, they are commonly employed as "healthy volunteers" for the first trials of new pharmaceutical preparations as well as for other investigations.

Those conducting such trials assert that, provided there are no threats of punishment for non-participation or undue promises of reward for those who do assist, prisoners should not be ruled out as subjects. It has been said that in these circumstances "there seems to be no good reason for depriving this group of the satisfactions of participation on an informed basis, satisfactions that to them are often great indeed, bolstering their self esteem and furnishing links to the general community and its values" (10). Of course it may be another matter in determining what equates to an undue reward, with the thin line between compensation for any possible discomfort and payment for involvement. In the United States "Prisons permitting this practice may have a detailed tariff of cash payments made for various interventions. In one case these range from 25 cents for a stool specimen to $12 for a bone-marrow aspiration" (11). Clearly defined scales of payment are of course easier to assess than other calculations which may enter a prisoner's mind, such as the value a record of participation in clinical trial work might have when he comes to be considered for parole. It is influences such as these which make the use of prisoners ethically difficult.

Finally, there are 3 groups of people, acting as healthy volunteers in preclinical studies, for whom some risk of exploitation exists : medical students, employees of pharmaceutical companies and employees of other concerns where the standardized nature of the work and their easy identification makes them particularly suitable. People in such groups may feel under pressure to participate in trials in order to gain the approval of academic staff or employers, or they may simply be over-enthusiastic about the work of their department, or the financial inducements may be considerable - and they constantly volunteer to participate.

For all these groups I have mentioned there is the problem of remuneration. It is reasonable to expect that there should be some compensation for time lost and possible discomfort experienced, but a line needs to be drawn before such payment becomes a positive incentive to participate. Otherwise there is a risk of people becoming semi-professional "guinea pigs", putting their own health at risk as well as possibly upsetting the results of trials. In the UK, ethical committees often advise on the trial where proposed payments, e. g. by pharmaceutical companies to medical students, seem excessive.

It is also important that payments should be made only to the strictly normal volunteers and not to patients who are receiving the medicine for a specific condition, albeit as part of a trial. There could obviously be grave dangers in the latter case, with patients having to decide whether to accept a particular treatment because of possible financial rewards.

Legal Liability

Although strict precautions are imposed, including the screening of experiments by medical ethical committees, death or personal injury which was quite unforeseen, and indeed quite unforeseeable, is sometimes suffered by a person who volunteers to participate in such an investigation or trial. In the UK, such a person would have no right of action and no cover would be provided by protection societies or Public Liability Insurance Policies, but it is the practice in special cases for an ex gratia payment to be made from public funds. The Royal Commission on Civil Liability has recommended in its recent report that such a person should have a cause of action, on the basis of strict liability, against the authority to whom he has consented to make himself available.

While it is generally accepted that society at large and, in particular, those responsible for such investigations and trials have moral obligations to those who volunteer to participate and that where "no-fault" accidents occur those who suffer injury should be compensated, there is some disagreement as to how this should be achieved, some advocating mandatory insurance cover against "no-fault" injury to which contributions would be required from a number of sources. There is also some misgiving that the application of the principle of strict liability to adverse reactions in volunteer patients to drugs would face insuperable problems in its implementation, in that the distinction between naturally occurring disease and drug-induced disease is often impossible to make in individual patients.

Where negligence has occurred the volunteer who has not in terms surrendered his rights, would have a right of action in tort and the Royal Commission has recommended that a no-fault scheme for medical accidents should not be introduced at present, but that the progress of no-fault compensation for medical accidents in New Zealand and Sweden should be studied and assessed.

General Conclusions

Because of the potential conflict between the roles of physician and clinical investigator some outside judgement of what is acceptable seems necessary to control clinical trials. However, whatever rules are drawn up by the administrators and lawyers these will only be fully effective if the medical profession itself is aware of the need for effective peer review and if the investigators themselves are trained in an ethical approach.

Doubts have been expressed about peer review by ethical committees on the grounds that "These mechanisms are self-selected groups; they do not have the sanction of any constituency in society, there is no adversary proceeding ... . Moreover, these juries are (composed of) senior men. They got to be senior by cutting and slashing their way through the ethics of clinical investigation, and they are suddenly supposed to tell young men that they cannot do the same thing... (These juries) are a superficial, veneer-like approach "(12). Such an attitude may be rather cynical, but it does make the point that the profession alone may have problems in regulating itself. However, the system as it exists, or is developing, in most industrialized countries, whereby a combination of regulatory authority and ethical controls provide a framework, but also with clear limits, does provide protection for the public while limiting research as little as possible.

While such arrangements exist in industrialized countries, much research is conducted in developing countries, and there may be discerned an increasing practice for initial trials of new drugs to be undertaken in those countries which do not have effective regulatory authorities. This points to the need for more specific guidelines which will assist appropriate authorities in the development of national procedures and the establishment of mechanisms which will facilitate their application.

Such guidelines could assist in the determination in particular of what constitutes informed consent in circumstances where the social and cultural background of those concerned is quite different from that which normally obtain in an industrialized country, and also in the determination of what amounts to undue inducement or pressure in the recruitment of subjects for research in such circumstances.

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CLINICAL TRIALS AND THE COUNCIL OF EUROPE

H. Scicluna

Every individual aims at happiness; it is therefore man's obligation, individually and collectively, to respect and safeguard the right of each person to full moral and physical fulfilment. It is precisely this right of the individual, that imposes on the modern state the duty to provide inter alia the best health services for the welfare of its citizens. Limiting ourselves to the one aspect of these services with which we are here concerned, namely the supply of medicaments, it would seem a corollary of the State's general obligation to safeguard health, that it ensures the availability of safe and effective drugs.

Problems of human clinical pharmacology arise out of the obligation to evaluate the safety and therapeutic efficacy of new drugs before marketing and involve mostly the reconciliation of the right of the individual to reliable and effective medicaments with the right of the person undergoing the test. In a resolution in clinical trials and a report on human clinical pharmacology shortly to be adopted, the Council of Europe has tried to reconcile the need for clinical trials on the one hand and the protection of the person undergoing the test on the other by recommending:

- a system enabling public health authorities to authorize a clinical trial or a system enabling public health authorities to be kept aware of planned clinical trials;
- basic common conditions for carrying out clinical trials on man, including
  - § preclinical requirements
  - § guidelines governing procedures for clinical trials
  - § conditions governing prior informed consent;
- improved facilities for initial clinical studies and therapeutic trials;
- a system for continuous exchange of information at national and international level, on the results of clinical trials.

1. CONTROL AND SUPERVISION OF THE CLINICAL TRIAL

1.1 A System of Authorization or Notification

1.1.1 Rationale of the system: Moral and humanitarian principles, economic considerations and technical possibilities considerably restrict the number of subjects as well as the number of systematic

studies that can be carried out on man as opposed to animals. Under these conditions it is essential not to waste human and material resources on unscientifically controlled studies, the value of which will be subsequently open to question.

The Council of Europe experts therefore felt it necessary to advise a system of prior authorization by or notification to the public health authorities. The option is left to the Member States to choose either a system of prior authorization or a system of notification in accordance with their national needs, legal system and particular practices. The purpose, in both cases is to protect patients during clinical trials, particularly by following the general clinical rules which guarantee that the investigator will keep all necessary objectivity in carrying out the trials.

At the same time, this system of authorization or notification envisages a number of prerequisites which are aimed at ensuring scientific progress, promoting initiative in medical research and improving the quality of clinical trials. This implementation could have numerous advantages, for example:

- unnecessary, repetitive, (1) or scientifically unacceptable trials would be avoided;
- the investigator would be better informed;
- the investigator and the patient would be better protected;
- the procedures would be sounder and drawn up better;
- the public health authorities would be better informed;
- adverse reactions, contra-indications and interactions would be detected more speedily.

1.1.2 Contents of the notification or prerequisites for authorization : The experts propose that for the purpose of this authorization or notification a dossier should be submitted which:

- gives the qualitative and quantitative composition of the new drug, the therapeutic indications proposed and all of the analytical, pharmaceutical, toxicological and pharmacological trials carried out, including the pharmacokinetic trials as well as a detailed procedure of the trials envisaged;

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1. Within the meaning of repetitions of clinical trials already carried out in some states participating in Partial Agreement public health activities.

- identifies and describes the drug to be used in the clinical trial;
- gives results of all preclinical trials and such specific information relating to quality and safety as may be judged to be necessary having regard to the proposed trial and contemporary scientific knowledge;
- describes the clinical use to be investigated and the procedure of the proposed trial;
- enumerates the clinical tests completed or in progress in other countries;
- gives the names, addresses and qualifications of the investigators and details of the institutions where the tests are to be conducted.

The dossier should also contain an undertaking:

- to inform the public health authorities of any changes in the dossier originally submitted;
- to provide any information available which casts doubt on the continued validity of the data submitted, including any information on adverse reactions, in order to help evaluate the safety, quality or efficacy of the drug in the uses recommended and to inform the public health authorities immediately in case of serious, unusual or unexpected adverse reactions;
- to submit to the public health authorities all the results of the studies either at intervals to be laid down or at least on the completion of the first trial and at the time of the drawing up of the conclusions;
- to report to the public health authorities any decision to abandon the clinical trials and to state the reasons for this decision;
- to have the clinical trials carried out in accordance with a duly approved procedure;
- to have the drug administered only by, or under the supervision and responsibility of, the investigator named in the authorization or notification. A change of investigator should be notified beforehand and his name, address and qualifications should be given;
- to provide each investigator with the required scientific documents as they are to be found in the official dossier submitted to the public health authorities;

- to submit drugs intended for clinical trials to pharmaceutical quality control by a responsible qualified person, so as to ensure consistency and constant pharmaceutical quality.

1.2 Preclinical Requirements

Before passing on to describe the conditions under which clinical trials are to be held, it should be pointed out that the Council of Europe experts maintain that a number of requirements should always be satisfied before a new drug is tested in man:

- the new drug to be used in the study should have an adequate pharmaceutical specification, and its stability under the conditions of the trials should be known;
- the pharmacodynamic actions and the potency of the active component should be established in a variety of animal models and with reference to all major physiological systems;
- specific acute toxicity tests should have been conducted in at least two species of animal, one a non-rodent, and the LD_{50} established in at least one species. The mode of death should have been determined and full autopsy examinations performed;
- specific sub-acute toxicity tests at three dosage levels and including investigation of behavioural, biochemical, haematological and histopathological changes should have been undertaken in two species of animal, one a non-rodent. It is recommended that the period of dosage should be at least two weeks to provide an adequate basis for single dose studies in man, and at least three months when repeated dose studies are contemplated;
- before any pharmacokinetic studies in man are undertaken, any analogous information derived from animal species should be available;
- in general, the inclusion of women within the childbearing age group is neither necessary nor advisable in pharmacokinetic studies;
- before proceeding to clinical trials other studies should be performed such as for teratogenicity and fertility. In some cases, other studies, e.g. for mutagenicity and oncogenicity, may again be necessary.

1.3 Common Guidelines Governing Procedures for Clinical Trials of Drugs

1.3.1 Preliminary Requirements: The procedure should be supported by an adequate rationale to justify trials in man, and the preclinical

data should be sufficient to support reasonable safety in man and to indicate suitable dosage regimens.

All clinical investigators should, from the outset, have access to facilities that are adequate:

- to monitor progress of patients and to detect drug toxicity at an early stage;
- to conduct or initiate the required pharmacokinetic studies;
- to undertake satisfactory follow-up of their patient at long or short term.

In the case of fixed-dose combinations, it is essential to have available data derived from animal and human studies of each of the components individually with respect to their toxicological, pharmacokinetic and pharmacodynamic characteristics. In general, similar data should be available in respect of the drugs in combination unless the data already available in respect of the individual components indicate that those drugs are unlikely to present any special problems or hazards.

1.3.2 Conduct of the trial: The aim of the study should be concisely and explicitly stated to the patient whenever possible. Appropriate procedures should be followed with regard to obtaining informed consent. The procedure should be both appropriate and efficient with respect to:

- selection of patients (in cases where women in the child-bearing age are included in clinical trials pregnancy should be positively excluded and trials in the animal should have shown no risk of teratogenicity);
- use of control groups;
- allocation of treatments;
- the proposed scale of the trial;
- assessment of the drug response, including, in the case of combination drugs, that of interactions;
- statistical analysis of the results.

The responsibility for coordination of the study (particularly in multi-centre trials) should be clearly established.

1.4 Informed Consent

The Council of Europe experts' view is that prior informed consent is always necessary in instances in which the research is not being

conducted in the subject's own interest. Where clinical tests are being conducted for therapeutic purposes, the patient's consent should also always be obtained unless it is not in his own interest to do so.

Prior informed consent presupposes:

- that it is given by a person capable of understanding the significance of the trials for which he would be a subject and who could understand the consequences that the trial might possibly entail;
- that consent is given freely and willingly.

The experts consider that capacity to give consent and complete freedom of consent is not obtained if there is a possible dependence of the subject on the person carrying out the tests: i.e. the relationship between patient and doctor, student and teacher, employee and employer in the drug manufacturing industry, prisoners and the authorities, as well as the position of mentally handicapped persons, children.etc.

In all the above cases, the experts concluded that the words "volunteer" and "voluntary" are inappropriate, and ought to be replaced by an expression such as "healthy or sick person of sound mind who has given his consent". The experts also think that, where trials are not in the subject's own interest and have no direct therapeutic bearing, it is desirable that consent should be in writing, although there is no such obligation in most states participating in Partial Agreement public health activities.

Where the trial carried out on patients has a therapeutic element, it is theoretically desirable on ethical grounds to obtain the informed consent of the patient, his family or his legal guardian. However, it is often difficult and delicate to apply this requirement systematically. In any event, even if written informed consent is to be granted by the patient, his family or his legal guardian in full knowledge of the facts, it might be necessary to impose certain restrictions in the patient's own interests. Under certain circumstances, oral consent granted in the presence of a witness and confirmed in writing by the latter, might be appropriate.

The Council of Europe experts further considered that leading medical representatives or others of teaching or training hospitals whose professional competence and conduct are beyond question and who are not involved in the trials in question could be invited to consider ethical and practical aspects and the rights of the patient concerned. Both the individual and public health interests would thus be protected from the possible dangers of such experiments. Those responsible for trials conducted in places other than the hospitals referred to above would have to apply to the special boards.

2. IMPROVED FACILITIES FOR INITIAL CLINICAL STUDIES AND THERAPEUTIC TRIALS

New drug laws and regulations of nearly all European States give rise to the need for controlled and elaborate trials for presenting evidence concerning the therapeutic efficacy of a new drug.

Investigations of this kind are best accomplished by physicians having experience in the design and practice of therapeutic trials. Furthermore, they should possess basic knowledge in pharmacology and toxicology necessary for understanding and evaluating the data obtained in preclinical trials.

In the past, clinical investigation of new drugs has been undertaken in the main by physicians with specialist knowledge in the relevant clinical field, but often lacking some of the facilities and experience required to undertake adequate and efficient controlled studies. As a result. the pharmaceutical industry has been required to give support and technical advice to clinical units.

There is thus a need for clinicians to fulfil all requirements for testing of drugs, preferably by bringing in clinical pharmacologists working in units or departments designed and equipped for this purpose. Clinical pharmacology is a new speciality of medicine which investigates the pharmacological action of drugs on man with the aim of evaluating their therapeutic efficacy.

A clinical pharmacologist should be trained in pharmacology as well as a clinical speciality, such as internal medicine, pediatrics, psychiatry etc. He has to know the basic facts of experimental design and statistics that are relevant to the design and analysis of therapeutic trials. Furthermore, he should act as a consultant in any problem of therapy so far as the pharmacological or toxicological aspects of drugs are concerned, and he should arrange teaching programmes. He should establish, if it is possible, a system for monitoring adverse reactions in the hospital and set up an information service for physicians.

A clinical pharmacologist will never be able to master all procedures that are essential for testing the intensity and duration of drug action, and he needs to collaborate with clinical specialists of all kinds. Thus, clinical pharmacology is an interdisciplinary subject and should be organized in this respect according to the traditions prevailing in the different countries.

It is sometimes argued that a clinical pharmacologist who specializes in only one clinical subject cannot contribute to the evaluation of drugs used in other clinical specialities. However, his general knowledge of pharmacokinetics, embracing information concerning absorption,

distribution, excretion and mechanisms of biotransformation, is really essential for a rational evaluation of the efficacy of drugs. Thus the clinical pharmacologist is in a position to provide an essential contribution to the investigation of any new drugs.

The experts strongly recommend that there should be groups capable of performing drug trials until such time as a sufficient number of clinical pharmacological units in European countries can be founded to cope with this research and to educate enough physicians in this field. Such a team should include a specialized clinician and a pharmacologist who would both provide appropriate knowledge in the field of clinical trials of drugs, and who should have at their disposal all facilities for determining the drug and some metabolites in body fluids. Cooperation from a pharmacist and a statistician will often be necessary.

It is also advisable that a clinical pharmacologist who is a qualified physician or a physician trained in pharmacology coordinates the drug-testing programme and advises the clinician on any pharmacological problem. The clinician is always responsible for the patient. The Governments of Member States who are responsible for authorization or registration of drugs should therefore facilitate the development of an adequate number of clinical pharmacological units or departments capable of fulfilling the requirements of their relevant regulations whilst safeguarding the academic freedom of investigators.

3. SYSTEMS FOR CONTINUOUS EXCHANGE OF INFORMATION AT NATIONAL AND INTERNATIONAL LEVEL, ON THE RESULTS OF CLINICAL TRIALS, PARTICULARLY WITH REFERENCE TO ADVERSE REACTIONS

The experts deem it desirable that the Member States should consider an international system of free exchange of information between the competent national health authorities on the results of clinical trials, with particular reference to serious, unusual or unexpected adverse reactions.

The experts recognize that there may exist in the various participating States obstacles in the way of the exchange of information on adverse reactions arising from the application of the principle of confidentiality or possibly from specific laws in this respect. It however agrees that there should be free and uninhibited exchange of such information and for this purpose is of the opinion that the States concerned should take all appropriate measures to remove such obstacles.

Such an exchange is urgently needed as regards serious, unusual or unexpected adverse reactions, which should be reported immediately to the competent authority by the manufacturer, since he has the necessary information on the whole field of clinical trials, including those taking place in other countries. Minor adverse reactions will automatically

become known when the drug is considered for authorization or registration.

The experts further think that a system of pharmacovigilance for drugs in the clinical trial stage can produce practical results (e.g. the termination of the trials and special safety measures) only if there exists in each participating State a system operated by the competent authorities, for the authorization or notification of clinical trials.

LA NOTION D'ETHIQUE MEDICALE : REFLEXION D'UN HOMME DU TIERS MONDE

F. Johnson-Romuald

Je laisserai d'emblée aux nombreux savants et penseurs ici présents le soin de disserter en long et en large, en hauteur et en profondeur, sur "l'expérimentation médicale et les droits de l'homme", thème passionnant et sujet toujours actuel s'il en est.

Cet être à la fois limité et illimité qu'est l'homme est d'abord et avant tout un être vivant. En tant que tel et même s'il estime sans objet ou superflu de s'interroger sur ses origines ou sa finalité, il ne peut pas aisément résister à la tentation de se demander à lui-même le "pourquoi" et le "comment", c'est-à-dire les conséquences possibles de ses propres activités.

Dans ce monde éminemment dualiste, où les contraires sont constamment associés, l'homme se sent à la fois fier et quelque peu effrayé par ses propres créations, car son esprit créatif, j'allais dire divin, lui suggère qu'une création entraînera nécessairement une autre création, et, de création à création, on peut fort bien ne pas exclure l'éventualité d'aboutir tôt ou tard à des résultats non désirés.

Le savant le plus détaché, le chercheur le plus exclusif, le scientifique le plus froid, ne peut donc échapper à cette possibilité de se retrouver un jour ou l'autre face à face avec lui-même au sujet de ses propres découvertes.

S'agissant de santé, l'instinct de survie sommeillant en chaque individu se trouve directement visé. Quiconque (c'est-à-dire pratiquement chacun) ayant eu l'occasion de vivre dans sa chair, et ne serait - ce que quelques instants, en compagnie d'une affection aussi banale qu'une céphalée, une rage de dents, un panaris, une crise hémorroïdaire, etc., peut avoir verifié combien précaire se révèle cet equilibre plus ou moins instable du corps physique que nous appelons santé.

Si j'ai tenu à faire tout de suite ces rappels élémentaires de choses qui sont à chacun de vous tout à fait familières, Mesdames et Messieurs, ce n'est pas dans un but autre que de vous souhaiter de tout mon coeur courage et persévérance dans vos discussions, car de telles discussions sont pratiquement sans fin, le sujet étant par définition inépuisable.

Je porterai donc le plus vif intérêt à nos débats, et ceci d'autant plus que l'expérimentation médicale, ou ce qui a été présenté comme telle, a parfois revêtu à diverses périodes de l'histoire et même

jusqu'aujourd'hui, des aspects tels que les hommes sensibles aux droits fondamentaux de l'être humain ne peuvent pas ne pas se sentir profondément concernés, sinon révoltés. Les abus auxquels une telle expérimentation a donné ou peut donner lieu ne sont que trop réels et aucune occasion n'est de trop pour les condamner, les prévenir ou simplement tirer la sonnette d'alarme. Mais nous ne devons pas oublier qu'il s'agit là de phénomènes reflétant au minimum un certain environnement, un environnement technologique plus ou moins sophistiqué de la civilisation dite industrielle. Or, le fait est malheureusement que le contexte socio-économique et technologique peut être différent dans de larges zones du monde moderne.

Et c'est ici que vous me permettrez, Mesdames et Messieurs, d'introduire dans le schéma désormais classique "d'expérimentation médicale" la notion un peu inattendue "d'expérimentation non médicale" c'est-à-dire un point de vue plus terre à terre, qui ne débouche plus seulement sur de hautes considérations générales et philosophiques, mais accorde quelques instants d'attention au vécu quotidien et actuel de centaines de millions de nos contemporains sur cette même planète TERRE.

En effet, pour ces hommes et ces femmes, j'allais dire pour ces "sous hommes" et ces "sous femmes", "l'expérimentation médicale" n'est pas un concept ni une activité réservés à des spécialistes en la matière mais bien une réalité quotidienne, puisqu'ils ont tout loisir, tout le long de leur vie à chaque instant d'expérimenter ce que j'ai appelé plus haut "l'expérimentation non-médicale".

Car de médecins, ces hommes et ces femmes en connaissent peu ou pas : le seul médecin - s'il y en a - desservant leur région, peut avoir à s'occuper de 200 - 300 000 habitants. Si les statistiques nationales d'un pays ramènent ce chiffre impressionnant à quelques 30 ou 40 000 habitants, on peut sans crainte d'erreur grossière soupçonner que les 2/3 de l'effectif total des médecins du pays se trouvent concentrés dans la capitale, et que dans les zones rurales les chiffres précédents n'ont rien d'excessif.

Il existe bien des auxiliaires médicaux, des infirmiers, des agents de santé, etc..., mais le dispensaire ou le centre de santé où cet excellent personnel sert - souvent avec beaucoup de dévouement - se situe dans le village le plus proche, c'est-à-dire à des kilomètres de là, et le moyen de transport le plus approprié pour y arriver est la marche à pied. Si on a le bonheur de résider dans le village possédant le dispensaire ou le centre de santé, le diagnostic souvent valable de l'infirmier n'a qu'une portée limitée, puisqu'alors le médicament manque tragiquement, car la maigre dotation trimestrielle - si elle a pu être honorée - s'est "évaporée" de longue date, et en attendant la prochaine dotation - si elle arrive - il faut (pour ne pas perdre la face) faire semblant de soigner.

Ce tableau n'est pas artificiellement noirci. Voici quelques chiffres récemment cités : (1)

500 millions d'hommes souffrent du paludisme
300 millions de cas de bilharziose
la malnutrition atteint plus d'un milliard d'êtres humains
l'espérance de vie, dans tel pays, est de 35 à 37 ans
la mortalité infantile de 0 à 1 an est de 180/1000
la mortalité estimative de 0 à 3 ans est de 300/1000

Selon les documents publiés à la Conférence internationale sur les soins de santé primaires (Alma Ata, URSS, 6-12 septembre 1978) :

"Plus de la moitié de la population mondiale n'a pas accès à des soins de santé primaires.

"Les dépenses publiques de santé par habitant dans les zones urbaines sont environ 14 fois supérieures à ce qu'elles sont dans les zones rurales, dans les dix pays de l'Asie du Sud-Est, Région comptant au total 965 millions d'habitants.

"Dans la Région africaine de l'OMS, qui groupe 44 Etats représentant un total estimatif de 273 millions d'habitants, les dépenses annuelles de santé sont en moyenne inférieures à un US dollar par habitant."

Ces statistiques sont d'une éloquence suffisamment brutale pour se passer de commentaire.

Dans son numéro de juillet 1978 consacré au 30ème anniversaire de la déclaration universelle des droits de l'homme, le magazine de l'Organisation mondiale de la Santé, "Santé du Monde" portait comme légende de la photo de couverture : "La Santé, l'un des premiers droits de l'homme".

Dans un enceinte aussi huppée que celle-ci, nous pouvons donc gravement et à juste titre traiter "des droits de l'homme et de l'expérimentation médicale". Je le répète, l'importance du sujet mérite qu'on s'y penche, qu'on y vienne et qu'on y revienne et c'est ici que vous m'autoriserez à rendre à ce sujet mes respectueux hommages au CIOMS et à ses animateurs.

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1. Réf. notamment : Claire Brisset : "Le désert médical du Tiers Monde", dans Le Monde, 6-9/10 septembre 1978.

Le savant, le scientifique, le philosophe, le chercheur, ne sont pas à ma connaissance des êtres désincarnés. Ils ne peuvent donc se contenter de disserter des problèmes qui se posent à eux, uniquement comme dans un laboratoire vitré, aseptisé, climatisé et isolé du reste du monde. Leurs cogitations, si théoriques soient elles, gagneraient probablement une dimension supplémentaire à ne pas passer sous silence ou à ne pas se contenter d'allusions plus ou moins vagues sur les vices trop réels, les tares trop criantes d'une donnée de base de leur temps, surtout si celle-ci concerne plus de la moitié de l'humanité.

J'aurais probablement préféré le silence s'il s'agissait simplement pour cette conférence de s'acquitter d'une telle responsabilité en lançant, par exemple, une fois de plus un appel solennel - et quasi stérile - à la solidarité internationale.

A mon avis, il s'agirait essentiellement de nous rappeler qu'à côté de l'expérimentation médicale des hôpitaux et des laboratoires, peut exister et existe effectivement - et sur une large échelle - l'expérimentation vécue quotidiennement de la "non-médecine". Telle l'ombre qui met en relief la lumière, ce contraste peut être pour plus d'un d'entre nous source de précieuses inspirations, et pas seulement dialectiques ni théoriques.

Il n'est que de nous souvenir que parmi les 30 articles de la Déclaration universelle des Droits de l'Homme, l'article 25 traite plus spécialement du droit à la santé:

Je cite(2)

"Art. 25. 1/ Toute personne a droit à un niveau de vie suffisant pour assurer sa santé, son bien-être et ceux de sa famille, notamment pour l'alimentation, l'habillement, le logement, les soins médicaux ainsi que pour les services sociaux nécessaires; elle a droit à la sécurité en cas de chômage, de maladie, d'invalidité, de veuvage, de vieillesse ou dans les autres cas de perte de ses moyen de subsistance par suite de circonstances indépendantes de sa volonté.

2/ La maternité et l'enfance ont droit à une aide et à une assistance spéciales. Tous les enfants, qu'ils soient nés dans le mariage ou hors du mariage, jouissent de la même protection sociale."

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(2) Halter, S. et Dilen, H.: "La déclaration universelle des droits de l'homme, trente ans plus tard". Santé du Monde, juillet 1978.

Les textes de base rédigés par la Secrétariat de la Commission des Droits de l'Homme des Nations unies étaient les suivants:

> "Tout individu a droit aux soins médicaux. L'Etat doit protéger la santé et la sécurité publiques". Et: "Tout individu a droit à une bonne alimentation et à un bon logement et à vivre dans des conditions agréables et saines" (3).

C'est depuis la proclamation de la déclaration universelle en 1948 que le droit à la santé est devenu un acquis de la communauté internationale, et la même année, l'Organisation mondiale de la Santé a vu le jour.

Vous savez tous que dans sa constitution, cette Organisation proclame sa volonté "d'amener tous les peuples au degré de santé le plus élevé possible".

Comment se fait-il donc que 30 ans après la création d'une telle organisation et avec des résultats aussi spectaculaires que la perspective désormais certaine d'éradication de la variole, la circonscription de foyers endémiques du choléra, l'éradication dans certains pays comme l'Ile Maurice du plaudisme, etc., la situation sanitaire ne semble guère sensiblement améliorée dans de très larges secteurs géographiques du monde, restant plutôt stationnaire sinon s'aggravant au point d'autoriser cette affirmation osée mais tropvraie de"Désert médical du Tiers Monde" (4).

C'est que tout a été mis en oeuvre, la bonne volonté, le dévouement, la technique et la technologie, mais un seul point - fondamental - a manqué de recevoir une attention à la mesure de l'ampleur du phénomène. Ce point clé tient en une expression simple: la prise de conscience.

Je vois d'ici beaucoup de ceux qui m'écoutent ou me lisent lever les bras au ciel : "Mais nous, on a conscience depuis longtemps, on sait tout cela depuis belle lurette, mais que faire? Ces pays malheureux sont pauvres, n'ont pas d'argent et ne sont pas près d'en avoir. Il faut attendre leur développement économique pour que leurs problèmes sociaux, notamment de santé, commencent à être résolus. Pour patienter, on peut toujours leur envoyer quelques secours d'urgence".

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3. Halter, S. et Dilen, H.: "La déclaration universelle des droits de l'homme, trente ans plus tard". Santé du Monde, juillet 1978.

4. Réf. notamment: Claire Brisset: "Le désert médical du Tiers Monde", dans Le Monde, 6-9/10 septembre 1978.

Ce raisonnement fort répandu - et digne peut-être d'une organisation comme la Croix-Rouge, ignore simplement qu'un homme libre et responsable ne peut se contenter de l'être pour lui tout seul, mais peut et doit chercher à encourager dans la mesure du possible les autres à le devenir.

On peut également, et à fort bon compte, se frapper la poitrine en disant: "Moi, je veux bien faire quelque chose - mais quoi? Je ne suis pas un technicien de la santé. L'OMS et les autorités nationales de santé s'occupent de la question. Il n'y a qu'à attendre".

Vous le savez mieux que moi, Mesdames et Messieurs ici rassemblés, vous êtes des penseurs dans les divers domaines de l'activité humaine: scientifique, philosophique, ou même simplement humaniste sans qualification technique très particulière.

Or, chacun le sait, la structure préalable à toute nouvelle structure matérielle dans le monde, c'est l'idée. Je n'ai pas besoin de vous rappeler Platon : "Les idées sont des choses".

Mesdames, Messieurs, vous m'autoriserez alors à vous rappeler que vous disposez d'une arme particulièrement efficace pour reculer méthodiquement et graduellement les horizons jusqu'ici assez classiques et un brin théoriques de l'éthique médicale vers une approche plus pragmatique des cruels aspects actuels du Monde moderne.

Un forum comme celui-ci, en dehors de son audience internationale coutumière, pourrait donc prendre aussi la forme d'un canal privilégié pour des réflexions en faveur d'une prise générale de conscience plus aiguë de ces graves problèmes.

Il pourrait donc :

1) contribuer à sensibiliser l'opinion tant des pays développés que des pays en voie de développement eux-mêmes sur l'urgence de la situation;

2) contribuer à sensibiliser les gouvernants de tous pays, car plusiers auraient besoin de l'être d'avantage. Si les gouvernants sont à juste titre placés par leurs populations au sommet de la hiérarchie politique du pays, ils n'en demeurent pas moins en effet des humains aux prises avec toutes les contraintes de la limitation humaine : physique, mentale, morale, affective, etc.;

3) ce faisant, appuyer plus ou moins directement les efforts des organisations spécialisées, non-gouvernementales ou d'hommes de bonne volonté, qui ne cessent - comme l'Organisation mondiale de la Santé par exemple - de tirer la sonnette d'alarme;

4) peut-être susciter un mouvement progressif de solidarité, non en faveur de dons matériels toujours limités dans le temps et dans leur ampleur, mais en faveur d'actions plus concrètes et à plus long terme, comme:

a) possibilité de s'attaquer immédiatement à ces problèmes, d'abord avec les moyens propres des pays;

b) encouragement d'études épidémiologiques plus poussées;

c) mise au point de nouvelles molécules thérapeutiques;

d) action en faveur de l'assainissement de l'environnement;

e) rappel des diverses priorités, en particulier celle de poser clairement les problèmes;

et cette liste n'est pas limitative.

Il serait peut-être temps de conclure.

On sait qu'un geôlier participe, selon des modalités certainement différentes mais à plus d'un titre comparables à celles de son prisonnier, à la peine privative de liberté purgée par celui-ci. En d'autres termes, il semble peu contestable qu'un lien dialectique existe entre un prisonnier et son gardien.

De même pourrait-on oser suggérer que l'homme bien portant, s'il reste indifférent devant un malade, sous-estime simplement le malade en sursis que lui-même recouvre, soulignant ainsi - une fois de plus - l'espèce de solidarité intrinsèque liant les humains.

D'autre part, on accepte plutôt rarement de participer activement à des débats d'une si haute portée générale, uniquement pour le goût de la rhétorique ou de la dialectique. Pour se montrer fructueuse, la participation de chacun présuppose qu'il se sent profondément concerné par le devenir de l'homme, la condition qui est celle de l'individu et de l'humanité. Ce qui m'autorise, Mesdames et Messieurs, à égratigner un peu votre modestie et à vous assimiler par définition à des hommes et à des femmes de bonne volonté, c'est-à-dire, à des hommes et à des femmes de bien.

Dès lors, vous comprendrez aisément que quelqu'un qui a l'honneur de partager avec vous le privilège redoutable du maniement familier de ce merveilleux outil qu'est l'intellect, ait tenu à ne pas rater cette occasion de rappeler les responsabilités particulières dont du reste chacun de vous n'est que trop conscient.

Vu donc du tiers-monde, "l'expérimentation médicale à l'égard des droits de l'homme" acquiert ainsi un nouvel éclairage.

Miller, G. E.: Mr. President, in your eloquent opening remarks you alluded to the fact that oaths and codes represent a profession's noble aspirations but the real protection of human rights depends not on what is in man's mind but what is in his heart. Mr. Williams in his printed paper was even more blunt, pointing out, and I quote "whatever rules are drawn up ... these will only be fully effective if the medical profession itself is aware of the need for effective peer review and if the investigators themselves are trained in an ethical approach". I'm afraid the uncomfortable truth is that far too little attention has been given to this matter either in the basic education of physicians or in the preparation of research workers through their graduate training. It is true that this is changing and at least in the United States we've not only added courses in the human values but have added such professionals as ethicists and humanists to faculty members and have even established a formal society for health and human values.

Certainly these developments are helpful but, in all candor, one must note that the curriculum additions are more often designed to provide information about ethical issues than to change student attitudes that will ensure incorporation of that information in some kind of ethical behavior. Lecturing about the issues, discussing them is not enough. We must truly have learning experiences that grip and transform students - not merely inform them about things that they should be doing.

There are many tools now available that reflect this kind of instructional strategy but too rarely are they known by medical faculties and even more rarely are they effectively used by most medical teachers. Unless these strategies are more generally employed, I think it's fair to conclude that we may, even with this heightened effort, end with students who are better informed about human values but essentially insensitive to their application. Let me give a concrete illustration. One element of sensitivity is certainly captured in the principle of informed consent and certainly the legal requirements are generally being fulfilled. But the real question is whether sufficient attention is being given to the human requirements.

In the September 22 issue of Science there was a fascinating article on performance of institutional review boards to protect the rights of human subjects in research. I note only one of their findings, that less than seven percent of the informed-consent forms was as easy to read as Time magazine. More than seventy-five percent were written in the very difficult range of scholarly or scientific writing. This in the face of the fact that more than half of the adults in the United States have a reading level below the tenth grade, which is about the level of Time and the Reader's Digest. Now certainly this suggests some insensitivity among the research workers themselves. It was further reported that twenty percent of the subjects complained about a lack of information concerning the experimentation in which they were asked to engage and ten percent cited a need for more care or courtesy by the research workers

in dealing with them as human subjects. The investigators, the authors of this article, concluded that, although the ethical conduct of research involving human subjects requires that researchers have a certain degree of skill in communicating with and relating supportively to others, training in the techniques of effective communication is not an ordinary part of the education of researchers.

My plea, then, in our discussions is to consider the essential nature of altering the instructional practices with medical students and in the more advanced educational programmes to train research workers. The use of instructional techniques and evaluation procedures that are available to influence attitudes and values but are not now widely used. And obviously this means, then, that faculty members must first acquire some new pedagogic skills before we really can expect that medical students and research trainees will achieve what is required in their learning, if we are truly to fulfill the obligations which are the subject of this Round Table Conference.

Vilardell: I have been concerned with finding out at our last World Congress of Gastroenterology how much in the way of ethical committees were set up in different institutions. And they sent a questionnaire to all the three thousand members of the Congress to find out. I didn't get much of an answer - one hundred and forty-seven - and sixty-one of the answers were positive. Most of the committees were set up in hospitals in North America, the United States and Canada. Second followed Western Europe. Third, the Socialist countries. Latin America was fourth with the Asian Pacific. The Asian Pacific group was mostly Australian, and gave positive answers.

Besides that, at that meeting we had ten percent of papers related to new diagnostic methods. And I had been concerned with that because this has obviously some implication in ethics and this is to me medical experimentation, too. And nowhere could I find any statement about the protection of the patient concerning the use of new instruments or technical devices for diagnosis. This is disturbing to me because all those papers reported some rate of error or complications due to the technique itself. Of course, this is related to the technical skill of the operator a great deal, but I really wonder whether something can be done in order that any new procedure or technique that is going to be available for diagnostic purposes should in some way or another be submitted for the consideration of an ethical committee or a peer review of some sort.

Gellhorn: Thank you, very much, Dr. Vilardell. I wonder if we could get some information. May I ask what is done in the United Kingdom with regard to ethical review of new procedures? Does that fall in the same category of the clinical trial of a new drug? Mr. Williams?

Williams: Mr. President, I think that one finds that this is really in a grey area. Because normally when new procedures of this kind are involved you are also dealing with drugs as such. And if that is the position the matter will become a matter for a clinical trial certificate or exemption, and in any event will become a matter for the appropriate ethical committee. But I do think that it is, as I describe it, a grey area, and there may well be circumstances in which the terms of reference of the ethical committee are so narrowly drawn that one may well find that it is not the subject of consideration by such a committee, and this is a matter to which attention needs to be directed.

McCarthy: In the United States, we had legislation passed about a year and a half ago requiring review of medical devices by the Food and Drug Administration and now all new medical devices must be reviewed by institutional review boards, which are essentially ethics committees. So that, although the details vary somewhat because devices are not quite the same as drugs, our essential procedures are to give drugs and devices a similar kind of review before they may be introduced into general use.

Bouramoue: Je dois d'abord remercier l'ICCA et le CIOMS de nous avoir fait l'honneur de nous inviter à cette séance très importante qui comporte essentiellement le sujet des droits de l'homme vis-à-vis de la recherche scientifique. L'essentiel a déjà été dit; je dois néanmoins stigmatiser l'incursion des chercheurs dans la sous-région africaine dans ce sens que la plupart du temps les chercheurs étrangers opèrent dans un champ où les interessés ne sont pas conscients et c'est déplorable; cela a été signalé par M. Williams, je le souligne à nouveau parce que certains chercheurs croient avoir trouvé dans certains pays sous-developpés le champ où ils peuvent déployer à loisir leurs activités de recherche sans pour autant que les pays concernés puissent en tirer profit.

Le deuxième point concerne les prisonniers. Je crois au bon sentiment d'Amnesty International, mais, je dois avouer que cette organisation n'a pas toujours le courage partout où il le faut. Son expression est fonction de la situation du moment et du pays auquel elle a affaire. Je crois que les essais qui ont lieu, qui se font sur les prisonniers, sont extrêmement condamnables parce qu'on parle du consentement informé, mais dans certains pays souvent le prisonnier est informé et on lui tend une dragée: c'est par exemple la réduction de la durée de la peine d'emprisonnement du fait qu'il se soumet à l'expérimentation. Il s'agit là, à mon sens, de moyens qui ne sont pas très humains.

Neki: I wish to take this opportunity of drawing our attention to some more fundamental issues. The ethics of medical research has to be understood in the setting of a general code of ethics. And if we ask

ourselves to what general code of ethics do we owe our religions, I'm afraid that most of us would chose to remain silent. Because I have a feeling that the undeclared general code of ethics is materialistic advancement. My fear is that any code of medical ethics or code of ethics of medical research cannot run counter to the spirit of the general code of ethics. And we have therefore to pay attention to it.

Dr. Curran has talked about the question of trust. My fear is that the basis on which human trust flourished is fast disappearing. And therefore, unless we pay attention to this aspect, merely talking of a code of ethics of medical research would not be so fruitful.

At the pragmatic level, our policy of professional promotions is linked with research productivity. Because this is one professional aspect which is easily quantifiable. Clinical acumen is hard to evaluate and therefore is often neglected in evaluation for professional promotions. And therefore there is a tremendous rush of research at the rate of 1.35 seconds as you have alluded to. And this has lead to a lot of bad practice in research.

And, lastly, I again wish to underline, the almost total absence of and neglect of humanities in medical education. I wish to particularly say how much emphasis is laid on research methodology in our teaching and how little on ethics of research. And, finally, to put the record complete, we have had two excellent historical introductions to medical ethics, but neither of them seems to have mentioned or alluded to the World Psychiatric Association Hawaii Declaration of last year. And I wish this august assembly to be informed about it, because this declaration advises physicians not to be coerced into detaining individuals in the mental hospitals for reasons political rather than medical. And I thought this was an important declaration which needs to be mentioned here.

Riis: I want to return to the point of Professor Vilardell asking us about attitudes on investigation on therapeutical measures. I would say in accordance with Helsinki Declaration No. II, therapeutics and diagnostics and preventive measures are put in the same category. So I would see no difference in judging such projects when they deal with a diagnostic idea. But the problem is not that we don't see the ethical problems in such kinds of research. The real problem is that we have a very bad and weak science tradition in evaluating research measures in medicine. So I think that we should consider upgrading this aspect of medical research and as soon as we do so we'll meet the ethical problems which are there, and which are hidden at present because most doctors trying to investigate diagnostics don't tell patients that they actually are investigating and often do this in retrospect, giving bad results.

Carballo: I would just like to present a very brief account of CIOMS' study on ethical review committees. Two years ago we undertook

a pilot study on the role of ethical review committees. This project was designed as an international comparative survey on the functions and practices of ethical review committees. Originally, we selected three countries to be included in a preliminary report. These were the United Kingdom, the United States and Sweden, mainly because of the availability of material on ethical review committees in these three countries. But additional correspondence and site visits and review of the literature provided preliminary data on a number of other countries which have set up ethical review committees such as Australia, Belgium, Canada, France, India, Israel, the Netherlands, New Zealand, Nigeria and Switzerland.

As we are gathering more data, we feel that maybe as an international agency we can contribute in the following manner: we would like to enlarge the basis of our study to identify all countries where ethical review mechanisms and procedures have been established and make a very broad comparative survey. We would like to study more in depth practices of ethics committees in different settings and determine the possible influence of such practices on the formulation of ethical principles at a national or international level.

And, finally, by promoting a broader exchange of information between countries with experience in this area, and studying the conditions and circumstances in which research is conducted in other parts of the world, we would like to try to provide some guidance to other countries which would be willing now to set up their own mechanisms for the ethical review of research activities on human subjects.

SECOND SESSION

PRIORITIES AND ETHICS IN RESEARCH PLANNING

Moderator: B. K. Adadevoh

RESEARCH SPONSORED BY INDUSTRY

M. Weatherall

Rights and Duties

The first point that I want to make is a very simple philosophical one. It is hardly within my brief, but it will shape all I have got to say, and I believe that attention to it might simplify some of our later discussion. The point is this, that one cannot consider rights without also considering duties. Whenever a human right is stated, it implies an obligation on someone else to do something for the possessor of the right. If I have a right to food, other people must either provide that food or at least not stand in the way of my getting it for myself. If I have a right to freedom of speech, other people have a duty not to suppress me when I speak freely, and not destroy what I have said. And when I recognize the rights of other people, I incur a duty to act so that the rights are in fact realized. Rights and duties are the positive and negative sides of the same process. I prefer to talk about duties, particularly for myself and those for whom I am concerned, because duties imply personal, positive action by specified persons, whereas it is not always clear who must do what in order to preserve rights.

Duties of the Pharmaceutical Industry

The pharmaceutical industry has duties towards three groups of people: to the public, to its employees and to whoever has provided it with the facilities by which it operates. For the public, its duty is to use its resources to provide the best and safest medicines which it can provide. For its employees, it must provide rewarding employment, both financially and in the less tangible ways which are sometimes called job satisfaction. For the provider of facilities, it must offer some return, either, in a capitalist society, as a dividend on the invested capital or, in a socialist society, justifying the investment of public money by a return in public service.

The nature of the political system is unimportant, except that in a strictly capitalist society no relief is available if the business fails to break even, whereas in a state supported industry financial failure can be overlooked as long as the population is willing to pay sufficient taxes, or if other state organized industries are sufficiently profitable to carry the loss. Whatever the system, it is preferable for the operating costs to be less than the return obtained for the products, even if all the hopes of a profitable return are not fulfilled. In addition, it is optimal for the industry to undertake research to discover new medicines. Again in a capitalist society, the business incentive to research is the expectation of adequate return on the cost. In a socially oriented community, the profit in terms of human well-being may be balanced against the expenditure of

human resources, but total resources are always limited and it is still necessary to determine how much effort is to be expended in the hope of achieving a given result.

Strategy for Research by Industry

I will deal with this matter in capitalist terms, because it is easier to think about money, which is easily measured. But the same principles apply if the input and output are measured, less tangibly, in terms of human endeavour and human reward. The strategy must take the following into account.

a) The expected return on the research, in the long term, must outweigh the cost of the work, including provision of facilities, payment of staff and purchase of materials.

b) The money coming in to the business must be sufficient to cover costs through the period between starting any research programme and its eventual fulfilment. This period is likely, in present circumstances, to be a minimum of seven years, and probably is longer.

c) The majority of pharmaceutical research programmes now fail to result in a marketable product, so much or most of the money spent on research is wasted and never recovered.

d) As most research is carried out by institutions already in being, the direction of the research is largely determined by the technical knowledge and equipment of the staff already employed.

e) In the absence of external financial support, preference must be given to discovering drugs for which the market return is likely to be greatest.

f) In devising a research strategy, a company must conform to its own ethics, to the local ethics of the communities where it is conducting research and of those were it is marketing drugs, and, increasingly to a worldwide ethical standard.

In addition, there are some current limits and pressures, which are particularly discouraging to research. These difficulties include:

a) Objections to experiments on animals.

b) Public demand for safe drugs, and attribution of responsibility for safety to the manufacturer rather than the user of the drug.

c) Objections to experiments on man.

d) Increasing technical sophistication, associated with a demand for standards of purity which do not necessarily confer any practical benefit.

Practical Decisions by Industry

1. The first decision for a pharmaceutical firm is whether to undertake, or, more usually, continue undertaking, research. The decision depends on an understanding of human needs and on the prospects of an acceptable financial return. The greater the chance of profit from new remedies, the lower the cost of research, and the more adequate is current income, the more reason there is for undertaking research. Conversely the less the financial return on drugs currently being sold and the greater the quantity of research needed, the more reason there is for not initiating research and for abandoning what is already in play. This decision is not dependent on political structure. A government-sponsored research organization would still have to justify to its treasury reasons why expenditure should be incurred on research more costly than a subsequent pay-off justifies.

2. The second decision must be on the scale on which research is undertaken. The resources needed to discover, develop, assess and finally market a new drug are now very substantial. The chances of success are so small as to become negligible except in a moderately large organization. From my own experience, I suggest that a research and development staff of less than 300 people would be inadequate to bring any area of pharmaceutical research to fruition. The larger the research institution beyond this level, the greater the opportunities for mutual support between related but semi-independent activities. Beyond the size of about 1 000, the difficulties of communication and coordination increase so much that possibly more is lost than gained from expansion. But if one accepts a research activity of 300 - 1 000 people, this represents a cost of several million pounds a year as the minimum stake in the game, and the sum which must be recouped from current income whatever its source.

3. The next decision relates to the areas in which research is pursued. Biological research is full of surprises, and strict concentration on a particular target is apt to be sterilizing. When an unexpected observation appears, it may be well not to reject exciting possibilities because they divert work from the chosen end. For instance, if a new drug, synthesized as an anthelminthic, turns out to have useful muscle-relaxing properties, should one ignore the observation, or consider developing that drug as a muscle relaxant? And if one does the latter, what has happened to the resources intended for discovering a new anthelminthic? In practice, one must preserve a balance between working within fields in which one has experience and not neglecting stimulating and unexpected findings. But it is important to recognise that rigid restriction of targets is likely to reduce the chances of any success at all.

4. Given the uncertainty of the outcome of research, what is the duty of a pharmaceutical firm which discovers a potential remedy for a rare disease or a disease confined to poverty-stricken countries? In either case, the financial return over many years of marketing the drug may be insufficient to pay for the cost of its development, let alone its continued production and sale. In practice, some firms of high repute and competence do in fact devote substantial resources to unrewarding discoveries. But there is a limit to what can be done in this direction, and the tighter the financial controls on the industry, the sooner this limit is reached.

5. Suppose that the company accepts its ethical responsibility, pursues the drug in the interest of humanity, and fails to recoup the costs from its other activities, and in consequence goes bankrupt. It will then be unable to meet its obligation to its shareholders, or to the taxpayers who have supported it, and to its employees, who depend on the financially competent management of the company for their sustained employment. Perhaps in the interests of the employees, the state would make some sort of financial rescue operation. But the prospect of such help is questionable and its possibility is not one which would appeal to any management with pride in its self-sufficiency and business ability. Certainly it would not be within the responsibility of the company's research planners to advocate such a course, however ethically attractive the course might seem to them in terms of human welfare.

Conclusion

I conclude that a pharmaceutical business, whether financed independently or managed by the state, has a duty to keep its research expenditure within bounds. Indeed, it is not obliged to undertake research at all. But if it does, research directed towards targets which will benefit large numbers of prosperous patients is a more rational proposition than research directed towards rare diseases or diseases of poverty-stricken communities. The extent to which an industry can afford resources for less rewarding projects depends on its overall income. The smaller the profit margin, the less practicable it is to undertake any such unrewarding research.

EXTERNALLY SPONSORED RESEARCH

Harold H. Phillips

Biomedical and clinical research have come to be recognized as necessary to be conducted locally on site in the developing countries, with the realization that it is not always possible to transfer the results and findings of investigations carried out in the more advanced countries to many of the developing countries. The health problems and needs of the developing countries are quite clearly very often entirely different from those of developed countries, and it is necessary in developing countries to enlarge the scope of clinical research to encompass research problems with community health connotations.

At the present time the manpower resources of most of the developing countries do not appear to be sufficient, to permit them to investigate their numerous health problems and carry out biomedical research entirely on their own. Furthermore most of these developing countries lack the appropriate facilities - especially equipment of the appropriate kind - as well as financial resources to sustain important clinical research projects at the pace and intensity necessary to ensure early solution of problems.

The result is that very often local biomedical and clinical research scientists in developing countries require the assistance and technical cooperation of medical scientists from developed countries whose governments are favorably disposed to granting or donating or sponsoring clinical and biomedical research which in the donor's opinion are relevant to the development of the recipient countries. This leads to conflicts regarding priorities in clinical research because developed and donor countries see the problems differently from the developing countries. Donor countries it has been advocated, must focus on global priorities. In the wider context this is very desirable, and in any case priorities are global if, among other things, they are the priorities of a large enough number of countries. Thus global priorities are also very often local priorities.

As soon as we begin to discuss clinical research of any kind we nowadays fall onto the horns of an interesting dilemma. We recognize the need to combine medical research with medical care (i.e. clinical research) while simultaneously worrying about the morality of subjecting our patients to trials of new procedures and drugs.

What does clinical research sponsored by external agencies involve? It can be said to embrace attempts to refine knowledge already gained usually elsewhere, and to be concerned with the application of both old and new technology, procedures and drugs, to find out what we do not

know about the causes, the pathophysiology, and the management and treatment of disease in the recipient, usually developing, country. The technology, procedures and drugs may be tried or on trial, and procedures may be appropriate, inappropriate or frankly unethical. We cannot however avoid clinical research since many problems can only be solved in that context in humans. It is manifestly unwise to introduce new drugs or procedures based solely on trials in animals, for then the humans would become the victims of uncontrolled experiments.

The need for "adequate control" of clinical research implies that there could be situations which need to be controlled, and indeed there are administrative and experimental procedural situations which, if not adequately controlled and supervised, could pose dangers to humans especially infants and children, and the ignorant and trusting. Clinical research is, relatively speaking, in its early stages in the developing countries and this would be an appropriate time to set up guidelines for such research especially when sponsored by external agencies.

Topic of Area of Investigation Must Be Relevant

Generally speaking, external sponsors usually, and recipient countries often, seek to write an agreement on the sort of research to be conducted. The first point therefore that requires control is both administrative and scientific. The topic of area of clinical research to be the subject of external sponsorship must in the first place be relevant to the problems in the recipient country, and the results of investigation must if possible, lead to advances or improvements in the management of that particular problem in that particular developing country specifically, and if possible be applicable in many other developing countries.

There are usually a few medical scientists in recipient countries who are acutely aware of their circumstances and have usually identified problems for solution. Priorities may be difficult to establish, since these problems are almost all of national and economic importance. These clinical scientists are therefore uniquely placed to suggest or initiate appropriate areas of clinical research aimed at solving local problems. The local researchers are aware not only of the problems, but of socio-cultural moderating factors, and those of the population who stand to benefit.

Research that does not take account of local social and cultural practices and circumstances can be sterile, for one should look for collective social benefits as well as benefits to the individual.

Role of Local Counterparts

It is my considered view that in all clinical or other research sponsored by external agencies, it is essential and imperative that there should be local counterparts to any foreign medical scientists who come

to carry out investigations. One obvious advantage of this is that this is a means of increasing the institutional capacities in the host country with regard to trained manpower, and of increasing the experience of local scientists.

In many areas of research great advances have been made and we have reached stages where further clinical scientific probing could raise ethical and moral problems. In advanced countries it would be difficult, because of civic consciousness and their knowledge and awareness of their human rights, to subject groups of people to certain types of experimental procedures and treatments. The temptation must be great to carry out such research in less developed countries where very often people may not be aware of their rights, and where enthusiastic acceptance of help could put them in jeopardy, and where the conditions are such that it is relatively easy to carry out procedures which could be considered unethical.

The temptations could be greatest where the local counterparts in sponsored research are so overloaded with their other duties in patient care, and are concerned with fighting with difficult living conditions, that they are taken away from their clinical research duties, leaving the foreign personnel who are often less bothered by other problems, to do the work alone. It is in such circumstances that problems involving questionable practices or irrelevant investigations at the expense of human comfort have sometimes arisen. In the hospital setting such questionable practices are nowadays less likely, especially where the hospital is a teaching hospital. It is also in such circumstances that investigations, which were not in the original protocols because they were ethically suspect, are often insidiously introduced with the result that findings of investigations may be actually hidden from the local counterparts and only come to light when they subsequently appear as publications.

Adequate Controls

National Committees: What steps can be taken to ensure that the research itself is adequately controlled? It is my view that developing countries should set up National Committees to advise on ethical aspects of clinical research, as well as the design of the investigations, and in this context the experiences of developed countries can provide a useful guide for developing countries. Many clinical scientists in developing countries are aware of steps which are being taken in the advanced countries with regard to certain forms of experimentation in the clinical context. For example, there is a strong body of opinion which would for the moment at least, reject outright any procedures on the living foetus in utero. With the paucity of information about human growth and development in many developing countries, efforts are now being made to acquire this information. It must be tempting to want to know the patterns of growth and development of the human foetus also in the developing

countries. So far the methods being used are probably mainly non-invasive such as by the use of ultrasonic tomography.

It is essential for legislation to be enacted on the type of foetus to be used, and here the attending doctors should help in making these decisions. In many developing countries however difficulties may arise in this context because often the attending doctors are also the research obstetricians.

Monitoring of investigations: The monitoring of actual practices and procedures in clinical research is difficult. However, this is also one of the most sensitive aspects of the problem. Too rigid an adherence to experimental protocol can pose serious problems, and it is therefore necessary to ensure that whenever necessary a protocol is not permitted to lead to human discomfort and the compromise of health. Uninformed and ignorant people who are the subjects of clinical investigations whether outside or inside hospital, need to be protected from the excessive enthusiasm of research clinicians - be they local or foreign. The developing countries often offer "virgin" territory in many experimental areas, and the temptation to exploit these without regard to the consequences has to be controlled. Apart from National Committees therefore, local hospital or other appropriate research monitoring groups should be formed to ensure ethical and moral practices and to protect trusting but ignorant ordinary people.

The interest in traditional healing and medicinal plants has recently led to attempts to investigate these scientifically in developing countries. It is important that in designing clinical trials of these medicinal preparations, enough flexibility is introduced to prevent patients from being denied proven remedies while investigating the alleged virtues of local medicinal plant preparations.

Control of drug trials: One of the most controversial areas in clinical research has been the trial of drugs and other medicinal preparations. Some drug companies in developed countries have from time to time been accused of dumping bad drugs on the developing countries. Whatever the virtues of such accusations the important thing is to ensure that in clinical research the investigations, both local and from sponsoring agencies, should ensure that their experimental design permits them to guarantee the safety and comfort of their patients at all times. Trials of new vaccines and preparations of this kind need to be especially carefully controlled, since very often infants and young children are the subjects of such trials and investigations.

Unethical requests: From time to time, sponsoring agencies or organizations from developed countries are alleged to make requests which create ethical difficulties. For example, requests to be allowed to purchase blood from developing countries to be sold in developed

countries create several problems. Not the least of such problems is that in developing countries it is often extremely difficult to get people to donate blood. However, human nature is such that for money such people may give blood; and one could say that by so doing the sources of blood for hospital care could be drastically affected. It would obviously be unwise to encourage situations of this sort.

Agreements: It is my judgment that all agreements regarding externally sponsored clinical research should be signed by the appropriate competent authority on behalf of scientists and departments. In university medical schools this is usually easy to achieve, since it is university policy. For by this means the institution gets to know the whole situation, and legal and other matters for example financial, are properly covered. The authority can then ensure that no person is in jeopardy.

Publications policy: It is my considered view that in all sponsored research in developing countries agreement ought to be reached on publication policy before the work begins. What is more it is imperative that such publication agreements ought to be strictly adhered to. It has the merit of ensuring that protocols have as far as possible not been varied without the consent of local recipient country clinical scientists. It has the further merit that joint authorships of the publications, as agreed, prevents the possibility of interpretations which do not take into account cultural and social factors.

Legislation

All the controls suggested may be difficult to apply unless they form the basis of suitable legislation, on a national basis. Such legislation enables local scientists to insist on ethical practices and procedures, and prevents all and sundry simply going into a developing country to investigate problems without reference to local problems and personnel.

WHO SPONSORED RESEARCH

J. F. Dunne

The constitution of WHO is couched in the broadest terms since its basic objective is to work for "the attainment by all peoples of the highest possible level of health" and, in fact, its responsibility as an intergovernmental coordinating authority extends across the entire health field. Its full-time secretariat is accountable to Member States through an Executive Board and an annual World Health Assembly of delegates from all participating countries. Year by year new resolutions are adopted by the governing bodies and foci of interest inevitably change but, over the past decade, promotion of research in fields as diverse as health systems development and biological control of disease vectors has become an important and conspicuous function of the Organization.

Fortunately, the need to define priorities and to justify the operation of a highly selective research programme is simplified by the international character of the Organization and its consequent responsibility to complement rather than to compete with nationally administered research programmes. Priority is therefore naturally accorded to basic health issues that are otherwise denied the attention they might justifiably attract and the immediate and self-evident problems of the developing world are an obvious and predominant concern.

Wherever it is performed and whatever function it subserves, medical research tends to be a highly speculative and expensive undertaking. In fact, it is now widely appreciated that until the use of available resources is adequately coordinated and rationalized many of the more pressing health problems of the world are likely to remain refractory. The Organization itself obviously does not have the capacity to offer direct support to more than a very small sample of the projects that call for serious consideration, but a development of major importance has occurred within the past few years. Sensing the need for increased coordination of effort, many governments and other funding agencies have been persuaded to offer generous support to two specialized programmes in which WHO functions as the executive agency. The first, relating to human reproduction, is now well established, while the second - co-sponsored by the United Nations Development Programme and the World Bank, and directed to research and training in tropical disease - has attracted funds in excess of US $25 million in only its third year of operation.

Ideally, sponsorship should exert a catalytic effect, and investment aimed to develop the potential of existing key institutions is regarded as offering the most favourable prospect of ultimate return.

Since, in virtually every instance, the quality of the work performed is as dependent upon the capability of personnel and interchange of ideas as upon provision of financial support, training programmes are integrated as far as possible with research objectives. Moreover, since a wide range of the Organization's activities promote contact between representatives of widely dispersed research centres sharing common interests, they foster an obvious - if immeasurable - degree of informal collaboration. In the past, these contacts have been established almost exclusively with academic and government sponsored research institutions. In recent years, however, the experience and technical resources essential to innovative drug development have become increasingly concentrated in the international pharmaceutical industry, while, at the same time, the containment (not to speak of control) of some diseases endemic in the developing world, and notably malaria, has become precariously balanced. Whereas no one could reasonably deny that the prime objectives of WHO stray away from commercially attractive areas of development having crucial importance to an independent research-based industry, the Organization is committed to exploring ways of bridging this gap and establishing an integrated approach to research in tropical disease that embraces private as well as public interests. Everyone is aware that the pharmaceutical industry cannot act philanthropically, but an effective input from its scientists is of critical importance to progress in tropical medicine and it is perhaps worth reflecting that, in the longer term, no other technical advance would do more to stimulate the flagging world economy than the successful conquest of the endemic communicable diseases.

Nonetheless, the reality is that, although more than 2 000 million US$ is invested each year in drug research, work on the chemotherapy of tropical disease has dwindled to the point of extinction in most companies. Even among those that have maintained an active interest, few allocate as much as 1 percent of their total research and development budgets to relevant projects. It is often said that the scientific leads do not exist to justify expenditure, but progress that has been made over the past twenty years suggests intensified interest would yield a tangible reward. Although filarial infections, leishmaniasis and trypanosomiasis have been starved of attention, leprosy has benefited fortuitously from research on tuberculosis (since rifampicin and clofazimine have appeared just when dapsone resistance threatened to set back treatment of the disease); research into veterinary anthelmintics has yielded some half dozen promising schistosomicides and, of course, each major tropical military campaign provides an ironic but valuable legacy of antimalarials.

Everyone recognizes that the search for new drugs is complex, dauntingly expensive and beset with frustration, but the tantalizing fact is that few new compounds synthesized within the industry are systematically screened for activity against these diseases. If closer

collaboration between the industry and WHO can redress this problem, and provide the stimulus for improving facilities for the clinical testing of promising compounds and for coordinating an expansion of basic research into related technical problems, it is likely to pay handsome dividends.

The general objectives of such a programme are unimpeachable. However, any research including a strong clinical element calls for finely balanced ethical judgements on the use of human subjects. Since ultimate responsibility for the safety of subjects and patients does not reside at international level, WHO has a clear obligation, in its capacity as a sponsor of research, to establish adequate consultative procedures with governments and institutions involved with its programmes. It also needs to consider its own position as a signatory to existing international codes of research practice and the expectation of both donors and benefactors that it will act as a responsible custodian of ethical standards. This calls for an internal system of assessment and, for this reason, the major research divisions within WHO have built up formalized procedures for canvassing expert opinion on strategies required in developing specific programmes and the technical standard of individual proposals. Ethical review of research, however, is regarded as a direct responsibility of the Secretariat and an independent review of all proposals is now undertaken by a Secretariat Committee on Research Involving Human Subjects, which meets under the chairmanship of the Deputy Director-General.

Since projects are performed in communities which are subject to widely differing socio-economic conditions, educational opportunities and cultural influences, and also because nations themselves view ethical issues from quite different perspectives, this task is far from straightforward. Within many developed countries clinical trials of new drugs have been subjected to detailed statutory controls, institutional review committees have become the norm rather than the exception, and critical consideration of the quality and validity of informed consent has largely excluded involvement of children, handicapped patients and many categories of institutionalized individuals in medical research. But where should the balance be struck? As the situation stands, progressive constraints can be applied on medical experimentation in developed countries without immediate and evident prejudice to important public health objectives and in the knowledge that any work that is frustrated by the application of stringent controls might still be undertaken elsewhere. For developing countries the choice is more agonizing. Should, for instance, all research on children be rejected out of hand in regions where infantile diarrhoea, malaria and malnutrition take an appalling premature toll of life? Sceptics might pause to recall the harm that resulted from the indiscriminate use of sulphonamides, chloramphenicol and massive doses of vitamin K in the routine management of neonates in some of the most technically advanced countries

before evidence from systematic surveys and prospective trials was belatedly brought to bear on the associated hazards. Similarly, can the need for individual informed consent be resolved with the development of promising new larvicides to which whole communities rather than individuals may be incidentally exposed during field trials? When such questions arise an element of compromise is inevitable in the decision-making process, and these judgements can only legitimately be taken at local level by competent people aware of and involved with the problems. This is a basic tenet of the Organization's research policy and, whatever the local statutory requirements may be - and notwithstanding its internal and independent review procedure - an assurance is required, before a proposal is funded, that authorisation has been obtained from the competent health authority in the country concerned and that it has been reviewed by an appropriate institutional committee.

Taking the short view these multiple checks appear cumbersome and occasionally frustrating, but experience has shown that the system is practicable. Moreover, in the current healthily-critical climate of opinion a candid, independent assessment of the ethical aspects of research not only protects the rights and welfare of the subjects involved, it also protects the continued existence of research itself.

INFLUENCES OF ETHICAL GUIDANCE COMMITTEES ON MEDICAL RESEARCH - A CRITICAL REAPPRAISAL

Fritz W. Fischer & Heinz Breuer

Problems of medical ethics and ethics in medical research are, insofar as they are reflected by public opinion, symptons of contradictory social tensions and a widespread uneasiness as to progress. Everyone considers progress in the prevention and treatment of illness desirable and necessary. The citizen's attitude towards research is, therefore, positive, in an abstract sense. His or her attitude is also positive in the concrete instance - if a sickness touches him or her personally. This attitude changes, however, when the discussion turns to implementation. Then distrust, reservations, doubts and fears are often articulated. Politicians react to this uneasy public opinion. They appoint committees and organize hearings. Experience shows that in the end there are always the same demands: improvement of the protection of the individual and his rights by more visibility and by mechanisms for more self-regulation by the medical profession, as well as by increased control from outside.

The declarations of Helsinki (1964) and its Tokyo revision (1975) are a reflection of this development. The declaration of Helsinki was an appeal for ethical behaviour in research. In Tokyo the attempt was made to regulate and to control ethical behaviour. This trend has continued - at least in Europe - and has led chiefly to discussions of the strengthening of control mechanisms already in existence.

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Discussions of ethics that are underway in the Federal Republic of Germany are being conducted against a specific background. This background has been provided by history. Here the non-German thinks of the events between 1933 and 1945 which led directly to the Nuremberg Code (1947) and essentially influenced the Declaration of Helsinki (1964). However, the German observer sees the background as being more differentiated. He includes the years before 1933, a period governed by a high ethical tradition. He also thinks of those physicians and scientists who continued the tradition under the 1933 - 1945 dictatorship.

Wagner(1) has recently pointed out that as early as in 1931 the then Minister of the Interior issued guidelines for new forms of medical

1. Wagner, H.-J. Heilversuche und Experiment aus richtsmedizinischer Sicht. Beiträge zur gerichtlichen Medizin, XXXIII, 24 - 32, 1975.

treatment and for carrying out scientific experiments with humans. These guidelines were published in the "Reichsgesundheitsblatt" (National Health Gazette). The guidelines are clearer, more concrete and more far-reaching than both the Nuremberg Code and the Helsinki recommendations.

Some of the most important guidelines may be reported here in brief:

1. Every new form of treatment must in its justification and its implementation be in harmony with the principles of medical ethics and the rules of medical art and science.

This question must always be carefully examined and weighed: Are the ill effects that might be caused in an appropriate relationship to the expected benefit?

A new kind of treatment may only be undertaken if previously, as far as possible, it has been tested in experiments with animals.

2. A new kind of treatment may only be undertaken if the person in question, or his legal representative, after previous pertinent instruction has unequivocally declared his agreement with the undertaking.

3. Medical ethics reject any exploitation of social disadvantage in reaching a decision about a new kind of treatment.

4. In clinics, including those for outpatients, hospitals or other institutions for the treatment or care of the ill, a new treatment may only be carried out by the senior physician himself or by another physician on the senior doctor's express order and on his full responsibility.

5. About every new kind of treatment there is to be a record, showing the purpose of the measure, the reason for it and the way of carrying it out.

For purely scientific experiments without special benefit for the individual undergoing tests the following additional guidelines were valid:

6. i No experiment may be undertaken without the existence of an agreement.

ii No experiment on human beings may be made if instead it can be conducted on animals. An experiment with a person or persons may only be undertaken if first there has been procurement of all available data regarding

laboratory tests and experiments with animals. The requirement rules out any redundant or nonessential experiment on humans.

iii Experiments with children or persons under 18 years of age are inadmissible if they would even only slightly endanger the child or the young person.

iv Experiments with dying persons are incompatible with the principle of medical ethics and for that reason inadmissible.

These guidelines were valid up to 1945. They could not, of course, prevent all that happened in Germany after 1933. Even today the possibility of such aberrant developments cannot be automatically excluded everywhere.

In the years after World War II there was a strong movement to return to ethical traditions in Germany. The generation that was studying in those first postwar years occupies today the leading clinical and scientific positions in Germany. Within the professional scientific associations it is representatives of this generation who decide which research should receive financial support. The high degree of this generation's sensitivity towards ethical problems has been preserved up to the present day.

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The German legal conception pertaining to medical ethics is based on articles 1 and 5 of the Constitution and on general legal norms. Details are regulated by professional rules of the Chambers of Physicians of the states. Laws, professional rules or other written regulations or procedure in matters of clinical research did not exist until recently. This restraint, practiced for three decades stemmed from the conviction that in civil and penal law there existed sufficient stipulations with which experiments with humans would need to be in harmony.

On 1 January 1978 a new drug law (Law for the Reorganization of Pharmaceutical Legislation) came into force. In paragraphs 40 and 41, it contains detailed rules for the protection of humans in clinical tests of pharmaceuticals. Many recommendations of the declarations of Helsinki and its Tokyo revision have entered into the new law: limitation of risk, informed consent, direction of the investigation by an experienced physician, and legal competence of the test persons. New and indicative is a key regulation pertaining to insurance law (§ 40, paragraph 1, No. 8 along with § 40, paragraph 3); according to this, insurance protection will be granted in case of harm even if there has been no negligence ("accidental harm").

It may be expected that the principles formulated in this drug law in the future will also influence the legal norms in other fields of clinical research. The Tokyo recommendation of introducing controls by ethical review committees has not been embodied in the present version of the drug law.

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The Deutsche Forschungsgemeinschaft (DFG), which is the central research promoting organization in Germany, has managed without the existence of ethical review committees since its foundation. Every applicant is asked to present his test programme in detail and to comment on ethical and legal aspects. Every application is submitted to several evaluating experts.

In this connection it may be mentioned that the DFG has its evaluating experts elected for four years each by the scientific community in direct secret, voting; and apart from the elected evaluating experts the DFG can hear as an evaluating expert any qualified scientist. This arrangement results in a supraregional and independent system of evaluating experts with the highest possible degree of specialized knowledge.

All evaluating experts are expressly asked to take a position in regard not only to the scientific but also the ethical and legal aspects of research projects. Applications that raise ethical problems are always negotiated orally in the main committee that decides about the approval and financing of applications. If even the slightest doubts as to the ethical admissibility of a planned project remain during the discussion, then support is rejected. Grants can be linked with conditions. Not rarely the condition is set that a supervisor of the applicant takes full responsibility for tests with humans, along with the selection of test persons and their enlightenment as to the project.

In 1973, the DFG asked that in a number of special Research Areas(2), local ethical review committees be established in order to

2. Special Research Areas at selected universities involve institutionalized grouping of researchers of different disciplines for carrying out long-term coordinated work in a specific field of research. The program covers all disciplines, but so far emphasis is placed on medicine, the natural sciences and technology.

gain experience with this instrument of control. As of now the advantages and disadvantages of local committees can be assayed only in part.

An advantage of local examinations is doubtlessly that there the clinical experience of the researcher, for example in practicing invasive methods, his special working conditions and certain technical details of an experiment, can be better judged than by an evaluating expert at a distance.

A decisive disadvantage stems from the strong specialization of clinical research. At a given location, often only the project leader himself can really judge the risk/benefit ratio of a planned experiment. The members of a local committee, by reason of the subject, are often not competent to evaluate a risk. A further problem results from the local personal relations and dependencies that are bound to exist everywhere. Not least for this reason, some special research areas have declined to establish local committees. The doubts thus expressed stem partly from the experience that local committees in some individual cases are inclined towards permissive decisions.

For the above-mentioned reasons, the DFG concentrates on keeping its own well-functioning review system operative. The respective supraregional evaluating reports may be supplemented by recommendations of local committees, but the local comments may by no means obviate the evaluating reports. So the DFG repeatedly points out to its evaluating experts that the existence of local committees does not release the evaluators from their duty to critically examine the ethical and legal admissibility of experimental programmes. The DFG expressly reserves the right to reject research projects for ethical reasons alone, even if they have been approved by local committees.

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Clinical research in the Federal Republic of Germany is financed not only by research-promoting organizations but also from funds of the clinics themselves. In the latter case, no external procedure for obtaining expert evaluations, as it has been described for the DFG, exists. Here an examination of clinical research projects by local committees appears to be better than no examination a all. Not least for this reason, the DFG has asked the Federal Chamber of Physicians (Bundesärztekammer) to work on the establishment of local committees. The Bundesärztekammer meanwhile has worked out a procedure. The committees are to restrict themselves to the evaluation of ethical and legal aspects of research projects; they are expected to advise and not to decide.

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Neither the DFG nor the Bundesärztekammer is at present thinking of establishing a National Advisory Board. Important problems that can be resolved by a general rule, as for instance examination of pharmaceuticals and X-ray protection have recently been regulated by laws and ordinances. Most ethical problems do not at all lend themselves to consideration on general principles, but require, instead, individual discussion and decision.

* * *

In the preceding paragraphs we have dealt largely with control mechanisms. A thoughtful consideration of the ethical aspects of medical research also extends, however, into quite other dimensions. For instance, there is the question of what degree of risk a society considers it can ask of its members. For comparison, other risks, for instance in industrial work or in sports, would have to be considered. Everybody should be free, at the same risk, to contribute to the progress of science.

A basic motive of authors of all pharmaceutical laws and all orders on procedure in matters of ethics has been and is the protection of children and other minorities. While this endeavour always finds broad public agreement, it has, however, not only positive consequences. The restrictions at the same time result in our knowing particularly little about many therapies in pediatrics and in pregnancy. These therapies are thereby burdened by special uncertainties and a comparably high rate of unexpected incidents. The strong emphasis on individual protection in human experiments reduces individual dangers but brings about, at the same time, new collective dangers. It can be unethical to examine a therapy scientifically; but it can also be unethical to apply a scientifically unexamined therapy. The researcher in his day-to-day practice is confronted here by contradictions that are hard to resolve.

Also unconsidered in all laws and procedural regulations are the wishes of the ill and the motives of healthy volunteers. In the latter group, financial and idealistic motives may be intertwined; an additional factor is, however, often the pleasure of taking a calculated risk.

The tension between ethics and science can in its last analysis be resolved neither by declarations nor by control mechanisms. This is similarly true for the tension between science and medical practice, or that between the training of students and the well-founded interests of the ill. In the guidelines of 1931, mentioned above, the conclusion states: "As early as in academic instruction there shall be reference at every suitable opportunity to the special duties that are incumbent on a physician in undertaking a new treatment or a scientific experiment, as well as when publishing its results."

With that, what is probably the most crucial point emerges: namely, the prevention of unethical behaviour. We should talk more often again with the younger generation of physicians and researchers about ethics and ethical behaviour - and less about rules for checking on whether the newcomers do in fact conduct themselves ethically.

MAJOR PRIORITIES

A.A. Sampaio

In the disturbed world in which we are presently living, it becomes necessary to have a clear insight to enable us to take in good time the necessary measures to prevent the catastrophe which is beginning to take shape. For thousands of years there was a very restricted number of privileged persons. Not only the mentality of the epoch, but also the lack of all kinds of necessary means made it impossible to alter this state of affairs.

Scientific discoveries, and consequent technological advances observed in the last century and chiefly in our century, have created hitherto unimaginable possibilities from which, unfortunately the largest part of mankind does not benefit.

Great revolutionary movements, such as the French and Russian revolutions, have created for mankind expectations that cannot be ignored by scientists, who should feel a high sense of responsibility to the society to which they belong. If researchers are to continue to deserve the credit to which their profession and talent entitle them, it is necessary that preference be given to the study of the major problems of mankind.

Through modern means of communication it is easy to know, almost immediately, what is happening in the remotest parts of the world and, thus, it will never be possible to maintain peace if we disregard the poverty and misery under which the largest part of mankind is living. The researchers' contribution is of paramount importance for the achievement of a new socio-economic order that should be the main objective of all nations.

In the health field we witness the spectacular progress achieved in this century, permitting the control of a great number of diseases; but we observe, at the same time, the progressive increase of exigencies of the populations, which render health services more expensive every day and, therefore, beyond the resources of the majority of nations.

Present knowledge - if duly applied - would permit the control or eradication of communicable diseases which, until the end of the XIXth century. were the largest cause of morbidity and mortality of man. However, control of these diseases uncovers others of a different nature whose solution is difficult - such as cardio-vascular diseases, cancer, mental diseases and accidents due to factors of various nature - the mechanism of which we still do not know sufficiently well to institute an efficient prophylaxis.

In view of the present complicated situation, it seems to us that the ethical duty of researchers is to give priority to those problems that have the largest impact on the health of communities, and usually vary from country to country. It is necessary to create a new mentality, based on the help of rich countries to poor countries, tendered with a spirit of solidarity, and not with self-interest in mind.

Problems differ from region to region, from country to country and even within the same country. There are however some problems which interest the whole world and are indeed worthy of the highest priority. In developed countries, the more important problems are chronic-degenerative diseases, mental diseases and accidents and, in the developing countries there are also the communicable diseases. However, the chronic-degenerative diseases will become as important as those observed in the developed countries and all research in such a field will benefit - in the long term - those countries still in course of development.

For obvious reasons, maternal and child health should deserve priority attention from researchers, as part of the primary health care that WHO considers as fundamental for health and peace. I cannot help emphasizing, in this meeting, the priority importance of family planning in maternal and child health, but also for the control of population. This subject raises problems of a social, religious, economical and ethical order and, I therefore feel that it is opportune that this meeting should warn the world without sophism of the dangers of overpopulation Medical science largely contributed to the explosive expansion of the world population, and researchers should therefore contribute towards the solution of this great problem.

It has been observed in many countries throughout the world that the population increases at a rate higher than economic development and, therefore, family planning is a health measure of fundamental importance to prevent the birth of children with very little possibility of having an acceptable quality of life. It is obvious that birth planning results in an aging population, thus creating the problem of elderly people, which involves multiple facets for which no suitable solution has yet been found. The problem of aging offers a vast field of investigation not only of benefit today to a high percentage of the population in developed countries, but also in the future to the non-developed countries.

Another problem that deserves the attention of scientists is the constantly increased cost of health services, which greatly concerns public health administrations and governments in the whole world. I feel certain that by well planned and well managed health services a great deal of money could be saved; thus, a vast field of investigation - which so far has not received due attention - is now opened in this field.

Concluding my intervention, I wish to stress the importance of scientists in the resolution of problems that are presently tormenting mankind. However, while the freedom of scientists should not be limited, their research should be concentrated on problems of social interest. The scientist should, in addition to his specific training, have a sociological preparation supplying him with inspiration and motive in the choice of his themes of research.

Daoud: We have been hopefully referred to as the developing countries in the hope that we'll be developed. But while that occurs, we are facing urgent problems regarding not only the funding of research projects in our different problems but more important than that finding interested parties 'either industry or other countries or WHO that can fund the elaboration of new drugs for diseases which are prevalent in our countries and for which it was made very clear by industry that, because it is not worthwhile, they are no longer interested. So where are we going to go from there? Well, if we go to our national resources, they are very limited and they are only enough perhaps to fund some sort of basic field research like surveys of prevalence of a certain disease - what sort of ages it affects, what sort of areas, and morbidity and so on. Which leaves us with a problem and not a solution.

Well, if we get on to friendly countries, this has to be tied with politics, with international politics, with likes and dislikes, with other things which do not come straight away into medicine as such. Where do we go from there?

Well, we look to WHO. WHO can help us in funding problems perhaps in doing some preliminary research, but the funds so far available are not enough when spread over the six diseases and other diseases over the wide needing countries. To have any developmental research, especially in vaccines and in drugs where we need very much help, where do we go from there?

I honestly don't know. We know the problems, we can define them. It is too early for us to bother with the finer points, to put it bluntly, of ethical or unethical conduct. I think we haven't got interested enough people, because even industry now will be interested in such diseases that affect the individual, perhaps in tranquillizers and other things which the developed countries need. And we are not interested in that and we will not be a market for clinical trials of tranquillizers. We don't need tranquillizers. New emergence, for example, of things like new resistant organisms in malaria. No drug for onchocerciasis. No sure drugs for kala-azar. No new developed drugs for the thousand and one helminthic diseases in our countries. The need for the development of new vaccines for diseases which are existing because there is no other economical way of dealing with our problems. I'm also coming here because so far we have no ethical review committees. The problem is left completely to the discretion of the research worker. We think that he's ethically conscious enough to try as far as possible, when an opportunity of trial of vaccine or drugs comes, to make sure that it is not obviously unethical.

We want to try from your deliberations to take back home the general viewpoints of all the countries to try to develop our own ethical points with a big latitude to invite people from different countries to come to us with a goodwill to try to help us in solving our problems. Thank you very much.

Browne: Thank you, thank you very much, Mr. Chairman. Having worked in Africa for thirty years and luckily concerned with drug trials in leprosy and other diseases, I wish to say how much I've appreciated the interventions, particularly of Dr. Phillips and Dr. Dunne and Dr. Daoud this morning. These are extremely practical issues, not only in the matter of the trials of new drugs and the application of new investigative techniques, but also in the ethical implications in the developing countries of these new procedures. And one of our great opportunities in this forum today, Mr. Chairman, I think, is to encourage young scientists in the developing countries to adopt this attitude of query, of investigation, of inquiry into the application of what is now available in the privileged affluent countries of the Western World, and to encourage these young scientists, not only in the technical, mechanical, scientific principles, but also in the underlying ethical considerations that have meant so much to us in Western medicine in the past.

It is true that there is a terrific potential market, and here I address myself to the pharmaceutical companies represented here. We think in terms of malaria, schistosomiasis, onchocerciasis, trypanosomiasis, leishmaniasis, leprosy, tuberculosis, and these are diseases affecting hundreds of millions, even thousands of millions, of the population of our one world. Surely here's a terrific challenge to the pharmaceutical companies. I know the argument often is: the World Health Organization, UNICEF, voluntary agencies and governments are our potential customers, they will not pay much for the drugs for which they wish a large-scale use. But we think in terms of human need, there is a terrific challenge.

Another point, too. Very often, as I have observed in working in a developing country, an expatriate investigator is sometimes like an extremely clumsy bull in a very delicate, national china shop. And he will do irreparable damage unless he treads very carefully with great respect to the cultural attitude of the people. They are not passive material for his investigation. They are human beings with their own cultural history to which we do well to pay due respect. Hitherto, it has been mainly a question of mutual trust, mutual respect and integrity. But in the future, we shall have to surround this mutual trust and integrity with standards to be applied by governments and by research organizations, unless we are to commit irretrievable harm to many populations.

And so I would utter a plea, not only for the terrific opportunity for research into these diseases, but for the application of accepted moral and ethical principles in our conduct of research. Thank you very much, Mr. Chairman.

Hurley, T: In our first session, Dr. Gellhorn indicated that he hoped that from this session we would derive some insight into the effect of source of funds on ethics and medical research. And while agreeing very heartily with what has been said, I think it would be a shame if this session did not address itself briefly to the influence which national funding can have on medical research and ethics in medical research. And I'd therefore like to take your time briefly to consider this aspect.

Next, I would like to say that I think it arose from the first session that medical experimentation is essentially medical practice. And in the final analysis, responsibility lies with the investigator. It is not possible for this responsibility to be shifted either to committees or in informed consent to the subject or patient. Having said that, I think it would be useful to look in practice at the guidelines as they've been discussed and agreed to and how at a national level these are implemented and what affect national funding can have on the implementation of these.

These guidelines, I believe, are not only accepted and imposed on the individual investigator, but they are accepted at all levels in the community and must be accepted at all levels in the community. Our experience in Australia, I think, has perhaps been relevant in this regard. We assumed that because medical research societies accept these guidelines and that individual medical researchers accept them, that they will be accepted by the community.

I think that it is our responsibility, both as individuals and as nationally representative research bodies, to draw the attention of our community to these guidelines and the importance of adhering to them. We had occasion to do this in Australia almost by chance when we had a problem in relation to the ethics of a particular project which related to cannabis research and we convened a group of representative people in the community, legal people, representatives from students, from trade unions, from all sections of the community and put this problem to them. They, in turn reviewed the Declaration of Helsinki in relation to the existing guidelines in the community and improved on them in that regard. I think that this was a useful experience, both from the point of view from the research community and also the community at large.

It's also essential, and this came out in the discussion earlier, that any review of the ethics of medical research should be done prospectively. This also, we have found in Australia, to be most appropriately done at the time at which research funding is concerned and it

is done by the peers who visit and review projects which are put to them.

It's all very well to talk about the legal restraints which may exercise the direction of medical research, but in the final analysis often a more effective restraint is the absence of funding or the presence of funding. And I think that this is a clear responsibility of the national funding body. The experience again in Australia has been that projects may or may not be supported on the grounds of scientific merit, but they also on occasion may not be supported in relation to their ethical content.

So I think, in spite of the fact that the final responsibility lies with the individual investigator, the national body which supports medical research financially also has its responsibility in enforcing the guidelines which are adopted.

Oluwasanmi: If you go through some of the papers on trials in Africa, it is interesting to see that the trial officer goes around to get the consent for the trial by a chief or something of that nature. I think the time is long past for thinking of those people as being the custodians of the lives of the rest of the population. And anybody who does that really wants to escape the real issue of facing the population and trying to get what I will call a genuine consent. We are all debating the question of the rights of man, that everybody has a right to life and to the preservation of his limbs, I don't see any reason why at this stage anybody should still think of getting consent from tribal chiefs, but this still happens.

The other thing is, of course, that governments are created for the mutual protection of people who are in the geographical area of consent. And I think this is where a governmental control system or a governmental clearing house system should be set up in all developing countries, for drugs coming in and for trials of this nature, for trials of drugs inside the country. It is interesting that some of us who are trained overseas have used some drugs for quite some time while in those countries and then many, many years later they are now reintroduced as beautiful new drugs into the developing countries, when all the problems associated with these drugs have already been known, and some of them are even now taken off the market. And I'm speaking in this respect to Dr. Weatherall from industry. I'm not making any direct accusation against you, sir, you are my teacher. But I'm just saying that sometimes industry, when they put in the little write-ups with the drugs, leave out certain of the complications that they have already observed after a long usage in their own area. I suppose the whole idea is to make profits and this, as far as some of us are concerned, is not really good enough for the developing countries.

Now, talking about foreign-sponsored research, again I feel that what is good for the goose is also good for the gander. This is an area whereby when anybody who is going to do a research in a developing country should submit his protocol to his own country of origin, his own country committee or whatever kind of committee of ethics in his own environment before he takes it across. I think such protocols could have double vetting, both at the source and at the place where it is going to be used. This is why again I advocate that the developing countries should have a body that should be able to do some vetting of some of these trials. And, in Africa particularly, there's a new craze for drugs of all types. People are getting more aware of the use of what I'll call Western Medicine. And then they are getting addicted to tablets and injections, particularly the latter. And it is very important that people don't just come and try all sorts of things without a local clearance as well as clearance from their own country. Because by giving this double clearance, then one can feel happy that what is done then is at least within ethical limits.

And finally, on the question of collaboration, no externally-sponsored research program should exist without local collaboration. The same thing applies to WHO-sponsored programs. Local collaboration should be part and parcel of every trial of human experimentation in whatever form. One for the protection of the people and two, as Professor Phillips pointed out, for the development of local talents and techniques in this area.

Now, I will finally appeal to industry to look into the possibility of even training local people from the developing countries, particularly in areas where the drugs that are being used or are going to be used in the management of diseases that are prevalent in those areas, so that they can at least acquire the expertise in the lab, they can learn about the manufacture of the drug itself, and maybe in cooperation with this industry set up local plants that make or modify the drugs as required.

Riis: I want to comment on a point raised by Dr. Breuer. He pointed correctly to the vast area of medical ethics involved in everyday, non-trial clinical practice campaigns.etc. And he pointed out that we should be interested as much as in experimental ethics, in the ethics of this everyday, clinical work. And he is right because public opinion considers a doctor working in daily clinical situations as much more ethical than the doctor involved in clinical trials. And I think we, the medical profession, have ourselves emphasized this illusion by pointing to the fact that doctors usually know what they do and their decisions rest on a sound scientific basis. And everyone here knows that there's a lot of things we do not know and in a way it's unethical to go on treating patients without asking questions.

In the public discussion of these facts, one sometimes hears the point of view that those two complicated ethical aspects in a way neutralize each other by a strange and metaphysic phenomenon. Of course, they do not. We have to inform the public opinion that we need to raise the standard of ethics in our daily clinical work. And the only way we can do this is to invest interest in controlled studies of diagnostics, therapeutics and prevention.

So the answer to this dual question - ethics on the experimental side, ethics on the daily work side - is not either/or, but both, and the common denominator is the patient, our fellow man, whose interest in high ethics would be precisely the same whether he's situated on the patient's side in a non-trial situation or as a participant in a controlled study.

Violaki: I have just one question that perhaps Dr. Weatherall could answer. When, in his presentation, he describes the duties of the pharmaceutical industry, he mentioned that the pharmaceutical industry for each employee must provide reward in employment both financially and in the less tangible way which is sometimes called job satisfaction. On the other hand, Mr. Williams under Session I when he presented this morning his contribution, said that in addition certain studies are carried out within pharmaceutical companies on members of their staff, where there is no coverage by ethical committees. May I have the views of Dr. Weatherall on this subject?

Weatherall: I suppose that it's inevitable that anybody who is tarred with the brush of industry becomes the target for brickbats. And I'm sure this gathering is much too sensible to think that the hurling of brickbats is the only necessary procedure to make industry come to its senses and behave as you would wish it to.

I must stress one point, and that is to remind you how much the pharmaceutical industry has contributed in the field of tropical medicine, and is continuing to contribute in the field of tropical medicine in the sense that, for instance, of our own research activities a still sizable quantity is going into such matters as chemotherapy of the major tropical diseases, of contracts with WHO, of collaboration and of work in this field. I feel I'm sitting slightly pretty in that my own company is, as you know, owned by a private trust and every penny of profits we make is distributed by that trust in the interests of medical research. And there must be many people in this room who in one way or another appreciate what Wellcome has contributed to social benefit out of the profits which are always regarded as in some way disreputable.

However, of the specific points that were made, one point that I would like to make is that we do spend, and other firms in the industry also spend, substantial funds on training both for technical services in

relation to diagnosis and so on in Third-World countries, and this is an activity which we continue, which is associated with help to the proper use of drugs - I didn't come here with the figures in my pocket - but this is something which we do, and wish to do, and will continue to do. I also very strongly indeed deprecate a suggestion made by somebody that industry said that research in tropical or Third-World diseases was not worthwhile. All I said was that we had to balance our books. And that the more restrictions and restraints that arise, the more difficult it is to have the spare reserves to do those services for the Third World which we all wish to do and consider infinitely worthwhile in human terms.

On the question of ethics and volunteers within the industry, I can't speak for the practices of other companies, I can say only that within our own company, first, I come back to my original point that I made about duty and responsibility. We don't have an ethical committee formally labelled by that name for our in-house studies. We do recruit volunteers on the strict understanding that they are in no way ever invited to volunteer but only that notices are put up saying that if people wish to volunteer they should. As a person who habitually volunteers for experiments myself, I should most bitterly resent any body that set itself up and told me that I hadn't got a right to volunteer if I wanted to. And we take the utmost precautions that our volunteers are in no way under constraint, nor are those who do not volunteer in any way under constraint. And, of course, as far as the practices go, looking at it from a quite pragmatic point of view, just because the industry is such a target for brickbats, there is no organization that has to be more careful about what it does in any in-house studies, because if anything goes wrong, a glare of publicity and a complaint about what's happened will probably be much sharper than would ever happen in a hospital and certainly than would ever happen in a remote community or even in a general practice in a First-World country.

Dunne: Just in the interest of détente, I don't think Dr. Weatherall was aiming at me when I said that research on tropical medicine was not worthwhile. The fact is though that in many companies it's not undertaken these days, which is sad. On the other hand, I'm sure that everybody in this room does understand and appreciate the tremendous help that the Wellcome Foundation over the years has given and I just want to make the point that we can't look anywhere else for drugs except to the pharmaceutical industries, so we've got to find some symbiosis, and brickbats are just out of the question.

Adadevoh: I think that Dr. Weatherall did make it clear to us how expensive the nature of drug development is, and within this concept of the overall expenditure I think he did mention that ninety percent of research expenditure is for R and D. I stress this because too often we are all blaming the industry for not doing this or doing that,

without thinking how much in fact they do invest in the development of one particular drug.

He has stressed also the economic interests, which of course apply to the public sector, to the investors and also to the employees. Each one of them has economic interest in any drug development. Whereas the complexity of the interests, when you consider each group against the other, the question of risk-taking in drug development - and I think his five-year rule which has passed on from his teaching days to his industrial days must be borne in mind when we are criticising or trying to assess situations with new drugs.

Whether industry should do or not do research and what obligations they have, is the vexing problem which fortunately enough has met with the interests of a few organizations, principally the World Health Organization and also the National Institutes of Health. For those of you who know about this, I apologize for just reminding you again. These are two organizations that have become very involved in collaborative effort in drug development with industry. And are funding industry to do this job. So here we see an aspect of a new dimension in trying to encourage industry, waiving the profitability to the industry at a low level in either screening drugs that are on the shelf developed for some other sources but may be useful for the variety of conditions which Dr. Daoud has referred to. So we need to note this, and here the CIOMS can perhaps take up a vanguard role. How to do it, I think, it is a matter which can be discussed in-house.

Dr. Phillips did focus specifically on the need for writing-in adequate training for locals, the question of counterparts, the issue of publication. And I must stress that that has been a vexing problem. Publications which arise from research without paying attention to development of research reporting, even by the counterparts and the locals in an environment where the research has been done. Again this is an aspect in which the CIOMS can play a role.

Dr. Dunne's contribution, I would like to see as an example of what an international organization could do in trying to meet the needs of some of the problems that we have been discussing. He's described to you the two major programs: the tropical disease program which is in its seventh year. Between the two of them, I think there are now between US$ 40 - 45 million. And the in-house committee which he is the is secretary to looks at the global issue of ethics and they do consider this against the international assessment by committees where relevant. And I think that this is a very good example of what an international organization could do.

The various other speakers, I think, did focus on various aspects of matters which are relevant. Dr. Stanley Browne shared his experience

with us from his work in developing countries and is advocating a much more aggressive involvement of young scientists and adoption of an attitude of inquiry. All of which I think could be handled within a national committee.

Dr. Hurley, we are grateful to him for giving us an example of what happens nationally and for also focusing attention on the national responsibility, particularly with regard to funds.

Professor Oluwasanmi's contribution reminded us of a number of problems which Dr. Weatherall has made comments about: the need for industry to train people is in fact within the concept of the collaboration being undertaken by WHO, and hopefully by the NIH - I'm not familiar with that. But I do know the WHO collaboration includes training for young scientists from developing countries in the industries themselves.

We were reminded by Dr. Gellhorn to focus attention on the impact of source of funding as it may affect ethical criteria. And I believe this organization, the CIOMS, expects us to narrow down on what are the salient issues. Considering most of what I have listened to from here and from there, there are three summary points for consideration. The first of which is the need for this national committee, which is urgently needed, and for which national responsibilities must be clearly seen both in the organization and in the funding. The attitude of inquiry and this mutual trust which has similarly been the basis for collaboration should be seen against the need for establishing priorities, guidelines, rules and regulations, training schemes, etc. And I think here the CIOMS is already aware of their need to do this. I do know that the CIOMS is very anxious to get national committees established in this form. And it may well be that this is one way of meeting the needs of outside sources of funding against ethical issues of local needs.

The second summary point for consideration is the issue of institutionalized review committees of the nature of which WHO operates right now. The main question is whether this can be done by other international agencies. And I think it is worthwhile on your behalf if CIOMS looks into this. The issue was raised by Professor Oluwasanmi that it might be useful to vet research at source of origin, that is the origin of the overseas scientists where the funds are coming from outside. Much of this would be desirable. I think the onus would still have to rest on the national committee. I say this because there are going to be problems - I give the example of depot privera - where if now you wanted to support any research in that regard from the US, you would not succeed in getting US approval. On the other hand, the home country may wish to have this drug for use. So there's a need for flexibility but not withstanding that we can recognize the need for the national committee and and the second need for an institutionalized review committee of the

nature of which WHO runs at the moment. And, of course, ask ourselves what role the CIOMS can play in promoting this kind of activity.

The third summary point is the whole question of the industry in terms of clinical drug development. We heard from a number of contributors, and I think also stressed by Dr. Stanley Browne from his concern from the tropical parts of the world - Dr. Daoud also stressed it -- the issue of drug developments. I think here the problems are such that are being handled at the moment, as I did say, by WHO and NIH in collaboration between industry and research organizations. There is no doubt a need for further development of this kind of approach, and whatever CIOMS can do I think also needs consideration here, particularly for developing drugs of relevance to worldwide disease. The fact that an industry does not concern itself with a drug which you and I may consider important for our own country is something which we all recognize but we also should recognize why they have not considered it important. And I think the example of WHO and the example of NIH - I'll mention those two that I'm familiar with - could be used as a platform from which CIOMS could assist in developing some strategy for dealing with issues of this nature. We must not forget the economic interests of investors, the economic interest of employers which most often times, you know, has precedence of an economic interest of the public.

THIRD SESSION

ETHICAL REVIEW COMMITTEES

Moderator: Sir Douglas Black

COMPOSITION, AUTHORITY AND INFLUENCE OF ETHICAL REVIEW COMMITTEES

Povl Riis

The principle behind the setting up of ethical review committees is the well known one that a second and independent look is a reliable way of reducing or eliminating bias in individuals. In other words the review committees rest on the principle of so-called independent judgement. In Denmark the adoption by the World Medical Association of Helsinki Declaration II in October 1975 almost immediately initiated the preparation of setting up scientific ethical committees.

The preparatory work took place during 1976 and, in 1977, the first step had been taken by the Danish Medical Association. The following groups participated in the work: Danish Medical Research Council, the universities of Denmark, the Danish Odontological Association, the Central Health Administration of Denmark, the Association of Danish Apothecaries, the Association of Danish Pharmaceutical Industries, the Association of the Danish Agencies of Pharmaceutical Import, the Danish Central Society for Medical Sciences, the Danish private hospitals, the Ethical Council of the Danish Medical Association, the Committee for Postgraduate Education of the Danish Medical Association, the Association of Danish Counties, besides representatives from Danish Society for Research in General Practice, psychiatric research groups and the Host Organization: the Danish Medical Association. Observers from the Norwegian Medical Association were invited.

The preparatory group had as its base the Helsinki Declaration II, and introduced its work by stating the important differences between version II and version I:

1. The declaration now comprises not only medical research but biomedical research in its broadest sense, in other words all research that includes man as a research object.

2. Besides treatment, version II comprises diagnostics and prevention.

3. It is a "must" that every research project on man be based on an extensive research protocol.

4. It is explicitly emphasized that the publication of biomedical research results with man as a research object always must include reporting on the ethical aspects of the project.

5. The patients' right freely to decide if they will enter a research project or not is strongly underlined.

6. Spouses now are able to act as a guardian in cases when patients are not able themselves to accept participation or evaluate the scope of informed consent dealing with biomedical experiments. In some cases spouses act as guardians where time does not permit more formal procedures.

7. The use of control groups is explicitly mentioned as a methodological necessity, with strong emphasis on the main rule that patients in control groups always have to be secured the best proven diagnostic or therapeutic standard known at the time of experiment.

8. The possibility of suspending informed consent is linked to the demand that the reasons for such a suspension have to be stated in the research protocol and that the interests of the patient must be the starting point of such possible suspension.

9. Version II of the Helsinki Declaration has solved the illogical statement of version I that clinical research could be accepted if the result was beneficial to the patient. In version II, it is accepted that research projects based on lack of knowledge could never secure a positive outcome. In other words all original scientific activity includes a certain amount of unpredictability.

10. In version II. it is stressed that the scientist. besides protecting the rights of the patient and the healthy research subject, is obliged to consider the protection of laboratory animals and the ecological system.

11. One of the most important innovations of version II is the demand (1. 2) that the "experimental protocol" "should be transmitted to a specially appointed independent committee for consideration, comment and guidance".

In its work the Danish preparatory group made the following definitions:

By biomedical research it understood all systematic collection of data with man as the research object. In this way the field covers not only the basic scientific project of medicine and clinical science but also social medical and epidemiological research. Odontology and pharmacy were included in the Danish work because the national research policy and research administrative structure comprise all three disciplines.

By generally accepted scientific principles was understood the consensus present internationally concerning principles on planning, carrying through and interpretation of biomedical projects. The most obvious consensus is expressed indirectly by the editorial policies followed by a majority of international publications and scientific societies.

A person is considered scientifically qualified if he/she has received a theoretical education besides practical experience, within the field of biomedical science, expressed in his or her earlier scientific publications.

A person is considered medically qualified if he/she possesses such an education and experience within the scope of the project's clinical aspects - or within the scope of a given basic scientific experiment's possible side effects - that he/she would be qualified to prevent, diagnose or treat morbid states and/or refer such patients or research subjects to relevant clinical institutions.

By a dependent relationship is understood such circumstances that it is to be feared that research subjects' or patients' decisions on participation in a given project could be influenced. Such duress might stem from economical dependency, educational dependency, fear of losing access to specific methods of treatment, etc.

By an experimental protocol is understood a comprehensive collection of all documents describing a given scientific project. The following items have to be included: the original idea of the project, the approach, the practical design, methods of observation, statistical methods, ethical aspects, information sheets for patients and besides, all formulas used.

It was important for the preparatory group to stress the sphere of application, when creating a system of Danish scientific ethical committees. Besides the three disciplines human medicine, odontology and pharmacy it had to comprise all university institutions, all clinical departments whether university or non-university, all private hospitals and laboratories, all general practitioners, all high schools of dentistry, the public odontological service, the general practising dentists, the drug industry and other biomedical industries.

The Danish system is founded on the so-called self-declaration in which the responsible leader of the project declares his/her analysis of the project in relation to ethical aspects, taking as a starting point version II of the Helsinki Declaration.

The approved Danish structure of scientific ethical committees comprises two different levels: regional scientific ethical committees

and a central scientific ethical committee. Every research protocol including man as research object, has to comprise a self-declaration and to be forwarded to a regional scientific ethical committee. The regional scientific committees will have six members, three biomedical scientists and three lay representatives. The biomedical scientists could be doctors, dentists or pharmacists. The lay representatives could be any citizen with an interest in and knowledge of present-day society.

Scientific members for the regional committees can be proposed by any group of scientists, societies, boards, etc., within the region. The Danish Medical Research Council has accepted to be the body nominating the three scientific members of a given region. The lay members can be proposed by any individual citizen or societies, unions, clubs or other organizations. Lay members are nominated from such proposals by the regional county councils. The period of consideration will be maximally one month. At least four members - two lay members and two scientific members, including either the chairman or the vice-chairman - will have to participate. Principles of suitability for membership are expressed in some detail.

The regional scientific ethical committees has the right to ask experts to evaluate specific research protocols. Moreover, a regional committee can forward a protocol to the central scientific ethical committee for secondary consideration.

The central scientific ethical committee will comprise ten to twelve members representing the central health administration of Denmark, the Medical Research Council, the Association of Scientific Societies, the universities, etc. Even the central committee will have lay representatives. The functions of the central committee will be: to consider appeals from scientists not accepting the recommendation of the regional committee; to collect annual reports from all regional committees and issue a public report on scientific ethical committees; to advise local committees on specific projects; and to counsel government, the parliament, etc. The secretariat of the central committee will be provided by the Medical Research Council.

The system of scientific ethical committees will have to be adopted by all national granting agencies and all scientific journals with editorial offices in Denmark.

Conclusions

The composition of ethical review committees will have to be mixed. In other words. both the scientific aspects of research projects and the ethical ones will have to be represented by specially appointed members.

Scientists are, of course, not without the ability to consider the ethical aspects of a given project. But their evaluation will always carry a suspicion of bias, whether present or not. Ethical aspects even of complicated scientific projects will have to be considered by lay representatives too. In the analysis of methodological and ethical aspects of a project, the scientific members of a review committee will be able to help lay members, but the latter then have the right to decide if they can accept the participation of citizens in the experiment or trial. Voting is not intended as a common decision procedure in the review committees, because one member abstaining would be sufficient to cast serious doubt on the ethical quality of the project. Yet parity between scientific and lay members is considered necessary because both groups enter the debate within the committee with equal weight.

The authority of ethical review committees is strongly dependent on their legal status. If introduced by a national law on the protection of research subjects and patients, the authority can be very high. A serious disadvantage would be the red tape involved and the difficulties in describing the very many special circumstances in biomedical science in the text of a law. The system outlined, comprising a structure of semi-official review committees constituted in agreement with ministries, universities and scientific societies, will probably not reach the same degree of authority as a legal system. On the other hand, the publication of Helsinki Declaration II and the creation of a comprehensive committee system will, according to Danish juridical experts, carry much weight in case of infringements, and thus act as a strong prophylaxis against violations.

The influence of ethical review committees is expected to be very strong. In Denmark the publication of Helsinki Declaration II and public knowledge of the planning of regional and central scientific ethical committees have already created a strong consciousness among citizens and scientists.

It is important to stress the necessary balance between protecting human rights in patients and research subjects, and, on the other hand, not unnecessarily blocking the progress of the medical sciences, including basic sciences and clinical science. Too strongly restrictive measures would certainly increase the protection of human rights, but would at the same time make the same citizens losers because innovative medical research would be hampered.

SCOPE OF REVIEW PROCEDURES OF ETHICAL REVIEW COMMITTEES

Gustav Giertz

In the original version of the Helsinki Declaration (1964) no demand was made for the ethical scrutiny of research projects. The Declaration addressed itself directly to the clinical investigator, and it was assumed that he himself would make the necessary ethical deliberations. Under these circumstances it was immaterial whether a measure was designated as patient-care or as research.

With the very setting up of ethical committees and with the very introduction of the demand for scrutiny in the revised Declaration, the question has emerged in a partly new light. In certain situations, the formal handling of medical development work is dependent on whether it is classified as patient-care or as research. In Sweden the need for drawing a borderline has further been emphasized by the pronouncement of the Parliamentary Standing Committee on Education that clinical trials ought to be subjected to ethical scrutiny.

In certain respects, however, the Declaration is still formulated as if it were directed towards individual doctors engaged in practical clinical work. Thus, among other things, the Declaration prescribes that a doctor must have the right to utilize a new method if he thereby considers that he can help his patient. A medical measure of this kind need not have anything to do with research, but even in such a situation the doctor may need to be able to fall back on generally accepted principles of action. However, here the necessary deliberations fall outside the scope of activity on an ethics committee for research.

In an effort to obtain a general view of how matters stand in practice, I carried out two studies at the request of the Swedish Medical Research Council: (a) a follow-up of all the projects assessed by the ethical committees in Sweden up to and including 1974 (project studies); and (b) an examination and compilation of the somewhat more than 700 lectures reported in the book of summaries from the national conference of the Swedish Society of Medical Scientists. A short account of the project study will be given in another connection at this conference.

In Sweden there is no legislation on ethics in medical research. However, scientific institutions in Sweden have developed a formal organization to deal with these problems. In the late 1960s, committees on research ethics were established in the medical faculties. These committees at first consisted solely of faculty members actively engaged in research or in medical care, but were later expanded to

include one or more non-medical members - for example, persons nominated by the health-care authorities. The Swedish Research Council has set up a working group for the purpose of preparing recommendations or rules for grants for planned research involving experimentation on human beings and for cooperating with the faculty committees and international bodies in this field.

The following is mainly an account of the results of examining the lectures delivered at the national conference. The aim of the investigation has primarily been to try to elucidate what should reasonably be characterized as patient-care and what should be characterized as research. It seemed that better knowledge of these circumstances ought to promote the possibilities of adequately assessing which studies should be subjected to ethical scrutiny. The evaluations made are my own personal ones.

Localization of the Research

The examination shows that the medical research that led to results suitable for presentation at a congress of the character of the national conference was principally carried out at clinics attached to university hospitals and the like. Of the 46 lectures presented by doctors from other hospitals, most of them concerned purely patient-care problems, such as case-reports, retrospective investigations, and demonstration and investigation of methods and interventions introduced elsewhere. Only three of these lectures dealt with what can be termed scientific experiments on human subjects. The investigation thus indicates that the scientific work carried on at Swedish hospitals not attached to medical educational centres is not of such scope that it should in itself warrant a decentralization of the committee activity.

About 50 of the lectures were given by people who had been working at institutions not attached to hospitals. It is thus clear that biomedical research is performed to a not inconsiderable extent at institutions which are not directly interlinked with medical care or attached to medical educational centres. This applies, for example, to some military medical research, some pharmaceutical research, environmental and nutritional research, and industrial welfare. It applies also to much of the research relating to psychological and sociological problems. The material from the national conference is, however, not suitable for elucidating the extent to which this occurs.

Scope of Review Procedures

This material has been assembled in groups with the aim of elucidating as clearly as possible the problem at issue. In the Swedish compilation the text has been supplemented with tabulations giving the titles of the lectures in question, so codified that the interested reader can

readily find the lectures in the book of summaries. A layout of this kind could naturally not be attempted here.

Laboratory Studies

Approximately 150 lectures concerned laboratory studies. The aim here was generally to develop apparatus and methods, to refine diagnostics or to throw new light on special medical problems. The work had largely been done at institutions and laboratories having research as one of their main tasks. Since neither healthy experimental persons or patients directly took part, the need for ethical assessment did not generally arise. However, some aspects ought to be studied.

If it is assumed that biological material sent to a laboratory has been taken in the amount and in the way required by the clinical situation, it is likely that no ethical objection could be raised against the use of the material also for research purposes, provided that this were done without neglecting the investigation originally requested. Thus, a pathologist ought to be able, without having to consult a committee, to perform anatomical studies on certain parts of an operation preparation sent in. A chemist ought to be able to use surplus blood for obtaining normal values, for checking the reliability of his apparatus or for carrying out more special studies. Nor should it cause misapprehension if in the interests of research a pathologist retrospectively examines and re-evaluates previously assessed material. However, if the sampling itself is modified in virtue of the research aspect, the situation is altered. The review procedure which should then take place is dealt with further on in this article.

In general, the results obtained in research of this kind are scarcely of interest to the patient and there is seldom any reason to communicate them. In certain cases - and this applies especially, perhaps, to certain cell studies - the results may divulge information of a personal kind, for example, concerning the genetic make-up. It may then be difficult to come to a decision as to whether one should inform the person or not. These questions are, however, scarcely relevant to research ethics and ought not to be judged by ethical committees.

It is obvious that laboratory research and the development of apparatus can in certain cases entail risks for those taking part - for example, via intoxication, spread of infection, fire or explosion. However, it ought to rest on authorities other than the ethical committees to supervise the safety of the personnel in these respects.

In the new version of the Helsinki Declaration (Tokyo, 1975). it is recommended that special caution should be exercised in research which can affect the environment. Of the 11 lectures in the section on environmental hygiene reported in the summary book, 8 had emanated from

institutes of hygiene - in certain cases in collaboration with non-medical institutes. A large proportion of the lecturers were non-medical. It is obvious that not all research which can conceivably have an injurious effect on the environment and in which doctors have in one way or another taken part can or should be subjected to assessment by the medical ethical committees. The committees have neither the time nor the expert knowledge required for such a task. A general demand should therefore not be made for such scrutiny. On the other hand, it is clear that in some of these cases these committees are well fitted to make the necessary ethical deliberations. It should rest on the project leaders themselves to decide where assessment should take place.

Finally, it should be borne in mind that in certain cases it is not the research methods used but the aim and results that can give rise to doubts. For example, the aim has been questioned in certain genetic manipulations. One can justifiably maintain it is unethical to carry on inferior development work - for example, to construct apparatus which is intrinsically hazardous. When deciding on projects referred to them for assessment in other respects, the committees should, as far as possible, also weigh up these factors. It is, however, unreasonable to imagine that all medical development work should be judged for aim and quality by an ethical committee. A reasonable point of view is probably that the researchers should be stimulated to consult the committees as soon as they feel doubtful concerning the ethical scrutiny of a project and where the question falls within the field of competence of the committees. In Sweden a special expert group now follows the development of genetic research.

Autopsies

About 10 lectures were based on studies relating to autopsies. Most of them dealt with relevant clinical questions or technical procedures in, for example, medico-legal procedures. However, in four cases it was a matter of purely scientific projects without relation to the clinical aims of the autopsy. In three cases it was a matter of studies on the fetus.

In Sweden, autopsy and transplantation work is statutorily regulated. However, neither the directives from the National Social Welfare Board nor the law state in detail what a hospital autopsy ought to or may comprise. However, one might assume that it is justified to perform all the investigations required for elucidating as completely as possible the problems in question, if this can be done without distressfully ill-treating the dead body. In this connection, special permission ought not to be necessary for carrying out scientific research. Scarcely any objection could possibly be raised when, for example, anatomical studies are performed on organs anyhow removed in a routine autopsy.

It is harder to decide under what circumstances it should be considered legitimate for research purposes to make an autopsy more comprehensive than initially required. Since autopsy work is statutorily regulated, it appears formally most correct to refer doubtful cases to the National Social Welfare Board for assessment. On account of the varying character of the situations that arise, it would not appear possible to issue standard regulations for extending the scope of an autopsy. The assessment must in each individual case be performed with reference to the extent and aim of the intervention and to the human aspects. In borderline cases, ethical committees could be consulted with advantage.

Organization and Economy

About 20 or so of the lectures dealt with questions of organization and economy. It is in the nature of things that studies of this kind are generally not associated with the ethical considerations of the type which the ethical committees have to deal with. Of course, this does not mean that many decisions on organization do not have ethical aspects. For example, in the data processing of medical information the value of protecting the personal integrity of the individual should be weighed against the need in medical care for easily accessible information. Accordingly, this is largely a problem requiring an ethical decision. Even if it is desirable to subject such decisions to ethical scrutiny, the suitability of relegating assessment to the ethical committees must be questioned. The make-up of these committees is not suited for making such evaluations, and most of the work involved can hardly be designated as biomedical research.

Mere Patient-Care

Under this heading, 127 studies were assembled. Here clinical questions were entirely dominant and the scientific element was of such a kind that it was clear that ethical assessment was not necessary.

It is of value if doctors present to their colleagues cases and situations which, for various reasons, fall outside the range of the ordinary. Most communications of this kind only report the patient-care situation as such, but in some cases, purposeful studies were undertaken in an attempt to start from the individual case and to try to elucidate the problems involved. The latter procedure can thus be characterized as research, but if only established methods are used and if the investigation has largely been in the interests of the patient, there is hardly any reason to consult an ethical committee. If one is to judge from the examples given in the book of summaries, this is generally the case. On the other hand, it is clear that an occasional case can lead to advanced research of such a kind that it ought to be assessed by a committee.

Even when it is a matter of planned studies concerning diagnostics, the situation can be such that assessment must be considered unneces
Here are two examples from the book of summaries. "Use of urography preoperatively prior to prostectomy" and "Acute angiography in massive gastrointestinal bleeding". In both cases it is a matter of well thought-out prospective investigations with a clear aim, but the scientific set-up has not involved any departure from what can be designated as measures based on patient-care. Thus, this is a matter of medical projects but hardly of medical experiments.

It is of very great importance that the result of a given treatment is followed up and checked. In one or the other of these follow-ups it may be questioned whether every individual investigation has been absolutely necessary from the standpoint of every individual patient. As a rule, however, the patients are likely to be thankful that checks are made, and understanding for investigations of this type is likely to be so great as to make assessment superfluous. It ought to be sufficient for the doctor to tell the patient what the investigation is all about. The proviso is that follow-up should only comprise accepted clinical methods and thus not entail the taking of unjustified risks or causing the patient undue inconvenience. If this is the case, in accordance with what is discussed further on in my report to the Council, the committee's assessment should be sought.

About 50 or so of the lectures discussed here related to clinical reviews of various kinds, which all had in common the fact that they were based on reported material about patients and in this was reflected the experience and attitude of the clinician concerned. It was hardly a question of research in a narrow sense, and examination of the studies brought no ethical problems to light.

Introduction of New Methods

In 75 of the lectures, reports were made of experiences with new diagnostic aids and therapeutic methods. The new procedures were applied in routine medical care and no more comprehensive experiments were arranged for demonstrating the value of the measures. It was thus a matter of methods of treatment performed under medical responsibility. These lectures have been divided into the following groups:

1. Testing out of methods introduced elsewhere;
2. Modification of existing procedures;
3. New indication areas;
4. Previously untested methods;
5. Methods involving the utilization of materials alien to the body;

6. Situations where the doctor-in-charge must have asked himself whether the tested material was really equivalent to or better than other available methods.

In the cases assigned to the first four groups, my understanding of the situation is that the doctor in question considered the adopted measures to be medically indicated, and that the measures thus have not entailed any departure from what was justified from the patient-care angle. Since this was a matter of medically based measures performed under medical responsibility, they ought not in my opinion to be introduced under the concept of biomedical experiments.

However, the situation is somewhat different when it comes to introducing diagnostic methods and surgical and certain other more technical clinical methods of treatment on the one hand, and testing out drugs on the other. The point is that the testing out of drugs is statutorily regulated, while the other new orientations in patient-care mentioned here are carried out entirely under the responsibility of the doctors taking part.

In surveying the activity of the committees I rather formed the impression that the generally shared opinion is that assessment of medically indicated measures is not a task for the committees. Among other things, one case is discussed in the project study which ought best to be assigned to group 1. Plans were made to treat by means of stereotactic operative measures patients with anxiety and compulsive states who had shown themselves resistant to other forms of treatment. The committee stated that the proposed investigation was to be considered as treatment of an illness by already established methods, and that it should therefore be looked upon as medical care and therapy control. The committee therefore considered that there was no reason for it to take a standpoint in the matter.

It would probably lead to untenable consequences if we in Sweden were to get a number of authorities - the ethical committees - which each should be assigned competence to decide which ethical measures were in line with the requirement of the medical regulations for 'science and tested experience'. It is not the worth of the diagnostic or therapeutic measures in themselves that should be evaluated by ethical committees, but whether scientific testing takes place in an ethically acceptable way.

The committee in Lund, in particular, put forward similar views on the testing of drugs. Thus, on various occasions, it declared that it does not consider that from an ethical standpoint it has cause to judge situations where the chief clinician has considered a measure justified from the patient-care angle. However, from discussions which have taken place, it appears that certain circles appear to believe that all

drug trials - therefore obviously also the simple testing of new preparations or of preparations registered for new indications - ought to be subjected to ethical evaluation. However, under no circumstances should such demands be raised unless they are approved by the authorities which are responsible for drug registration in this country. The point is that it must be made absolutely clear that in simple testing in certain cases it is a matter of patient-care pure and simple, over which other authorities than the committees have the duty of exercising supervision.

The cases assigned to group 5, which all relate to operative work, give rise to a special situation. The point is that there is one item in these cases that the surgeon can find difficult to assess - namely, the advantages and disadvantages of untested prosthetic material. A lecture which dealt with infected arterial prostheses illustrates how difficult it can be to evaluate risks in the field discussed here. Patient-care and the patients themselves would appear to be best served by the efforts on the part of specialists to gradually try to improve methods and to rely on self-examination, which at any rate in this country constantly occurs when specialists meet to discuss their experiences with each other.

However, situations exist where testing can be required. Such is the case when a doctor wishes to use a new method whose reliability he feels unable to judge and where he is thus himself doubtful of the value of the method in question. From the project study, it was clear that the committees were also to a great extent consulted by doctors who felt uncertain before trying out new principles of treatment, such as immunological therapy trials. A clear example of the difficulties that can be encountered in gradually seeking to evaluate a new therapeutical procedure is afforded by a project series that had as its aim the elucidation of the use of prostaglandins for inducing abortion. Another area where systematic efforts are being made to evaluate a method of treatment which is controversial in our country is acupuncture.

The basic rule ought to be that the doctor-in-charge should be entrusted with the duty of himself deciding when a medical-care measure needs to be evaluated from an ethical viewpoint. The situation varies somewhat in the evaluation of surgical and medical principles of treatment. As regards operative techniques, it is most often primarily the operator himself who, on the basis of his experience and his knowledge of his own technical ability, is best equipped to judge the situation in question. As regards new drugs, the individual doctor often finds it more difficult to judge any advantages or disadvantages associated with a new preparation.

Clinical Trials Linked to Patient-Care

In 115 lectures, studies were reported where measures were adopted which were not necessary solely from the standpoint of the

patient's situation, but where the aim undoubtedly was to elucidate the nature of the disease concerned or to create a basis for improved diagnostics and therapy. Thus, even if the interventions were not of immediate use to the patient concerned, in many cases the doctor had justifiable cause to assume that in the long run the results would benefit the patient. Thus, patient-care and research were here so closely interlinked that it was not infrequently difficult or impossible to draw a borderline.

The research methods used have varied. In certain cases they hardly resulted in any inconvenience to the patient - as, for example, in the withdrawal of one or two extra samples of blood. In other cases one could expect moderate trouble which soon passed - as, for example, in connection with biopsies or lumbar punctures. Quite often the research steps simply meant extending the clinical investigation by an item or two - for example, an extra X-ray examination or a metabolic study, where the questions at issue are the radiation risks, or the unpleasantness or the additional time taken up by more comprehensive tests.

In trials based on more advanced clinical physiological methods, however, the research situation was not infrequently trying for the patient. In certain experiments it was also difficult to assess the risk of complications. In the project series, starting from the material studied, I have tried to make clear which complications one must take into account.

In all the studies discussed here, the research had as its aim the deepening of knowledge of the disease in question. And as previously stated, it has often concerned investigations which might benefit the patient in the long run. The less troublesome an intervention is and the greater its value for the patient is judged to be, the less is the need for ethical evaluation. For example, where the research element only entails the taking of one or two extra blood samples it ought, in my opinion, to suffice if the doctor obtains the patient's informed consent.

In my report to the Council, I stated that it would be valuable if guiding norms could be given, stating which commonly occurring interventions - in themselves scarcely far-reaching - do not require special assessment. Further, it would help the committees if expert groups elucidated the risks attending certain more advanced technical investigations - such as catheterization of vessels, lumbar puncture and liver biopsy. From the project study it can be seen that such investigations have also been asked for by the committees. These expert groups ought at the same time to be given the task of working out guidelines for how complications can as far as possible be avoided.

Clinical Trials Not Linked to Patient-Care

It is relatively unusual for trials to be carried out on patients where the aim does not have any relationship with the patient-care situation in question. This was the case in 10 of the lectures. The project study gives a rather detailed account of trials of this kind. These were generally investigations where it was not possible to perform similar experiments on healthy subjects. This applies to studies under operative interventions or to metabolic experiments with the use of biliary or intestinal fistulas created on medical indication. Investigations under narcosis constitute a borderline case. Such projects ought naturally to be subjected to ethical evaluation.

Interviews and Health Check-Ups

More than 50 lectures were assigned to this group. In biomedical research there is not only the risk for bodily injury but also the risk that the set-up of the experiment and its implementation may in one way or another cause the patient worry and thereby produce mental suffering. One has to reckon with complications of this type particularly in interview investigations and social follow-ups. If investigations are made only with the aid of available documents and records, and the patient is thus not contacted in person, this risk does not arise provided that the cover of confidentiality is effective and the work is carried out with due discretion.

Health check-ups and screening procedures should also be set up and performed in a way which guarantees, as far as possible, that the subjects investigated are not caused unnecessary anxiety. Special caution is required in studies where a population group is randomly chosen for special studies or where genetic genealogical research is carried out.

In general, there is every reason to scrutinize the set-up of projects of this kind and to try to follow up the psychological consequences. Physical complications are most easily recognized by the researcher in question, and he thereby constantly obtains increasing experience and becomes better able to avoid the taking of unnecessary risks. On the other hand, it is much harder to evaluate the degree of injury that an unpsychologically set up project can cause. Here the committees need to pool greater experience. On the whole, it is urgent that the psychological aspects should be given adequate attention in the assessment of all medical research.

Comparative Studies

In 18 of the studies the scientific element consisted in trying - without the use of the placebo technique - to compare different diagnostic or therapeutic methods. Especially when it was a matter of diagnostic procedures, the comparison simply consisted in carrying out several

investigations on the same person and then analyzing the advantages and disadvantages associated with the methods tried out. In order to obtain comparable material in many of the studies a random distribution of the material was made. Some of these were open studies, in others the blind technique was used.

In the nine studies where the placebo technique was used, it was usually for drug tests. In some cases a placebo was used initially or for a short time, but in most cases it was obviously considered that a group of patients could be left untreated for a long time. The aim then was to elucidate whether the treatment had any effect.

A number of ethical aspects can naturally be imposed on controlled clinical studies and research projects using the placebo technique. The question has been raised whether it is fitting to give insufficient or misleading information, or to limit the possibilities of choice on the part of the patient for alternative treatment. All projects that are associated with questions of the nature discussed here ought, in my opinion, to be scrutinized. Obviously, however, differences in opinion exist as far as the ethical considerations are concerned. In my report to the Council I have therefore proposed that the entire complex of problems should be made the subject of a special inquiry with the task of working out proposals for guidance. It is a matter of stating norms that promote sound development towards better methods of treatment, without limiting in a troublesome way the right of self-determination of the patients.

Experiments on Healthy Subjects

Healthy subjects took part in 49 of the studies reported. The project study elucidates in detail a series of special questions associated with research on healthy persons - for example, selection of experimental subjects, information and payment.

With few exceptions, it seems reasonable that all biomedical experiments on healthy experimental persons should be referred to an ethical committee for assessment. Exceptions should be made primarily for projects where the inconvenience is minimal for the experimental subject or where no foreseeable risk exists. Further, it should be possible to leave it to a researcher, if he so wishes, to decide by himself whether or not experiments should be performed on him.

Conclusions

Examination of the material has shown that more than half of the lectures reported obviously did not concern investigations which need to be ethically assessed.

Unanimity probably exists on the general necessity for scrutiny of biomedical experiments on healthy persons.

On the other hand, as regards studies on patients, the doctor has to face the question of whether the adopted measures ought to be considered a natural element of patient-care work - for which he is under the obligation of answering to the authorities involved - or whether they ought to be characterized as a research experiment. In the original version of the Helsinki Declaration no demand for ethical scrutiny was made, but the Declaration simply addressed itself directly to the clinical investigator. With the very setting up of ethical committees and with the very introduction of the demand for scrutiny in the revised Declaration, the question has emerged in a partly new light.

In certain respects, however, the Declaration is still formulated as if it were directed toward individual doctors engaged in practical clinical work. The Declaration provides, among other things, that a doctor must have the right to use a new method if he thereby thinks that he can help his patient. A patient-care measure of this kind need not have anything to do with research, but even in such a situation the doctor needs to be able to fall back on generally accepted principles of treatment. However, the necessary considerations fall outside the scope of the sphere of activity of an ethics committee for research.

In order to emphasize this, the Swedish Medical Research Council's joint group recommends - incidentally, in agreement with a proposal put forward by the European Medical Research Council - that heading II in the Declaration, "Medical research combined with professional care (Clinical research)" should be altered to "Medical research intended directly to contribute to the benefit of the individual patient" and that heading III which now reads "Non-therapeutic biomedical research involving human subjects (Non-clinical biomedical research)" should be altered to "Biomedical research involving human subjects but not intended to contribute directly to the benefit of the individual". These alterations are considered to provide a better definition of what is really intended and to facilitate decision-making on what should be the subject of ethical scrutiny.

When reading the current version of the Declaration, one gets the impression that the authors have clearly grasped the problem related here. The point is that the term 'biomedical research' is mentioned in most places; but in the paragraph that enjoins scrutiny, the expression 'experimental procedure' is used. The expressions are not synonymous and one can only assume that the choice of words resulted after careful thinking. The difference is significant. If the only scientific element in a study consists in the doctor's procuring further information about the type of disease - for example, through taking an extra blood sample or a biopsy - this can rightly be termed research but scarcely an experiment.

On the basis of this reasoning, the Declaration could be interpreted to imply that each doctor in his work ought to pay regard to the norms set

up, but reference to a committee need only take place if a research step has the character of an experiment. The investigation that I have carried out illustrates rather well the different situations encountered here. Examination of the material from the national conference has led to the following personal viewpoints:

1. In the introduction of new methods purely for the purpose of patient-care, ethical scrutiny should take place to the extent that the authority supervising patient-care finds necessary or the doctor himself finds justified.

2. In studies that are linked to the patient-care situation, I am of the opinion that it should rest on the doctor-in-charge to decide whether scrutiny should take place or not. Certain guiding norms ought to be worked out.

3. In experiments which are not related to the patient-care situation, scrutiny should be compulsory.

4. Interview investigations and investigations directed toward selected groups of the population should generally be scrutinized.

5. Random investigations with or without a placebo element ought, as a rule, to be scrutinized. Guiding norms ought to be worked out.

The Swedish Medical Research Council's Standpoint

The Research Council's joint group has, with the help of the discussions that have taken place, worked out new directives for the ethical committees. All biomedical research projects in the country that comprise experiments on human beings (patients, healthy persons), where the said experiments are not intended directly to benefit the individual, shall be scrutinized by an ethical committee. This includes the testing of unregistered drugs and registered drugs tested with new indications. In ethical scrutiny, the principles laid down in the revised version of the Helsinki Declaration (1975) shall apply.

In order to create guarantees as far as possible to ensure that development work at clinics should be subjected to a preliminary ethical assessment, it is prescribed that all projects that conceivably fall under the definition of 'biomedical research projects including experiments on human beings' and that are in progress or are planned to be carried out at a clinic or institution, shall be described by the respective project leader in a project summary drawn up after a special pattern. Apart from describing the aim and methods of the project, the number of subjects, etc., the project summary shall contain information elucidating the investigation from an ethical angle - for example, the patient-care/research delineation, risks of complication, etc. The document shall be submitted to the chief clinician, who shall note on it whether in his

judgement the measures ought or ought not to be subjected to scrutiny by the research ethics committee. These project summaries shall be filed, thus providing the clinic or institution with better possibilities for reporting ongoing or concluded studies. In this way, material is also collected that can subsequently serve as the basis for more advanced decision-making.

ETHICAL REVIEW PRACTICES AND PROTECTION OF HUMAN RIGHTS IN MEDICINE IN THE GERMAN DEMOCRATIC REPUBLIC

S. M. Rapoport

Ethical Principles of Health Protection in the GDR

It is well known that the German Democratic Republic has a state-run national health service. The state is under the obligation to make provision for promoting, preserving and restoring the citizens' health and to do everything in order to prevent disease. From this obligation of the state it follows that all persons have equal rights to receive optimum health care. The Declaration of Alma-Ata has defined health as a "fundamental human right". This right is guaranteed to all inhabitants of the GDR by the Constitution, in which it is stated in Article 35: "Every citizen of the German Democratic Republic has the right of the protection of his health and his working capacity."

All scientific research is closely related to prevailing social conditions. Both the objectives and the organizational pattern of modern medical science and of the system of health care are an integral part of the social organization of human society. Human dignity is maintained not only through the respect for personal integrity, but also through responsible action by society for those in distress due to disease. Man creates the riches of society through his work. Is it not the duty of society to care for him when he falls ill? The manner in which society discharges this task is a measure of its quality.

Man is the centre of all efforts of medicine. An ancient Greek philosopher described man as the measure of all things and the great humanitarian German philosopher Immanuel Kant once said that man should never be regarded as a means only, but always as an end in himself.

The health protection guaranteed by the Constitution of the GDR enables people to lead a life free of material cares as far as their health is concerned, last but not least because medical care is provided free of charge. This is an important social achievement of socialist society. We do not share the concern that free medical care may lead to "excessive care". On the contrary, we have found that the people are grateful for this fundamental principle and recognize that society's obligation and responsibility for individual health does not in any way lessen the responsibility of the individual for his own healthy way of life.

These social foundations make it possible for medical science to develop freely and for every physician to make full use of his knowledge

and skills for the benefit of his patients in keeping with the humanitarian calling of the medical profession. Physicians and patients are not concerned with economic interests or worries that might disrupt the doctor-patient relationship. Thus, every citizen of the GDR may have full confidence in his doctor. He knows that the physician is not dependent on his illness as a source of income. He knows that his physical, mental and social well-being are the goal of medical activity.

Medical science investigates all aspects of life processes. Human life as the object of medical research is much more than just the chemistry of highly integrated matter. Human life means social and mental activity, it means development of physical and mental capacities. Any research into biological processes must help to develop man's capabilities to the full. This is possible only in a humanitarian society. There is little use in striving for ever deeper insights into the biological conditions of human life if there is not at the same time a social programme which allows everyone the full benefits of modern medical knowledge. Social well-being is both a condition for, and a consequence of, physical and mental well-being.

New developments in science and technology are not accepted from one day to the other. They require extensive proofs. In some cases, as with certain vaccinations, the voluntary cooperation of the people is a precondition before they can be put into practice. The increasing number of volunteers for medical screenings and for vaccinations, e. g. against influenza in the GDR, indicates not only an enhanced awareness of health responsibility, but also greater trust in medical developments and in the society that organizes such measures on a large scale.

The great ethical responsibility of the physician is an important consideration in research into human life processes and in dealing with patients. Man is a person and not an object. Hippocrates said that nothing detrimental to man should be done. The present - and far more so the future - potential of biology and medicine must not serve biological and social manipulation of an antihumanitarian nature. Society and the conscience of physicians must be on guard against such misuse. Weighty decisions and high-risk interventions, if unavoidable according to medical judgement, must serve the patient's health and not the doctor's prestige or, even worse, his profiteering. Although such negative conduct is ruled out in a socialist country, advancing science and technology still create conditions under which medical conscience may be exposed to conflicts.

While scientific-technical progress solves many problems that have occasioned ethical conflicts in medicine it also creates new problems for the medical profession. Consequently, there will always be ethical decisions confronting the physician. Physicians in the GDR may rely on the help of society, which, through legislation, enables medical decisions

to be taken and gives the doctor and the patient the protection of the law and with this an added sense of security.

Ethical Standards in Medical Research and in the Translation of Research Findings into Medical Practice

General principles: The ethical and moral principles underlying the substance and methods of socialist health protection are also fully expressed in legislation. Legal provisions ensure the protection of health of individuals and govern the rights and duties of health authorities and institutions and of persons. What is more socialist legislation converts ethical and moral principles into juridically fixed obligations that are enforced in a conscious manner both on a voluntary and an administrative basis, and which reflect the humanitarian nature of socialist legislation in this field.

In the GDR, medical research is based on state plans drawn up by the scientists concerned and subject to review and approval by the appropriate state authority (from the Minister of Health down to the director of the institute or hospital, according to the level involved). Research projects are presented, according to their importance, before local or central boards of scientists appointed by the Government. The research workers make statements on the goals and methods to be used in the intended research, including information on animal experiments and measures for ensuring absolute safety for human subjects (e.g. in clinically controlled trials). Work on a research project cannot begin prior to approval by the scientific board and the Government. The boards may request progress reports on approved research projects, with meticulous examination of any risk to human subjects. A number of legal provisions, among them the Medicaments Law, and especially its stipulations on the testing and clinical trial of medicaments and similar products, as well as the instructions issued by the Ministry of Health on scientific projects in medical research, ensure the strict observance of ethical standards. An important role is also played by the medical societies, which have the responsibility among others of advising the Ministry of Health on ongoing and prospective medical research and on therapeutic standards.

A few examples from medical research in the GDR will now be cited to illustrate the actual procedures including consideration of legal provisions implementing the constitutional principle of comprehensive health protection.

Artificial organs, organ removal and transplantation: Organ transplantation - Ordinance of 4 July 1975: Organs from deceased persons shall have absolute priority over organs from living persons. This involves fewer medical and legal consequences and no problems with regard to potential health damage to the donor. When having recourse to organs of deceased persons, determination of the death of a patient

is sometimes a difficult question. The present definition of death of a patient under resuscitation is focussed on cerebral death. For legislative purposes, the main point is the emphasis on the unequivocal and substantiated determination of death. No definition of death has been used in the text of the ordinance that might restrict the considerations of new medical knowledge. In the interest of the patient it is stated that the determination of death must be independent of any intention to remove an organ. This means that the medical team that determines death must not carry out the transplantation.

Organ removal from deceased persons is considered highly justifiable as a measure to save human lives, and as a humanitarian act when serving transplantation purposes. The ordinance is based on the ethical principle of mutual help in its fullest sense so that organ removal is not conditional on the agreement of the donor during his lifetime. If the deceased person, however, has made a stipulation to the contrary during his lifetime, this must be respected as his last will, in keeping with the right of the citizen to have his personality respected.

In the GDR, very little use has so far been made of living donors and mainly organs from deceased persons are used for transplantation. Nevertheless, conditions for the removal of organs from living donors had to be laid down. Provided that the donor gives his consent, there is the problem of possible damage to him. Physicians are confronted with a difficult problem: Is the organ removal compatible with the ethical requirement for physicians not to do anything to the detriment of health, although the intervention will ultimately save another human life?

It is for this reason that ordinance lays down that organs may be removed from a living donor only if no damage to his health is to be anticipated. Any organ removal that in the light of medical examination may damage the health of the donor will not take place even if the donor expressly wants it. Since the living donor's consent is required for the removal of an organ, he shall be informed fully and without reserve of the possible consequences and risks so that his consent will be well-founded and free from misconceptions. It should always be made perfectly clear that organ removal is irreversible. The consent shall be given by the donor himself (and not by proxy) and the donor must have reached the age of majority. He may withdraw his consent without stating reasons.

Organ donation is always a sacrifice made with the intention to help another person dear to the donor. That is why he may make his consent subject to the condition that the organ be transplanted only to a specified recipient. The donor has no material claims on the recipient since in a socialist society any commercialization of organ donation is out of the question. In consideration of the laudable moral stand of the donor the ordinance lays down that compensation by the state shall be provided for any resulting material disadvantage. The first clinical liver

transplantation performed in the GDR in 1978 was preceded by an exhaustive study of international experience and by large-scale animal experiments. When the preliminary stage had been completed, the responsible Deputy Minister of Health presided over an expert meeting dealing with such fundamental aspects as the state of experimental findings (e.g. preservation techniques), operative skills, organizational problems, immunological precautions, legal conditions, indications, monitoring programmes, etc.

On the basis of a plan of action approved by the Minister and covering the medical and organizational guarantees and the clinical performance of the first transplantation, a multi-disciplinary communication was established at the clinical institution concerned (the Medical Academy in Dresden) in order to assess the donor-recipient situation, and the scientific and organizational conditions prevailing were reviewed several times. Immediately before performing the liver transplantation, it was necessary to obtain the specific consent of the Minister of Health, particular consideration being given to the indication, i.e. the actual situation of the potential recipient (i.e. male, aged 44, adenocarcinoma of the biliary tract with very little chance of survival).

The GDR has a specific programme for the further development of treatment centres equipped with artificial kidneys and of centres carrying out kidney transplantations. The research work in this important field receives particular attention from the Ministry of Health.

Development of endoprostheses: The first clinical trials with endoprostheses for the human hip joint developed in the GDR were preceded by numerous animal experiments (for compatibility, implantation of endoprostheses, etc.). The experiments were supervised and evaluated by scientists appointed by the Minister of Health. On the basis of the experimental results in animals and on materials and technology, a meeting of specialists under the auspices of the Ministry of Health decided to launch the first stage of clinical trials (on 20 patients). Detailed decisions were made on all conditions of the trial, and especially on indications, clinical assessment, etc. The same procedure was applied to all subsequent stages.

Genetic research and genetic family counselling: The GDR has undertaken several research programmes on genetic problems. The programmes were approved by the Minister of Health or the President of the Academy of Sciences of the GDR. The ethics of a socialist society, as well as the Marxist-Leninist world outlook, rule out any intent of human genetic manipulation. The Ministry of Health recently adopted a programme for a comprehensive "counselling Service for Human Genetics" in the GDR on the basis of numerous research findings and international experience. The programme defines in a detailed way the fundamental policy and principles of genetic counselling, the functions of

counselling centres, and their collaboration with appropriate scientific advisory councils and governmental agencies. The programme rules out any misuse and offers scientific advice on family planning to all persons who are afflicted with, or might pass on, genetic diseases and who for that reason wish to remain childless.

Health protection for children and young people: It is one of the most noble duties of socialist society to ensure the healthy and happy development of the young generation. In keeping with this goal there has been set up (Ordinance of the Ministry of Health, 21 September 1970) a system of advisory boards with the purpose of reducing mortality of infants and children. Their duties include the investigation of every death, including the stillborn, of any child less than fifteen years of age. These boards comprise not only medical experts but also social workers and a representative of the office of the Attorney General. They submit analyses and proposals for improvement of medical and social care including problems of hospital planning, postgraduate training and information of the public. This system has proved to be a highly efficacious means for the assessment, control and improvement of the quality of medical practice. Research into human reproduction and into health protection for children and young people is geared to this objective. Central research projects are supervised by the Ministry of Health with the assistance of its scientific advisory boards. Permanent central supervision covers ethically important lines of research, viz. the biological, clinical and social aspects of contraception and legal abortion, the care of high-risk pregnancies, the investigation and treatment of sterility and infertility, problems of artificial insemination, cryosperma, extracorporal fertilization and implantation of the ovum, early detection and treatment of disturbed development in the prenatal, perinatal and postnatal periods, etc. The following results of research are of special significance:

- Immunoprophylaxis of Rh-incompatibility
  (The GDR is the first country to have introduced this mesure by law and to treat all cases free of charge.)

- Medicinal prevention of hyperbilirubinemia in the newborn, with the result of almost complete discontinuance of exchange transfusions.

- Development and practical application of a technique for immediate diagnosis of malabsorption and digestion in infants.

- Development and practical application of nation-wide screening techniques for the early detection and treatment of disturbances of development in childhood and of anomalies of genetic origin.

- Preparation and practical application of a nation-wide programme of periodic health surveillance for persons aged 0 to 18 years (including appropriate occupational guidance).

- Development of a highly effective anti-measles vaccine (in collaboration with the USSR) and implementation of vaccination that resulted in the reduction of the incidence of measles from about 90 000 to about 4 000 new cases per year.

All these results and applications indicate the ethical standards and goals of medical research in the GDR. Further examples might be cited from the fields of oncological research, the investigation and control of cardiovascular diseases, occupational health, medical aspects of environmental protection, the investigation and control of infectious diseases and from other main fields of medical research in the GDR.

The testing of medicaments for use in human medicine: The testing of medicaments is governed by legal provisions issued on 17 May 1976. The underlying principle is that the testing of medicaments is a basic condition for their use on a scientifically substantiated basis. Investigation of medicaments in human subjects is authorized only where pharmaceutical and animal studies indicate that there is a minimum risk to the subject. Investigations shall be carried out in a suitable manner and as prudently as possible. Specific guidelines lay down clearly defined legal requirements applicable to the investigations in human subjects (objectives, conditions and scope). They prescribe a phased programme, which is highly differentiated owing to the different elements in the testing of medicaments.

Tolerance is determined in Phase I. The objective of Phase II is to determine efficacy, suitable indications and side effects. Phase III serves to demonstrate clinical efficacy and safety as compared with the currently most effective medical treatment by controlled clinical trials. Phase IV has as its main purpose the follow-up observation of the medicament after registration, with regard to efficacy, side effects and pharmaceutical quality. Phases I - III are conditional upon authorization granted by the Ministry of Health. Exacting demands are placed on those carrying out the investigations, which shall be performed only after the subjects have been adequately informed as to the experimental procedure and the possible effects, side effects and risks. Consent of the subjects is an indispensable condition. Subjects have the right to withdraw their consent at any time and without stating reasons. As a matter of course, the subject's state of health shall be evaluated in a most careful way prior to and following completion of the investigations. The conditions for the testing of medicaments involving certain groups of persons are even more restricting. This applies, e.g. to incompetent or partially incompetent persons and to pregnant women. There is a regulation on

compensation for damage arising in connection with investigations of medicaments and the damage entitles to compensation, from which there are no exemptions.

Legal Principles for the Provision of Comprehensive Health Protection

Adequate care of the mentally ill: The particular concern of the socialist state for citizens with mental diseases is expressed, inter alia, in the provision of care in inpatient establishments with a view to protecting the life, health and personality of the patients and to eliminating any risks to society. This objective is reflected in the Law of 22 June 1968 on the Hospitalization of the Mentally Ill. The Law provides that, as a rule, the hospitalization of the mentally ill is conditional upon medical diagnosis and the consent of the patient or his legal representative. Hospitalization is terminated when care is no longer required or upon request of the patient or his representative. If the request cannot be complied with because of a risk to the patient or to society, the District Medical Officer of Health may order hospitalization for up to six weeks. Without the consent of the patient or his legal representative, hospitalization for more than six weeks can only be ordered by the local civil court as a result of civil action. In addition, the head of the inpatient establishment is obliged to review the need for further hospitalization periodically (every six months). It is strictly prohibited to carry out any procedure not designed for therapeutic benefit of mental patients. This legislation is called for because of the particular care and protection required by these persons. This prohibition applied also to prisoners and detainees.

Professional ethics of the physician: The ethical and moral principles of the health services of the GDR are reflected not only in patient-orientated health legislation, but also in legal provisions for the medical profession, which apply to physicians and auxiliary medical personnel alike. For example, the Ordinance on the State Registration of Physicians sets out legal principles for the exercise of the medical profession. These principles are essentially of an ethical and moral nature and are also written into the solemn vow taken by medical graduates. The principles are:

- The physician performs his professional duties in a responsible, careful and conscientious manner on the basis of the achievements of medical science.

- The physician continuously enhances his knowledge and applies it in practice. He maintains his general medical skills on a level permitting him to give emergency medical care.

- The physician gives his patients medical care in keeping with his speciality. In emergencies, he renders all medical aid

possible under the circumstances, irrespective of his hours of duty and medical speciality. If necessary, he assures further medical care of the patients.

- The physician creates a relationship of confidence between himself and his patient. He gives the patient adequate information on his disease and on the medical treatment and care required, and creates thereby favourable conditions for the active participation of the patient in the restoration of his health.

- The physician keeps confidential all facts made known to him in the exercise of his professional duty or by his patients.

Conscientious observance of medical carefulness: Every medical action shall be exercised in a conscientious and careful manner, i.e. in such a way that the patient is neither endangered nor injured. The scope of legally required carefulness depends on the state of the art of medical science. Any standard of professional conduct based on up-to-date medical knowledge is binding when it has been found substantiated and to be safe. With regard to the individual physician, there must have been the objective and subjective possibility of acquiring this standard of conduct in the context of obligatory continuous postgraduate training.

The carefulness required of the physician must be considered in the context of the main responsibility of the medical establishment in providing the patient with careful treatment with a view to restoring his health or alleviating his suffering. The health establishment must do everything to pursue and, to the extent possible, achieve the success of medical treatment. However, this does not imply any legal obligation to attain this goal. There are objective criteria for carefulness, it should not be considered merely as a personal professional opinion of the physician that receives attention only in the case of breach of duty.

Under criminal law, the physician is not culpable when he has to perform a high-risk intervention in order to restore the health or save the life of the patient. There is no negligent behaviour if the desired success of treatment is not achieved although the physician has observed the necessary care in performing the intervention. Such conduct is not punishable and no criminal proceedings ensue. The same applies if the physician choses one among a number of possible courses of treatment that may involve a certain risk, on the grounds that another treatment offers no or but little prospect of success. His option is irreprochable from a social point of view and does not entail any responsibility under criminal law.

Material assistance to persons in the event of health damage: The ethical and moral principles and the social and legal security of persons

in the field of health care are reflected in an impressive way in the new Civil Code of the GDR, which entered into force on January 1, 1976. In addition to claims arising from legal provisions in medical insurance and the Labour Code, the Civil Code guarantees comprehensive material and social protection to persons. The improvement on previous provisions lies in the fact that the material liability of the health establishment exists in general whenever there is a causal relation in which the damage and a medical intervention performed (or neglected, although called for) by the health establishment involving the breach of duties of that establishment. It is important to note that the burden of proof concerning the liability of the health establishment does not rest with the patient. The establishment itself has to submit evidence to disprove its liability. This regulation provides the legal guarantee required for careful medical treatment and for adequate assistance in case of damage. At the same time, it is in the best interest of physicians because unfounded claims may be rejected in a substantiated way after careful examination - mainly through state commissions of medical experts.

Increased material assistance in the event of injury despite correct and competent practice: The gist of an Ordinance of 16 December 1974 is the humanitarian principle of increased material assistance and social security in the event of injury occurring as a result of medical interventions for which nobody is liable, i.e. which has occurred despite correct and competent practice and is grossly-disproportionate to the anticipated risk associated with the intervention. An assenting condition for the application of the ordinance is that the risk associated with an intervention had been considered to be relatively small, that severe injury as a result of the operation could not have been anticipated in the light of careful medical examination and that, contrary to all expectations, severe health damage has occurred as a result of the operation. There must be a gross disproportion between risk and damage.

Another condition for the application of the ordinance is that the medical intervention had been performed according to correct and competent practice and to have been associated with surgical or other "instrumental" procedures. Still another condition is a causal relation between the operation and the damage. This connection is to be established by medical expert opinion (commission of medical experts). The final condition is serious damage to health, which is defined to mean severe deterioration of body functions or damage to the body resulting in major changes in the patient's working and living conditions. Recognition of all these conditions by the commission of medical experts entails a claim to increased and comprehensive material assistance, which is intended to create conditions for the person very close to those that would have prevailed if the damage had not occurred. This may also apply to third persons, e.g. to the dependents of the injured person.

The ordinance is a significant part of the social programme of the Socialist Unity Party of Germany and the GDR Government and has important social implications.

Compensation for damage as a result of vaccinations, according to the principle of objective liability: The legal provisions of 27 January 1975 on damage as a result of vaccinations state that persons may claim compensation for any unexpected damage occurring as a result of vaccination and other prophylactic measures, irrespective of whether the vaccinations have been voluntary or compulsory. The guiding principle of this ordinance is that persons taking part in vaccinations, etc. are acting in the interest of public health. Therefore they have a claim to protection by society in the event of injury. Under certain conditions, the mere probability of a causal relation between vaccination and injury may substantiate the claim for compensation. No breach of duty needs to be involved; liability exists according to objective criteria. Compensation for this type of health damage is granted according to principles of civil law.

Neither the increased material assistance under the Ordinance of 16 December 1974 nor the compensation for injury as a result of vaccinations is conditional upon application by an individual. The health establishment is bound to take all the necessary steps to safeguard the rights of persons (compulsory notification). This compulsory notification guarantees full satisfaction of the claims. The interest of persons to have their claims carefully appraised is further met by medical expert opinions. It should be emphasized that in such cases, as in numerous others, the decision is not taken by individuals, but by competent collective opinion (the commission of medical experts). This team-work in decision-making has given optimum results and ensures that ethical and moral principles prevail in the health service of the German Democratic Republic.

FORM AND FUNCTIONING OF ETHICAL REVIEW COMMITTEES IN CANADA

James Miller

I have been asked to comment on the structure and function of ethical review committees in Canadian institutions, which are primarily faculties of medicine or health sciences and their associated teaching hospitals. I have been unable to carry out my assigned task properly because I am currently living in Japan and there has not been sufficient time for me to survey the current situation in Canada. However, I can describe to you what the situation has been till within the past year or so and what the new guidelines of the Medical Research Council of Canada are.

In 1976, the Council established a Working Group of Human Experimentation that had two major terms of reference. These were, first, to review current procedures and, second, to make recommendations to the Council regarding principles and procedures that should be implemented. I shall limit my comments to the Working Group's views on the institutional review committees, and refer those interested in other issues to the Group's full report(1).

Since 1966, the Council had required local review committees to evaluate all research proposals involving human subjects. The committee was to be convened by the head of the department in which the proposed research was to be carried out and was to comprise " ... a representative appointed by the Dean or the institutional administrative office, two individuals knowledgeable in the field of the proposed research but not associated with the proposed project ... and one or more individuals who would represent a general point of view". A specific form reporting the decision of the committee was to accompany each research proposal forwarded to the Council for assessment and funding. This, then, was the situation when the Working Group began its study in 1976.

The Group found that in practice the procedures of the review process varied greatly in the 16 Canadian health science faculties. Some were complying with the minimal requirements, as outlined above, while others had gone beyond this and had established permanent institutional review committees that dealt with all proposals for research on human

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1. Ethical Considerations in Research Involving Human Subjects. Medical Research Council Report No. 6, Ottawa, 1978, p. 64.

subjects. In larger institutions these committees had responsibilities extending beyond health science faculties to other faculties and departments in which research on human subjects was carried out. Concomitant with these developments, some institutions had formulated formal regulations based on the recommendations of committees established to review the ethical aspects of human experimentation.

On the basis of its study the Working Group recommended that a review committee should be established centrally in each institution, should have at least a core of permanent members who are rotated so as to achieve continuity, and should contain both lay and scientific members. Since, in the Working Group's opinion, the first step in the ethical assessment of any proposal is determining its scientific validity, the presence of appropriately informed individuals on the committee is essential. If additional technical opinion on a specific proposal is required then external expert advice should be sought. The Group justified the presence of lay members as follows: "The requirement for a review of the ethical aspects of a research protocol is, in effect, a statement that research must be assessed according to the community's sense of proper conduct. It therefore seems inconsistent to leave this process exclusively to one sector of the community. For this reason, lay members, drawn from outside the medical research community and even from outside the university community are essential to ethics review committees and might even form a majority".

The Group recognized that the enlistment of such lay persons may be difficult; but it should not be impossible for most Canadian universities and hospitals already have lay members on various advisory and administrative boards.

The Working Group's report was accepted by The Council and released in January 1978. It should be stressed that the Working Group, and I believe it is fair to say the Council as well, does not believe in the issuance of hard and fast rules that will be administered from some central authority in Ottawa. Such rules would be difficult to interpret in practice and even more difficult to enforce. Rather the Group considered its function to be the establishment of guidelines on the structure and function of local review committees and other matters covered in its terms of reference. The implementing of these guidelines is better left in the hands of local committees whose members are aware of local singularities that may influence decisions on specific research proposals. Since it is less than a year since the report was released, there has not been sufficient time to determine how it has affected review committees in all Canadian institutions. However, on the basis of information obtained by a Working Group during the process of its study, and through personal experience since the report was released, I believe most institutions will attempt to comply with the guidelines as closely as possible.

DISCUSSION

Fischer: This is a small contribution on a limited experience with ethical committees. Some points may be of interest for those who have not yet established ethical committees and who intend to discuss whether they should do so and, if yes, how to handle it. Let me first say that in the Federal Republic of Germany a new drug law came into force in January 1978. This law goes to the greatest lengths in dealing with formal ethical norms. Many recommendations of the Helsinki Declaration have entered into the new law, but the recommendation of introducing controls by local ethical committees has not been embodied in the present version.

The German Research Society, which is the central research-promoting organization in Germany, has gotten along without the existence of local boards since its foundation. But in 1973, the Society asked that in a number of faculties in special research areas local ethical review committees be established in order to gain experience with this instrument. Up to now, we have ascertained advantages and disadvantages. One advantage of local examination is doubtlessly that the specific experience of a researcher in special working conditions and certain technical details can be better judged than at a distance. This advantage stems from the strong specialization of research. At a given location, often only the researcher himself can really judge the risk/benefit ratio of a planned experiment. The members of a local committee, by reason of a subject, are often overtaxed if asked to evaluate risks. Some misjudgement which we have seen may result from this fact.

Another decisive disadvantage may result from local personal relations and dependencies. We have gained the experience that just in borderline cases local committees are inclined towards permissive recommendations - much more permissive than the referees of the German Research Society, who are elected on a national basis by the scientific community and who form a supra-regional system with a high degree of specialized knowledge and a high degree of independence. It is for this reason that the Society has repeatedly pointed out to its referees that the existence of local committees does not release them from their duty to critically examine the ethical and legal admissibility of experiments with humans. The Society expressly reserves the right to reject research projects for ethical reasons alone even if they have been approved by a local committee. And it is not least for this reason - the reason of personal relations and dependencies - that some faculties and many special research areas have declined to establish local committees up to now.

Clinical research in the Federal Republic of Germany is financed not only by research-promoting organizations but also from funds from the clinics themselves. In the latter case, no external procedure of evaluation exists, and here an examination by local committees appears to be better than no examination at all. Not least for this reason, the German Research Society has asked the Federal Chamber of Physicians to work on the establishment of local committees. An advisory board of the Chamber has meanwhile worked out a procedure. Neither the German Research Society nor the Federal Chamber of Physicians is at present thinking of establishing a central scientific ethical committee as you have proposed it. The reasons are these: Important problems that can be resolved by a general rule, as for instance drug testing or X-ray protection, have recently been regulated by law and ordinance. Most other ethical problems, we fear, do not lend themselves to consideration on general principles but require instead individual discussion and decision.

You may have recognized that I made an ambivalent statement. To summarize, including the remarks of Professor Breuer, I would like to mention three points. First, in Germany we fear that on the international scene discussion perhaps concentrates too much on new control systems. We think it would be wise to reflect more on prevention than on control of unethical behavior. Second, in the research-promoting organizations we shall concentrate on keeping our well-functioning system operative. Point three, we shall try very carefully to supplement our review system by local boards. What we intend is supplementation, not substitution. We do not intend to surrender to local committees alone full responsibility in matters of ethics.

Binns: May I briefly describe the establishment of ethical review committees in England? In 1967 the Royal College of Physicians of London published a report entitled "The Supervision of the Ethics of Clinical Investigations in Institutions". Because of differing local circumstances, this did not attempt to formulate rules but recommended that wherever clinical research was undertaken a suitably-constituted committee should approve all proposals. In 1970, an inquiry showed that virtually all university hospitals and about three-quarters of responding non-teaching hospitals had established such committees. In 1973, the College issued a further short report and since then a series of meetings has been held to serve as a forum for discussion and advice. These are attended by the chairman of ethics committees in England and Wales, together with a panel of experts under the chairmanship of the President of the College - at present Sir Douglas Black.

It is not possible here even to summarize all these deliberations, but the following points seem particularly relevant to the present discussion. The basic approach has been that clinical research investigations - and that's the preferred term - are essential for continued medical progress, and that ethics committees should seek to protect the

individual without unreasonably hindering the advancement of medical knowledge. Committees should examine all proposed investigations regardless of whether in the case of a drug an administration authority has approved it for clinical trial or for marketing. It follows that every institution where clinical research is conducted should have a committee. In some cases it will serve a group of hospitals but the area should not be too large or it will not function efficiently. In practice, there's been considerable variation both in composition and method of operation. It should normally be a small and separate committee. The medical members should be clinicians who are themselves experienced in clinical research, and it should include one or more laymen. Lawyers have been particularly helpful in this respect. Some committees have appointed priests, nurses, junior doctors or other hospital staff and many have arranged to co-opt further specialist advice as required.

Since a large committee becomes cumbersome and slow to operate, various techniques are used to expedite the work, such as giving the chairman discretion in non-controversial cases, or consultation on the telephone. It's been found to be a great help for all submissions to carry a standardized summary, together with the necessary supporting documents, and for the committee to have an agreed review system. Some hospitals have found that most of the work can then be done by circulating papers to committee members, any of whom can request meetings to settle more difficult cases. And so the number of meetings has varied from one to twelve per year. It is generally agreed that all payments made in connection with the study should be reported to the committee. But opinions have varied on the responsibility of the committee to monitor and follow up its own decisions.

So in short, the present position is that institutions throughout the country have developed an ethical review procedure along the lines recommended by the Royal College of Physicians. All investigators have a strong moral - though not strictly a legal - obligation to comply. The committees have developed somewhat differently according to local circumstances. There is fairly general opposition to centralization or to having an appeal committee, but these periodic meetings of chairmen held by the College have provided a valuable forum for discussing controversial problems and have helped towards developing a reasonable consensus where no final solution yet seems possible.

Burrell: At the suggestion of Dr. Gellhorn, I shall talk about New Zealand and about some data that I obtained from there this year on a trip where I went and visited the major institutions and talked with members and, in some cases the full membership of ethical review committees that they have there. So I'm talking about a practical situation as I find it in New Zealand.

Just to refresh your memory, New Zealand is really a small country - three and a half million people spread out over two islands that together total about a thousand miles. They're the antipodes of Portugal, in fact, and no part of the country is more than sixty miles from the sea. But there are four major centers: Auckland, Wellington, Christchurch and Dunedin. Two of those have full medical schools and two have clinical schools. And then there are about ten other secondary centers, which are called cities because their populations are over twenty thousand and by definition in New Zealand, a city is anywhere over twenty thousand. And of those secondary centers, six have populations ranging from about twenty to eighty thousand people, and in those secondary centers I met with ethical review committee people as I did at the four major centers.

Ethical review committees have existed in New Zealand since 1973 and varying reasons are given for their existence. But I would tie it down to some correspondence I saw from the then Director-General of Health. He suggested that it would be a darned good thing if they set up ethical review committees. And, presto, within a matter of six or eight months there were ethical review committees in most of the centers.

All grants that are going to be approved by the medical research council of New Zealand must have first of all clearance by an ethical review committee from the appropriate institution. The functions of the individual committees relate principally to the consideration of the various ethical aspects of clinical research, as you would expect. But remember there are also the resident ethics committees, and from time to time they get other matters referred to them. And I find, for example, fascinating items such as an inquiry into the qualification of a foreign-trained person who claimed to be a physician and who was rendering what amounted to medical care. And in another center they looked at the way in which a budget had been allocated. They felt that the budget was not allocated ethically correctly. The complaint had been put to them. So when you're the only dog and pony show in town, you get everything referred to you. Ninety-five percent of their activity relates to clinical research, however.

Committee membership was fairly uniform and consisted of a small number, usually of senior people from the institution concerned. And in only a couple of cases outsiders - people from outside the institution. These lay people were hardly lay people in a sense. One was a retired coroner of a city; the other was the retired ex-matron of the same institution. No true lay persons in the sense that we are used to in the United States.

The chairmanship of the committee was in some cases an ex-officio matter for the superintendent of the hospital. In some places it was more of a rotating nature; in one place in fact it was a dentist, who was the chairman of the medical committee of that hospital and he had become

chairman of the ethical review committee. And in some places the chairmanship had devolved on the most interested person. That person, in one case, in Auckland, had been responsible for pulling together some guidelines on research and some ethical standards that I'll mention later.

I don't think from my observation of it that the New Zealand experience restricting the membership to physicians primarily is bad in that situation. I thought about the remark made by Dr. Neki this morning. It was, if I heard it right, a very sad observation. The basis on which human trust flourished is fast disappearing, he said. Well, I did find human trust flourishing still in the ethical review committees in New Zealand. The selection procedures, as I said, vary. The terms of membership range from one, two, or three-year terms up to an indefinite period, and of course the amount of traffic that they handle varies tremendously. In some of the smaller centres there may be only one or two research projects in a year. In the major centres they're very busy. While all of the committees adhere to general codes of ethics such as the Helsinki Declaration, several use the locally prepared Auckland Hospital Board Code, to which I referred earlier and which was drawn up by a very keen physician who is an ethicist in Auckland.

All the committees feel that they've learned a tremendous lot while they've been in existence and they've become more critical, they feel, rather than less critical as the years have gone by. And several of them used the occasion of my visit to sit down and have an open discussion on what ethical committees should be doing and are doing and where they might be improving things. One interesting item was that in the town of Palmerston North, which is just a hundred miles from the capital, Wellington, I find a real feeling of isolation and loneliness, and the hospital board, the Department of Health, and the Medical Research Council are all finding ways of helping that hospital. It feels it's an ethical island in a sea of disinterest. And I guess from that point of view my visit was of some use there.

Some committees meet, as I say, very infrequently as required; some meet every month. They all said that they don't believe in committees that routinely meet once a month or once every x weeks. They just don't have enough time to get into that sort of thing. Protocols and other data are circulated in advance, and it's required that all committee members read that material and be conversant with it when they attend meetings. The names of the investigators are always clearly identified. There's no anonymity in that part of the process at all.

While the committees generally encourage the presence of one or more of the proponents, the investigators, as they're discussing a particular protocol, they reach their final decisions in the absence of that proponent. Majority vote doesn't appear to be the method for decision making and I noticed that somebody earlier said that if one

person does not agree with the protocol, that should be enough not to even proceed to a vote on it, in a sense. And indeed consensus is the way that they operate in New Zealand. They're not as formal in New Zealand or Australia, I believe, as people are in Europe or in the United States. But each member of the committee has no hesitation in making his or her feelings felt. The decisions that are reached are relayed to the proponent, to the medical committees - or whatever one calls them - of the hospital, that is the faculty or staff committees, and to the hospital board. And brief studies of the actual proposal are available for those two groups. Nothing is mentioned outside of the committee about the depth of the discussion in the committee.

The committees vary a little, as I've suggested, with regard to the types of project which fall within their review. But in the area of scientific research, all review drug research, some also review new surgical procedures, and most review psychological testing proposals which would seem to be very much on the increase, incidentally, in New Zealand. All adopt a very broad overview of their role and feel obliged where appropriate, and that's quite frequent, to recommend protocol design modifications. And if those are not accepted, willingly, graciously, by the proponent, the proponent is told to go away and think it out and come back again. There have been some rejections of protocols. Very few but some. Informed consent and the benefit/risk ratio appear to be the aspects that cause the greatest discussion at the committee meetings. Consent, by the way, is verbal and not written.

Extra attention is given where appropriate to protocols that include special groups such as children, students, etc. And the presence in at least two of the cities of special hospitals for women, with their very efficient committees meant that fetal and abortion problems did not get discussed in the general committees in the hospitals in those towns. And they had not become issues in the other centres. Incidentally, at the Women's Hospital in Auckland I was quite interested and saw quite a bit of the activities of another ethical committee they have - it's an ethical animal research committee. They feel very strongly that at this stage they had need of that.

It appeared to me that in New Zealand the local hospital ethical review committees are really reporting to their own institutions - the hospitals themselves and their fellow staff. There wasn't any sense of obligation to report to to the Ministry of Health what was coming out of it. And my contacts with the Director-General of Health and the Director-General of Mental Health were used as the occasion for them to obtain from me information about the committees. Although they knew they existed, they didn't really know how they were working at that stage. And they, I believe, are now going to take a more direct interest. And it sounds as though they'll meet with the chairmen of the various ethical review committees some time during each year or two-year period.

The New Zealand Medical Journal does not require a statement that an ethical review has taken place for an article to be published, but the editors look very closely at anything submitted and have within the past five years rejected one paper on the basis of what they felt was an unethical study. And that was referred back to the author, and the author did not choose to resubmit it. And on that occasion the hospital at which this was conducted did have an ethical review committee, and it appears as though this may have slipped by because it was one man doing something really outside the hospital. That situation may have been corrected, I think, since then. There's no provision for supervision, or for ethical review, of research conducted outside hospitals as far as I could determine.

So, in summary, there are a number of very active ethical review committees in New Zealand. They work well, I think, on the whole, and they're trying to work better.

Nir: I would first like to take the opportunity to say that I'm very glad in a way that this afternoon's session turned out to be in a very practical direction. One of the things that I expected from this gathering, in addition to the exchange of information, that some practical guidelines and some practical advice for people of various countries to obtain for setting up of their own organizations in their own countries. And I shall go along the lines which have been started by my previous colleagues and make a small number of comments regarding the practical points which have been discussed here.

First of all, I would like to state that I don't like the term human experimentation. Not only because this has got some unpleasant reminiscence of the not far past which we had experienced in the last war, but because when we are talking about drugs, and I am dealing with drugs in the review committee, the problem is different from when we are talking about human experimentation. In drugs, we usually apply drugs to humans after they have been tested on animals, and we do these additional tests on humans only to confirm some of the pharmacological information that has been obtained and to identify additional points which we were unable to do on experimental animals. That's why I think that what we are actually dealing with is not experiments but just clinical trials - one may call it an experimental clinical trial - and that's usually the purpose of all tests that we are doing on humans with drugs.

And that is also why we consider that a clinical study of drugs is actually a well-controlled medical practice. This morning we heard from one of the colleagues that actually a clinical trial is not any more than a medical practice. I would put that the other way round - I would say that each medical practice is actually a clinical trial. There is never enough experience in our hands to say that we know everything about the drugs and more and more information comes out with the continuation of

this treatment. And if the physician is not able to weigh exactly the pro's and the con's of a drug when he does the treatment, he's not unable to treat. That's why I would say that actually what it is is a clinical treatment, a clinical trial, equivalent to medical treatment, with a drug.

Now the first question would be, if so why not leave it completely to the medical profession? And especially that we know that even when a trial of a drug is approved by the so-called ethical or review committees the responsibility still remains with the medical doctor or researcher. My answer is very clear on the basis of the experience which I've got serving as the chairman of the Israeli review committee for the last ten years. It is that nobody wanted not to have an evaluation. Clinical trials are not restricted any more to very specialized clinical researchers. We have to give these trials to clinicians to a large extent. That's why the clinical research, the clinician and also the third party, the drug company or the institute which is producing the drug, all parties are interested in having this drug evaluated. And this morning we had the suggestion from Dr. Curran - and I would like to tell him that his suggestion has been introduced in Israel five or six years ago - that we are not satisfied only just by giving a permit to do a certain trial but there is a committee with a permanent secretary that monitors the whole trial. The trial is usually restricted to a certain number of months - maximum one year - and the researcher has to apply for continuation of the trial and he will not get a permit to have it extended unless he has given a report and the report has shown that no harm may be expected from the trial that he has been conducting.

So this works very well, and people are very happy about it. And there's another point, Mr. Chairman, you said that you prefer a regional committee to a central one. In Israel we don't have this problem. It's a small country and we have the advantage of being a small country that the central and regional committee is actually the same. So I think it's better to have one committee because it gives a homogenous approach, a homogenous evaluation, rather than leaving it to certain areas where you may get people who are too close to the researchers, too much involved, and it's our experience in having a central, national, independent committee not only with specialists but with general clinical pharmacologists, with clinicians with much experience in internal medicine, who will do the evaluation, that we rarely have to reach for the assistance of specialists. We have had hundreds of applications and rejected one-third of them, and we didn't encounter during these 10 years any problem either by having some adverse unexpected effects or any people who would not accept our decision. So, all parties involved like this way of having an independent, scientific body. Although this is a governmental committee, most of the members are faculty members, although there is representation of the paramedical aspect. I think that it is very important that we maybe did not mention this morning that justice should

not only be done, it should also be seen to be done. And the fact that if somebody is carrying out a test in humans with a new drug and he could state that this independent, scientific body had evaluated and reached a conclusion that there's no objection, this gives a very good feeling to the researcher himself - much better than the formal consent that one would receive.

Now the question is, which drugs should be considered for clinical trials. And the key is the status of the drug itself. I think, most European countries have got a list of drugs which are approved for marketing in their own countries. So we've got our own list of drugs which are approved, and any drug which is not on the approved list in Israel would automatically require a clinical trial. Moreover, drugs that have been approved for specific indications cannot be used for different conditions without the approval of the review committee.

Thieme: I would like to note that it would be desirable to ensure that capable women are involved in all ethical review committees in a satisfactory number to put in a female viewpoint and judgement in this field. Notice that half of the human subjects are female. Also, it is necessary that more women should belong to research committees, because I believe that there would be a difference in the definition of priorities in the selection of research projects that should be furthered first. If you look around this conference, one could believe ethics is only a problem of men. But I assure you that women are very sensitive in this field.

Borchgrevink: I would like to ask a question to the panel in general, probably to Professor Riis in particular. I shall be brief. Two questions. How do you select the people for the committee? Do you have fifty percent lay people, fifty percent professionals? And just being a doctor, is that qualification enough to sit on a committee? Or being a professor in itself, is that enough - present company excepted of course - but is that enough in itself? And what about the lay people? Do you just pick up an ordinary man from the street who is probably good enough actually? Or do you take a lawyer or a philosopher or a politician or someone who has the confidence of the people in general?

Riis: A scientist is a scientist, and it's difficult to define. But it's not just a professor of any speciality. And that's why we couldn't place a selection in the local areas. Because they could point to people they considered to be competent and willing. Therefore, we ask the central board, which is the medical research council, to try to combine these two things. Otherwise, we think we had too many dignified members of the local society. And the lay members are the kind of people used for court work as lay representatives. But, of course, you find that some politicians have already been pointed out because it's very difficult to ask for people being interested in society, being able to speak out in public and then avoid politicians. And I've no personal allergy

towards politicians, but of course I would like to see at least some factory workers or union members or priests. But we never pick them up in the streets.

Serrao: Je veux vous présenter une proposition très simple, mais je crois bien importante. Malgré les comités de révision éthique en ce qui concerne la recherche médicale, l'expérimentation et d'autres actions portées sur des sujets humains, nous croyons nécessaire et urgent d'adopter une récommandation sur le droit des médecins à l'objection de conscience. L'objection de conscience peut se présenter dans certaines situations, comme la dernière défense du médecin.

Tygstrup: I have a comment and a question both specifically concerning randomized clinical trials. The comment concerns the remark by Dr. Burrell that no study was accepted unless the opinion of the committee was unanimous. I believe that as far as randomized clinical trials are concerned, the ideal setting for such a trial is the situation where the establishment was divided concerning which treatment to prefer. So I would think that this could give a little biased selection. The question is to Dr. Nir and that concerns the monitoring of trials. And I am especially concerned with a long-term trial which offers many difficult and special problems. And I wonder whether your review committee evaluates the results after unblinding.

Nir: We had recently such a problem to solve. There's a clinical study going on to continue for five years. But they have got the computer to take out all the adverse reactions that do occur and have them summarized on a special sheet and sent up. So as long as we know that there are no drop-outs and there are no adverse reactions which are of concern, we allow the study to continue under the same conditions as previously.

Daugaard: Only a few points to elaborate on Professor Riis' answer to Professor Borchgrevink. Because I think the allergy of Professor Riis towards politicians is a minor problem. But there is a real problem in Denmark that these politicians actively engage themselves in medical ethics independent committees and this will not be an independent committee. How will active politicians act as independent lay people. Will research be a political issue? Will the political people exercise their political opinion as lay people from the street? I feel it's a very dangerous development and I am afriad that this can set up a mixture of committees which is not independent and which mix the funding of research with the ethical review of research.

Marketos: I'd like to ask Dr. Nir concerning the basic methodology of the double-blind clinical trials using the so-called placebo group of patients. Do you think, Professor Nir, that the

principle of this experimental methodology is not dangerous and that it is not in agreement with the ethical medical standards?

Nir: You can't make a generalization. If we think, for instance, that a group of hypertensive people have been freed from the treatment and found by the treating physician satisfactory without treatment. So there's no harm that these people will come to under a placebo unless the blood pressure starts to rise, when you would have to take them out of the study. But in principle if no harm is expected by no treatment, it's always preferable with the tests that we do to have no treatment than treatment.

Refshauge: I think, Sir, that it's very fitting that two of the major papers this afternoon came from Scandinavians. It was Scandinavia that indeed stimulated the revision of the Declaration of Helsinki. In June 1974, I had the pleasure of meeting with the representatives of the Scandinavian Medical Association in Copenhagen. And I'm saying this not because I'm a quarter Dane, but because this really happened. And they suggested to me that the current Declaration of Helsinki was now outdated and could be looked at again and they proposed that they set up a Scandinavian expert group to look at the Helsinki Declaration. And this they did. The original Helsinki Declaration was submitted purely as recommendations guiding doctors in clinical research. And it sought to be no more than that. It was, I believe, not intended to be a rigid document. It was a set of guidelines that could be adapted to local conditions. But nevertheless there seemed to be obvious advantages in seeing it as an international statement. And Professor Giertz, who gave a paper this afternoon, at that stage called it a declaration that reflects the conscience of the world. I hope he still thinks so.

The Scandinavian committee finalized their deliberations early in 1975. And with the help of Dr. Daugaard, who has just spoken, and who was the chairman of the medical ethics committee of the World Medical Association; and with the help of some very willing and wonderful experts from WHO, the final document, the Helsinki Declaration No. 2 has now been adopted.

In early March 1976, a meeting was held in Geneva called the International Conference on the Individual and the Community in the Research, Development, and Use of Biologicals. This was held at WHO and it was co-sponsored by CIOMS, the US Department of Public Health, the International Council on Biological Standards and the World Medical Association. And it was from that meeting that CIOMS got, I think, an extra impetus to develop its ideas on medical ethics in human experimentation.

At that meeting, it was recognized that the Helsinki Declaration was still only guidelines, and it was felt that there were areas still not

covered and perhaps rather vague. It was suggested at that stage that, as in the Geneva Convention, which has a lot of articles which tend to be vague, that there could be for each article, set up over a period of years, a definition of the article. For instance, what biomedical research means, and so on. Types of review committees. Unfortunately, I resigned from the WMA later that year and I couldn't get my Scandinavian friends to help in the study of the feasibility of that project.

But a more important point was stressed at that 1976 conference and that was, although ethics committees which were stimulated by the Scandinavian group could be set up, they could not replace the conscience nor the trust in the investigator. And therefore there was a need for more emphasis on medical ethics in the medical curriculum. And I believe this is a very important point.

Finally, I'd just like to say a few words on the ethics review committees in Australia, as earlier this year I completed a survey of some six institutions carrying out research projects for the National Health and Medical Research Council which is being represented here by Dr. Hurley. Firstly, this covers some 150 projects over a period of about eighteen months. The size and composition of the committees was similar to that expressed by representatives from the UK, and I won't go over that. The code that was used by the various institutions was either the Helsinki Declaration No. 2 in its entirety, or modifications adopted by the institution. Only about four projects out of the 150 were rejected, and there was one delay of three months, and that was to get extra information from the investigator. The committees do meet as frequently as necessary to consider all the applications, so that there is no delay. And in some of the institutions they do have a supervisory role from time to time. From the survey, I believe that the discussions of the committee should be in private, as this allows full and frank discussion of any problems that may arise. But the recommendations certainly need not be confidential.

Although the committee should not delegate its responsibility, it should not hesitate to seek outside expert advice to assist it in its deliberations. I believe that the committee should try to reach unanimity. But a single minority vote out of a committee of five or seven, I do not believe, should prevent a project from proceeding. And I believe that a committee should have sufficient authority that, should it recommend against a project on ethical grounds, the project cannot proceed. The committee, I believe, should be willing to review or reject a proposal should new relevant information become available or the proposal be modified to conform with the ethical code or guidelines in use by the committee. And that caused one delay.

Concerning informed consent, which was of course the greatest problem amongst all the committees, there is a special problem with

regard to mass surveys. And here I may mention that in Australia between 1973 and 1975 we had a blood-pressure survey carried out by the National Heart Foundation in which over 100 000 people were screened and 4 000 of those had mild hypertension, and were asked to participate in the investigation - half of them getting a placebo and half getting treatment. And this is a five-year project, and although the survey itself finished in 1975, 2 500 have had their second annual review. And I believe that in these sorts of processes in the mass trials, it should be clear that the principle of consent by each individual definitely applies to the earlier stages of a research and development programme. For example, the first administration of a drug to a small group of humans and to a second and larger group of individuals. But, in the late development phase, and especially in areas where there are mass trials, perhaps some other form of informed consent might have to be used.

Although the various codes and statements tend to highlight special groups of subjects, I believe the committee should pay particular attention to those in which a special relationship raises ethical issues. Patients of the investigating doctor, students, prisoners, children, etc. And I think the problem before any committee in these cases is the true value of that informed consent. As the cultural and ethical views of a community vary from nation to nation, it would be impossible to allow for all these in one general statement. However, I am sure that any committee established for an international role such as developed by CIOMS would keep this in mind in insisting on the ethical compliance in research projects on Humans.

Vilardell: I just wanted to make a little point concerning the ethical committees. We may have the impression that everything goes very well everywhere and it's simply this. I don't think that's the case. All the speakers who have been talking today were either from Scandinavian countries or English-speaking countries. Israel, you speak English very well, too. But certainly in other countries, things don't go as well. And if I may again quote the survey that we had at the World Congress of Gastroenterology, I found out that most of the people at the meeting had absolutely no idea of the Tokyo amendments to the Helsinki Declaration. They didn't know at all about them. That was six months ago. They knew about the Helsinki Declaration. They didn't know about the Tokyo amendments which are so important and have so much changed the whole field. There were more people answering that they know about an ethical committee in their own hospital than people knowing about the Tokyo amendments. So I surmise that probably many committees are working in hospitals unaware of the Tokyo amendments.

Riis: I would like to point to what Professor Vilardell said. Are there no snags within this? And I will try to do it by making a sort of checklist for those of you who have not created such a system. I would say from the beginning as a preamble that I think that

several systems could probably work and I won't try to sell you one of the Nordic ones. You have to ask yourself: Do we want regional covering? Do we want to include general practice, industry, epidemiological studies? And do we want to have full scientific covering? Do we want to include diagnostics, therapeutics and prevention? And not only create a system of clinical pharmacology. If I were a logician, I think I would express it in this way. Do you want a system being exhaustive and exclusive within your region? Do you want a system picking up all scientific ethical problems? And do you want a system where every project group exactly knows which kind of a system they're going to link to? And my argument for this starting point is that the citizen, at least in my country, I think it's global, is completely unaware of the dangers he's in, the risks he runs, the degrading treatment he might suffer from, whether it stems from a controlled trial in a hospital, whether he's a patient in general practice or whether he's employed in the medical industry or whatever situation he must be in.

The second question is: Do we want local committees instead of central ones, or a central one? The more local you make them, the less bureaucracy, but the more biased. And if you go to the extreme of thinking of the researcher as the one-person committee which is the old-fashioned system, you might educate him better and you'll have a very nice non-bureaucratic system but certainly rather much biased. But I'm in many ways in favor of this. I would point to the fact that ethics can be a disguised or masked excuse of a different nature in local circumstances. You can look upon a project, you can find that you don't like the researcher, you don't like the methods used, and then it's much easier to say this is unethical because this is in a way undebatable to point to bad ethics. It's much more difficult to say we don't want to use the money.

And the next question is do we want a central committee? Certainly you get much more bureaucracy, but you get less bias. And, at least in the Nordic countries, people are used to having an appeal body. So even if we're in favour of a decentralized system, the Nordic citizen, including the scientist in the Nordic countries, will often demand a system where he can address himself if he has got a "no" from some sort of board or authority. You might say that in this way we try to minimize the number of paranoiacs or even martyrs within our countries. This might be a specific trend within these Nordic tribes, but I think it's rather universal and you have to ask yourself the question do we want an appeal body, because then you must create a sort of central body, too.

Giertz: I very much agree with Dr. Riis and his suggestions. I think that local committees are the best. Not local in every hospital. We have in Sweden localized them to six places in each region. And I think that's a good thing. Because you must have

experienced people in every field. What is very necessary for a research committee is that the persons who are there really know what they are discussing. They must know and they must have experience and you must be in a committee for a long time to really realize what problems you have to judge about. And then about laymen. We started to have no laymen. We decided that because we thought it was very difficult for a layman to really make the right assessments in this rather difficult process. Nowadays, we have laymen, but just a few we need in each committee, and they are elected by the authorities of the hospital. So the hospital has an insight into the scientific work done in the region. I have some experience from another body. The Swedish Society of Medical Sciences has made a delegation for medical ethics where we try to make guidelines for the profession not only in research but more in other problems. And there we have laymen who are elected by the workmen's union, by the employer's union, by the university people and by the press. And I must say that I am extremely impressed with the work that these members are doing. So I don't hesitate to have them if they are elected in the right way. On the other hand, if you in the hospitals get people in our local committees who are most interested in not the ethical problems because always there are other problems - economic problems - what does this cost? Though you will have a quite new judgement, it's not research. They will try to review it in quite another way than we think ought to be the job of the committee.

There are a few projects that have been rejected in Sweden. But very, very many have been discussed. If we take the researcher into the committee and you discuss the problem, you make clear for him what we think is not too good. And then he alters it, and then it passes. And I have never had one where we haven't all been agreed - the research worker and the committee. But then in some instances the research worker has withdrawn his project. I think, to sum up, that we should be very careful having new regulations and more paragraphs. But we shall always discuss new paragraphs to remain conscious of the problems and to discuss our experiences.

Rapoport: Just a very few words. First of all, I very much join in my two preceding speakers in the following points. I think what you need is a spirit of general discussion and awareness. And I think this is served in various ways. Among others, it's by the fact that, as in our country, the medical and the para-medical professions include the nursing profession constantly present issues of ethics by philosophers, by physicians, by legal people. And I think they usually stimulate further discussion which is both public and is also discussed in the committees. I think this is one particular way in which you create an atmosphere. The second thing I feel is that what you do need is a system of committees. I don't think the question of central or local is really the whole issue. Some of the questions, for instance in

genetics, are so specialized that you do need a system of committees for that alone, and it's not easy to unite it with the business on the drugs. And the same goes for other fields, for instance radiation for which we also have a hierarchic system. For I do feel that the more committees, actually the better it is. If they work with the spirit and with the full conscience of and participation of the medical profession and of the lay-people, and if they do not feel themselves to be juridical bodies who pass final formal decisions.

And perhaps one word to Dr. Vilardell. The Tokyo Helsinki Declaration is well known in our country and I think some people are also conversant with the English language.

Black: Thank you very much. I'm not going to try to sum up the discussion, but I would like to bring out one or two points which seem to me to have gained something very like a consensus. I thought there was consensus that there should be lay membership of ethical committees, different types of lay membership was accepted at least by the majority. Then, I thought there was support for the idea that grant-giving bodies should require an ethical clearance from the appropriate committee before giving the money. Then, I've nothing really to add to what Dr. Riis said about the question of local or general committees. In relation to Dr. Nir's point, I think the operational unit is a unit where all the doctors know one another sufficiently to be able to form a judgement on their probable ethical conduct. And Israel may well be such a situation. Then I think I disagree with Dr. Riis on the business of one single vote killing a research proposal necessarily. And I think I'll come to a reason for that in my very closing remarks.

Before that, I'd like to take up Dr. Mabeck's point about general practice because this is very important. It's undercared for, if that's the right word at the moment. I think, at present, a great majority of clinical research done by family practitioners is in the context of controlled clinical trials. And I'd thought that they're almost agents and that the real ethical responsibility lay with the company, and with those who advise the company, on the nature and setting up of the trial.

Finally, I'd like to remind you of the point that Professor Curran made. He said that an ethical review committee was there to apply general principles to specific cases. And that meant to me that the committee must work with a good spirit. Now some people place restrictions on research, not because they think the research is unethical, but simply because they don't like research in general. It's rather like the puritans in our country who banned bear baiting, not because it was unpleasant for the bear, but because it gave pleasure to the spectators. So I think we have to be careful that we don't get people on ethical committees who are hostile to research. I think we want

people who have a positive attitude towards research, but at the same time are ethically conscious. So I would add one to the list of duties of the research committee, and that is that they have a duty to support research and not just to look at it.

FOURTH SESSION

SELECTION AND RECRUITMENT OF SUBJECTS

Moderator: Sir William Refshauge

SELECTION AND RECRUITMENT OF HEALTHY SUBJECTS IN RESEARCH

D.W. Vere

It must be agreed that some knowledge, needed for many worthwhile reasons, cannot be gained without human experiments, but few experiments are devoid of risk. For some procedures like venepuncture or liver biopsy, the risks are well known for the group, if not for the individual subjects. In new procedures, and always with new drug development, the risk is unknown, even for the group. Many volunteers do not understand the concept of risk. Some cannot understand it even when it has been carefully explained. Medical and other scientists are in a position of great power and prestige in relation to volunteer subjects. People may volunteer, or fail to volunteer, for the strangest reasons. Thus abuses can readily occur, and should be prevented.

Aims and objectives: These are some suggestions for ethically acceptable goals for human research: (a) to increase knowledge by the best practicable methods; (b) to minimize risks and inconvenience to volunteers; (c) to avoid all exploitation of volunteers; (d) to retain a proper respect for research; (e) to minimize the expenditure of scarce resources.

Selection: In each situation it is necessary to consider why normal volunteers should be selected at all. Why not animals, or indeed patients, at this stage in the growth of scientific knowledge of this subject?

It is always necessary to remember that volunteer selection is heavily biased by self-selection and by environmental factors. Self-selection is a powerful influence; the motives of volunteers vary enormously, and can be dangerous to themselves, to others and to the research project. An article about volunteers(1) was recently reviewed in a weekly newspaper, and was misunderstood to be an appeal for volunteers for drug tests rather than a discussion of the problems associated with such appeals. Even though no experiments had been described, many people then wrote to volunteer, and many of them disclosed their motives. Despite a clear statement that healthy persons were needed, most of these volunteers were, or had been, ill. Some hoped that they might be given a new remedy that might improve their

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1. Vere, D.W. "Testing New Drugs - the Human Volunteer". J. Medical Ethics: 1978, 4, 81-83

health. Some were simple, warmhearted people who had misunderstood almost every aspect of the work in hand. A few seemed to be of unsound mind. In fact only two out of about 30 were stated to be in full health, of appropriate age and sex, unmedicated and comprehending. One or two suggested that, such was their public spirit, they would be willing to accept risks unquestioningly. It would be easy to exploit such people, yet wrong to turn their helpfulness aside. This incident was most instructive.

Environmental factors largely determine selection. Employees in drug firms, the food industry, hospitals and research institutions are those most likely to see requests to volunteer. Medical students, idealistic and keen to become involved, are another such group. Should they bear the weight of this work? Are they not peculiarly vulnerable in that the pressures upon them to volunteer are very direct, and they may do so repeatedly, thus multiplying the risks they undergo? Are they not, by their profession, already incurring environmental risks which are akin to the risks of the tests for which they volunteer? When the experiments involve new drugs, young adult males are also selected, partly because teratogenicity and fertility testing awaits the later stages of drug development and so precludes the use of women. For other reasons children and the elderly are excluded. This raises questions about how representative the results of such research can be when applied to man in general.

Why should the normal elderly be excluded if disease does not exclude them? The reasons usually advanced is that if something went wrong they would react less well than would the young. But in many studies, for example with isotopes, older subjects are preferable. Volunteers may seem healthy when they are not. In some groups of young volunteers from industry abnormal concentrations of liver cell enzymes have been found in peripheral blood and the history then indicated that they were heavy drinkers. This prejudices their value as "normal" subjects. It is important always to supplement medical histories by material from the general practitioner and works medical officer. Quite apart from the need to gain assent to research procedures from the general practitioner, it is important to share his knowledge of that person as a patient. This should be added to a clinical examination in all relevant aspects made by the researcher himself; the adequacy of these examinations should be ascertained by the ethics committee.

Volunteers may also be self-selected according to how well they understand the small amount of information that they have at the start of a research procedure. The wording of a notice can have a markedly selective effect. Much is written about how to treat volunteers once they are such, but little about who they are and how they came to be selected.

It is, I would argue, part of the natural function of ethics committees to ensure that these aspects of volunteer selection are written into the protocols of tests; but not all volunteer studies are sent to an ethics committee.

Recruitment: I have already said that in each case it is necessary to ask whether normal volunteers should be recruited at all. If they are to be recruited, then the smallest number should be used that are likely to supply a useful and scientifically valid result. Human volunteers represent a scarce resource; it is unethical to use avoidably either more or less than are needed for an adequate test. One important aspect of this problem is the way in which numerous volunteers may be used to test procedures or treatments that contribute little to human betterment, while more worthwhile but less financially rewarding projects are neglected. Many further questions arise:

How should volunteers be recruited?
Who should recruit?
How can they be recruited without exploitation or duress?
How can the risks of investigations be explained and how can they be minimized?
Should any incentives be given?
How can goodwill be best mobilized ?

In each community there must exist some healthy adults who can and should contribute to the public health by volunteering for human experiments. Many of them also wish to do this for sound reasons. The problem is to find them and to use this resource of goodwill whilst avoiding people who might be harmed by their participation. So, the existing methods - biased as they are by self-selection and local pressures - have important difficulties. It is easy for an investigator, in his relief that someone has come forward, not to ask himself why that person may have volunteered, and whether they may be harmed by this. Busy investigators looking for volunteers naturally turn first to those in their immediate environment. This is no bad thing in some ways, for those nearest to them are often best informed, most aware of the dangers and other aspects both of the tests and of their perpetrators. But there are disadvantages too; those nearest to an investigator may be most liable to pressure, most beholden to him as juniors, as patients, as friends, as financial dependants. And local volunteering isolates the process of research from the community which, in the last analysis, has to pay for it whether by taxation, by prices or by foreign aid. This kind of separation fosters misunderstanding, ignorance and alienation. How much better it would be if an opportunity could be given throughout the community for any who wish to participate to offer their services? This opportunity would bring great problems but also great gains in social cohesion.

This naturally raises the question of who should do the recruiting and the explaining (for they must and do go together). The Medical Research Council of the UK suggested(2) that it should be the investigator, in the presence of a third party. Clearly, the investigator must take prime responsibility and be the prime agent. Non-scientists may wish to help in recruiting, but when left to themselves their support can be more hazardous than their opposition. The object is, after all, to avoid exploiting the volunteer, and this can only be assured if: (a) the tests to be made have been reviewed independently; (b) an adequate explanation of all aspects of an investigation are given to him, and understood by him, i.e. he should understand all that he can and needs to know to decide responsibly about himself, and what cannot be understood should be safeguarded by someone else who can understand it on his behalf; (c) the subject is exempt from all duress and inducement, be they financial, career, relationship or otherwise directed; (d) the subject's safety is guaranteed as far as possible, including his mental and physical safety, insurance and medical provision, and safety in the laboratory environment, and having regard to his family and dependants. Reports of adverse reactions to drugs should be submitted, without editing, to a confidential register kept by the national drug regulatory authority.

These are stringent criteria; they must be balanced to some degree against an informed volunteer's right to incur risk knowingly as an act of altruism. However such situations need be few, and should in general be avoided as much as possible. History is littered with examples of needless self-sacrifice, though these contrast refreshingly with selfish efforts.

Explaining risks is difficult. Even in the present state of quite satisfactory general education in Britain it is impossible to explain risks meaningfully to many people(3) and we find that we have to use an independent "subject's friend" or guarantor to show that the best possible explanation has been achieved. There is need for public learning, for adult education here, away from the immediate environment of laboratory work, for some appreciation of the nature of risk is useful in one's general approach to living, quite apart from scientific experiment. In countries at an earlier stage of development the problem is even harder, and the temptation to exploit peasant communities must be intense even in

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2. Medical Research Council, Annual Report for 1962-63, Cmnd. 2382, London, HMSO, 1964. Also British Medical Journal, 1964, 2. 177-178.

3. Vere, D.W. "Risks of Everyday Life - Drugs", Proceedings of the Royal Society of Medicine, 1975, 69. 106-107.

a paternalistic attempt to "do them good" in the long run. This attitude fails to respect their humanity and, when they later discover it, leads to rejection rather than gratitude. However, it is amazing how much can be achieved by patient, careful explanation to the more gifted natural leaders of such communities. It is right and necessary to abjure temporary gains that risk rejection later on. This rejection can go beyond the investigator and his work. It can spill over into a wider rejection of the drug firms, of drug therapy, of scientific research.

What about incentives? Human decision is a see-saw, tipped one way by discouraging factors and the other way by incentives. So incentives there must always be if there are to be volunteers. But how can we be sure that they are good incentives? Most would agree that any deceitful incentive is bad. One could wish that the prime incentive in us all would be to help other people, as well as oneself, and that that should be a sufficient stimulus to volunteers, i.e. that the incentive should be internal. Many investigators, no doubt moulded by experience, decide otherwise and offer gifts. What is a proper gift? I have discussed this problem elsewhere(4), for I have reason to think that gifts may not be what they seem to be. Material gain is a strong deluder. So are collective opinions. Sadly, what seems lacking is strong, individual, independent, ethical judgement.

How can goodwill be mobilized? People have barely begun to find out; research is still largely a "cottage industry" for all its scientific sophistication. We have found trade unions willing to help in locating volunteers, to be largely on the side of their members' interests, but liable to confuse political appearances with public benefit. Thus they can stimulate volunteers for reasons beyond the desire to further new drug development; reasons which they no doubt consider to be important, but which are better kept out of this reckoning. Managements are similar in that way if different in others; in short, there can be quite a lot of well-meant dishonesty. Could there be some independent organization, similar to a national blood transfusion service, with human well-being as its sole interest, or should we continue to use ambivalent organizations if only to keep them in touch with their need to make ethical decisions in the community, and so to avoid that isolation and alienation of research to which reference has already been made? One thing is clear. When research workers consider their own convenience rather than the public good, useful work is inevitably impeded, however long that moment of truth may take to arrive.

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4. Medical Research Council, Annual Report for 1962-63, Cmnd. 2382, London, HMSO, 1964. Also British Medical Journal, 1964, 2: 177-178.

Major discrepancies exist in several directions. Industry, in the main, pays volunteers for more than their reasonable expenses and loss of earnings, whereas many university departments do not, some because they believe the practice to be unethical. So, the debate here is about what should be done if, as may happen, no one volunteers for useful tests unless he is paid. I have even heard of one case where workers began industrial action to force up such payments.

The amount of information offered varies from that which is so little as to mislead and so induce that subject to volunteer, to that which is so much as to mislead and scare him away. Certainly, the very valuable doctrine that this is primarily the private responsibility of the investigator has led to disregard for any kind of uniform standards for the information offered.

I conducted a survey this year of all the volunteer studies and clinical trials that had been made of new products marketed in Britain within the last 4 years. Manufacturers who kindly completed the questionnaire revealed that about a third of these studies were not approved by an ethics committee. This seemed to happen chiefly in certain European countries, no doubt because they have another system in place of ethics committees. But there can be no doubt that some of the trials reported elsewhere would have been unlikely to pass a British ethics committee. Even allowing for local differences of customs, there is certainly no uniform standard about how volunteers should be recruited and cared for. This is the more remarkable when one considers the international character of the drug industry. New guidelines proposed in the USA by the National Institutes of Health are an attempt to gain some uniformity. Presumably they will not apply to tests of products which are not destined for the USA market. They may also impose new delays and difficulties for products which are directed to that market. And it is important not to hedge volunteering about with so many restrictions that work is driven from highly organized countries into other places.

Industrial confidences seem to prevent access to ethics committees in some places, but need and should not do this. The stage at which animal tests are deemed to be sufficient to permit tests in man varies from country to country. Here is surely a point where scientific agreement could be reached. New drug development in various countries often seems to be unrelated to the needs of the general populace of those countries or to their level of development. Insurance cover for volunteers is another aspect that lacks uniformity. In Britain, this is among the matters reviewed in current proposals for law reform. As courts tend to award ever-higher damages for drug injuries it becomes increasingly difficult to secure adequate insurance cover for clinical experiments. A growing emphasis on bioavailability testing will increase the number of tests made in healthy man, so increasing drug exposure and reducing

the scarce pool of volunteers(5). To the ethics problems there must be added legal difficulties; they overlap but are not the same. But courts will certainly take the rulings of ethics committees into account.

Summary

To summarize the argument, recruitment, selection and explanation about experiments are all inextricably mixed together. Explanation is usually considered only in relation to consent but it is equally relevant to recruitment. Whether or not someone volunteers, and what induces him to volunteer can be influenced sensitively by the ways in which communication occurs. Volunteers tend to be either professional colleagues and workfellows of the researcher, who may be well informed but may tend to volunteer too often under local inducements, or to be uninformed people of goodwill, or self-seeking for all kinds of odd reasons, who volunteer for something they have not understood or could not understand. In peasant communities this latter problem becomes acute. In particular, the explanation of risk is very difficult, evoking diametrically opposite but equally meaningless responses among groups of naïve subjects. Financial incentives are curiously difficult to evaluate from an ethical point of view.

Who should do the recruiting, and who should supervise its ethical quality? Since there are large, untapped resources of goodwill in the community, one might argue for national organizations to do this, rather like the blood transfusion services. However, giving blood is largely without risk even if there has been financial exploitation in places from time to time. The danger of a national drug trial volunteer service would, in my opinion, be that in the present state of public information about drugs, even in the more developed countries, many would volunteer for inappropriate and harmful reasons. This is not some paternalistic wish to stop such public systems. It is a plea that public education about medical therapy needs to come first. When people can understand a problem, they should be allowed to react as they wish towards it. The objective is to avoid exploitation, which, I believe, still occurs in many subtle ways, disguised behind the truism that "people want to volunteer". So, I am proposing that:

(i) public consultation about the risks and benefits of research in healthy volunteers;

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5. Association of the British Pharmaceutical Industry. Report of the Committee to Investigate Medical Experiments on Staff Volunteers. London, 1970.

(ii) The supervision of the ethics of experiments can only be done by the investigators themselves, together with their informed but independent peers. Though some nations do not yet accept the idea, I submit that this can only mean local ethics committees to which all human experiments must be submitted. Journal editors won't do; much human experiment is never published. And ethics committees should include amongst their tasks not only the proposed research procedures, but also the methods of recruitment of, and explanation to, volunteers. Sound investigators are happy to have their methods surveyed by competent colleagues. But enthusiasm and self-belief can delude the best of scientists at times; detached judgement is needed. This can only be supplied by those who are not parties to the work but who are competent to join the group that authorizes it. So, ethics committees should provide safeguards in terms of information given, independent review, payment and withdrawal criteria.

(iii) Progress could be made towards uniformity of standards for volunteer tests between nations. A little progress has been made in reducing the needs for repetitive tests. The need for uniformity should not outweigh legitimate differences between nations where these can be identified.

(iv) Some developing countries might do best to promote only new research developments that are in the interests of their own people. But a general rule to this effect would be extremely damaging; after all many procedures and remedies which have benefitted the whole world have been tested within the nation of their origin. The best yardstick may be the level of education of the volunteers, with the suggestion that the strong should help the weak and not the reverse. New knowledge is needed, for example about normal physiology and about new drugs. It is crucially important that the process by which it is gained can be respected. People can only respect work which can be seen to be helpful broadly to their own community. Other policies will result in loss of confidence in research and in those who do it, for a cheap advantage seized today is tomorrow's loss.

SELECTION AND RECRUITMENT OF PATIENTS FOR BIOMEDICAL EXPERIMENTS

K. Gibinski

Selection and recruitment of patients for biomedical experiments seems to look better, and in some respects easier, than that of healthy subjects. This is especially valid as far as diagnostic and therapeutic procedures are concerned. The opportunity of being better examined by a new and promising method, or with new sophisticated equipment, or of being treated in the most modern way, is often considered by the patient as a lucky happening. It is enough if a doctor says he has a new apparatus, or that it is available in the neighborhood, that it is electronic, fully automatic and infallible, to get the patient's approval. The happy patient does not think that doctor is just gathering personal experience with the new tool; even if the doctor frankly says he is the first or the third case examined this way, the patient will enthusiastically believe in the new method because his faith in the continuous progress of omnipotent science and technology has been deeply implanted by the mass media. And he does not realize that everyday life presents such a complicated multifaceted and changing system that it is not to be compared with the relatively simple experimental conditions of each innovation discovered in a laboratory.

In fact, medicine originally grew out of observations of man in health and disease, and experiment in man is as old as medicine. What has changed during the centuries is the accessibility of the hidden organs, and the dimensions and accuracy of measurement. A famous example in the history of medicine is the observations on the function of stomach made by the American surgeon Beaumont on his patient Alexis St. Martin. Heroic experiments of many bacteriologists carried out on themselves have been widely admired, and there are many well-known recent experiments and field studies on human adaptation to changing environment, e. g. to heat. We admire the present experiments on man carried out in space. And we have only recently realized that, in fact, each administration of any registered drug to man is a small experiment, because we can never predict the individual tolerance of any particular drug and the patient's response to it may be unexpected. Thus, our every-day practice may be regarded as unintended experimentation to gather experience(14) in the worst possible way: by trial and error. By such practice, without first studying the usefulness of a new drug in man, we are planning errors that can sometimes have terrible consequences for many subjects. These errors could be minimized by both previous and prospective well-controlled studies.

New research achievements originate from knowledge and logic, and must be based, step by step, on a series of proper experiments.

The final evaluation takes place after many years with respect given to the risk/benefit and cost/benefit ratios(13). A real breakthrough is rare. In most cases innovations bring relatively small, though important, numerical gains or losses. Clinical trials must therefore be regularly designed to assess results accurately and reliably.

We cannot abandon our duty towards society by avoiding carefully planned studies in man and choosing instead the worst method, that of treating patients and waiting until sombody claims that the drug should be banned because of its delayed toxicity or its oncogenicity, etc. The conviction that organized study is an experiment while simple treatment is our medical duty is false. It is the controlled study that is much safer for patients than the free use of new drugs, even though they may already have been registered. Our society must learn and must face this truth, and willingly take part in evaluation of all approved innovations in therapeutics tested in man for efficacy, safety, superiority to the old measures, economy, etc.

But, therapeutics is only one, perhaps the most common and most controversial field of so-called "human experimentation". Each systematic trial of a new device or of a new therapy is usually considered and initially undertaken with great optimism. It is believed, for a number of reasons, that the new method will prove to be highly superior to old models or to a standard therapy: preliminary experience seems to provide good evidence for this. This initial optimism, however, very often turns out to be unjustified. This situation existed in the past as it does at present, for example, in such large diagnostic areas as angiography, isotope techniques, endoscopy, cardiac monitoring, clinical enzymology and many others. Although none of these techniques is younger than 20 years, their place in diagnostics does not seem to be definitely established. Sometimes rapid progress and development of innovations stimulates the replacement of previous methods by new ones, although the former have not become obsolete or been sufficiently explored.

Selection of Patients for Diagnostic Procedures

Studies intended to evaluate new diagnostic procedures present a different problem. They aim either to bring a confirmation or to deny the diagnostic working hypothesis. Their positive or negative results are expected a priori, and therefore patients do not think of them as experiments. To tell the patient that a new treatment will bring either positive or negative results gives it the appearance of an experiment.

Usually no substantial objection can be raised against the specific character and accuracy of diagnostic methods and procedures that have been previously sufficiently tested in animals. Cost can also be calculated before application to man. The problem is that of their tolerance, because many new techniques are invasive and even

aggressive to man. Their findings are expected to confirm or to deny the diagnostic hypotheses first postulated; sometimes the finding may be inconclusive, and in such case the examination appears to have been performed in vain.

It is the responsibility of the doctor to decide which case should be selected and assigned to a hazardous procedure. The doctor, however, facing the world of diversity represented by the patient population can rely on nobody but himself before he acquires some experience. It may happen that after a few initial misfortunes he gives up, and does not use the method any more, although later on it may turn out to be acceptable in the light of worldwide experience. Until this common experience is acquired no doctor can hide behind a written "informed consent" of a patient. The problem is that of his personal qualifications and responsibility(12). No regulation can help him. The only solution seems to be to select the proper places and the proper doctors who would be able to select the right patients for such procedures, and these doctors should be nominated by a sort of professional standard review board(9).

It is not possible to explain to patients all these nuances. All we have to do is to assure them that everything that is being applied to man has been appropriately pre-tested, and that a highly competent body is supervising each project. The problem is not how to explain the matter to the patients and to look for volunteers, or how to recruit them, but to reach such a situation in which we could select the most suitable patients for the trials from many volunteers ready to contribute to the progress and safety of medicine.

Selection of Patients for Experimental Therapy

The situation in therapeutics largely resembles that in diagnostics. People are fed with news announcing miraculous drugs and methods of treatment (e.g. anti-atherosclerotic diets or weight reducing diets) before they have been proved really effective or safe in man, etc. There is a substantial difference between demonstrating a quick pharmacologic effect of a new drug, e.g. lowering the blood pressure or plasma cholesterol concentration or blood coagulability, and proving that such particular treatment is really beneficial to the patient in long-term therapy of the relevant disease (23).

Again, people have great confidence in new potent drugs because they have learnt that they are really active, and superior to many doubtful former preparations that quickly disappear from the list of registered drugs; and in that they are right. People insist on having new drugs prescribed that are more and more potent and bring prompt relief.

The law of supply and demand begins to work, and the physician follows it, sometimes being ashamed that he has never heard of and does

not know the preparation the patient demands. This is a double pressure; that of the insistent patients, and that of the doctor's consciouness of possible defects in his education.

Any diagnostic procedure has to confirm or to deny the doctor's hypothesis, and this is its object. In the case of therapeutic measures, it very often is difficult to predict if the final goal can be reached at all. This is true even if the goal is a symptomatic relief, e. g. from extra-systoles, pyrosis, diarrhea, insomnia or headache. Again, though the pharmacodynamics and potential toxicity are basically known from pre-clinical studies, something unexpected may be encountered due to different bioavailability or pharmacokinetics, and the hidden peculiarities of any human individual (3, 5, 16). Even the results gained in well-controlled, prospective, multicentre, clinical trials are unlikely to be valid for the whole range of patients suffering from a given condition(15).

Pathophysiology

Sometimes experiments made in man neither result in a diagnosis nor help the patient. They are basically planned to solve some obscure problems of pathophysiology or morbid mechanisms that cannot be solved in healthy subjects because these do not meet the requirement of having an altered function or a damaged organ, nor in animals if no suitable animal model is available. Sometimes experiments in normal physiology are also carried out on patients if a justified assumption exists that their illness or disability does not affect the organ or function under study. This is an essential requirement for selection of volunteers. Inpatients are especially convenient material for experiments because they are for a longer time in the hands of the medical staff in a research hospital medical centre, their living conditions may be easily unified there and they can be under surveillance in the best way. All experiments in this group are usually planned very carefully and safely, and are not really a threat to the subjects (8). Being unconnected with any possible benefit, the consent of the subjects is fully objective and conscious. However, although these patients have no motivation to be subjected to the experiments because they cannot expect any profit for their own health, they may feel dependent and grateful to the staff for the medical care and nursing offered to them in their illness. They may feel themselves to be in an awkward position if they refuse, and thus their consent may not be so voluntary as it is considered. I fear that many new drug studies, so-called "first time in man"(5), are done in this way. The study may be a single test of bioavailability, of pharmacokinetics or even pharmacodynamics.

The recruitment of patients for biomedical research should be considered separately in the three particular fields I have mentioned.

Recruitment in Diagnostics

The situation in the field of diagnostics seems to be the simplest. Any procedure should be allowed if it really can bring valuable data necessary for the diagnosis, providing no other less offensive procedure can bring similar results. The conditions for recruitment are: proper indication, lack of contraindication, low risk/benefit ratio, sufficient training of the staff and the necessary facilities. Thus, it is not so much a problem of recruitment of patients, because they present themselves to us at random, but that of recruitment of responsible doctors. Gathering and evaluating the current clinical material and comparing it with other, e. g. older, methods is necessary for further improvement.

Social ethics demands that special techniques, more aggressive and bearing more risk should not be commonly accessible to the medical staff, but should be allowed only in centres that apparently meet requirements. This requires special national bodies to select and survey such centres, such as the Professional Standard Review Organization in the USA(9). Its task is to monitor and to supervise the quality of medical care in order to create the proper conditions for good practice, rather than the fear that unsatisfactory practice will be discovered.

Recruitment in Therapeutics

The problem is completely different if we do not have to diagnose the patients but to assess the value of a drug. If a new drug seems to be life-saving in a particular case, its use may be much justified, although there may be a risk of severe side effects. In this case the situation may be similar to that of a risky procedure that is expected to provide an important diagnosis. In a helpless situation, no chance of administration of a new drug that is under trial should be refused to the patient, in disregard of its doubtful safety. The excuse that the homogeneity of the clinical material will be disturbed in such a case cannot be accepted. The evaluation of a drug may be much more difficult in these conditions, but it is the problem of not refusing the drug rather, than of allocating a patient to the trial.

Real problems arise when a drug to be tested is not unique for a given disease or when it is not a life-saving one. It becomes more difficult if the new drug is one among several others exerting similar effects. The problem to be tested, then, is that of a higher efficacy, or of higher specificity, or of less toxicity, or of more comfortable administration or of lower cost. The only sensible introduction of a new drug is when it offers an advantage in comparison with other drugs. The difference may be very specific and clearly apparent in polysymptomatic disease; it may be related to age or to sex; may disappear in complicated cases; may be abolished by other drugs taken simultaneously and so on. These conditions concern mostly chronic diseases. Thus a new problem arises of proper selection and suitability of patients for the trial. The necessary conditions must be declared for each study. Each study must

comprise quite a large series of patients. They must be divided into comparable groups at least two, sometimes more. Each group must be numerous enough to warrant proper statistical evaluation. In the case of a rare disease, gathering a satisfactory number of patients suitable for the trial conditions may be very difficult, and may prolong the study considerably.

Basically all patients meeting the requirements should enter the trial. However, they must be warned about the experimental character of the intended therapy. The more nervous do not agree to sign their consent. Thus, there is self-limitation of the number of patients which further diminishes the number of subjects tested. The main task of a physician is to take care of a patient for whom he is responsible. Some authors (10) postulate that a doctor can recommend - with a good conscience - participation in a randomized trial only if he feels that the prospects of benefit seem equivalent to all the methods of treatment. When the value of two comparable drugs is unequal, the allocation of patients to one group or another imposes on the doctor a serious moral problem. This is most striking if a placebo group is used. A placebo seems to be the most reliable basis for comparison(21, 22) because the so-called (positive) placebo effect may be disregarded, which diminishes falsification of the results. However, there are only very few instances in which a placebo may be used for no patient would agree to take an absolutely inactive preparation, and to deceive him is unacceptable. For ethical reasons it is also unacceptable to give the patient a placebo in life-threatening situations or in an acute disease. Administration of a placebo for a long term in chronic diseases prolongs ailments and precludes amelioration, and that is why it will be accepted neither by ethicists nor by the patient himself.

Lack of knowledge of the natural history of most of the chronic diseases always requires a very long treatment in order to avoid false conclusions due to spontaneous remissions. Some of these diseases affect patients both with good and with bad prospects, and therefore the outcome of the trial usually remains unpredictable for a long time. The ratio of these different patients may vary considerably in the trial groups, and this may influence the final result more than the drugs administered.

In some diseases the risk factors are quite well known. Systematic controlled trials of an active intervention against these risk factors open a new way for reducing them, as well as the related morbidity and mortality(6). To what extent is the detailed explanation and informed consent of large social groups needed to start such a study? We know that in some regions iodized salt was distributed to shops instead of pure salt in order to reduce epidemic goitre, without the written consent of each citizen in these areas. Were human rights unacceptably disregarded by nation-wide vaccination and immunization made obligatory by governments in order to combat and eradicate some infectious diseases?

Moral Problems

All the difficulties listed above make the problem of recruitment of suitable patients to the trial difficult. A view has been expressed(20), and is shared by several authors, that the patient should play a more active role in his own treatment, while the physician's role is to help, guide and encourage him (not discourage by horrifying explanation). It is essential for the final result of the treatment that the patient is motivated and willing to cooperate.

The patient has certainly the right to get necessary explanations that he wants. Such explanations must always be at the level of his comprehension. The doctor's approach to the patient must be individual; it often determines acceptance or rejection of the proposed diagnostic or therapeutic procedure. We should always keep in mind that the patient is under the pressure of his emotional state due to the disease itself, to the strange social environment in the hospital, horrifying apparatus, etc., which may highly influence his decision. The doctor's task should be not to derationalize his decision by talking about matters that are absolutely strange to him, but to help him to understand the rationale of the therapy.

The Patient's Consent

Though "informed consent" is a separate subject to be discussed later, it should not be entirely omitted in the discussion of the recruitment of patients for experimental therapy or similar purposes.

The doctrine of informed consent as formulated by lawyers(1) seems to be an example of soft law because of the many exceptions that are not clearcut. A large book has recently been published showing all the complexities of this seemingly simple procedure(2). Instructions about getting a written record of patient's consent presented under item 4. 1. in the "Principles for the Clinical Evaluation of Drugs" issued by WHO(21, 22) seem very well balanced. On the other hand the bureaucratic attempts at "practical" formalization of this task, such as the already published form of written consent established by the State legislature of Ohio(1) may be considered as frightening.

It becomes evident that insufficient research has been devoted to assessing risk and benefit, as well as cost:benefit ratios of many new diagnostic, therapeutic and prophylactic measures just coming into use, as also those practiced for several years(10).

It seems absolutely certain that public understanding of vital health matters is inadequate as can be seen, for instance, from the rising alcohol and tobacco consumption all over the world(4, 6, 19). Many other instances could be quoted here. Which is the less ethical? Not to explain in detail all the possible injuries connected with the diagnostic method and simply inform the patient that up till now acquired experience of the

intended procedure is very limited; or to arouse in the patient fear and doubts resulting in his renunciation of a diagnostic method and, thus possible later therapeutic consequences? Is it ethical that innovations in medical practice are unintentionally confined to courageous people only, while made inaccessible to those of more timorous character? Or is it ethical that more educated people can easier evaluate their risk/benefit ratio and decide under severe emotional stress to undergo the proposed examination or therapy, while the simple-minded, frightened by learning of hazards and underestimating the danger of the disease of which they know very little, because for some psychological reasons they have not been informed in detail by the doctors?

Surgery

Increasing frequency of adverse reactions to drugs has resulted in the opinion expressed already that mankind was entering a period of safe surgery and increasingly unsafe pharmacotherapy(18).

Requirements imposed upon the registration of new drugs have increased considerably, as have the numerous voices in defence of the human rights of the volunteers and patients subjected to drug evaluation trials. An incomprehensible situation has been created by rigorous requirements for minute designs and protocols of intended studies on new drugs, for their approval by ethical committees, for controlled performance in man with full documentation and careful follow-up observation; while surgical operations may or may not be tested in animals, may be introduced in practice with or without a reviewing body, and need not necessarily be subjected to a long-term follow-up study(7). It is a traditional habit that everybody signs his consent on his patient's record when entering a surgical ward. Very often he does it before it is decided what kind of operation will be done, if any. Some planned operations, e.g. jejuno-ileal bypass, have found many partisans despite very critical evaluation by many other surgeons, the former disregarding the clamour questioning the ethical justification for such a crippling and sometimes debilitating operation.

The surgeons have, however, strong arguments: without the initial period of operation for mitral stenosis with a mortality rate exceeding 50%, we would never have arrived at the quite safe valvulotomy of today. This does not mean that surgeons want to avoid any control. They advocate a continued surveillance maintained at a necessary minimum level to allow for a long-term evaluation of results and the risk/benefit ratio; instead of a separate permission for each project being required they maintain that new procedures should be carried out only at institutions approved for such purposes and working under the surveillance of local and central agencies designated "institutes of health assessment"(7).

I fear that at the present time we cannot overlook that there is an aspect of art in medical practice which cannot be absolutely schematic, and defined in all possible details by rules and bye-laws(17). We must fight for some human rights of freedom for doctors too, so that they can do everything beneficial to the patient even if something is not included in formal terms, dictionaries, handbooks, legal regulations or written tests for special qualifications. A surgeon who, after opening the abdomen and facing a strange situation, is prompted to alter the former plan of operation, is allowed to improvise the procedure according to what he actually finds. Why are new adaptations of surgical manoeuvres and procedures acceptable, while adaptive innovations in pharmacotherapy are said to be unacceptable experiments even if they are cautiously prepared and verified in preclinical studies?

I do not intend to contest the rule of informed consent given and signed by the patient. However, its importance should not be overestimated. The patient's decision will always involve a factor of confidence or trust and never will be based on comprehension alone.

I think that the shadow of the Second World War and the memory of cruel experiments on man judged in the Nuremberg trials influence our thinking on all the present activities concerning human rights and experimentation in man. I believe, however, that the heart of the matter judged and condemned at Nuremberg was not human experimentation as the irreplaceable source of knowledge, but cruelty and dehumanization.

A patient's or a volunteer's signing of the "informed consent" form cannot be considered the main key for the promotion of biomedical research in man on a large scale.

It is clear that we cannot refuse to all doctors, neither to confer on all of them, the right to make free biomedical experiments. The decision to fire is not conferred on every soldier in the army, but on the highest commander only.

Final Remarks

The most promising approach to overcome the present barrier in human experimentation seems to be in:

1. Formation of an independent State body that: a) watches the policies in health services and the most important social health indices; b) organizes nation-wide mass surveys; c) authorizes some doctors or groups of doctors to carry out innovative studies, taking into account the facilities they have at their disposal. The authorization should be limited in time and must be renewed after X years; d) surveys the regional ethical committees that evaluate draft proposals for studies in man.

2. Changing the common human attitude, adverse to any experiment in humans, by stimulating the consciousness that without society's active and ready participation medicine will not be able to further improve social health(11). An atmosphere of confidence must be created. Searching for a few patients for a clinical trial or experiment must be replaced by selection of the most suitable from among numerous volunteers ready for experimental therapy, or for other study intended to promote progress in medicine and to improve health.

My opinion is that of a clinician who started his professional activity 40 years ago, and who witnessed all the changes occurring in this profession in the time-span in which both medical science and medical practice, underwent an enormous change. Only by considering the problems discussed above in a perspective approach that permits a backward and forward view offers a possibility that permits of taking a position that would fit a given time and a given level of development, say 1978, and that will inevitably be forced to change further in the coming years.

Although progress in medical science, in modern equipment and techniques, and in medication is enormous, and is able to accomplish astounding therapeutic victories in particular cases that were impossible in the past, the same heroic methods and facilities, applied on a global scale, so often produce iatrogenic disease and death that did not exist formerly. The capabilities of medicine, great as they are, have been oversold. Certainly there are doctors aware of the real limitations, but the organized profession, e. g. the health service as a whole is overconfident in medical omniscience and omnipotence. Only few realize that we are "doing better while feeling worse". Because medical practice is not able to keep pace with scientific and technical progress, because the latter is not verified sufficiently as to how and to what extent it can bestow a real benefit on man. Another very important problem is how we can expect a physician to live in an ultratechnological and impersonal society without acquiring the characteristics of this society. To expect that doctors only will preserve all the old virtues such as humanity, compassion and devotion, while society abandons this old-fashioned burden, may easily appear an absurdity. Such are the roots of dehumanization of medicine.

I think that in this rapidly changing world with an unknown future and fate, we have to be careful not to deprive medicine either of a scientific background or of a scientific approach (scientific is only that which can be measured); or of commonsense in our medical thinking, and the habit of thinking; or of some kind of art in personal contact with the patient; or of the personal responsibility of each doctor. Overregulations and bureaucratization hinder human skill in adapting to meet the infinite variety of problems and situations the doctor encounters in

his everyday practice and has to solve. That is why I think that the rules we are talking about must be soft, but the surveillance of scientific activity must be as clearsighted and keen as possible.

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SELECTION AND RECRUITMENT OF INSTITUTIONALIZED SUBJECTS

J.S. Neki

Medical research, with man as the research object, has increased tremendously over the last half a century all over the world. Among the reasons for such increase are (a) the pharmaceutical industry, which has provided the medical profession with a large array of new, potent and often life-saving drugs, and which promotes biomedical research as one of its vested interests; and (b) the great consideration given to research productivity in the matter of professional promotions in the medical field, especially to prestigious academic positions. Forces of prevailing competition make it obligatory for ambitious medical men in the academic field and certain drug houses to undertake research and publish results as quickly as possible. Cutthroat competition, not unexpectedly, can lead to unscrupulous practices - hence the need for protecting human rights, man being the object of most of such research. This has called for regulatory measures. These have been of two kinds: (i) statutory and (ii) peer-review type.

One of the areas for such regulatory procedures has been selection and recruitment of subjects. However, selection and recruitment of researchers has received scant attention. Hence I seek indulgence to talk about it parenthetically. Besides intellectual excellence and creative urge, the personal characteristics needed in a researcher are ethical scrupulousness and honesty, perseverance and a high threshold for frustration. However, hardly anywhere is a premium placed on looking for these fundamental qualities in the research worker. Selection of subjects has, on the other hand, received considerable attention, especially in the matter of 'informed consent'.

Institutionalized Subjects

The one area from which subjects are more copiously drawn than any other are the institutions. Institutionalized subjects are preferred involved in medical research for a variety of reasons. They are more easily available in large numbers in a compact geographical area. They remain available over relatively longer periods of time with a lesser risk of drop-out compared with subjects from most other sources. They live under uniform living conditions (while in the institution) and these conditions can be well controlled. The subjects can be subjected to as intense or prolonged observation as required. Moreover, in case of any adverse effects of the research procedures, there is a ready availability of emergency and other remedial and restitutive procedures.

Medical institutions, particularly hospitals, have ingrained traditions of patient care. Demands of research and of patient care may be congruent with each other in some cases (as, e. g. in retrospective studies of treatment procedures), they may be overlapping in others, or

the two might be independent of one another (as, e.g. in some community surveys). However, problems arise when research aims interfere with patient care or conflict with it. Conversely, there are qualms of conscience if methods employed for patient care have not resulted from modern scientific research (as, e.g. certain homeopathic or folk remedies, or such procedures as acupuncture). Nonetheless, sound traditions of patient care in these institutions can insulate the patients against onslaughts of research not directly related to patient care.

In the treatment of the sick person, new therapeutic measures may be employed by the treating clinician if in his judgement these offer hope of saving life, restoring the patient to health or alleviating suffering. In such a case, consistent with patient psychology, the doctor must obtain the patient's freely given informed consent, or that of his legal guardian in case of legal incapacity of the patient. Subjects from institutions have a strong dependency relationship with the treating physician, and can succumb more easily to giving formal consent to research procedures. How far such a consent would be ethically appropriate, is a moot question, for one can easily discern an element of veiled and unwitting coercion in it - arising from the dynamics of the doctor-patient relationship itself.

The ready availability of resuscitative and other emergency measures in the institutions can sometimes encourage the researcher to show excessive bravado in going ahead even with some of the potentially hazardous research procedures. When the researcher is confident that the wherewithal to manage side-effects of his research procedures is available, he can become extra bold.

Again, in the institutions, there is a greater chance of abuse of goodwill and deception. The blind written consent (for surgical operation and anaesthetic of any kind) obtained from all patients who are admitted to surgical wards of most of our hospitals is one such instance. It should be borne in mind that the responsibility of clinical research always remains with the researcher; it never falls on the subject, even after written consent has been obtained.

Another peculiarity specific to institutionalized subjects is their mutual contact. Patients in the ward often exchange notes - especially if they are suffering from the same condition, receiving similar treatment and more so if participating in the same research project. I have personal knowledge of double-blind trials of drugs, where although the researcher was unaware of who was receiving what - the pharmacologically active drug or placebo - the patients had all guessed this correctly on the basis of their mutual discussions of the effects experienced by them.

Finally, some of the institutions, particularly psychiatric hospitals and homes for the mentally retarded, are often less open to public view and review. In such institutions, there is a greater likelihood of patients being treated as guinea-pigs in an unscrupulous way. I am personally aware of patients treated with intrathecal administration of a crude alcoholic extract of a herb (without any antecedent animal studies) carried out in a poorly staffed large-sized mental hospital. I am also aware of a sizeable series of prefrontal leucotomies carried out on mental retardates in an institution during the initial zeal period of this procedure. Notwithstanding these limitations, institutionalized subjects have been and will continue to be objects of biomedical research in a major way.

Selection and Recruitment

For the selection of subjects, the primary criteria obviously would be the inclusion criteria of the research project. Similarly, the limiting criteria would be the exclusion criteria prescribed in the research protocol.

However, these determine only potential subjects. Recruitment of actual subjects from among the potential ones would depend on their motivation. Due caution needs to be exercised in motivating these subjects and evaluating their motivation. How much information about the research project needs be provided to the prospective subject and how much withheld is a moot point. There is, one the one hand, the possibility of telling too much, which is fraught with the dangers of causing injury to the process of motivation as well as fracturing the doctor-patient relationship. On the other hand, one may tell too little, or suppress essential information, and thus obtain only uninformed consent.

One has also to be mindful of the emotional state of the prospective subject and of those of his personality characteristics that have direct relevance to motivation. Paranoid patients are not only hard to motivate but are also overcritical and suspicious. They are also impulsive, and often aggressive and litigious. Hence great caution needs to be exercised in taking them up for research purposes. The depressive personalities are more prone to give up and hence more likely to drop out. The obsessionals ask too many details. The anxious patient often wavers indecisively. Such patients are the researcher's bugbear. However, it is the immature and the dependent persons that put themselves passively and often uncritically into the hands of the researcher. It is the duty of the researcher to build safeguards that should protect such a person from exploitation.

The Question of Consent

The question of consent has been debated more copiously than any other ethical issue concerned with medical research. Criteria of adequate

informed consent have already been discussed in great detail in the paper by Professor Dickens. Certain aspects of consent from institutionalized subjects may be discussed here.

Most subjects in psychiatric hospitals and homes for the mentally retarded are, by virtue of the character of their specific disorder, incapacitated from giving their consent. Consent can be obtained from their legal guardians on their behalf and, where possible, in addition to their own consent; but would this consent be valid? An important issue worth bearing in mind is that such a consent obtained from a guardian alone does not provide a tenable ground for defence in case of a law suit. This implies a great dilemma. One cannot obtain adequate informed consent from the psychotic, for example; but on whom else can one conduct a trial for instance, of antipsychotic drugs or psychosurgical procedures? Needless to re-emphasize that it is precisely this kind of patient population that has suffered the greatest injustice involving violation of human rights at the hands of enthusiastic but unscrupulous researchers.

Another important segment of patient population which one must not ignore is the illiterate patient, who constitute a major bulk of such populations in the developing world. The illiterate person, being less well-informed and less sophisticated, asks the doctor fewer questions, and often has more implicit faith on him. This faith can easily become subject to misuse and abuse. What safeguards can be built against such misuse? One might also ponder over the fact that written consent from an enlightened and literate person signifies one thing and that from an illiterate person quite another.

Control Subjects

Control subjects are often drawn from institutions - the reasons being the same as for experimental subjects. Hospital populations can be used by selecting subjects who do not suffer from afflictions of the organ-systems, that are under the experimental enquiry. Alternatively, recruits for the control group can be drawn from institutions from where supposedly healthy subjects are available. One such kind of institution is the jail. When volunteers are drawn from jails, how far can their consent be considered adequate? These subjects are often motivated by such incentives as parole, amelioration of term conditions, reduction in term period, etc. When thus motivated, the consent obtained becomes constrained and therefore questionable. How far is such a person, for example, in a position to withdraw his consent?

The Question of Numbers

Since subjects are available in good numbers in institutions, large series of subjects can be drawn from them. One comes across, in literature, many studies where the primary attempt has been to impress by virtue of largeness of the series. Even the demands of statistical

sampling have limitations, and larger series unwarranted by such demands are clearly unjustifiable.

Conclusion

Before concluding, I would like to say that, before considering the selection of subjects, certain other basic issues ought to be attended to. As far as possible, research should have a direct bearing on diagnosis and/or treatment of patients, it should have kept in view proper indications and contra-indications and should have high benefit/risk ratio. In the scientific application of medical research it is the duty of the researcher to remain the protector of the life and health of the person on whom this research is carried out. To carry out research, properly trained, adequately motivated staff of an adequate and befitting personality make up need be employed. Finally, greater ethical caution needs to be exercised when selecting subjects suffering from legal incapacity.

Recommendations

Every institution from which subjects for research are recruited must set up a Research Ethics Monitoring Committee that should ensure:

A. Initial evaluation: going into the following issues:

i) Does the proposed research procedure ensure sufficient safeguards with respect to safety to the life and health of the subjects to be taken up for study?

ii) Has free and informed consent of the subjects involved been obtained? How has the "freedom" been ensured? Has sufficient information relating to the research project been provided to the subject? Have the risks of procedures involved been adequately explained? Have the test-procedures involved been evaluated independently with regard to their safety?

iii) Has the possibility that the subjects may have been recruited under duress been reasonably excluded?

iv) If any incentives have been employed to compensate the subjects, are they judicious and not acting as a positive allurement?

v) In the case of illiterate or mentally retarded subjects, has it been ensured that they have understood the nature of procedures to which they are going to be subjected?

B. Ongoing monitoring: The Monitoring Committee should review all reports (which should be obligatory for investigators to submit),

regarding any ill-effects of the research procedures and advise in the light of its findings whether the research should go on as it is, have its methodology modified or be abandoned altogether.

C. Retrospective review: A retrospective review of every completed or abandoned research project should be made by the Monitoring Committee and guidelines drawn up for any future research projects of similar nature.

ETHICAL CONSIDERATIONS IN THE SELECTION AND RECRUITMENT OF CHILDREN FOR RESEARCH

Robert E. Cooke

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has finally completed the several assignments given to it by the Congress of the United States of America(1). The Commission studied and reported on research involving the fetus, on research involving prisoners, on research involving the institutionalized mentally infirm, on the practice of psychosurgery and on several other subjects including research on children.

The Commission labored longer and had more difficulty in arriving at its recommendations regarding children than it did with any of its other charges. Research involving children presented more areas for difference than in all previous deliberations. The selection and recruitment of subjects were at the heart of the arguments. Can a subject be enrolled in a research project in the absence of sufficient maturity to understand and appreciate fully the benefits and risks of research? That question remains the key issue for this conference as well.

Hauerwas in his paper to the Commission on Ethical Issues in the Use of Human Subjects affirms this belief:

> "The ethical issues raised by the use of prisoners and the poor seem simple when compared to the problems involved in the use of children and other non-competents. In order to develop certain kinds of drugs or procedures we can do all the animal and adult testing we want and still we must finally test on children - i.e., a test group who by definition cannot give informed consent. Paul Ramsey has argued that no one, parent or guardian, even with the best intentions has the moral status to consent for a child to be made subject of medical investigation solely for the accumulation of knowledge (except when epidemic conditions prevail). To quote: 'Where there is no possible relation to the child's recovery; a child is not to be made a mere object in medical experimentation for the good to come'.(2) If it is objected that this severely restricts possible

(1) Report of the National Commission.

(2) Ramsey, Paul. The Patient as a Person, New Haven, Yale University Press, 1970, p. 12.

> advances in childhood medicine, Ramsey argues that the moral progress of the race is more important than the scientific. Thus, testing of children is the paradigm instance that at times it may be necessary to choose between morality and knowledge even though we normally assume that we do not have to choose between them."

Unfortunately for our peace of mind research involving children can not be dismissed with the injunction, with which almost all would agree, that the moral progress of the race is more important than the scientific. Because of the extreme immaturity of the human species at birth, large numbers of normal infants may be seriously harmed or fail to survive in the absence of scientific progress. In contrast to most species, the human infant is totally dependent for many months and requires repeated interventions in order to survive. What interventions are necessary, when should they be made, how much should be done, are questions that require precise answers to prevent serious harm to many normal persons.

The premature infant, for example, is not an abnormal part of our species but a perfectly normal human being in the early part of life. Such normal individuals will be seriously damaged or die in large numbers unless interventions are appropriate. The central nervous system is immature, as are the respiratory, the gastrointestinal and the urogenital systems. Adaptability is so limited that if the interventions are not tuned very finely, there is no survival. We are not talking about having people lead happier and nicer lives, we are talking about survival. That fact introduces into the area of infant and child research a new imperative - not a scientific imperative that we must have more knowledge, but a survival imperative. If interventions are not appropriate, large numbers of individuals die or are seriously damaged.

If oxygen is not administered to immature infants, many deaths occur. If too much is given, blindness results. If chloramphenicol to prevent sepsis is given to prevent babies from dying of infection, the death rate increases from the "gray baby syndrome". A drug such as Gantrisin which is well-tolerated by adults produces kernicterus and severe athetosis and cerebral palsy as a consequence. Yet the answer is not simply going back to the old way. We know, for example, that breast milk in a substantial number of babies in some parts of the world is inadequate as a feeding mixture and that infants will not develop and thrive. Thus, a serious problem exists in regard to research in infants and young children who cannot ever give responsible consent. If interventions are inappropriate, there is no benefit but there also may be very serious harm. Too much water to a baby can produce serious damage. Too little water can produce damage also. Those of you as old as I may remember the days when premature infants were not fed for three to four days so they would not die from aspiration. Cerebral palsy and death were probable consequences of the hypernatremic dehydration that some suffered.

How do we ascertain such consequences? Do we rely on trial and error as with the use of oxygen where literally thousands of babies were blinded, or do we carry out research? Do we learn something about normal human development so that we can anticipate problems and avoid a rise in infant mortality as a consequence of the use of a drug such as chloramphenicol? Research in infancy, I would conclude, is necessary to prevent widespread harm, in contrast to later in life when, if no research is carried out, there would probably be significantly less benefit in the world but in general not an enormous amount of harm would result.

Many years ago Darrow, Pratt and I(3) were concerned with the effects of heat stress on young infants. The reasons for that interest were that a very large number of infants live under circumstances in which there are significant heat stress and high morbidity and mortality, that evidence from adults might not be applicable to infants, and that there was no information available as to what feeding mixture was appropriate and what water intake was proper under such circumstances. To answer such questions we carried out extensive balance studies on a series of infants - four weeks to six months of age - in a controlled environment comparable to hot summer temperatures. Changes in body water and electrolyte that occurred over a number of days were calculated from precise measurements of intake and output, including skin washings, blood chemistries and body weight. The infants, all black, came from an orphanage in which personal attention was extremely limited because of inadequate financial support. During these studies the infants received far better attention from our round-the-clock "foster mothers" (nurses) than in the orphanage. In our minds, the improved care compensated for the fact that we had to draw blood from these babies using techniques which at that time were not without pain or risk. These infants were also subjected to the additional discomfort of being restrained for the purpose of collecting urine and stools for a number of days in an unpleasantly warm environment. The infants at the end of that time did have the great advantage, compared with other infants from that orphanage, of being placed in foster homes. Retrospectively my guess is that in the long run those infants were probably not harmed and may actually have had benefits by virtue of their unconsented participation.

On the other hand looking at these experiments from my present perspective and that of existing Institutional Review Boards or from the standpoint of the Commission's recent report I would conclude that those experiments could not be done at the present time for many reasons

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(3) Cooke, R.E., Pratt, E.L., Darrow, D.C. "The Metabolic Response of Infants to Heat Stress", Yale J. Biol.Med., 1950, 22: 227-249.

including discrimination in the selection of subjects. Yet, was the work worthwhile? Without going into detail let me say that the balance studies showed remarkable retentions of sodium during heat stress, which produced rather serious intracellular dehydration, despite weight gain, leading to significant illness and fever. As a consequence of those experiments there was a major change in the feeding practices for infants throughout the world with a substantial decrease in morbidity and mortality everywhere.

Why would these studies now be considered unacceptable? Is it because the risks were excessive? Certainly not. Adults are common participants in more dangerous research. Is it because the benefits to the subjects were minimal? Certainly not. Adults are common participants as volunteers where there are no benefits. Is it because the subjects were infants and there were no direct benefits or is it because the subjects were abandoned infants - orphans, poor, underprivileged and of a minority group? Would the experiments be acceptable if the subjects were normal healthy white infants of upper-class educated scientist parents?

Putting the argument in a more general form: is there a morally relevant and morally significant difference between the orphan and the child in a caring family? There are frequently great differences because of crowding, inadequate finances, personnel turnover, chance for abuse, etc., but, more importantly, parents have a duty to their children which does not exist for other caretakers.

Although a few parents do abuse their children, parents as leaders of the family have a moral obligation to its members. As Hauerwas points out the family is a "natural", in Aristotelean terms, not a contractual institution of society.

> "We do not ask to be born into families, we simply are born into families of one kind or another. In a decisive sense the family is not a voluntary institution and the kind of responsibilities that accrue in it are thus different. Morally children are not simply smaller, younger, dependent and less 'rational' than adults. Morally the meaning of 'child' is relative to the interests and needs of the community as mediated through the family. In other words to speak of family and child is exactly to speak of duties of parents and children toward one another that are grounded in the concrete expectations of particular communities. The argument is not one of rights of children but rather one of responsibilities to them irrespective of their ability to make claims upon us. It is not one of

personhood. We care for children because they are children not because they are persons."(4)

The orphan, then, is not protected by the bonds of a family and is not an appropriate subject because there are not naturally loving parents acting on his behalf. If the orphan is eliminated as a subject are all infants eliminated as subjects for such experiments? That question requires substantial analysis. The answer to that question depends upon the answer to the more fundamental question: Can parents give consent for the involvement of their child in research unless for the benefit of that child? Does one, including the parent, have the moral right to volunteer another for someone else's benefit? If research on infants and children is so necessary are there ways that it can be ethically justified in the presence of the roadblock presented by lack of consent of the subject?

To answer that question it is necessary to look at what consent represents. Why is consent important from an ethical perspective? Most people would agree now that even though no risk or harm was involved, except for observational activities in public places, consent of someone is necessary if you are doing something with that individual. That means that consent is important for more than the protection of the individual from physical, mental, social or economic harm. Further, most people would agree that consent might possibly provide some protection, but from the writings of Katz it is clear that such protection is limited. Persons are frequently coerced unknowingly. For example, a patient who has a 100 percent fatal disease cannot easily resist the trial of a new therapeutic measure. He is going to die without it - and might live with it. There is obviously not very much freedom of choice in that particular situation. Thus there is a great deal of subtle coercion. Even more subtle than that is the physician's relationship with the patient. The patient respects the doctor, the patient is somewhat indebted to the doctor. So it is very difficult, I think for consent to be free of some kind of coercive influence.

If one reads consent forms carefully, I think you would have to agree that in the cancer chemotherapy area, for example, one would have to be a good clinical pharmacologist to understand what is meant. Indeed the Institutional Review Board preliminary report to our Commission indicated that the reading level of most consent forms is about third or fourth year college level, not that of subjects. The comprehensibility was at a very high academic level, and the comprehensiveness was at a relatively low level. Thus in the consent process, as Freeman points out,

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4. Hauerwas, S. "Must a Patient be a Person to be a Patient: or My Uncle Charlie may not be much of a Person, but he still is My Uncle Charlie." Connecticut Med. J., 1975, 39: 815-821.

people can give responsible but uninformed consent. Consent is poor protection. Institutional Review Boards can provide far better protection against physical or mental harm than consent.

Yet consent is said to be important for two other reasons. Respect for the autonomy of the individual and the dignity of the individual. Even though there is no risk, we expect consent out of respect for the freedom of the individual to choose, and out of respect for the person as an individual. How then do these aspects of consent apply to the infant or young child? Autonomy means freedom to choose. Ability to determine one's own course of life. However, such a concept is meaningless when applied to the infant. The infant does not have any autonomy. He cannot even choose what he wants to eat. He has to be changed when somebody else decides. He is totally dependent, and for a number of years he is relatively limited in terms of his freedom of choice. The notion of autonomy applied to the infant is a meaningless one. Consent to recognize autonomy when autonomy is not present is nonsense. When the individual matures, when he becomes older, he acquires gradations of autonomy. We allow choice to occur at different levels. Children can learn to drive at a certain age but we don't allow it at a younger age. We don't allow a child to look at "wicked" movies until he is 16, but at 12 he can look at Peter Pan. There are graded freedoms to choose. We have graded autonomy - a graded freedom to choose.

To return to the infant who has no autonomy: Consent to recognize autonomy is meaningless. Consent out of respect for the dignity of something or someone, does not have to be given by the individual. For example, we don't allow cadavers to be mutilated. Before one can do an autopsy, permission from a caring person must be obtained. We have certain respect for dignity also. We don't allow people to desecrate a mountain. We require some acceptance by the community. The consent to recognize dignity does not have to be given by the mountain. It can be given by some other individual in a proxy situation out of respect for individuals or things. The experiments that were rather horrifying to the Commission in which the dead fetus was decapitated and perfused to study brain metabolism lacked respect for the dignity of the human fetus even though people might have agreed to abortion. Decapitation of a fetal dog and perfusion would probably not generate that kind of revulsion. Consent then can be given to recognize the dignity of other individuals.

How, then, do we justify carrying out research in the individual when it is not for his benefit? Richard McCormick takes the position that one can make the presumption of what an individual ought to do. Natural law doctrine indicates that individuals owe something to other members of the human species; they have an obligation to assist. If one then makes a presumption of what a child would wish, the child would not only wish to do this, but he ought to do this. Unfortunately I cannot agree with that approach in its application. The reason I cannot agree with it is that if

applied, one should be able to draft adults for non-beneficial research because adults ought to assist. No one is recommending the drafting of adults as research subjects, therefore, no one should draft infants. That is simple justice.

When a child is viewed not as an autonomous individual but rather as a dependent part of a family there may be a substantial difference. Trust, love and care for the child is an integral part of family. The obtaining of consent by the family for actions toward that child is out of respect for these bonds, not out of respect for the child as an autonomous being. Proxy consent which Bartholome has interpreted to be primarily an attempt to protect the child can equally be seen as an attempt to protect the integrity of the family unit. It is true that parents may not always know what is best for their children. The important issue is that the historical tradition of family expects that the family should know. "In other words proxy consent (or permission) as an institution (or procedure) is one way to insure that whatever is done to the child is done in accordance with the moral conventions and traditions of that family."

My position comes very close to that of Hauerwas. Infants and children are part of families and are part of the human race. They are not to be automatically excluded from research. They are not automatically excluded because they cannot make decisions on their own behalf - because they cannot give consent. If the family participates in research, if the family heads - the parents - give permission or consent to participate, then the younger members can be enrolled, I argue, even though they cannot comprehend or possibly even object. Permission on behalf of the infant to participate alone is considerably different from consent on the part of the family as a unit to become involved. The family as a unit is recognized by society as having considerable freedom to choose what is best for itself.

People in a family have the same names, a family begins usually with certain legal actions - marriage. The family is not dissolved without legal intervention - divorce. The family can essentially do what it pleases with its members unless there is significant harm to those members. Some families do not raise their children as well as one wishes, but society does not step in. If there is marked child abuse, if the parents are seriously injuring the child, then one can intervene. However, the damage has to be considerable. It is very difficult to have a child taken out of a family or the family's course of action changed for psychological harm, even though it may be long-lasting. Society does not invade the autonomy of the family. Families can choose. What I propose is essentially that research related to members of a family is acceptable providing there is family consent for participation of the family.

What does that mean? It means that the family is enrolled, the parents as well as the child and infant, providing both leaders of the family, both parents, agree; providing the family continues to participate in the studies, that some senior representative of the family is present when there are procedures carried out, and providing they are there as participants to withdraw from the experiments whenever the activities are uncomfortable to the family. What I am saying is that consent of the parents to participate, essentially family consent, recognizes the freedom of families to choose. A family does not have to participate in the research, or they can participate, but it must be a unanimous choice. Thus in research of a non-beneficial type both parents must agree; the family must be participants, not simply the infant, and the family is there to withdraw if procedures are painful. The parent can judge and the family and infant can withdraw. This is not proxy consent for another individual, it is consent for family participation.

That kind of consent exists in sociological research. The chief or the senior members of a tribe can consent for the tribe. The heads of organizations/associations can consent for the members providing you are not harming individual members. What kind of safeguards then do we require if we recognize that the family can provide consent for participation of the family. First, both parents must consent. A one-parent family may not be the most desirable to enlist. If there is no family, as in the case of the orphan babies, research could not be done with such individuals unless they could benefit immediately because these individuals are not representative members of a family.

Non-therapeutic research on infants then, is acceptable under such an approach: (1) providing that animals, adults or older children who are consenting mature minors have been studied previously when feasible, (2) providing no alternative means are available, (3) providing the sought-after information is highly valuable to prevent harm and do good, (4) providing every effort is made to utilize the same procedures being carried out as part of usual medical and nursing care, (5) providing the least invasive and the least uncomfortable procedures possible are utilized, (6) providing the risk is no more than minimal, (7) providing there is no unfair discrimination in the selection of subjects and (8) providing there is careful scrutiny of the motivations of the family that volunteers to participate so that thoughtful family consent is possible.

When interventions are carried out as a part of research that may benefit the child, few physicians, lawyers or ethicists raise concerns. Permission is granted by the parents or other caretakers with the obvious expectation that all "therapeutic" approaches are directed towards the best interests of the child. Unfortunately, that may not always be the case. In the application of rules related to the conduct of research or, for that matter, the provision of services, it is important yet difficult to

distinguish always between research on behalf of the caretaker and research on behalf of the individual child.

In the study of a group of patients who are hyperactive, are amphetamines given to the child for the benefit of the child or his teacher or his parents? Certainly improved behavior makes life far easier for the teacher and the parents. Yet if the child is appreciated more by his caretakers and his performance is improved, is he not benefitted? It is not an easy distinction. A number of years ago in Cleveland carotid-jugular anastomosis was developed to revascularize the brain of children with Down's syndrome so that through retrograde flow there would be a greater volume of blood going to the brain. Was that for the benefit of the parents or for the child? It turned out to be of no benefit but it certainly was a procedure that could be questioned. Gastrostomy for the severely defective was a common practice in the Sunland Training School in Florida until a short while ago to assist feeding. A tube is put in, feeding time is shortened, and the budget is reduced in that institution. Such actions were for the benefit of the caretakers, not the child certainly.

As far as "therapeutic" research is concerned, the child who is not able to consent should not be in the forefront of research. When feasible, where survival of that individual is not at stake, research should be carried out in adults or consenting older children prior to therapeutic research in the younger group; and every effort should be made to plan therapeutic research so as to conform as much to the treatment routines as possible, so that as little discomfort and as little risk as possible are generated. When the experimental subjects are beyond infancy and early childhood, but not adults, they may bear some responsibility for decision-making regarding participation in research, whether classified as "therapeutic" or "non-therapeutic", but attempts to translate the principle of graded autonomy or graded responsibility for making one's own choices into specific ages were not particularly successful.

In principle if one follows the reasoning of Hauerwas regarding the child's place in the family as an element of consent by the family for the child, then the degree of emergence of the child from the family confines is a rough index of the extent of decision-making to be allowed. Participation in school is one mark of such partial emergence from the family, and some assent or dissent could be recognized if given by the schoolboy or schoolgirl. Likewise, independent living out of the family could certainly be recognized as an indicator of the "adulthood" of the individual. With children between these two limits, approximations must be made, which are based not only on the degree of independence permitted by the family but also on the seriousness and complexity of the problem.

Dissent should certainly be recognized if no benefit will accrue, but not if death or serious disability would be the alternative to participation in research aimed to benefit the individual. In this regard it is important to distinguish between consent and permission, and amongst consent, permission and objection. Some critics of the report of the Commission have not properly perceived the differences. Consent is used in the traditional sense in ethics, and as such requires full explanation and understanding as well as freedom from coercion, so that a responsible choice can be freely made. Permission is essentially such a choice made on behalf of another but is morally different since it is not the free choice of the affected individual. Dissent or objection is not the absence of consent but is an expression of unwillingness to participate. The child age 7 for example cannot be expected to comprehend freely the merits of participation in research but can be expected to agree to or object to spending 3 hours taking a psychological test, or having a ven puncture or being measured, restrained, etc. The parents receive the full explanation from the investigators and give their uncoerced permission. They explain to the child what will be done and urge his cooperation. Such a process to my mind makes research feasible if risk of harm is slight, and recognizes the autonomy of families to choose what is in their best interests as a family.

In summary, then, I have argued for the unique importance of research especially concerned with young children even though that is the group least able to consent, assent or object in a meaningful way. I have argued for participation of the family in recognition of the importance of that unit in society and as a protection for the child's wellbeing and dignity. The ethical bases for these arguments have been presented only sketchily and hopefully will be developed in years to come as the debate continues.

L'ESSAI DES MEDICAMENTS SUR L'HOMME SAIN: SITUATION DU MEDECIN-EXPERT EN FRANCE

Jean Cheymol

En 1965, convaincu que de multiples essais de médicaments, réalisés sur différentes espèces animales alourdissaient inutilement les dossiers d'expertises, un group d'experts de l'OMS, dont j'étais membre. a proposé un protocole en quatre temps adopté depuis dans la majorité des pays. Il comprenait :

1. Une étude analytique du produit et de ses métabolites éventuels et la détermination de la toxicité chez l'animal;

2. Un essai prudent et limité sur l'homme sain, volontaire et éclairé pour établir - non l'action thérapeutique - mais le niveau sanguin, le métabolisme, ce qui est devenu depuis en s'étendant la pharmacocinétique du produit;

3. Sur une espèce animale métabolisant comme l'homme le produit, l'étude pharmacodynamique la plus complète possible;

4. Aborder alors sur l'homme malade, les essais thérapeutiques qui seront déterminants.

Cette façon d'opérer - révolutionnaire à l'époque - fut admise rapidement et recommandée dans des rapports de l'OMS en 1966-1968 et 1970. Si les essais chez l'homme malade furent acceptés sans résistance par la quasi-totalité des pays, il n'en fut pas de même pour l'utilisation de l'homme sain. Admis dans les nations anglosaxonnes, les pays latins furent plus réticents.

Qu'en est-il en France ?

On y trouve une situation ambiguë. L'Ordre national des médecins et les juristes étant nettement hostiles à cet emploi, l'Académie nationale de médecine et l'Administration hospitalière parisienne l'admettant sous conditions, le ministère de la Santé restant indécis entre ces deux positions, le médecin-expert risque de tomber en cas d'accident ou d'incident graves sous le coup d'articles du Code pénal le condamnant sévèrement. Analysons rapidement les différents aspects de cette situation périlleuse.

Opposition à l'emploi de l'homme sain

Ordre national des médecins: S'appuyant sur le serment d'Hippocrate - juré par tous les médecins de France - sa position se résume ainsi : la médecine cherchant à transformer l'homme malade en

homme sain, ne peut accepter de faire de l'homme sain un homme malade. Il se base également sur l'article 2 du Code de déontologie français "le devoir primordial du médecin est le respect de la vie et de la personne humaine"; et sur le Code international d'éthique médicale qui "interdit au médecin de donner un conseil ou de poser un acte médical prophylactique, diagnostique ou thérapeutique qui ne soit justifié par l'intérêt direct du patient".

En 1974, il rappelle sa doctrine dans un communiqué à la presse..., "adopter cette seule expression d'expérimentation sur l'homme sain... risque d'entrainer des abus de toutes sortes... toute expérimentation humaine est contraire au principe du respect de la vie humaine qui est inscrit en tête du Code de déontologie". Strictement fidèle à cet impératif, l'Ordre se refuse à l'emploi de l'homme sain, même volontaire et éclairé qui ne retire aucun intérêt direct des essais réalisés sur lui.

La Justice: Le Code pénal n'interdit pas la tentative d'expérimenter sur l'homme même sain, pourvu qu'il soit volontaire, éclairé du risque encouru, mais condamne l'expérimentation comme illicite s'il y a accident (articles 309 - 311 - 318 du Code pénal, prison et amende possibles) sans oublier les réparations financières à fixer comme dommages par le Code civil.

Il existe une jurisprudence (déjà ancienne) dans ce sens. Le Conseil d'état (la plus haute instance juridique en France) a une position identique.

Acceptations sous réserves par l'Académie nationale de médecine (1952)

Elle considère que les essais médicamenteux sur le malade dans l'intérêt de sa santé sont non seulement le droit mais le devoir du médecin. Elle accepte l'expérimentation proprement dite sur un non-malade quand on ne peut étudier une question très importante autrement. Par contre elle conseille la plus grande prudence de la part des expérimentateurs et demande des garanties pour le patient volontaire.

L'Administration des hôpitaux de Paris (1976) admet la pharmacologie clinique chez l'homme malade ou sain; elle organise le contrôle dans ces établissements par des Comités d'éthique médicale.

Indécision entre ces deux positions inverses

Ministère de la santé : Son administration accepte et même demande "chaque fois que cela est possible "des renseignements de pharmacologie humaine... mettant en évidence la biotransformation (métabolisme) et les éléments pharmacocinétiques essentiels . Elle admet donc implicitement l'essai sur l'homme sain, mais avec une

absence de netteté regrettable; elle ne parle pas d'homme sain ou d'homme malade mais utilise uniquement un terme neutre : patient.

Exigeant dans une loi récente (10 Juillet 1975) des essais de tolérance cutanée ou muqueuse pour des produits cosmétiques (qui ne sont pas des médicaments) donc sur l'homme sain, elle n'a pas encore sorti (3 ans après) le décret d'application de cette loi. Donc réticence et perplexité!

Population et corps médical : Il est illusoire d'attendre un assentiment universel à des règles d'éthique médicale! Selon les cultures nationales, les imprégnations religieuses, les populations réagissent différemment. Anglosaxonnes, elles ne soulèvent pas de difficultés majeures à l'utilisation de l'homme sain, latines elles y sont en partie hostiles. En France le respect illimité de la personne humaine s'impose et le Code s'inspire du droit romain jaloux de cette doctrine. La législation sanitaire s'en ressent. Il est frappant de noter que parmi les ministres de la Santé de la Ve République (soit depuis 1958) une majorité a une formation juridique et non médicale.

L'opinion est sensibilisée par les souvenirs atroces des pseudo-expériences nazies dans les camps hitlériens, état d'esprit exalté par les médecins déportés et les familles isréalites cruellement éprouvées. Même les "dix règles de Nuremberg" promulguées par les juges américains le 19 Août 1947 à l'issue du procès des médecins nazis furent accueillies avec une certaine réticence. Il en fut de même pour la Communication de l'Académie de médecine du 25 Novembre 1952. On peut déceler une certaine rythmicité dans ces courants d'opinion envers la science. Vers 1944, la connaissance des crimes hitlériens entraîne un refus justifié de toute expérimentation sur l'homme. Quelques années plus tard, les prouesses de la science - universellement admirée, dans les différents domaines allant de la médecine, chirurgie, cybernétique, astronautique, etc. - créèrent un engouement justifiant tous les sacrifices.

Sous l'influence du temps (nouveaux philosophes, écologistes, mass media, etc...) la science perd actuellement une partie de son prestige, la population lui trouve un relent d'hitlérisme, ceci entraînant un phénomène de crainte, sinon de rejet. On constate dans une partie du public se rendant dans les hôpitaux une certaine appréhension de servir de cobayes pour des expériences sans en être informés. D'où des plaintes non fondées mais signalées à grand bruit par une certaine presse. Le corps médical lui-même est indécis et souvent partagé sur ce problème.

Conclusions

A l'issue de ce trop rapide tour d'horizon des différentes instances susceptibles d'influer dans un sens ou dans l'autre sur le sort éventuel, en cas d'accident, de l'expérimentateur français opérant sur l'homme sain, on comprend mieux l'inquiétude inconfortable qu'il ressent. Avec une certaine hypocrisie, on semble lui dire : on ne vous empêche pas d'utiliser des hommes sains, volontaires et éclairés sur les risques encourus, mais si vous avez des incidents ou accidents graves vous serez condamné lourdement et cela par trois juridictions :

- professionnelle - infraction au Code de déontologie (Ordre des médecins),
- pénale - articles 309 - 311 - 318 du Code Pénal
- civile - indemnité compensatrice des dommages exercés.

Pour sortir en France le médecin-expert de cette impasse, il est nécessaire :

- de créer un courant d'opinion favorable aux essais en en montrant l'intérêt, mieux la nécessité,
- d'officialiser et de généraliser les Comités d'éthique et de coordination des essais protégeant le patient contre tout abus(1).
- d'obtenir des pouvoirs publics une position claire sur les devoirs et les possibilités du clinicien-expérimentateur.

Mais comme il s'agit d'apporter des exceptions aux cas visés par des articles du Code pénal, la voie législative risque de s'imposer. Elle sera longue et semée d'obstacles!

1. Ils existent déjà, sans être imposés par la loi dans des organismes de recherches (INSERM) et de grands hôpitaux.

ETHICAL PROBLEMS IN MEDICAL GENETICS

N. P. Bochkov

Intensive development of science, including medicine, has always confronted society with new moral and ethical problems. In this context, serious attention should be given to medical genetics on which is focussed the interest of different specialists (physicians, biologists, mathematicians). Undesirable consequences of eugenic errors concerning the improvement of human nature that arose during the early years of human genetics as a science, are well know. During this time genetics has made big strides and today man is on the verge of obtaining powers that, according to the opinion of prominent scientists, will enable him to predetermine his biological destiny.

Discoveries in medicine and their realization in the practice of health services concern the interests not only of society as a whole, but also of individuals. Experimental medical and clinical investigations in the USSR, from the viewpoint of ethics, correspond to the principles of Soviet society as determined by the Constitution of the USSR, the Laws of the Soviet republics, the Health Service Law of the USSR, and most important, the whole of the way of life of the Soviet people. The principle "Everything for human welfare" is a fundamental one. It is common in the USSR that one aspect of medical ethics, namely deontology, is paid much attention in the training of medical personnel of various specialities.

Patients with hereditary diseases and their families form a large group of the population with regard to which many ethical issues arise in the processes of medical care or scientific investigations. It should at once be pointed out that all the principles of medical ethics for this group of patients are fully respected. However, the peculiar nature of genetic diseases (life-long course, severity, continuity) and also their property of passing from one generation to the next, pose specific ethical problems. In our opinion, a general solution to any ethical issue in medical genetics should be based not only on the principle of Hippocrates "not to injure a patient", but also not to injure members of his family in a broad sense of the word, including future generations of children.

Thanks to progress in medical genetics, methods of early diagnosis of hereditary diseases have been developed, as well as their prevention by way of genetic counselling and protection of human heredity from damaging effects of new environmental factors. In this report, ethical issues of these three sections of medical genetics will be considered, as also the approach to them in the USSR. At the same time further developments in genetics, in particular, genetic engineering, may pose other ethical problems, some of which have already been discussed at a conference in Asilomar. Other aspects are still awaiting discussion.

Diagnosis of many hereditary diseases only at the clinical stage was earlier considered as "a doom" for the family. Early diagnosis has changed this situation, because treatment has now become possible. At the present time, so-called screening methods have been developed for early mass diagnosis of hereditary diseases (phenylketonuria, hypothyrosis, cystic fibrosis and so on). Centralized diagnostic systems are organized in many countries. Active diagnosis of hereditary anomalies in all newborns is justified from the ethical point of view only under certain conditions that are fully observed while carrying out such programmes in the USSR.

First, it is absolutely obligatory that a preliminary diagnosis be confirmed by an investigator or a physician, because in screening methods there is always a possibility of a false positive analysis (diagnosis). If the diagnosis is not independently confirmed, then even healthy children may stay with a diagnosis of a severe disease, and this causes great moral damage to the patient, the parents and other members of the family.

Second, early active diagnosis of hereditary diseases (before they are clinically manifest) is ethically right where a dispensary system is available for patients diagnosed, for their preventive treatment or social assistance, as well as genetic counselling for parents. If such a system is not provided by the government, then the early diagnosis of the disease has only an experimental value and offers no benefit to the patient.

Third, programmes for mass diagnosis of clinically unmanifested carrying of the gene as, for example, for Tay-Sachs disease, or haemoglobinopathies, should be provided by highly qualified genetic counselling of couples and should be based on voluntary, not obligatory, examination.

Fourth, in carrying out a diagnostic programme on hereditary diseases with a view to determining their frequencies for scientific purposes, without any possibility of rendering aid to patients (for example, if therapeutic or preventive methods are not yet developed), all diagnoses should be "blind". Moral principles are thus not violated as regards certain people, provided that the examination itself does not harm the health or interests of those examined.

The next question that I should like to consider is the prevention of hereditary diseases. As is known, the main method of preventing hereditary diseases is genetic counselling, as one kind of specialized medical aid. Patients are informed of the probability of the birth of an affected child, and depending on the prognosis they are recommended to abstain or not from childbearing. Here consulting geneticists should not only be thoroughly informed in their profession, but also really humane towards patients, whatever contradictory notions they may have. Their main task is to bring to those referred to them the necessary genetic

information. The final decision concerning childbearing is a right that always belongs only to the patients themselves. Medical geneticists in the USSR help the family in solving questions about childbearing, but do not insist that their advice should be followed.

Progress in genetic counselling has given rise to new ethical issues, namely: carrying out prenatal diagnosis; establishing discrepancy between biological and legal parenthood ("false parenthood"); premarital counselling; and examination of relatives of the patient. Under modern conditions, all these issues are solved individually in each case. There are, however some general approaches in solving them.

Prenatal diagnosis is nowadays the most efficient way for a family to avoid the birth of an affected child. This procedure is carried out at the fourth month of pregnancy when a woman already has maternal feelings. Because of these, methods of prenatal diagnosis must be especially precise. If the methods have not been sufficiently tested, they must not be carried out. Otherwise the pregnant woman and her future child will be serving as experimental objects, and this is in contradiction with moral principles of medical services in the USSR.

Sometimes in the process of counselling the question of true parenthood has to be solved. The fact of "false parenthood", if it is established while ascertaining the diagnosis of the health of the future progeny, should not be discussed by a clinical geneticist. This is a question that should be put only by the patients themselves. Otherwise an irrecoverable moral harm might be done to the family, without any benefit to the health of the future child.

In a number of countries, premarital genetic counselling on an extensive scale has been discussed. However, such a measure is not justifiable if there is no special medical evidence of, for example, hereditary disease in a family. From the ethical point of view, "analysis" of the pedigree of bride and bridegroom is not always justified. Nor is it scientifically valid, because the search for possible congenital diseases in certain couples only would require extensive programmes of investigation that are in practice not feasible.

One delicate question in genetic counselling is the examination of relatives. Since conflicting claims of a wife and husband concerning the reasons for the birth of an affected child might be aggravated as a result of the examination of relatives, it is necessary to be tactful and to preserve medical secrecy as regards any examined relative.

In conclusion, let me dwell on one more question very important from a social point of view - protection of human heredity. As is well-

known, some of the products of the progress of science and technology, such as ionizing radiation or chemical agents, may damage heredity. The sense of moral responsibility of scientists who pose the question of excluding mutagenic factors from the human environment is quite understandable. Progress in genetics has opened up an opportunity for testing new factors in the environment for their mutagenic activity. Such measures reflect concern for health from the individual and the population aspects. In general, it might be said that the use of new drugs, food additives, pesticides and so on, without testing their mutagenic activity is an extensive genetic experiment constituting a violation of ethical norms. Legal regulations on the testing of drugs for their mutagenic activity exists only in a few countries, including the USSR since 1976. In this country new drugs are allowed for us only if mutagenic properties are absent. These tests must be carried out, for all aspects, on experimental animals and human cells. If the preparation possesses any mutagenic properties but must be used because of an urgent need (for example, cytostatics for the treatment of cancer), then the patients should consult a geneticist after treatment.

Shelopoutov: I have listened with great interest to the statements made up to now and am looking forward to hearing those which are scheduled for today. The first observation that I would like to make in this regard concerns the overall approach to the subject of this Round Table. I believe the position of every specialist who embarks upon the matter of ethical and human rights aspects of medicine and of medical science and, in particular, those of medical experimentation is extremely difficult. Indeed, on the first day of this Round Table, I think confronted, one has to deal with a large variety of incoming elements such as medical ethics, moral obligations, human rights, duties and responsibilities, etc. All these notions have different meanings and cannot be used interchangeably, especially this is true as regards human rights and medical ethics. There was almost no confusion on this matter at the present Round Table. For example, Dr. Curran, Dr. Williams and Dr. Riis considered the respective issues from the point of view of professional ethics. Professor Johnson-Romuald took, in my view, a human-rights point of view mainly in terms of the right of health and medical care. Dr. Weatherall looked at the matter from the point of view of rights and duties, etc. At the same time, there is a sort of division of labour in this regard between existing international documents. On the one hand, we have major human rights instruments such as the Universal Declaration of Human Rights, the International Covenants, etc., recognizing the basic rights, for example, the right to life, the right to health and adequate medical care, the right to food, the right not to be subjected without one's free consent to medical and scientific experimentation, etc.

On the other hand, the documents adopted by the international medical community, such as the Declaration of Helsinki, the International Code of Medical Ethics, the Declaration of Tokyo of 1975, The Declaration of Sydney, statement on death, etc. deal with the matter entirely from the medical ethics point of view. This situation, Mr. Chairman, would not have made any difference provided the notions of human rights and medical ethics represent one and the same phenomenon. But they do not. Take, for example, the question of informed consent. What does it mean in terms of medical ethics? It means that, according to Article 9 of the Basic Principles of the Helsinki Declaration, each potential subject must be informed of the aims, methods, anticipated benefit and potential hazards of consent to participation at any time. Does this position cover all aspects of the problem? I'm afraid it doesn't. We can ask ourselves what will happen if the doctor does not provide the subject with all adequate information. The Declaration does not say anything in this regard. What does the informed consent mean from the point of view of human rights. It means that the subject has the right to be informed. In case he is not, this right is considered to be violated. And the doctor in this case is responsible for this violation. In my view, this situation

needs to be clearer. This right, as well as the right to health or the rights of patients, does not only raise questions of medical ethics. A society's health needs, and the health benefits which its members have a right to expect, exceed the framework of exercise of a profession. However closely it may be involved in the development and implementation of solutions in this field.

Therefore, it was not by chance that - I think it was Dr. Browne who said yesterday - that trust and moral ethics should be supplemented with norms and standards. Without attempting to elaborate further on this subject, I would simply like to state, Mr. Chairman, that, as for the relationship between human rights and professional ethics regarding medicine and medical sciences, not everything is entirely clear. Therefore, my first suggestion will be that people concerned should start thinking whether or not the time has come to look at the whole area you are involved in, not only from the point of view of medical ethics but also from the human rights point of view. In this regard, it may be useful to think of having some human-rights dimensions for the documents already in existence which were widely referred to yesterday. It in no way means that the issues of medical ethics should be forgotten. But they should be complemented by a new dimension. In any case, perhaps to begin with, CIOMS could organize a meeting on this subject.

My second and last point is as follows: Going through the list of participants, I have noticed that many of those present today in this room are to a greater or lesser extent concerned with the teaching of their respective disciplines. It does not happen very often that UNESCO has a possibility to address so many distinguished specialists representing various branches of medicine and medical sciences who at the same time are active in educational fields. Therefore, I wouldn't like to lose this rare opportunity, and would like to inform you of some of the results of our work concerning the overall subject of this meeting. In this regard, one of the major concerns of UNESCO is the problem of development of awareness and that of increase of knowledge of human rights aspects of medicine and medical sciences. Both among professionals and general public. In other words, the problems of education on this issue.

May I refer here to what Dr. Fischer said yesterday? That the main task is to prevent the abuse of science and technology rather than to correct it. Education serves this purpose, too. In UNESCO's view, this is the matter of paramount importance since mere existence of ethical codes in human rights does not apply their automatic implementation. They must be known to the people concerned and this is one of the simplest but most decisive preconditions of their implementation. In order to obtain a background information on the state of affairs in this field, the International Institute of Human Rights in Strasbourg, at the request of UNESCO and in consultation with WHO and CIOMS, carried out

in 1977-78 a world survey on the teaching of human rights and professional ethics, in faculties of schools of medicine and medical sciences. This survey was prepared on the basis of a questionnaire which was forwarded to all the 955 faculties of schools of medicine and medical sciences in 107 countries listed in the World Directory of Medical Schools published by WHO in 1973. These questionnaires were filled in and sent back by 145 institutions in 43 countries. The results of the analysis of the replies are most interesting. They show that the situation is far from being satisfactory. The teaching exists more often than not in embryonic and dispersed form. Teachers are often considered to be insufficient in number and inadequately trained and equipped to provide such teaching. Whereas the need for it, judging by the replies, is very great.

On the other hand, the interest that students take in this field is very keen. Some replies speak for themselves and need no comment. Highly interested; great interest; active participation; enthusiastic response; students are interested and would welcome such teaching; considerable interest. etc. It may be interesting to note here that such issues as medical and surgical experiments on human beings, informed consent, professional secrecy, organ transplantation, are also mentioned as subjects of the teaching courses, papers and meetings. These questions are also given a high priority among the subjects relating to human rights and medical ethics that should be taught at the faculty or school of medicine. Though the replies indicate that all the subjects should be taught, since all are important, priority is given to the following. Firstly, the rights of the sick person. Eighty-two percent of replies followed by medical experiments, seventy-eight percent; the right to life, seventy-six percent; the right to health, seventy-three; etc.

Many faculties and schools of medicine expressed their desire to cooperate with other institutions. This undoubtedly requires an urgently needed contribution to the training of teachers, the establishment of programmes, the preparation of teaching materials and exchange of experience. This work has also been started by UNESCO by organizing in Vienna, in September 1978, the International Congress on the Teaching of Human Rights.

The last but maybe the most important point which I would like to make is the elucidation of the inter-disciplinary aspects of research and reflexion on human problems to be undertaken by the philosophy division. Another project will be a follow-up both of the above-mentioned world survey on the teaching of human rights and professional ethics, and the International Congress on the Teaching of Human Rights. Namely, we plan to carry out a feasibility study concerning preparation of a joint WHO/UNESCO recommendation on the teaching of human rights and professional ethics in faculties and schools of medicine and medical sciences.

Downie: Mr. Chairman, as you said just before coffee, the speakers have put forward most of the problems. They've posed a number of questions for which I think they are hopefully expecting you to provide some of the answers. And they have expressed their own solutions to some of these problems.

Now as a number of references were made to the pharmaceutical industry, I thought it might be appropriate to offer some views on this topic coming from a doctor who works in that industry. Most of my comments will relate to practices in the UK, although some, of course, may have more general application. I will take the topics in the reverse order for reasons, I think, will become obvious. Simply that you take the easy ones first.

Studies of drug evaluation in young children are largely not a problem for the industry. Formal controlled clinical trials in young children are not permitted by law, although the application of the law has never really been put to the test in the courts. Therefore, it is the children who are disadvantaged in that they are given new drugs based on data from studies in adults. And the evidence of the efficacy and safety of a new drug in children has to be gathered in a rather haphazard way. And therefore, I would certainly commend you towards Professor Cooke's proposal as a possible solution to this very difficult problem. Similarly, the use of institutionalized subjects for trials other than therapeutic studies aimed at a specific disease is not permitted in the UK. And I must say that I shared all the views presented by Professor Neki.

Now, the selection and recruitment of patients for clinical trials is clearly the responsibility of the clinical investigator, guided by the industry doctor in the light of data from animal studies and, of course, any previous human experience with the drug. But the clinical investigator does not have the freedom that may have been suggested by previous speakers, when carrying out clinical trials in association with the industry. That even includes the selection of patients. Probably the only person who has absolute freedom in this area is a surgeon, provided he doesn't use a device.

The industry doctor, in accordance with his national drug authority, has to impose increasing constraints on the conduct of clinical trials. In the UK, the onus for complying with the regulations, and accepting the sanctions that may arise from any digression, rest entirely with the industry. The necessity to comply strictly with the requirements of regulatory authorities and, to some extent, with those of ethics committees and other interested bodies has now led to a degree of rigidity in clinical evaluation which I don't think is beneficial to the advancement of therapeutics, and in some cases I think it is clearly to the detriment of the patient. And I was extremely pleased to hear Professor Gibinski

specifically address himself to this problem of rigidity that is being introduced into clinical evaluation of new drugs.

Time doesn't permit me at all to itemize any of these constraints, but one of the most worrying aspects that I have come across is the recent trend following, I think, this degree of rigidity, is a disenchantment of many experienced investigators and their increasing disinclination to become involved in the evaluation of new drugs. Yet, the advancement of therapeutics, which I believe we all want, is totally dependent on the involvement of expert clinical investigators. One factor in the selection of patients, which I believe has not been mentioned, is their fitness, their resilience, their strength and their courage to endure the rigors of the narrow double-blind, the cross-over placebo-controlled trial, comparing one drug with another, which is becoming obligatory.

Lastly, and perhaps unfortunately only very briefly can I make a comment on healthy subjects, which I think are often referred to as volunteers. Both descriptions, I think, are incorrect. A healthy person has been defined as one who has been inadequately investigated. And a volunteer in our own present social climate has been defined as an altruist with a price tag and a very good anticubital vein.

But I'd like to reassure Professor Vere from the comments that were in his manuscript that company employees who are involved in studies are selected with the greatest of care and protected at all times, if only on the basis that the responsibility of the employer goes far beyond that normally seen in the doctor-patient relationship. On the other hand, I do share his concern on the place of the healthy volunteer in new drug development. Because I think this has been furthered by misguided concern for the unhealthy volunteer, who at least might derive some benefit from the experimental procedure.

In conclusion, Sir, I would like to put forward for discussion the proposition that we may be going too far in our attempts to protect at all costs the patient in the formal experimental situation, without much regard to when he is in the informal experimental situation, that is in the form of treatment. And I think we are going too far without firstly quantifying the risks that we are all concerned with at this meeting. And, secondly, we are not giving equal regard to the consequences for the majority of the patients, particularly those yet to benefit from the recent advances in science.

Mach: L'Académie Suisse des Sciences Médicales (ASSM) a rédigé le ler décembre 1970 des "Directives pour la recherche expérimentale sur l'homme", directives qui ont été envoyées à plusieurs

centaines d'hôpitaux, cliniques et instituts(1). Nous avons insisté pour que les hôpitaux non universitaires soient également informés, car dans un pays comme la Suisse où l'industrie pharmaceutique est si puissante, des pressions risquent de se faire sentir partout où il y a des malades.

Ces directives de l'ASSM établissent une distinction fondamentale entre les études expérimentales qui se rapportent premièrement au diagnostic, deuxièmement au traitement et à la protection de l'homme malade et troisièmement celles qui concernent les sujets sains. Rappelons les dispositions communes les plus importantes contenues dans ces directives:

1. Les principes fondamentaux de l'éthique médicale qui régissent le comportement du médecin sont également applicables à la recherche expérimentale sur l'homme.

2. Les recherches expérimentales sur l'homme ne peuvent être conduites que par des personnes scientifiquement qualifiées, dans des institutions suffisamment équipées et sous la responsabilité d'un médecin.

3. Les recherches expérimentales sur l'homme doivent se référer à des essais de laboratoire, en particulier sur l'animal, ou à toutes autres méthodes ou données dont la valeur scientifique est reconnue.

4. Les recherches expérimentales sur l'homme ne peuvent être entreprises que si les risques encourus sont médicalement en proportion avec l'importance du but à atteindre.

5. Toute étude expérimentale sur l'homme doit être précédée d'une évaluation soigneuse des dangers qu'elle implique par rapport aux bénéfices que peuvent en retirer le sujet ou la collectivité. Il faut en particulier tenir compte des modifications que pourrait subir le sujet dans sa personnalité et dans sa capacité de discernement.

6. Il est recommandé de créer des corps consultatifs auxquels les aspects médicaux et éthiques d'une étude expérimentale en préparation puissent être soumis.

C'est là l'origine des commissions d'éthique régionales, qui fonctionnent en Suisse depuis 8 ans. Elles sont sous la dépendance de

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1. Directives pour la recherche expérimentale sur l'Homme. Bulletin de l'ASSM, 1971, No. 27, pp. 156-160.

l'ASSM, mais leur existence n'est pas reconnue par la loi. Elles sont composées de médecins et en plusieurs endroits on a ajouté des laïques représentant l'équipe soignante, c'est-à-dire des infirmières, des travailleurs sociaux, des aumôniers catholiques et protestants, des psychologues et parfois des juristes. Là où ces équipes n'ont pas été composées l'ASSM va faire un effort pour qu'elles soient réalisées.

Comme m'a dit le rapporteur danois, l'autorité de ces commissions serait plus grande si elles étaient reconnues par l'état, mais elles perdraient une partie de leur indépendance. L'autorité de ces commissions qui ne sont pas officielles est grande, du fait même qu'elles existent et qu'on sait qu'elles travaillent consciencieusement pour le bien du malade. Nous ne pensons pas que dans un petit pays comme la Suisse une commission nationale, centrale soit nécessaire car l'ASSM peut remplir ce rôle d'arbitre si la situation l'exige.

Nous pensons par contre que ces commissions, qui devraient encore être renforcées selon le modèle danois et suédois, pourraient élargir leur champ d'activité et que certains problèmes de thérapeutique pourraient leur être soumis. J'aimerais citer l'exemple du canton de Zurich qui, il y a deux ans, nous a posé un problème d'attitude médicale qu'il n'arrivait pas à résoudre. La question des autorités zurichoises était la suivante: quelle réponse donner à un chirurgien du coeur auquel on demande de poser un pace-maker à un malade désorienté dans le temps et dans l'espace et âgé de 82 ans. Les directives de l'ASSM sur l'authanasie publiées il y a deux ans permettraient à une commission d'éthique de répondre aisément à cette question.

J'ai été frappé d'entendre plusieurs orateurs parler d'une certaine méfiance face à la médecine d'aujourd'hui et du fait que le prestige du médecin se heurte assez souvent à un mouvement d'Antimédecine!

Je pense que si nous voulons retrouver notre position morale, il faut que le public soit mieux informé de notre activité. Il faut qu'il sache ce que représentent ces commissions d'éthique et qu'elles travaillent honnêtement pour le bien et la sauvegarde du malade. Cette information du malade et des familles n'est pas une chose facile. Il faut commencer par donner à nos étudients et à nos assistants une éducation sociale. Il est nécessaire qu'ils apprennent à parler aux familles et à expliquer ce qu'est un diagnostic et une recherche expérimentale. Sur cette information les infirmières en contact avec la famille seront très souvent plus à même de donner des renseignements utiles. Il est important qu'entre les familles et les médecins il n'y ait aucun mystère et surtout jamais de mensonges. Il faut que règne autour de nos malades un climat de confiance et je dirais de transparence. C'est à ce prix que la médecine d'aujourd'hui pourra rester moderne tout en respectant ce côté humain qui lui est nécessaire.

Milhaud: C'est avec beaucoup d'attention que j'ai suivi les débats de cette conférence consacrée à l'expérimentation médicale et à la protection des droits de l'homme. C'est une question grave, à laquelle la principale réponse apportée est celle de la mise en place de comités d'éthique et de coordination des essais de médicaments. Dans les hôpitaux, dans les facultés, dans les écoles de médecine, dans les institutions, il convient de se demander si cette disposition est éfficace et quelle est son coût par rapport aux avantages. La protection de tels comités est illusoire dans les pays mêmes où elle serait le plus nécessaire - c'est-à-dire dans les pays où le pouvoir médical est détourné à des fins punitives par le pouvoir politique.

Dans les autres pays, on assiste à une inadéquation croissante entre l'objectif qui est la protection des droits de l'homme et les moyens mis en oeuvre. Est-ce que dans le monde occidental les droits des malades sont si gravement ménacés qu'il faille consacrer autant d'énergie à la protection de ces droits? - aux Etats-Unis, la seule année 1975, selon l'estimation publiée par Gray dans Science en Septembre de cette année, un tiers de million d'heures de travail pour les membres de ces comités. Le rapport coût/avantage n'est certainement pas favorable. Il faut bien considérer le coût, en particulier pour le progrès thérapeutique. L'innovation thérapeutique est faite dans un tout petit nombre de pays. Or, cette innovation est freinée par des réglementations de plus en plus contraignantes de la part de la puissance publique, réglementations qui le plus souvent n'apportent aucune sécurité supplémentaire pour les malades. Faut-il donc imposer de nouvelles réglementations contraignantes en ce qui concerne l'essai des médicaments chez l'homme?

Verspieren: Je voudrais souligner l'importance des questions posées dans les documents préparatoires et les exposés de la séance de ce matin, au sujet de la recherche biomédicale qui n'a pas de visée directement thérapeutique. Le Professeur Vere a signalé avec raison le danger "d'exploitation" des sujets soumis à l'expérimentation. L'opinion internationale s'est émue il y a quelques années des prélèvements de sang dans des pays en voie de développement au bénéfice des pays développés : cela avait une grande charge affective, ce transfert de sang a été vu comme ayant une signification symbolique. Il faut veiller à ce que des situations semblables ne se reproduisent pas, à ce que les groupes humains qui détiennent le pouvoir ne profitent pas de la situation de dépendance d'autres groupes humains.

L'image typique de l'utilisation d'une situation de dépendance est l'expérimentation biomédicale faite sur des groupes de prisonniers. Il y a eu des scientifiques dans le monde pour souligner que "pour bien des raisons pratiques, les détenus constituent le groupe le plus approprié au

recrutement des volontaires".(1) Peut-être, mais est-ce une raison suffisante pour les utiliser?

De même le Professeur Gibinski a dénoncé l'utilisation des malades hospitalisés pour des expérimentations sans rapport avec leur maladie. Ils constituent certes un "matériau pratique", mais...

On a parlé de même ce matin de l'expérimentation faite sur les enfants d'un orphélinat, d'enfants n'ayant donc pas la protection que représente le fait d'avoir un père et une mère. (Mais de l'expérimentation sur les enfants en général, je ne voudrais pas parler ici, car je n'y ai pas suffisamment réfléchi; c'est une question fort difficile...)

Enfin, que dire de l'utilisation pour des expérimentations de ceux qui se trouvent dans une situation financière difficile?

L'argument utilisé le plus souvent pour justifier l'expérimentation sur des individus est le bien commun de la société. Cet argument est juste, mais à condition d'en reconnaître les limites(2); Je pense surtout qu'il faut avoir le courage de se poser un autre type de question : l'expérimentation biomédicale ne repose-t-elle pas dans certains cas sur l'exploitation de la situation de faiblesse et de dépendance de certains groupes humains? Dans de tels cas, cela pose de graves questions : car, à mon avis, et à celui du Saint-Siège que je représente ici, la valeur d'une société se mesure au traitement qu'elle réserve à ses membres les plus faibles. Ceux-ci sont-ils, pour une société, un matériau qu'on utilise, ou des membres faibles qu'on protège avec un particulier respect?

Prendre au sérieux cette question peut poser, il est vrai, de grands problèmes à la recherche scientifique : les volontaires des autres catégories sociales seront-ils assez nombreux? Mais ce n'est pas une raison suffisante pour écarter cette question, cela en pose en fait une deuxième: celle de la régulation de la recherche par la communauté scientifique.

Car, est-ce toujours le bien commun qui est recherché par l'expérimentation sur l'homme? Le Professeur Weatherall a insisté sur les "devoirs" des entreprises pharmaceutiques. Je parlerais plus volontiers de leur "logique" comme il y a une "logique" du chercheur, et un

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1. Santé du monde, janvier 1976, 7.

2. cf. Paul VI - Allocution du 28 avril 1973 - D.C. 1632, 20 mai 1973 p. 454.

"enthousiasme" qui a été signalé plusieurs fois ici. A ces logiques, il y a une autre logique à opposer : celle des droits de l'homme, du respect de l'homme, surtout du plus pauvre et du plus dépendant.

Opposer ces deux logiques conduira sans doute à diminuer le nombre des hommes sujets à l'expérimentation. Il faudra alors choisir entre les expérimentations qui seront menées et celles qui seront écartées.

Les comités d'éthique dont on a parlé hier sont un premier pas sur la voie de la régulation de la recherche. Peut-être y a-t-il un deuxième pas à franchir : puisque l'expérimentation sur l'homme pose de graves problèmes éthiques, la limiter au minimum indispensable ; ce ne sera pas alors parce qu'une recherche est possible qu'elle sera effectuée, mais parce qu'elle apparaît plus urgente qu'une autre. Telle est la question des priorités qui a été abordée plusieurs fois ces jours-ci.

Je sais que cela est encore utopique. Mais ce n'est qu'à ce prix que l'expérimentation biomédicale sans visée directement thérapeutique conquerra l'estime de la population des différents pays, et que les hôpitaux ne seront plus des lieux où l'on craint de devenir un cobaye mais deviendront des lieux où toute confiance sera accordée aux hommes de science.

Peretz: If I could address myself first of all to the last speaker. Of course, I have and the industry has the deepest respect for what has been said and we must all be very careful that we don't upset or take little account of the dignity of mankind. But we're all on the horns of a dilemma. It was mentioned for instance yesterday that the poor and deprived people in the developing world are extremely short of new drugs for tropical diseases. And what is the pharmaceutical industry to do without the possibility of using human volunteers if we are to find adequate treatments for diseases like filariasis? So one does not have a clear black and white answer to these questions. If one's going to make progress, one has to think of the people who are deprived because they have not got medicines to treat their existing diseases.

Now, for a question, addressed to the panel as a whole, but particularly to Professor Vere. Recognizing that surgical procedures are at least as hazardous as the use of pharmaceuticals, could Professor Vere, and perhaps other members of the panel tell us how much of the time of these ethical committees is used on reviewing new surgical procedures?

Vere: I have no precise figures and I think that it's very important to say this. One only knows of anecdotal evidence and experiences in southeast England. But I can say that it is my impression

that whereas medical procedures are frequently and regularly brought before the ethical review committees, there seems to be a great deal of doubt in many doctors' minds about when and why surgical procedures should be brought before such committees. And so my impression is - others here may correct this impression if they have a different experience - my impression is that, on the whole, fewer surgical novelties, shall we put it that way, are brought to ethical committees than perhaps should be. But I suspect that one of the reasons for this may be that there are not the same clear-cut divisions and guidelines in surgery. So perhaps we should pay particular attention to that aspect. But I'm not a surgeon myself and I think it's very important to remember that in listening to these comments.

Neki: I think the question has been asked not merely to elicit information but to drive home the point that if new surgical procedures are not so much subject to review by these committees, why should the medical projects be subject to review. The answer is very simple. The answer is that surgical procedures as well should be subject to review.

Roche: Monsieur le professeur Cheymol a magistralement exposé le problème de la protection des médecins, et j'aimerais dire un mot sur la protection des malades et des sujets dans l'expérimentation des médicaments en France. Il y a dans notre organisation française trois garanties. La première garantie c'est qu'il existe une législation très stricte. L'essai des médicaments ne peut être fait que dans l'hôpital public. Et les médecins qui font ces essais doivent être acceptés par le Ministère de la Santé sur une liste limitative d'experts. Donc, en principe, convenablement choisis.

Deuxième garantie, on en a parlé, le médecin de l'hôpital, même fonctionnaire, a une responsibilité Pénale et criminelle. C'est-à-dire qu'il peut être poursuivi devant les tribunaux en cas d'accident dû à une imprudence. Et ceci est une garantie, car ça l'oblige à être très prudent dans ses essais.

Et puis la troisième garantie sur laquelle je voudrais insister c'est le problème de l'environnement
avec des étudiants en médecine qui sont actuellement assez indépendants pour des raisons très précises; c'est que tous les examens actuellement en France sont anonymes et par conséquent, l'étudiant, avec qui nous avons d'ailleurs les meilleurs relations, a la possibilité de donner son opinion de façon très précise en certains cas et de parler avec les infirmières dont vous savez l'importance. Et toutes les fois qu'on fait une experimentation dans un service, on doit expliquer à ce personnel l'intêret de cette recherche. Il est indiscutable que ce personnel n'accepterait pas une expérimentation contraire à l'éthique. Et ceci me

paraît une troisième garantie qui aboutit au fait que dans l'ensemble les essais en France sont effectués avec prudence. Et il faut bien reconnaître que le besoin de commités d'éthique ne s'est pas fait sentir de façon urgente ni dans la collectivité médicale ni dans le public.

Wahba: Two weeks ago the WHO European office organized in collaboration with the Federal Republic of Germany a symposium which is, by the way, a yearly event in Deidesheim which brings together clinical pharmacologists, drug control authorities and the industry from the member states in Europe. And several recommendations which came up there are very much in line with what has been discussed here. So with your permission, I would like to read them to you because they show that there is a considerable consensus.

The way in which informed consent is to be obtained should be carefully defined, inter alia, as regards to type of information to be given to the patient on the purpose of the study, the nature of the drug, and the risks involved. There should be special procedures for consent given on behalf of minors or persons not able to give informed consent, such as mental defectives and unconscious patients.

The clinical investigator bears the primary responsibility for a clinical study. The fact that informed consent has been given does not mean that the trial subject assumes responsibility for the entire risk, nor does the approval given by a review committee or regulatory agency lessen the investigator's responsibility. This has clearly been defined by Professor Neki.

In every country, there should be provision for adequate and broad insurance of trial subjects including the so-called healthy volunteer and those taking placebos. And prompt compensation for any injury resulting directly or indirectly from participation in the study. Facilities for such insurance should be guaranteed by the State, as is already the case in certain countries.

The WHO European office has undertaken a survey of ethical committees and general guidelines for human experimentation in the European region, which is a kind of follow-up and complementary to the study taken up by CIOMS and Professor Curran, and a short summary of the results that we have obtained so far is available at the registration desk.

Brand: I would like to make a short statement, which is rather similar to one that I made about two years ago at another CIOMS meeting which was held in Geneva. I would like to draw to the attention of participants that since 1971, the United Nations Division of Human Rights, in fact my own section, has published reports on the impact of modern

science and technology on human rights. We have covered, for instance, the impact of surveillance devices, automation, electronics, especially data banks, and the impact of science and technology on the whole range of economic, social and cultural rights.

More particularly, we have published studies on the protection of the human personality in its physical and intellectual integrity in the light of advances in biology, medicine and biochemistry. This somewhat grandiose title of the subject is not my invention, it comes from a General Assembly resolution. Experimentation on human beings has been covered in document ECN4/11/72 and 73, of which I have a copy here. Unfortunately, it is the only copy that I do have in Lisbon. But I would be very glad to send a copy to any participant in this meeting who wishes to have a copy and who would like to ask me for it.

Scicluna: First of all, I would like to express my agreement with Dr. Downie's view regarding the notion of volunteer. In fact, in our reports on this subject, our experts have made it clear that the use of the word volunteer is totally inappropriate. And they have proposed the use of the term healthy or sick person of sound mind who has given his consent - an informed consent. In fact, I think it is mostly a question of emphasis. The use of the word volunteer gives the impression that there is a mass of people yearning out of public spirit to sacrifice their health and their life. And this is not the case. Moreover, the use of the world volunteer throws the onus of the responsibility on the person who offers himself for the experimentation while the use of the words "a person who has given his consent", "a consenting person", throws part of the onus on the research worker in that he is the one who originally made the request to which the consent is given.

The second remark I have to make concerns the use of children. And here I'm afraid I have to express a dissenting opinion. Basing myself on this very definition, I think that when we say a healthy or sick person of sound mind who has given his consent this seems to rule out children. The thesis which has been developed here by Dr. Cooke, I find is a very clever one, but not fully adequate. It gives the impression - I fully agree that the family unit is a separate entity from its components - but I do not believe that some of those components, in this case the parents, have the right to put other components of that unit, in this case children, in any discomfort or hazards. The thesis developed gives the impression that the children belong to their parents. And, in my view, this is not so. I believe that the parents are the natural custodians of the children. And, as such, they have the duty, not the right, the duty to safeguard and protect their welfare. And I don't think that they have the right to put their children to any discomfort in the name of a public spirit, which after all does not belong to the children but to the parents.

I can see the point that was made, I think by Dr. Downie, that the experiments that are done on adults cannot be transferred onto children and therefore, in the long run, children might suffer from the fact that experiments haven't been carried out on children. I can see the problem, but I think that here we have a choice and it is evidently not for me to decide it. But I very much believe that it is a question - and here I believe with the representative of the Holy See - is a question that needs much further investigation.

Cooke: I can't help agreeing that everyone recognizes the problem from the Holy See on down. Unfortunately, there have been very few people that have made the attempt to try to explain in an acceptable way the solution to this problem. As I said, mine was an attempt to open the debate in an approach which I consider to be one somewhat different from the usual. Namely, to consider that the family has a certain autonomy, and that consent in general is a respect for autonomy, and that family autonomy has in general in society allowed parents to make decisions for the whole family. Some of those decisions we may be considering unwise, but nevertheless we allow families to make those decisions. I'm simply attempting to apply that same principle, fully realizing that there is always the question of what is in the best interest of the child or best interest of the family.

Family units may be strengthened by the participation - and let me give you an example - say a metabolic study which has no benefit to the child. Parental participation in that study, where the parents are there with the child throughout the whole time, where they are supportive, where the discomfort can be minimized very significantly represents, to me at least, an experience not unlike what families go through on their own behalf. Families go out and allow their children to swim, to do various things at a much greater risk. And yet we don't see society saying that those things are impossible. There are decisions that families make and this is what I was trying to bring out.

Riis: I do respect certainly the high moral levels or ethical levels we are now introducing. But I want to point to the fact that if we raise high barriers in some countries having clean hands, we often see that such problems are pressed towards centres of less resistance: the underprivileged members of developing countries. So if we want to state that no family member can ever give permission for a child of his family to enter a research project, then we would have to consider having to pay the price ourselves. We ought to create a self-suspensive system within this country and not be able to use the scissors and paste technique which is to try to get results from other countries or centres of the world. If we are willing to pay this price, it's all right, but often it can create an element of hypocrisy.

Hinchcliffe: May I add my voice to the speaker whose organization was becoming a little disenchanted with the term volunteer, and wanted to substitute it for a person of sound mind who had given informed consent. I think this is relevant to a concern that epidemiologists have, certainly in the field of hearing and its disorders. But some of the perhaps counter-productive studies have been those in which there was a sole consideration that it was a volunteer population, without having any regard to the fact that, as Professor Vere has pointed out, so many volunteer populations are unrepresentative.

There is therefore, perhaps, the consideration one might differentiate between active and passive volunteers. And, as we all know, there's no dichotomy between volunteers and non-volunteers. Many non-volunteers can be persuaded to become volunteers. The question therefore arises, to what degree should one, or is one justified in persuading people either by argument or by awards to become volunteers. This is so essential because otherwise, as you know, if a population isn't representative, and even if you do initially start out with a random population, a random selection, if you don't get a high yield because of the order of coming up effect and other phenomena, you might as well not have done the study. Therefore, I would like to ask to what extent one may go in using methods of persuasion, by argument or rewards, to ensure that you get a representative population.

Margulies: The first day and a half, what I heard suggested to me either that there was no problem, because there seemed to be no difficulties, or that there was a problem that wasn't being met because everyone seemed to have a system established which was operating very smoothly. And I had hoped for some kind of controversy and we are only just beginning to get into it. I shared those misgivings with some of my colleagues around me and in other parts of the hall.

I don't quite know where we are going overall with the discussion up to the present time, despite the fact that it is of profound importance to all of us. Let me just go back for a moment, if I may, without being too diversive. We have heard, among other things, that there is a need for some kind of a body to take a look not only at research involving drugs, but certainly surgery - I think anyone would add new kinds of diagnostic procedures to that. We heard from Dr. Weatherall that drugs cannot really be evaluated effectively for at least five years, and I think we would all agree that trials which are done under ideal circumstances must also be evaluated when those circumstances are not ideal, and go into overall use and practice.

We have also heard people say that the difficulty is really not in the area of research where people are well-disciplined, but in the overall delivery of medical care. And what we do need instead is the same kind

of a concept which is extended to all empiric therapeutic practices that characterizes the practice of medicine. We heard more than that. We heard from the Third-World countries some very reasoned and, I think, highly acceptable concepts, which included the idea that research should, to be ethically conducted, be consonant with national priorities. One should not be doing highly esoteric and sophisticated research involving huge sums of money and many people in a society in which the problems are those of overcoming death

We heard also on the very first day that we need some system of evaluation and of monitoring. Now, put all that together. And suddenly I find myself remembering the story of the sorcerer's apprentice, which I think came from this part of the world, where the apprentice learned from the magician how to use a broom to carry water, but he didn't learn how to turn the system off. So pretty soon the water kept coming from the well back to the house and flooded the
and told him how to stop the magic.

We are engaged in a discussion which is around risks and benefits. And those risks and benefits include the processes that we are instituting to overcome the risks and to get the benefits. How are we to know whether what we are introducing at this time is going to be worth the risk? What observations do we have of what was wrong before we began this system? What is set up to determine whether when we get through with it, we have reduced risks and increased benefits? And are we going to do that by a process of monitoring and review which becomes so cumbersome that in the final analysis people will turn their backs on it and say we want no more of it? It's too burdensome, it's too troublesome.

What I am concerned about is whether in the process of going after selective issues, we are not creating a kind of a monster for ourselves. Is there not a way of being selective so that in the beginning, for example, one can reject all bad research, which would reduce a very large percentage of the applications that have to be looked at. Is there not some way of being selective so that we know what the issue is that needs to be addressed? Certainly, there is not such widespread, constant violation of human rights, or of the needs of individuals, that we need to go, as we do in many systems, after every kind of research activity. And yet there is clearly a need for the protection we are talking about. There have been abuses, there are accepted enthusiasms on the part of researchers, and there are those who go beyond enthusiasm to be sadistic or to be charlatanistic.

I don't know if CIOMS is in a position to take on all of these responsibilities. But I, for one.am concerned about whether we are in balance, whether we are in a position to determine what the risks are,

if we have even begun to define the benefits in this undertaking, and if so whether we have any system to follow up to find out where we have been going.

I've also discovered in talking with many of my colleagues that the systems they have in place are troublesome. They do have problems. They have many problems. And we haven't heard very much about them. There are public statements that disturb the profession, professional statements that disturb the public. And if we are to involve ourselves more and more with minutiae we may find that what we are after both for good research and for the protection of humans will be lost.

Refshauge: I think that really sums up what I was trying to say at the beginning. That there surely is a balance between the protection, the moral right that we have, or the moral duty that we have, of the protection of the individual with the balance with medical progress. And I thought that this was the whole object of this exercise. And I think you have highlighted it.

Vere: I agree with what has just been said and note a little concern about the way in which some of the issues are being presented as I see it at the moment. I'm worried by movements which are going in one direction without perhaps noticing the equal and opposite pull in the other direction. There were three that I picked out particularly in listening to the debate so far.

First was the suggested rejection of the term volunteers. Now, just before we lose that word I think that one has to note that it has some value in discriminating between those who respond to a direct approach on the part of a research worker, and those who respond to an indirect approach. A notice on a board is not personally directed or something of this kind. And I think that there is a danger that we may get caught up in our own choice of words. There hasn't been time yet to think through the approach from our colleague from the Council of Europe but it seems to me that if his definition automatically stops consideration of investigation of children, for example, then there may be something wrong with the definition. And we need to look at it very carefully in both directions.

The second point was this plea that ethical committees may delay progress. Well, of course, indeed they may if they're misapplied. But it's always seemed to me that one of the chief roles of an ethical committee is to promote useful and valuable research. And the ethical committees with which I have had contact have certainly not delayed research as far as I have been aware. They've made it possible for research workers to get ahead and do worthwhile things more quickly and in an atmosphere of less suspicion than might otherwise have been the case.

And then on this very compassionate, humane and thoroughly supportable plea about the weakness of certain groups. Well, yes indeed, of course we must avoid exploiting the situation of weak groups. But surely on the other hand, their very weakness is a strong incentive to try to do something to help them. One of the chief motivations perhaps. And so, though work must be done with the greatest possible circumspection, I wouldn't decry the urgency which their need brings into the research arena. I think indeed this can be a very useful stimulant. And so I can only agree that there is an area which needs to be explored here, possibly in another conference. It's been opened up most helpfully this morning.

Binns: I just thought that since we seem now to be moving towards some conclusion and recommendations, I would like to make a point rather more explicitly than has been made so far, although it seems to be coming out now. I think it's very difficult for groups of experts, committees, official bodies and perhaps particularly for politicians to resist adopting idealistic standards. And it takes far more courage to be realistic. Nevertheless, the principle remains the same whether we're thinking of ethics, of drug safety or water purification, if you like. For each additional increment, the cost rises progressively so that we soon reach a point where the cost - whether we think of it in terms of money or diversion of effort or as disincentive - becomes out of proportion to the benefit gained. And in both technical and ethical fields, we're in danger of adopting perfectionist standards that look good, but in practice are so difficult to attain that they in fact operate against and not in favor of the public interest. Now, I'm concerned about the effect on innovation, and that clinical investigators will no longer be prepared to undertake this type of work. We must keep constantly in mind the ethical implications of not doing this type of work. Errors of commission are always much more obvious and certainly better publicized than errors of omission. But I believe that in the past far more harm has been done by exposing people to unprogrammed treatments and unassessed risks than by deliberate human experimentation.

Oluwasanmi: We've had a lot of discussion on the issue of protection of those who are the least privileged or who are not in a very good position to protect themselves. I think this is very important. And I was rather disturbed by the experiment that was carried out on those orphans. I think it is like using one group of people for a job and trying to rationalize that the benefits will accrue to some of them later on, whereas really the benefits accrue to another group of people altogether. I think in practicing experimentation we talk about teaching students about humane attitudes and a humane approach to patients. I think that we should demonstrate it ourselves. And it is in demonstration that really the students themselves will learn. And I hope that this type of experiment, which really concentrates on using either the poor, the orphans,

the underprivileged, maybe even the Third World, for experiments for which they would have no direct benefit, would stop. And people should believe that, if you want to do an experiment of that nature, you can do it in an environment in which the benefits will be most felt. There is no doubt that there should be experiments, of course, which will also be carried out among the people of the Third World. But I believe that this should be related more to their problems, which are completely different from the problems - at least the bigger problems - of the developed countries. Now this point was also made quite clear by Dr. Browne, and one of the Third-World representatives here yesterday.

About this question of tribal chiefs. That people take permission from tribal chiefs to experiment on a whole range of people. I think that this is completely unethical. I don't see how - what legal justification exists these days - to make a tribal chief the custodian of the life and limbs of the members of that tribe. And we are moving forward. The Third-World countries are moving forward. There are a lot of things we are trying to gain from you, and there are a lot of things we are changing. And it is really turning the clock back to be thinking of the tribal chiefs of the nineteenth century, whereas we are really moving near to the close of the twentieth.

And, I would like to put a question to the panel. And that is on the question of illiterates, the use of illiterates for experimentation. I think it was Professor Neki that brought this up. Who is a person to give a consent? Because he mentioned the custodian or the legal custodian of the illiterate. The illiterate adult is an adult. He has no legal custodian. I think, at least talking in the Nigerian context. Who is his legal custodian? I have in my own mind who his legal custodian should be and that is the government, with whom he has a contract for protection. And I think that this is the purpose for the existence of governments.

Neki: I would like briefly at this point to make two points that have not been made. I've been sensing all along that there is a wave of remonstration against imposing ethical standards. And this remonstration comes from two sources: the pharmaceutical industry, and the medical profession. And I think both have enjoyed a freedom that they are unwilling to part with. That is the reason for this reticence on their part to accept this. I have a feeling that both have already become the subject of public suspicion. And it is important for them to establish measures that will divest the situation of this kind of suspicion. The public suspects that men are used as guinea pigs. They suspect that people in hospitals are overinvestigated for purposes of research without letting patients know what are these investigations used for - that there is an infringement of human autonomy and dignity and abuse of trust placed in the doctors by patients.

Now, it is precisely to dispel these suspicions that we need to introduce measures. The fear is that these measures would curb research. Well, if they dispel public suspicion and restore public trust, it will make investigators more sensitive to human rights and to human dignity and perhaps also to our duty towards animals, because we are sacrificing far too many animals in our research. Let's be very realistic about it. Then it will reduce unscrupulousness in our research. That is what we are aiming at. Not curbing all research but reducing unscrupulousness in our research. The quality undoubtedly will improve not only in terms of ethics, but also in terms of reliability of that research because if research is being carried out unscrupulously it is entirely unreliable.

And therefore I think the great advantage would be improving the quality of research on which we are banking so much. Besides, I have a feeling that man will not be made a sacrifice to the so-called progress in medicine. Progress in medicine will remain and has remained subservient to mankind and not mankind subservient to medical progress. That is what I think is the crux of what should be the guiding principle in our discussions.

Cooke: I wonder if I could respond to the gentleman from Nigeria who is directing some of his critical comments at me. I accept his criticism, but I want to remind you that experiments done with orphans was thirty years ago, and I can cite for you hundreds of examples, thousands of examples, much worse than that that have been done within five or ten years. Thirty years ago I think our sensitivities were substantially less than at the present time. In regard to sociologic research, I refer to tribal permission just as someone might go to the president of this organization and ask whether it would be acceptable to send a questionnaire out to the membership. And rather than polling each member to see whether they would wish to participate in such a study the chairman of the society might give its permission for that kind of investigation. I think that's quite different from doing harm to individual members of the tribe.

Cheymol: J'ai écouté avec beaucoup d'émotion tout qui a été dit pour les enfants, pour ceux qui sont incapables de donner un consentement. Mais nous avons surtout parlé, nous avons surtout pensé à des expériences portant sur un produit pharmaceutique, portant sur une technique, surtout des expériences d'un petit volume. Et je me pose le problème : est-ce qu'on pourrait actuellement faire une étude épidémiologique importante dans les conditions que nous voulons arriver à imposer aux chercheurs? Supposons que nous ayons un vaccin nouveau à essayer. Je pense par exemple au BCG, qui a été employé chez des enfants en quantité considérable. On peut dire que tous les enfants en ont bénéficié, puis qu'on peut dire que la tuberculose est tout de même

en grande partie disparue grâce à ces vaccinations massives. Est-ce que l'on pourrait aujourd'hui faire des études épidémiologiques comme on les a fait à cette époque-là? Et cela ne remonte pas tellement loin dans le temps. Or, tout de même, si l'on met en présence les bénéfices pour l'éspèce humaine et tous les enfants qu'ils soient orphelins, qu'ils ne soient pas orphelins, qu'ils soient de familles aisées ou de familles pauvres, je crois qu'il faut penser tout de même à cet autre aspect du problème. Ne pas envisager strictement le petit problème d'une petite expérience faite peut-être par un chercheur un peu farfelu et qui veut essayer quelque chose parce qu'il pense avoir une idée. Mais regardons l'autre aspect du problème - les grand problèmes épidémiologiques - je crois que vous êtes obligés d'y penser et de pas les écarter, peut-être en surveillant au maximum et en prenant toutes les précautions voulues, mais qui exigeront peut-être de la part de l'espèce humaine quand même des sacrifices qui seront largement compensés.

Daoud: Really I want to take off where our friend from Nigeria left off. We have the special situation where elaboration of new drugs and clinical testing of these drugs has to be done in our countries. And this will bring in - what do we do about informed consent? As it has been explained by the previous speakers, even in very developed countries it is very difficult to get informed consent, because sometimes the experiment is of such a special nature, and so technical, that even college graduates will not be in a situation to understand what it is all about. All right, what do we do in such a situation like in our developing countries? Can we adopt a system of guardianship, where people can take the responsibility for their illiterate underprivileged brothers? As I think, one can take a practical attitude and say: yes. But with the following precautions. First of all, the protocol for the experiment and the trial of the new drug must have been passed by the ethical review committee in the country which presents the drug; which wants to do the trial. Secondly, the condition for which the drug is tested must be one of the priorities of the nation of the Third World where the trial is going to take place. And, thirdly, the protocol and the agreement of the ethical review committee from the initiating country should be reviewed again by a national ethical review committee in the country where the experiment is going to take place. And then after all these criteria have been satisfied, I think we will be justified in taking a line of guardianship by persuading the people, after taking all these precautions which I mentioned, that the experiment will be as much as can be discerned harmless, and could be beneficial both for the people who are the subjects of the experiment and for their fellow people.

Refshauge: I think Dr. Daoud highlighted a very important point, and that's informed consent, which is going to be the subject of our next session. I'm not sure that it wouldn't have been better to have it before this one in the light of the comments of Dr. Daoud. I don't think

that I could sum up this discussion this morning any better than Professor Neki did a few minutes ago. I think that there is a tremendous amount that's come out of this discussion that will be of immense help to Professor Gellhorn and Dr. Bankowski and his consultants.

I still believe that there must be a balance between the moral duty that we have to guard the individual human rights, and progress of medicine if we are going to obtain the goal of world health. And whether we like it or not, I think that the medical profession has got to regain the trust that we used to have by the community at large which comes from teaching and by precept and example. And I think that justice, not only has to be done, but has to be seen to be done in this world that we live in today.

FIFTH SESSION

INFORMED CONSENT

Moderator: William J. Curran

CRITERIA OF ADEQUATELY INFORMED CONSENT

Bernard M. Dickens

Consent is more than compliance with another's wish. Consent is a quality that may arise in human relationships of autonomous and informed equals, who volunteer to act in partnership. This quality can arise in medical experimentation, even when the free-will of the potential subject may be curtailed by a medical condition, and the information possessed by the potential investigator may be of a different order from that which determines responses of potential subjects.

This paper considers criteria for identifying the presence in the relation of investigator and subject of informed consent. Accordingly, it addresses in principle the basic relation of the medical scientist to the individual, competent adult subject. This model relationship discloses ideal standards which may be applied to the many variants of the model experienced in practice. It serves to show that, for instance, a potential subject affected by impaired perception, whether for instance of pathological origin or related to medical therapy, may be individually incapable of contributing the consensual quality required in the relationship of medical experimentation. It also discloses the need to communicate with the potential subject in language and idiom which is meaningful to that potential subject, and not in an unaccustomed language, including the language of medical science.

It is not the purpose of this paper to consider consent at the community level (see the paper of Professor Robbins). Similarly, although there is an interaction between informed consent and free consent, this paper will not consider the positions of subject populations liable to be affected by disadvantages, motivations or incentives extraneous to a proposed study. Such populations include minors, prisoners, students, nurses, laboratory technicians, military personnel, persons of low income, ethnic minorities, the unborn and auto-experimenters (see the papers for Session IV).

The Purpose of Informed Consent

The ethical (and legal) requirement of informed consent serves the interest of human rights; the origin of modern sensitivity to this concern lies in times when individual human rights were systematically grossly violated (see the papers for Session I). The primary reason for requiring consent is respect for the principle that all persons must be allowed to make decisions and to exercise choice on matters which affect them. The function of consent is to recognize the potential subject's dignity and integrity, and to implement and enhance individual autonomy. Informed consent redresses the potential subject's scientific disadvantage

by permitting his or her decision on collaboration to be as aware of private and public aspects of the proposed study as the investigator's thereby preserving the potential subject's intellectual dignity. Informed decisions contribute to potential subjects' individual freedom and protect them against manipulation and exploitation.

The aim is to achieve a voluntary and respectful partnership between individuals, both investigators and subjects, of common understanding and intention. It follows that the investigator must maintain the subject's consent in good repair; informed consent is not simply an initial condition of the subject's involvement, but a continuing condition of its endurance. The subject must therefore be kept informed of new matters relevant to collaboration, such as identification of different risk levels than were initially communicated, and changes in perception among the scientific community, since autonomy includes a right of withdrawal and of redesigned participation, to a lesser or greater extent.

Information for Consent

The qualitative nature of personal consent makes particular instances as individual as subjects themselves, but certain normative elements may be expected to be observed in procedures inviting potential subjects to participate in studies. A variety of codes and regulations (see papers for Session I) may be drawn upon to identify the following disclosures as contributing to informed consent.

1. The scientific need the study is designed to meet. This should give the reasons for the study, such as to create a specified new treatment, to test a suspect treatment, to verify another study's results and, for instance to improve upon a drug available through a particular manufacturer.

2. The general scope of the study, including its institutional or financial sponsorship, the centre(s) where it will be conducted and the intended subject population(s), including the basis of selecting the individual potential subject approached. If that basis is relationship to another, for instance, such as a relative affected by a disorder, the consent of that other person may be required before disclosure of that principle of subject selection.

3. An explanation of the procedures to be followed as they may affect the potential subject, and their purposes. This must include identification of any procedures which are experimental, either by novelty or by being therapeutically unnecessary.

4. Where the potential subject is a patient, the prognosis of remaining untreated should be disclosed when the study concerns a novel therapy.

5. Where the potential subject is a patient invited to participate in study of a new treatment, disclosure should be made of any appropriate alternative procedures that might be advantageous for the patient.

6. A description of risks and discomforts which may reasonably be expected from the procedure (and from alternatives where patients are concerned; see 5, above), including the possibility of the procedure being unsuccessful.

7. A description of possible side-effects of the procedure when it follows its reasonably predictable course.

8. A (restrained) statement of the benefits and consequences of the study reasonably to be expected. This should separate benefit to others from benefit to the potential subject; if the potential subject has no reasonable prospect of medical or health benefit, this should be stated.

9. An explanation of provisions to protect the potential subject's identity and confidentiality from (a) the investigators themselves and/or (b) those to whom the results of the study would be available, whether in publication or otherwise.

10. An instruction that any subject agreeing to participate in the study is free to withdraw at any time (so far as the treatment itself may permit; a drug treatment, for instance, may have irreversible short-term effects), without prejudice to rights of future medical treatment of subject or family. This concerns free rather than informed consent.

In addition, the potential investigator should offer to answer any questions the potential subject may wish to put, at any time, since informed consent must exist throughout the conduct of the study, not simply at its commencement. The concept of "risk" requires amplification, since it extends beyond medical or health risk. The US Department of Health, Education and Welfare guidelines note that "An individual is considered to be 'at risk' if he may be exposed to the possibility of harm - physical, psychological, sociological, or other - as a consequence of any activity that goes beyond the application of those established and accepted methods necessary to meet his needs." Accordingly, risk includes damage to self-confidence and self-esteem, and social embarrassment, for instance from suffering impairment and indignity, as well as the risk of suffering pain. Similarly, economic loss and damage to the status of a group, such as an ethnic group, with which the potential subject identifies himself or herself will require to be considered.

If "risk" is thus broadly construed to include, for instance, risk of emotional injury, it may provide the focus of information a potential subject must receive for consent to be informed. An investigator should apply a protective imagination to guard a potential subject against risk not only of physical detriment, but also against the psychological risk of feeling that there has been abuse of goodwill, deception, breach of confidentiality, exaggeration of likely benefit of a study or minimization of its adverse side-effects and of feeling that there simply has been a waste of the subject's time. Accordingly, a subject invited to participate in a minor procedure, as non-invasive, for instance, as giving a urine sample, or as passive as allowing access to a medical file, may nevertheless object to doing so for a study under particular sponsorship or on behalf of a particular cause.

For example, a study of rates of recuperation, morbidity and depression following induced abortion conducted by a specific method, may retrospectively compare statistics of such method with statistics of other methods and statistics of childbirth. A mother may be prepared to allow medical file inspection or to answer a questionnaire on her experience of childbearing. If she is doctrinally opposed to abortion unless to save maternal life, however, she may object to participation in a study showing which method of performing elective abortion is most advantageous, or that abortion may be preferable to childbirth in certain pregnancies.

The principles considered above are guidelines, to be applied to individual studies according to their conditions. The full design of, for instance, a multi-centre, complex, multi-phase study need not be explained, although the scope and purpose must be stated. Randomization of subject management need not be explained in terms of the basis of randomization, but it must be explained that treatment options have been predetermined, and allocated on the basis of the research design rather than the needs or characteristics of the individual subject. Use of placebos need not be identified, but a potential subject must be told that at some stage of the procedure he or she may not be receiving the treatment under investigation; if the subject is a medical patient and the study concerns his or her condition, placebo use may amount to withholding treatment, and this possibly should be disclosed. Double-blind studies need not be explained in detail, provided that subjects understand that their welfare will be constantly supervised at some level, and that codes will be broken upon predetermined adverse indications to find the particular treatment being administered to a subject at risk, and to render appropriate aid.

Any intention to depart from these principles should be stated in the research protocol submitted for institutional approval, and justifications for departure should be offered. Where the principles are

intended to be observed, the protocol should include proposals for renewing consent upon amendment of the informational basis of the study, such as perception of greater risk than was initially disclosed, or reduction in likely benefit, for instance because results of an immediately comparable study have been published.

The Scope of Nondisclosure

While informed consent is an indispensable precondition to the conduct of human experimentation, its requirements are not absolute. The quest is for adequately informed consent rather than "fully" informed consent. Levels of nondisclosure are ethically and legally permissible. It has been seen that such design features as randomization need not be detailed, provided that their consequences for the potential subject are explained. The object of offering and preserving potential subjects' choice is served by disclosure of general data they will want to know, but without requiring them to undertake a medical education.

If venepuncture is proposed, for instance, warning should be given of risk of temporary soreness at the site of withdrawal, bruising and treatable infection, together with information that no medical treatment, including the proposed therapeutically unnecessary treatment, is free of risk; further, an assurance should be given that if the attempted venepuncture proves unsuccessful after say, two attempts, no further effort will be made to include the potential subject in the study. Where children are concerned, moreover, specialists may be expected to be involved in the procedure rather than less trained practitioners and blood may be drawn only by pin prick and in a volume related to body-weight. This may properly be stated.

The medical risks of taking a common blood sample have been recorded to include a haematoma, dermatitis, cellulitis, abcess, osteomyelitis, septicaemia, endocarditis, thrombophlebitis, pulmonary embolism and death. Disclosing these acknowledged possible but unlikely incidents of the procedure might appear to distort rather than to preserve choice. Stating them in the abstract, rather than evaluatively indicating their remote possibility, may deny rather than offer informed choice. Clearly, however, the greater the injury and the greater the risk of incurring it, the greater must be the level of disclosure. It must be remembered, furthermore, that the test is not what level of disclosure the particular proposed subject of research is likely to require, taking account of his or her sensitivities, fears, both rational and irrational, and hopes. The intending investigator must therefore take care to learn or accommodate the individual characteristics of each potential subject.

When the proposed subject is also a patient, for instance whose treatment requires some innovative departures from the orthodox, selective nondisclosure may be permissible where therapeutically indicated. The therapeutic setting no less than the experimental requires informed consent, of course, but the former recognizes what is sometimes described as the physician's "therapeutic privilege" to withhold potentially harmful, distressing or otherwise dysfunctional information, for instance of more remote risk, in order to maintain the emotional stability and morale of the patient. The scientific investigator as such has no comparable privilege, but in proposing the patient's involvement in a study, the investigator may preserve the therapist's privilege of nondisclosure, for instance, of information regarding the patient's condition and prognosis, including the limits of alternative treatments.

The therapeutic privilege of nondisclosure must not be permitted to become an instrument of exploitation. It is confined to the therapeutic setting, and if a conflict exists between its preservation for therapy and the duty to give information for consent to experimentation, it must be resolved in favour of therapy by not inviting the patient to participate in research. If the patient's proposed involvement does not affect therapy, however, but consists of access to his or her medical file, testing a urine sample or for example material removed for diagnosis or therapy, such as tissue or the surplus of a blood sample, the potential investigator must adequately explain the research but need not discuss any aspect of therapy; indeed, even under questioning by the potential subject, the investigator should decline such discussion, even at the cost of forfeiting the potential subject's collaboration in the intended study. Under the same safeguards, the investigator may invite a patient who is to undergo for instance blood sampling, for diagnosis or therapeutic monitoring, to donate an additional limited volume for research purposes.

Further matters pertinent to a proposed study which should not be disclosed are approval of its objectives and methodology at scientific peer review, and approval by an institutional ethical review committee. Both review mechanisms should offer safeguards for a potential subject's welfare, but they can do no more than ensure that possible risks are contained within acceptable scientific and ethical limits and that the prospective subject is free to accept and free not to accept the irreducible risks, physical, psychological, sociological and other, which are an unavoidable element of the proposal. Intimation to a potential subject that such approval has been given may mislead him or her into believing that there is no risk, and that the study has been approved as safe. Accordingly, while the investigator requires such prior approvals, they approve only inviting a potential subject to take a risk. The subject's choice may be unduly influenced by learning that responsible committees consider the

risks reasonable and the risk-to-benefit ratio of the proposed study favourable; the decision on taking risk must be exercised individually by the prospective subject. The subject may take such advice as he or she seeks, but should not be told that committees have already considered the risks acceptable both in themselves and in the light of the anticipated benefit of the study.

Strategies of Informed Consent

Methods of seeking consent relate more to its freedom than to the quality of its information, but certain strategies may need to be employed or be available to exclude distorting influences. In particular, where a potential subject is also a patient whose attending physician proposes the study, the trust generated in the therapeutic relation may obscure the separate judgement the patient needs to exercise to collaborate in research. It may not be clear that the healing relationship is intended to be inverted, and that instead of the physician acting for the patient's welfare, the physician is presenting himself or herself as scientific investigator inviting the patient to act for the scientist's interest and advantage. Clearly, no one may be in a better position or more strongly motivated than the attending physician to ensure that the patient's welfare is not jeopardised, but the inherent quality of the interpersonal relationship changes at the point of research in a way the patient may not appreciate. As a grateful patient, he or she may not feel adequately autonomous to exercise the power to decline the physician's request in light of the information presented.

Accordingly, it may be desirable for a person not appearing as an authority figure in the patient's view to invite participation in the study. Nondisclosure of the identity of the principal investigator, the attending physician, may appear at first inconsistent with the requirement of informed consent, and a difficulty may exist in the patient's wish to discuss potential involvement with the attending physician. Nevertheless, in order to permit the prospective subject to evaluate involvement without being guided by perceived assurances, the matter of participation may be better introduced by a stranger appearing to offer no unspoken assurances, to whom the patient feels no sense of allegiance or gratitude.

Alternatively, the attending physician first raising the invitation to the patient to become a research subject may encourage the patient's consultation with another physician with appropriate knowledge, who is related neither to the patient's management nor to conduct of the prospective research. Another strategy is to inform the patient of the prospect of collaboration and ask that it be considered, but thereafter to leave it to the patient's initiative to raise the matter again; this technique does nothing, however, to ensure the informed calibre of consent. This may be approached by having an independent physician ask the patient who expresses an interest in collaboration questions about such matters as

the aim of the proposed study, what it entails for the patient and what benefit may be derived. A patient whose responses suggest inadequate understanding of critical elements would be excluded from the study.

The techniques of encouraging consultation with an independent physician and of having such a physician question the prospective subject, are available regarding any possible subject of medical experimentation. This may in principle go to the extent of having prospective subjects sit a written test, those showing inadequate awareness of information about the disclosed research not being allowed to take part. While in most cases this may be an extreme and unnecessary sophistication, it shows the inadequacy of the other extreme of presenting a potential subject with scanty information couched in comforting assurances, or with a barrage of scientific data, and seeking immediate acceptance and participation. At the very least, an intended subject should be given time such as 24 hours to digest and consider information, ask questions and take independent advice. This is so however minor the research procedure may appear, such as weighing and measuring or medical file inspection, since it has been seen that the risk against which protection must be offered has psychological and sociological as well as physiological aspects.

Consent Forms

Consent is a quality and not a document, and where that quality does not arise, its absence is not made up by a signed form. Consent should often be evidenced in writing, however, since a form may usefully show what information has been given. The following general rules of preparing and presenting consent forms may be proposed.

1. Principles of Drafting

   a) Language used that the subject understands;

   b) Simple and direct style, avoiding or explaining in lay terms scientific words, e.g. instead of "electroencephalograph" or "EEG" say "test to show brain waves";

   c) Be alert to hidden meanings; e.g. "new" drug may be taken as "improved" drug, so say "untested" or "experimental" drug;

   d) Avoid legalistic phrases;

   e) Volumes, weights, etc. in meaningful scales as well as scientific measures, e.g. blood in teaspoonful or proportion of Red Cross donation, biopsy tissue size "0";

f) Avoid evaluations such as "minimal risk", use e.g. "less than giving routine blood sample", "same as receiving blood transfusion", "same as taking aspirin";

g) Express in the second person, as an invitation, with brief acceptance clause in the first person (a matter of style but preferable).

2. Contents (not necessarily in this order)

a) Statement of general purposes of the study;

b) Statement of the role played by procedures involving and affecting the subject;

c) Statements of reasonably expected results of the study, including: i) benefits to the subject - if none, this should be stated; ii) benefits to identifiable groups ; iii) general benefits to medicine and to society;

d) Expression of invitation to participate;

e) Statement of why particular subject being invited, e.g. i) because normal; ii) because relevantly special/ abnormal; iii) because relative of particular person. (This may be omitted where subject a volunteer responding to advertisement.);

f) Description of procedures involving the subject, including i) purposes; ii) duration; iii) frequency;

g) Statement (if it is so) that experimental drug, etc. will be unavailable after study concluded (to avoid disappointment if beneficial);

h) Identification of procedures that : i) depart from acknowledged / orthodox treatment of patient's relevant condition ; ii) amount to withholding / withdrawing (routine) treatment, e.g. that involve placebo; iii) are allocated randomly or be pre-selection ;

i) Description of known and reasonably anticipated physical risks of the procedures involving the subject, including side-effects, discomforts and inconveniences;

j) Description of risks of psychological and social injuries or disadvantages;

k) Statement that subject's consent to experimentation includes consent for access to medical or other relevant record;

l) Statement of provisions protecting confidentiality regarding, e.g. i) identification of subject to primary and secondary research personnel; ii) publication of research results;

m) Statement of areas in which identity of subject will be disclosed and/or discoverable (Where optional, separate/severable request for consent should be included);

n) Statement of whether results of research/of procedures involving the subject will be available to the subject or, e.g. the subject's physician;

o) Details of scheme of remuneration, e.g. to meet out-of-pocket expenses. If none, this may be stated;

p) Offer to answer questions before and during the study;

q) Reservation to withdraw subject at instance of investigator or, e.g. subject's physician (or statement of adverse indications causing subject's withdrawal);

r) Statement that subject is free to withdraw from the study at any time, without prejudice to right to receive medical treatment normally available.

3. Formalities

a) Give subject a copy of the consent form to keep for his or her own reference;

b) Form should have institutional (e.g. hospital, university) heading, or refer to the institution under whose auspices the study is to be conducted;

c) Form should identify the particular study covered by reference to its distinguished nature or the principal investigator(s);

d) If primarily verbal information given for consent, the informant should be named;

e) No exculpatory clause or language should be used;

f) Witness to subject's signature should give capacity, e.g. as relative of subject, associate of principal investigator;

g) Date of consent should be given, and jurisdictional location (e. g. concerning age of legal majority).

Effects of Informed Consent

Autonomy and self-determination are ethically associated with the concept of individual responsibility. Similarly in law, a person who knows of a risk and freely agrees to undertake it becomes individually responsible for any injury he or she suffers. The subject's voluntary assumption of risk transfers the burden of such injury to the subject, and absolves a non-negligent investigator of responsibility.

Nevertheless, a conscientious investigator cannot abandon the informed subject to an injury unavoidably incurred. Every effort must be offered not only to minimize risk, but also to deal with injury which in fact results. While language exonerating researchers from liability for negligent and also non-negligent injury should not be used lest it may deter a negligently injured subject from pursuing appropriate remedies, a potential subject must be informed that in consenting to participate in a study, he or she is accepting the hazard of its unavoidable risks; it may be added that the investigator will give the subject all the assistance possible should injury occur. This should permit the potential subject to make arrangements, for instance for his or her family, in the event of injury. In addition, investigators may have to consider insuring subjects against the financial costs of incurring injuries caused both by their negligence, and in the absence of fault attributable to the investigators or those acting under their direction.

A subject who will be less than fully assisted and covered should injury result from participation in research should be made aware of that fact before being allowed to volunteer for that research. A subject not so aware may appear to have given less than adequately informed consent.

CRITERIA OF INFORMED CONSENT IN VACCINE TRIALS

F. C. Robbins

Attitudes about what constitutes the ethical conduct of research involving humans have changed greatly since the end of the second World War. We have become more concerned about the rights of individuals to determine their own fate to a maximum degree, to be treated with respect and justice and to enjoy a high degree of privacy. In many countries including the United States rather elaborate procedures have become customary, and to some extent mandatory, in order to assure the ethical conduct of research involving humans.

An accepted part of this ethical code is the securing of the consent of the subject or subjects. When the subject is unable to give consent himself, there is need to obtain an acceptable surrogate (e.g. the parents of a child) who then becomes the consentor. But consent is only half the responsibility here. Ethics dictates an obligation to truly inform the consenting subject or surrogate of the nature of the study. He must understand the purpose of the experiment, the anticipated risks and benefits, and the degree of discomfort he may experience. There should be freedom of choice, as well - freedom of choice to participate, not to participate or to drop out of the testing at any time. This choice should be made by a person capable of rational judgement and without any overt or subtle coercion.

I realize that there is not complete agreement as to what constitutes "informed consent". I realize, also, that in the opinion of some, consent should not be given by a surrogate. This sentiment would eliminate children as experimental subjects. Another view maintains that no experimentation involving humans is justified unless the subjects derive direct personal benefit. Such generalizations continue to be the topics of much debate, and I suspect probably always will be. However, I feel they must be answered in the light of the cultural mores and religious beliefs of a particular time.

In general, there seems to be broad agreement throughout much of our world that some middle position should be adopted that balances individual rights against the needs of society in order to permit the continued development of effective agents to control disease. The ultimate goal is, after all, the improvement of the quality of life.

It is my particular task to examine the problems associated with obtaining subjects' consent for participation in vaccine field trials. These problems are essentially those of controlled clinical trials. I am defining

field trials as tests of the efficacy and safety of vaccines that are conducted in open communities and which involve populations of hundreds or thousands of subjects. These field trials have been preceded by animal tests and small-scale clinical trials that have demonstrated an acceptable level of both safety and efficacy. Although the underlying principles of informed consent are the same for field trials as they are for more circumscribed experiments, there are special problems, some of which derive from the larger numbers of people involved. For one, the large size of the enterprise makes for depersonalization which, if not overcome, can jeopardize the entire experiment. For another, the simple mechanics of communication become difficult.

Other peculiar features include the fact that field trials invariably involve control populations. Often it is desirable to utilize placebos, and randomization of the study population with double blind procedures is usually employed. Since the control subjects ordinarily receive either nothing or a placebo, they derive no direct benefit. Furthermore, vaccine trials usually involve children, which again raises the issue of surrogate permission. Finally, follow-up studies are a necessary procedure.

We will now examine some of these specific issues in more detail along with suggestions and examples of how consent may be appropriately obtained and properly documented.

The key issues to be dealt with are:

1. the large size.
2. the problem of effective communication.
3. the need for controls.
4. the involvement of children.
5. the need to follow the population over a period of time.

Communication between the investigator and the subject is never easy but becomes even more difficult in a large trial. In general, the effectiveness of communication depends upon the relationship between the parties involved. The more personal and trusting the relationship, the better the communication. Effectiveness in this instance may be measured by the amount of information transmitted (and understood) and the numbers of persons who volunteer. A large study has a tendency to be impersonal and bureaucratic which may be accentuated if, as is often the case, governmental agencies are involved. Under such conditions it is not easy to motivate people to participate.

In order to establish effective communication with potential subjects the target population must be defined and the approach developed accordingly. A general ethical principle dictates that the study population

should be as broadly representative of the community as is commensurate with proper experimental design. Indeed, as a rule, broad representation enhances the study. From the ethical point of view the concern is to avoid exploiting certain groups that are peculiarly vulnerable, such as persons using government-supported clinics and hospitals or who, because of lack of understanding, are incapable of making informed judgements. It is interesting that in some of the United States studies in which the composition of the volunteering participants is described, such as the large trial in 1954 of the killed polio vaccine, there was a preponderance from the higher socio-economic levels.

In order to conduct a study in a community it is essential as a first step to establish rapport with and obtain the support and cooperation of the key agencies, organizations or persons. Of course, the responsible governmental officials must also be supportive. The physicians and other health professionals of the community are of special importance since many persons will turn to their physicians for advice. Indeed, the physician who has rapport with his patients is in the best position to recruit subjects, and a number of vaccine studies have been conducted in the United States employing as subjects the private patients of physicians convinced of the value of the study. It is important to keep in mind that, because of the peculiar position of trust the physician occupies in respect to his patients, specific precautions must be taken to avoid the subtle coercion that could be implicit in this relationship. This situation illustrates well the potential dilemma that always exists in recruiting experimental subjects. On the one hand, the personal physician as a trusted advisor is the best person to inform his patient about the study and to serve as a recruiting agent. On the other hand, if the physician becomes too much involved in the study and thus a partisan, his concern may no longer be primarily for the welfare of the patient. The obvious solution is for a physician to avoid involving his own patients in experiments in which he is one of the investigators. If his patients wish to participate, they should be counselled by a disinterested third party.

It is not easy to identify the appropriate influential entities in any particular community. In some societies cooperation of the tribal chief, religious leader or traditional healer may be absolutely necessary in order for any study to be done. A great deal of effort may have to be devoted by the staff conducting the study to fully inform these key persons. Supplemented by other efforts, such as information provided in writing and through the various news media, the area's key figures will be the principal source of information for the persons whose voluntary cooperation is sought. It is important that adequate time be permitted for this initial process to be effective.

It is not a simple matter to determine what information should be provided and how it should be presented. This is particularly true of data released through the mass media. It must of course state the reason why the trial is being done along with an accurate and fair portrayal of any risks, discomfort or intrusions upon privacy as well as the benefits to be derived by the subjects or others. When one is anxious to recruit volunteers there is naturally a tendency to overstate the benefits and under-emphasize the risks. However, arriving at a balanced presentation that is accurate and understandable and will not unduly alarm is vital for the integrity of the trial. It is here where outside opinions may be most helpful, such as those of a conscientious institutional review board or some comparable body.

It is critical that the information provided to the public be presented in terms that laymen can understand. I have often heard that persons of limited education or those who are unfamiliar with the scientific approach cannot be informed adequately in order to make responsible choices. This may be true sometimes but I believe that the material can be presented in terms that the public can grasp even though it may take great skill to do so. We should never forget that the purpose of this exercise is not to propagandize but rather to inform, so that each individual is capable of making the choice most appropriate for himself.

One of the most difficult issues to deal with is that of the necessity to employ controls. The concept is not necessarily familiar, even to some well educated persons. Furthermore, the controls may derive no direct benefit and indeed may seem to have been deprived of any possible benefit from the vaccine under test. The situation may be ameliorated somewhat by testing two substances simultaneously, using each one as the control for the other. An example of this is the recent combined trial conducted in Finland of meningococcal and H. Influenza type B polysaccaride vaccine. Difficult as it may be, it is generally necessary to clarify to potential volunteers the implications of the experimental design, including the probability of being assigned as a control.

Children are usually involved in vaccine trials. Thus, it is necessary to obtain consent, or permission, for their participation from the child's parents or legal guardian. The National Commission on the Protection of Human Subjects of Biomedical and Behavioral Research has recently submitted its report concerning research involving children to the Secretary of Health, Education, and Welfare. The Commission has suggested that the term "consent" be reserved for what persons of adult age give on their own behalf, whereas the decision rendered by parents or others on the behalf of a child or ward be called "permission". Furthermore, it is proposed that children 7 years and older be required to assent or indicate their understanding and willingness to volunteer.

This may seem like a semantic exercise but does highlight the difference between free consent by an individual and permission given on someone's behalf. The suggestion that 7-year-olds are capable of understanding and giving assent or consent has generated much discussion. Many persons, such as pediatricians and educators, have expressed the opinion that there is no particular age when all children achieve a certain stage of development, and that if a specific age is required, 12 years would be more appropriate. Earlier in this program Dr. Robert Cooke has dealt with the issue of the participation of children in research in greater detail. He supports the involvement of children in non-beneficial research under carefully controlled conditions, and proposes that children as they begin to develop a degree of independence from the family (e.g. when they go to school) should begin to play an active role in decisions concerning their own welfare.

A question that sometimes arises is whether or not it is ethical to reward persons for participating in clinical trials. As a rule this is not considered acceptable since it could be regarded as a form of overt coercion, and consent given under such circumstances might not be truly free. On the other hand, adults who fully understood the implications and whose need was not desperate might receive a modest reward without offending the ethical sensibilities of many responsible observers. The practice of rewarding parents or guardians who give permission would be particularly subject to abuse and probably should not be done under any circumstances. The only possible exception would be to provide some monetary assistance in order to make it possible for a particular family to participate (e.g. carfare to a clinic). One quite legitimate form of reward is to provide all controls with the vaccine, assuming it proves effective, after completion of the trial.

Once the subjects or their surrogates have been provided the appropriate information and consent or permission is obtained, there is need for a record of the transaction. The subject is asked to sign a form stating that he has been advised about risks, benefits, etc., that he understands the explanation and that he agrees voluntarily to participate. To many persons the signature on the form is the important matter and they believe that this absolves the investigator or sponsoring agency of legal liability. Gray has reported that a survey of Institutional Review Boards in the United States revealed that much of their effort concerned the content of consent forms rather than the substance of the interaction of investigator and subject. In point of fact, the signed form, and parenthetically it is probably more meaningful if the investigator as well as the subject sign it, does little more than vouch for the fact that an interchange has occurred. In large field trials where large numbers of persons must be bled and/or inoculated within a short time it is often difficult for each participant to receive a full explanation before signing a form. Ideally, the subjects should have been adequately informed

previously and in receipt of the form which they would bring to the reception point already signed. Again this emphasizes the importance of allowing adequate time before any procedures are undertaken so that the process of education can occur. It is also obvious that if the entire process is to be successful the various community resources already mentioned must be mobilized well in advance. This entire process that I have outlined here demands time and resources. However, not only is it necessary from the ethical point of view, but it will lead to greater cooperation and support from the public when people come to realize that they are partners in the enterprise and not just experimental subjects.

I have suggested that a signed consent form does not necessarily mean that the signator is adequately informed no matter how elaborate the instrument. Few efforts seem to have been made to evaluate the success of the educational process. It has been suggested that each prospective subject should be given a short examination which he must pass before being allowed to enter the study. This is an interesting idea and one that might be explored on an experimental basis. It would probably not be practical, even if effective, to employ it in field trials. However, it would be possible to do a random sampling of the study population without undue effort.

A properly conducted vaccine trial should provide for the long term follow-up of some or all of the participants, and they should be so informed. Since there is complete freedom for individuals to drop out at any time, it is important to do everything possible to retain their interest. A full explanation initially to all participants of the importance of follow-up and regular feedback of the results of the study can do much to heighten the motivation to cooperate.

The field trials of meningococcal vaccine conducted in Banbury, Connecticut, illustrate many of the features of a well conducted and successful study. The various community leaders and groups lent their enthusiastic support and as a result participation was high. The entire community became thoroughly informed about the study and its progress. Indeed, this became a matter of great community pride which assured a successful outcome of the study. Such a happy situation is not always possible but with proper care and management it should be the rule rather than the exception.

In preparing this paper I have been struck by how little one finds about the process of obtaining and verifying informed consent or permission in the publications reporting the results of vaccine field trials - or for that matter clinical trials of any sort. The monumental trials of killed polio vaccine in 1954 were described in great detail with reproduction in the appendices of letters to physicians, laboratories, health

departments, etc. but there is no mention of how informed consent or permission in this case was obtained, nor are the forms mentioned or reproduced. Similarly, little attention is given to this issue in more recent publications. I realize that journal space is precious and that it might be impractical to describe this process in much detail but it would seem desirable to mention it at least. Some consideration might be given to instructing authors to submit along with their manuscript a fuller description of the process of securing consent along with copies of any forms of printed material that were used. This could be referred to and made available on request to those with a special interest.

Summation

The reasons for obtaining informed consent or permission from participants in vaccine field trials are the same as for those in other types of experimentation. However the large size of the studies, the need to incorporate controls, the frequent involvement of children and the need for long-term follow-up all present special problems. Above all it is difficult to provide the personal relationship that can occur in the more usual experimental situation. It becomes necessary to work within entire communities and enlist the interest and assistance of government, community leaders and the mass media in order to provide the prospective subjects the information they need in order to make informed judgements. The information must be presented simply, honestly and in terms appropriate for the particular community. Above all it must be aimed at informing and not propagandizing. Frequent feedback to the participants and community is important. Making a record of the consent is necessary but it does no more than verify that a transaction took place. If we are to continue to test new and improved vaccines it is important that we invest the necessary resources to educate the public so that they will participate freely, with full knowledge of the reasons for the experiments, the benefits to be derived, the risks to be expected and the extent of any intrusion upon their privacy. Only if we are honest and straightforward even at the risk of not having enough volunteers to conduct the trial, will we be able to secure and deserve the trust that will make subsequent experiments possible.

DISCUSSION

Lasagna: First, some general comments. Regardless of what one may believe in regard to the divine source of such ancient codes as the Ten Commandments, modern codes (such as the Nuremberg code, the Helsinki declaration, etc.) and other recent procedures and checklists represent the deliberations of fallible humans at a given time in a given culture. This is important because it mitigates against their universal and eternal applicability and acceptance, and at least explains some of the discrepancies between codes and practice.

Second, in regard to rules and procedures, we must beware of the temptation to protect certain subjects from weaknesses that do not in fact exist. This can result in the denial of freedom to volunteer, in the name of morality and protectionism. The traditional posture of the arrogant autocrat must not be assumed by well-meaning bioethicists, who have no doubts about their own ability to make judgements on their own behalf, but do not trust others to do the same. In "The Informed Heart", Bruno Bettelheim noted:

> "To know only those things which your superiors allow you to know is more or less the condition of a small child. To be able to observe by one's self and to draw one's own conclusions characterizes the beginning of independence. To refrain from observing and to accept blindly other people's versions amounts to renouncing one's own ability for reasoning and even one's perceptive faculties. Not to observe matters which are of vital importance, and not to know what one needs to know, is utterly destructive of the human personality..."

It is dangerous, for example, to decide that some subjects are being coerced when in fact the subjects believe that the true coercion occurs when they are not permitted to participate in research. This is true of many US prisoners in well-run prison research units, and is certainly true of patients whose diseases are inadequately treated by standard medicines. A bioethicist's "subtle coercion" may be enlightened self-interest to the eager subject. No one is exempt from duress or inducement or reward, but the degree and kind can of course vary greatly from subject to subject.

In obtaining informed consent, I have a simple goal - to play fair with potential subjects, to tell them what is going on, including the fact that we do not know everything that may possibly happen. In trying to reach these goals, I believe that flexibility of approach is at times indicated with patients, but rarely so with healthy volunteers. Unfortunately, the flexibility cannot be easily dealt with at the cloistered level of the

Institutional Review Board, but can only be achieved on the barricades when one is talking to individual subjects. In obtaining consent, we should not be so doctrinaire and compulsive as to discourage most volunteers. I agree very much, for example, that nothing terribly useful is served by reciting to the subject the gruesome list of rare horrors that can follow a venepuncture.

I am surprised that it strikes anyone as unwonted pressure to give potential subjects the information that an Institutional Review Board has approved their research protocol. This information can surely be given without implying that there are no discomforts or risks and it is symmetrical to the negative information that should also be given to potential subjects when protocols have not been submitted to Institutional Review Boards, or have been rejected by such Boards. I consider it a desideratum that subjects in the future will expect to hear whether an Institutional Review Board has dealt with a research plan, and what the Board's action has been.

I agree very much with the recommendation that consent forms should be couched in language understandable to lay persons. But our own research shows that the amount of information is also related to effective communication. In an experiment of ours with short, medium and lengthy consent forms, the likelihood of volunteering was inversely proportional to the length of the form, but so was the comprehension of the information contained therein inversely proportional to the length. This was true among those who volunteered as well as among those who refused. In other words, excessive detail can constitute information overload and may actually interfere with comprehension.

Finally, towards the end of Professor Dickens' paper, he says that "...in law, a person who knows of a risk and freely agrees to undertake it becomes individually responsibie for any injury he or she suffers." It is a notion with which I personally agree, and would like to move towards, but my understanding is that at least in the United States it is in fact not the case that simply knowing of a risk and agreeing to undertake it puts the onus on the volunteer subject for any ill effects he may experience. It is traditionally said that a subject or a patient cannot "sign away injury" and I would welcome the comments of Professor Dickens and Professor Curran on this point.

Dickens: The point made in my paper is that the voluntary assumption of risks will absolve the non-negligent investigator. That is, if there is an irreducable minimum risk of injury attending a study, then one effect of informed consent may be to transfer the risk of that injury to the subject from the investigator. There's no protection for negligence. The American courts are in a sense not so much making the investigators or the medical profession liable, but are simply

requiring them to bear the loss on their insurance rather than requiring the individual patient or subject to insure. This is a peculiarity, I think, of the American legal system.

Curran: The peculiarity, I fear, may be broader than the American. The movement all across the world, it seems to me, does contain an element of protection, without fault, for subjects who do something of value for the community. And even though they do accept a degree of risk, perhaps they should not be forced to accept it all when a community is benefitting greatly from the studies themselves. This seems to me a trend in the Swedish compensation law at the present time. It certainly seems to be what was done, I agree, in the United States in the recent swine flu epidemic. After the fact rather than before, because before the fact it was thought that all of the risk would have to be taken by the subjects because of the great deal of information and very long consent forms that were in fact distributed in that study. But I think that the public pressure that occurred afterward saying that if this project and if this whole study was intended for the protection of the community as a whole and if all of this effort was so broad then we ought to protect those who perhaps have suffered. I suppose, though, that the basic legal principle you state is a sound one, and that in any effort to convey information to the person, that person should know and must expect that the risks after all are to be borne. The mere fact that they may be compensated for does not remove the fact that they may be blind or that they may have lost some function or, in fact, that they may die.

Dull: Both Professor Dickens and Dr. Robbins have discussed in great detail the concept of obtaining informed consent in research and in field trials. I'd like to make a comment or two about the practice of obtaining informed consent in distinction to the concept. I believe these comments apply equally well to research subjects or to participants in health programs where some risks attend. Some of the remarks grow out of our experience with the process of obtaining informed consent during the swine influenza vaccine program in 1976 in the United States, when more than 40 000 000 people received at least two and sometimes three documents which then were handed over to health officials to store for a period of years in keeping with statutory requirements.

All of us accept the fact that the responsibility to inform as a part of a personal decision-making process in health derives from at least social, legal and ethical obligations. However, in satisfying these obligations, the contributors to the process and the practice of informing can create what seems to many of us to be a complex and confounding product. The biomedical investigator or the health practitioner - either one presumably having reached the point of proposing a generally believed to be valid and not excessively unsafe health measure - wants to provide

understandable, comprehensive and comprehendable acts or at least reasonable expectations with which to persuade a potential subject or a potential receiver of health care to participate or to accept the health practice.

The lawyer, who may look after the legal obligations of the process, while wanting to avoid excessive legalism, nevertheless wants to ensure that the information is put in words and ways that a court could reasonably subject to critical analysis with respect to other research or other health matters that may have some relationship. Or what persons with expert qualifications might present to contradict or counteract the information that's given. The ethicist, looking at the process, and advocating that fundamental rights are not abridged wants to assure that anything overly promotional, or put in too-positive a way, be muted so that a neutral position is presented from which a person can freely make an unencumbered decision. In practice, therefore, the product of this arduous effort to compromise, in ways, the various intents and obligations probably not really satisfying any of the research, legal, ethical or sociological critics, is presented to potential subjects of research or health care.

The point I want to make is one known to all of us, and quite a simple one in that the intent and concept of informed consent is certainly a valid and an important one. However, perhaps it's difficult, or maybe nearly impossible in practice to inform fully about the complex scientific or health matters and at the same time create a fully legally sound document, if we are talking about forms, or process otherwise, with which to defend against claims of injury and at the same time present information devoid of implied encouragement for fear of over-promoting and denying the human right of free choice.

It may be necessary, therefore, to recognize that the process of obtaining informed consent has several elements. Obviously, one is to inform. Another is to seek a decision. And the third is to document that the process has occurred in a way so as to obtain as free and as objective a decision as possible. Perhaps by avoiding, if it is possible to do so, the creation of a single procedure or a single unified document, that tries to do all of these things, we might best seek ways to separate the process into its components, where people best able to deal with the components can take primary responsibility for assuring that they are suitable, and yet avoiding what seems to be destined otherwise to be a compromise and a confounding process. This doesn't mean totally independent efforts but rather a coordinated, unified approach which tries to minimize conflicting objectives and makes the practice more easily adapted to different needs and different circumstances.

Sondervorst: During the past two days we have heard much stimulating discussion on the exercise of human rights. We have had explained the deep-rooted meaning of the uncontroversial principles of the need to obtain informed, affirmative agreement before any participation in any kind of research. Informed consent by an adult or by a guardian, or assent in the case of a child, implies the right to know what will be done, why it will be done and what risks are involved. It also implies that the subject or patient may withdraw from such participation at any time without prejudice.

We have also heard of the grave responsibilities of the institutional or ethical review boards, or under whatever name they may go, in further and perhaps uniquely, protecting the individual who may not be quite as informed as he or she may think, or who may not realize or understand for a variety of reasons the health, the risks or the safety issues at stake always in some measure in any research. What has been said these last two days is not innovative. It is an accentuation of related meetings in the past and of what now is thankfully, current and accepted national and professional policy and practice in most, but unfortunately not all, countries. However, it was only yesterday, at this present reunion here, that one of our distinguished delegates very cogently pointed out that if we talk about rights and freedom of decision, there is also an obligation or duty on the part of some or all of us to ensure that those rights have meaning.

The pharmaceutical industry is probably the largest single experimenter with the human subject, and as such it has the awesome duty and responsibility of protecting the health, safety and well-being of those who have consented to the conduct of such experimentation and research as is required. Those of us from the industry present here are very conscious of this responsibility and fully endorse the declaration of Helsinki and the various human rights bills and the legislative ordinances governing clinical testing.

When a new therapeutic agent is being studied, much information has to be acquired and this must be done under conditions of strict control and subject or patient surveillance. Prior to the introduction of a new drug entity in man, the industry spends enormous resources in the chemical development and the quality assurance of the product. And in its preclinical testing in a variety of conditions, in animals, for pharmacological and toxicological effects. At this time, that is when this testing is on-going, these animal studies have been finished, an increasing number of countries impose the prerequisite of approval to proceed further with the study of the drug in man. Either by an IND or other form of clinical trial certificate.

Studies are designed to methodically and cautiously test absorption, distribution, excretion, metabolism, etc. of the new product. These are the Phase I bio-availability and pharmacokinetic studies and are usually restricted to volunteer subjects. The clinical pharmacology studies extend into a second phase where dose-ranging, therapeutic effect and initial safety are observed. These studies are usually of short duration, and have to be followed by expanded studies to confirm the efficacy and assess the occurring side-effects. These longer studies involve much larger patient numbers for longer durations, the extent of which depends on the nature and the therapeutic indication of the drug, as well as the disease treated.

Under favorable conditions, this results in official approval or registration. Yet, does the duty of protection, of surveillance, of the individual cease at this point? Does experimentation cease with registration or drug approval? To the contrary, this responsibility to the research subject or the patient now shifts to a vastly greater area. To the population at large. To the safeguarding of the health and well-being of the man in the street. This duty of continuing surveillance is so vast that it cannot be exercised by the pharmaceutical industry alone. It will not only involve the entire medical profession, but will indeed become a national and possibly supranational concern and duty. It will require much legislative guidance and governmental assistance in money and human resource. But we cannot shy away from the responsibility. It is this thought, this appreciation of duty to our fellow persons, imposed upon us all by the rights of others, that I hope we all will carry away with us when we return to our respective homelands.

Martins: My remarks are not really just on the problem under discussion. They are of a more general nature. On these two days, I've come out with the feeling that the members here present have some sort of guilty feelings about their attitudes so far. And I believe that, if we maintain as our primary concern the total welfare of the human being, that should not be so. I believe that the medical profession needs to present itself to the outside world with a dignified appearance; one not presumptuous but one of self-confidence and not of incapacity or doubt of itself. It looks to me that we have seemed to doubt our capacity to fulfil our ethical role in the community. I think, on the contrary, that one independent medical body is the most capable for decision-making; although obviously many times in cooperation, on specific topics, with other professionals or lay people, as required.

The public has the right to "common sense" information and it will obviously give its cooperation if it feels that we want to help it. But we must be realistic and distinguish intentions from their applicability. Major decisions in research should not be left solely to the individual but

should be screened, monitored and evaluated. Ideally this should be done through the medical profession, through their ethical committees.

We obviously need international codes of ethics as well as national codes to allow for the adaptions imposed by local conditions, either of historical, social or other background. Nevertheless, I strongly believe that the ethical controls should be kept within the profession, which should be the only one to lay down the rules and codes of ethics and implement them, although obviously accepting the right of society to appeal to the courts of justice if the doctors behaviour falls within the scope of common law. In Portugal we have just revised the problem and laid down a Code of Medical Ethics to which all doctors have to abide. There is a national medical council for ethics that defines the rules and revises them as needed. There are regional bodies to evaluate the problems or complaints that may arise. There is a disciplinary body, completely independent, elected solely for that purpose within the profession, that can go as far as to ban a faulty doctor from practice. We have the tools we need and we believe that dignification of medical practice must come from within the profession and not from outside the profession. We think that attention must be given to ethics and human and social goals of the profession during pre-and post-graduate training. We think that this is the only way in which we can keep the trust and confidence of our patients, who will look upon us as friends and as in the front-line of defence of their welfare and human rights. There is always room for improvement but I feel that, so far, there is no reason why the profession should be ashamed of itself. And that is really the message I didn't find in the previous discussion and which I would like to come out as a sort of conclusion.

And as a final remark, I would like that this gathering takes the view that it is considered unacceptable and to be condemned that any action should be taken against a doctor or that there should be any limitation of his rights, simply because of the refusal of that doctor to act against the code of medical ethics, as defined by the profession.

Robbins: I'd like to make a couple of comments in response to this. One is that, as a medical educator, I feel very strongly the obligation to educate in these areas. But I feel also very strongly that the medical educational establishment is not able to do very much beyond, because it is the role-models that students see that really influence them, not what they are told in school. Secondly, no matter what we may feel, about the inviolability or the inviolate rights of medicine, the medical profession - like any other group in society - is a social instrument. And we should not forget it.

Thirdly, this conference is predominantly about the ethical concerns in the field of research involving human subjects. I'd like to put a little different perspective on the participation of others in dealing with what the investigators do. In my opinion, this is in the tradition of good science. The scientific method is designed in the full knowledge of investigator bias. And we go to great lengths to design our experiments to overcome our known bias. And the fact that in those areas that involve ethical considerations, we may also have bias, and may need to design our experiments even to include the participation of others in reviewing this matter, is no criticism of us. It is purely good science. And I would like to suggest that that's a reasonable point of view. And perhaps would overcome a bit of this breast-beating and would make it more acceptable for others to view our plans and performance in research.

Kleczkowski: I fully realize that this session is practically the last technical session, and I would like therefore to ask your permission to share with you some more general reflections on possible benefits of this meeting. If one looks carefully at the title of our seminar, one might wish to see the context of our discussion much broader. We have been until now mainly concerned with clinical trials in the broader sense of the term with the only exception of field trials with regard to vaccines as proposed by Dr. Robbins. In other words, the main attention has been paid till now to developments of safeguarding of safety mechanisms of medical instruments with regard being paid to ethical aspects of such developments. Till now we haven't paid enough attention to the way of using these medical instruments in practice.

As a matter of fact, all of us are fully aware and even some reference has already been made by several speakers today and yesterday, to some issues related to day-to-day confrontation of medical decisions, from the top from health policy decisions, to the individual decisions made in doctor/patient contacts for with their everyday ethical implications. We are also aware that a lot of medical experiments are taking place in the field of medical delivery.

In general we can state that while being highly concerned with careful development of modern and safe medical instruments, you are much less concerned with the guiding system of the ways of estimating the value of these instruments to the recipients, that is to the population. And, as a matter of fact, most decision-making on the political level or day-to-day medical decision-making, are not carefully controlled. I am far from suggesting that we expand our discussion. We have to be realistic. The subject of mental health is complicated enough and important enough and has been already exhaustively discussed during our discussion. There is practically no room to try to expand our discussion.

However, before concluding our seminar, it would be worthwhile to note that there is a big field of medical experimentation and its implication in terms of human rights that has not been discussed at this conference. We have to be aware of such a fact, for instance, that around eighty percent of the global population is simply deprived of any essential medical care until now. Or that a high proportion of medical care consumers is not satisfied at all with the service provided. This is just one example.

I would like to go a bit further that probably we may use the Round Table forum offered by CIOMS to go further on these topics, to cover some missing aspects not being discussed until now. I'm referring to medical decision-making and its social, economic and ethical implications.

Scoville: Je voudrais revenir un instant sur une question de détail peut-être, mais qu'il me paraît éventuellement utile de préciser avant l'expression de conclusions générales. C'est à propos d'une notion qui a été évoquée ce matin car, si j'ai bien compris. d'aucuns ont voulu parler d'essais chirurgicaux.

La première chose que je voudrais dire c'est qu'il me paraît difficile, et je parle ici en tant que chirurgien, de comparer une intervention chirurgicale et un essai clinique médicamenteux sur l'homme. La seconde chose, c'est que, essais chirurgicaux ou expériences chirurgicales n'existent pas dans le travail d'un chirurgien un peu normal. L'expérimentation chirurgicale, comme nous savons tous, se passe au laboratoire de chirurgie expérimentale, où dix, vingt ou cent chiens sont opérés avant de lancer une nouvelle technique chirurgicale. Et, dieu sait si les sociétés protectrices nous le reprochent. La troisième chose est la question d'un éventuel comité d'éthique dans un cas de tentative chirurgicale. A-propos de cette sorte de comité d'éthique je dirais qu'il ne faut pas se compliquer la vie. Il existe. Nous le trouvons. Nous l'avons. C'est précisément le staff meeting où chaque détail est discuté et où le médecin traitant, le consultant, le cardiologue, le gastroentérologue, tous ceux qui ont intérêt à avoir bien soigné un candidat à une opération, viennent discuter. M. Mach ce matin a fait allusion à un cas vraiment exceptionel et il a bien fait de le signaler, mais ça reste vraiment un cas d'exception. Mais je crois que nous devons bien réaliser que dans toutes les structures hospitalières un peu normales c'est ainsi que cela fonctionne au cours d'une discussion très largement accessible à tous ceux qui s'intéressent aux futurs ou éventuels opérés. Je crois qu'il n'y a pas besoin de préciser plus.

Browne: May I without apology once again direct attention to the shifting population center of gravity of the world, which is now four-fifths in the developing countries and will in the future be of greater proportion

than that. We cannot extrapolate from our western society and our standards the entire concept of ethics and of informed consent. And I do sense an apparent danger of an unrealistic overemphasis on the rights of the individual as against his obligations to the community. I am all for the protection of the individual by informed consent to participation in drug trials or research of any kind, but I do also see that failure to act in time, and to act adequately, may be just as culpable as doing positive harm in another sense. And in developing countries today epidemiological investigations may be just as important a preliminary to successful therapy, so as to provide an adequate basis for therapy when that becomes available.

And so whole populations surveys are certainly on the cards. When the investigation employs non-invasive techniques - stool and sputum examinations - there is no problem. But when it comes to invasive techniques - taking of blood, lymph, skin snips, gland punctures, etc.- then we have a whole host of ethical problems on our hands. And investigators must be ethically justified in the procedures that they advocate and take part in. Similarly, for mass treatment, and it is here that governments intervene with their own ethical codes and their own responsibilities for the majority of the inhabitants. And the individual researcher may be on the horns of a dilemma as he considers his obligations to the individual and those to a society at large. And once again it is mutual trust and confidence that will be at the basis of all such relations.

We found that it was the application of the principles of informed consent that was most difficult to apply in a community, say in Central or in West Africa. We enlisted the cooperation not only of the chiefs and heads of families but those conversant with the local drum language. In fact we learned some of the languages ourselves so that we could convince populations that what we were proposing to do was in their best interests. And so once it was abundantly clear that vaccination against smallpox was in effect a protection, then we were able to go on to treatment for such endemic diseases as onchocerciasis and leprosy. And here it is not a question of regaining our raison d'être as doctors, but of retaining the goodwill of the populations we serve. And this can be done by having a curative system at the same time as developing investigative techniques. People would not then complain that you come here and take blood or lymph or whatnot, but you don't give us anything in return. They see that the doctors concerned with the investigation are really concerned with caring for individual patients who suffer from certain conditions. And this really gives the reason for the continuing investigation and eventually. the trials of new drugs. And so by attention to these sociological details, I think one can convince folk of one's desire to help and hence to apply on a large scale the investigative techniques that we in the West are so familiar with.

Violaki: In the discussion the last few days, considerable attention has been focused on the human rights of subjects involved in medical research. National and international reports or studies have been formulated. Institutional ethical review committees have been created. And in some countries clinical trials of medical products have been subjected to detailed and complex statutory controls. The community concept for vaccine trials is very important, because it involves on the one hand the most healthy population and also on the other hand the child population, and this morning we spent a lot of time about the ethical aspects. If you permit me, may I emphasize the following points.

Appreciation of the importance of greater attention to all the ethical aspects of human research as well as health care in the education of world health science personnel is essential. It is also necessary to prepare guidelines for the establishment of advisory committees on bioethics, and to review experience in countries with established ethical review procedures. There is also the necessity of including, as has been mentioned, non-medical members, and specifically women, on committees reviewing research projects, particularly those involving children. This will be an important issue in many vaccination trials. It is also important to emphasize to the community that sometimes we have not only rights but we have also duties.

Consumer behaviour - what factors such as availability and accessibility of services, influence consumer behaviour? What are the predisposing factors, such as motivation, health, knowledge, that influence human behaviour, and how can the growing power of certain types of health services be promoted? The acceptance of preventive procedures is very important. An effective programme of health education helps the prevailing levels of public understanding for preventive procedures. Public consultation about the risks and the benefits of research will help in these trials. The public can only respect a worker who can be seen to be helpful broadly to the whole community.

During these discussions it was pointed out that there is a need to develop guidelines for ethical review procedures having regard to the increasing research activity within the biomedical field that has developed in recent years. Although the welfare of human subjects involved in a research project continues to be adequately protected, it is nevertheless essential and desirable for WHO to assist developed and developing countries in involving mechanisms that would ensure observance of the principles of medical ethics in biomedical research. May I also associate my voice with that of the previous speakers who plead for some human rights and freedom for medical people, so that they can do everything beneficial to human beings.

Krebs: During these last two days medical experimentation has been looked at mainly as a one-to-one relationship between the individual or the patient and the researcher, that is the physician. However, it would appear that there is a part missing in this analysis. As there are also other groups involved in the research process. And the extent and the manner of their involvement can have, and ought to have, an influence on the way in which the research is carried out, and therefore on the results. Hence, it would seem important to give this matter due consideration. As far as nursing and nurses is concerned, I would like to call your attention to two points. One refers to nursing service and its management. The time that the nursing personnel needs to devote to the patient involved will depend on the type of research. When nurses act as data gatherers, this has a direct influence on the time devoted to patients participating in the research, and to the patients not involved, for whom less time may be available. So this has to be taken into account when calculating the staffing needs.

The second point relates to the nursing personnel individually. Last year at the International Labour Conference recommendations concerning conditions of employment and conditions of work and life of nursing personnel were presented. The recommendations contain the following clause: Nursing personnel should be able to claim exemption from performing specific duties without being penalized, where performance would conflict with their religious, moral or ethical convictions and where they inform their supervisor in good time of their objection so as to allow the necessary alternative arrangements to be made to ensure that essential nursing care of patients is not affected. It is therefore necessary to stress that both those responsible for the management of nursing services, as well as the individual nurses, need to be informed about the medical experimentation proposed, in order to be able to decide if they agree or do not agree to participate, and second to be able to make the necessary provisions for staffing to ensure that both the patient involved in experimentation and those patients not involved will receive the nursing care required, and to guarantee that it is acceptable in terms of quality and quantity. In this way it will be possible for the nursing personnel to make a responsible contribution to medical experimentation, so that it will meet the standards here discussed.

Riis: We have discussed the legal aspects and we have discussed the human rights aspects in that you show the research subjects due respect by explaining to them, and I think that this is very positive even if the cognitive content of what the doctor says is not always taken in to the same extent by the patient or volunteer. I want to stress a tertiary effect by having such informed consent discussions in departments. The information part acts as a sort of discussion of the rationale of diagnostic, therapeutic and preventive measures. And we very much need such discussions in clinical medicine. And thereby the informed

consent discussions have a very positive effect on the huge and uncovered field of patient information as such in non-research situations. And by this means I only want you to, let's say, adopt a less defensive attitude when discussing informal consent because in this way it has a very positive influence on our clinical conduct in other respects.

McCarthy: I would simply like to address a question to Dr. Dickens and perhaps to Dr. Lasagna. And that is to add perhaps one more element to the information that is conveyed in informed consent. It seems to me that if we are going to convey to the potential subject the information of possible untoward effects that may result from the research, then we ought also to convey to the potential subject what sort of short-term care may be available in the event of some kind of injury, and of what kind of long-term care may be available in the event of a serious injury or a chronic injury. And then finally what kind of compensation for loss of wages will be available to the subject in the event the person is unable to engage in gainful employ. It seems to me that if we are going to describe possible injuries, then we ought also to assure the individual or inform the individual as to what if any kind of care or redress for those injuries will occur. So I would like to hear comment from one or another of the speakers on that subject.

Curran: Quickly, I think the question is would you see, Professor Dickens, including in the concept of informed consent informing the subject of the availability of some compensation if injury does occur.

Dickens: Yes, I think that would be absolutely proper. There would be no question of that being an inducement. If anything it would reinforce the negative elements of the study and offer appropriate assurances.

CLOSING ADDRESS

Alfred Gellhorn

It is the purpose of this final session for me to attempt to summarise some of those things which we have discussed, and to draw some conclusions therefrom. This is far too sophisticated an audience for me to begin in the usual humble way by saying that I will be inadequate in my summary. I assume that you know that, so that I will not further pursue that disclaimer. I do wish to note, however, that the summary does not begin to do justice to the wealth of information contained in the papers and the discussion.

I would like to restate the purpose of this meeting, which was to focus attention on the issues relating to ethical review in clinical research. There are many other ethical aspects arising from the practice of medicine, which are appropriate concerns, but this meeting was specifically directed to the first issue. What is the need of the meeting? During the course of the meeting it has been questioned whether it was really necessary. In response to this I think that it is significant that we have present delegates from 40 countries, both developing and developed, and from 46 international organizations, all members of CIOMS, in addition to representatives from the World Health Organization, and from the United Nations and its several divisions. This would suggest that the subject is one of universal interest, and therefore I do not think we need apologize for having held the meeting.

What are some of the reasons for the worldwide concern regarding ethical monitoring of medical research involving human subjects? There is the overriding reason that we are concerned with morality in the practice of medicine and in the practice of research. But far more than that, ethical review of research has some very explicit objectives. It ensures the protection of the entire research enterprise. Without it, science is subject to accusations of arrogant disregard of human rights, but with it science can continue advances in biomedical knowledge and apply these in research on man.

Ethical evaluation of clinical research is necessary for the protection of the individual subject, whether he be in any of the categories that have been considered during the course of this meeting, i. e. healthy subjects, patients, institutionalized subjects or children. Ethical review of clinical research protocols is an important protection of the investigator; for an individual who conducts research without peer review, both of the purposes and the technical aspects but also the ethical conduct and the ethical organization of the research, is subject to charges which he can avoid by virtue of having had prior clearance.

There is also protection for the granting agency. This is of obvious concern to such organizations as WHO, the United Nations, and other international and national organizations providing funds for clinical research.

Very significantly, as has been brought out in the discussions, ethical review is important for the protection of a nation. Many countries in the developing world have forcefully drawn our attention to the need for ensuring that the relevance of research for their own need is properly considered. There is the importance of assuring that there shall be local involvement in whatever research may be conducted by outside investigators, and unless there is an established mechanism for this purpose, many of these important requirements cannot be met.

The following issue could be expressed as "How does one go about achieving this ethical review?" The historical presentation emphasized the fact that serious concern for this aspect of medical research is recent. Ethical codes have been drawn up, of which particular mention may be made of the guiding principles laid down by the World Medical Association in its 1964 Helsinki Declaration and its 1975 Tokyo revision. It was recognized, however, that the general principles need to be accompanied by more specific rules for their implementation and that they be better adapted to particular needs, whether these be of particulat granting agencies and whether they be of countries or for special types of research. These may be elaborated in two forms: (1) statutory regulations, enforced by regulatory agencies in many countries of the world, particularly with regard to drug research, and (2) the establishment of review committees (a means that has been particularly emphasized during the course of this meeting).

As to review committees, these can be of two types. There can be a central type of review committee established at the governmental level or perhaps by a non-governmental entity, such as an Academy of Sciences. Either of which has the advantage of authority, because of its central nature. Such a central committee has the advantage of being non-partisan, because those individuals who are selected will be individuals of eminence. It has the advantage of being able to deliberate on fundamental policy decisions, which then can be transferred to local levels. It can thereafter serve a useful function of appeal from a decision at a local level, felt to be unsatisfactory. Thus it is useful for the interpretation of existing codes, and could be enormously valuable to the developing countries where such a central authority could be of assistance in establishing research priorities. The disadvantages of central committees have to do with the fact that they are remote, that they may be politicized so that the selection of the members then may not be on the basis of their merit but for other considerations, and that the time element in their deliberations may so slow the research.

As an alternative to central review committee, or as an addition, there is the possibility of creating local committees which can be again of two types. The majority of local committees in the industrialized countries of the world are hospital-based. In some examples given a second type of local committee exists which is community-based. That is to say, it has a responsibility which extends beyond the university hospital and beyond the teaching hospital and thus may be related to the entire community. Such a committee would be more effective in monitoring the ethical aspects of (drug trials) research carried out by physicians in their ordinary (office) practice. The advantages of local committees are that they have knowledge of the local personnel who may be involved in the research; they also know the availability and the appropriateness of the facilities; they are able to take quick action. The disadvantage is that bias, in terms of being more concerned with the personal relationships with investigators than with the fundamental issues at hand. may play a role.

With regard to the composition of the review committees once they are created, the consensus seems to have been that it is of value to have clinical researchers, i.e. those who have actually been involved themselves in the conduct of clinical research, serving on them and that there should also be representatives from the laity. There was a forceful recommendation with regard to the latter and parenthetically may I say that we, the organizers of this conference, really overlooked this, and that we should have foreseen the important contribution that might have come from a greater lay representation to put forward the attitudes of non-medical, non-scientific individuals with regard to these ethical issues. A very strong and compelling recommendation was made that. inasmuch as a significant proportion of clinical research is carried out on women, it is important that there be women represented on the review committees. Our delegate from the International Council of Nurses also drew attention to the desirability of the involvement of nurses together with physicians in the conduct of clinical research, their importance to the success of the research, and their insight into the implication of the research.

The next issue that was considered related to the authority of review committees. The authority can stem from a variety of sources. It can be, as it now is in the United States, a matter of governmental or legislative action. Thus review committees must be in existence and must function. It can be at the international level, within or on behalf of an organization such as the World Health Organization, which now states that any research that is carried out in its farflung activities must have had ethical review. The authority may well rest with the requirements by funding agencies that ethical review has been carried out. There is also the important potential element contributed by scientific journals, which before publishing the results of the research demand evidence

that the research has been given review and approval by an appropriately constituted ethical review mechanism.

There was limited discussion of the implications of the source of funding. For the most part attention was focused on funding that came from governmental sources. The consensus was that research supported by private foundations, grateful patients or from the pharmaceutical industry should be given the same types of scrutiny and review by ethical review committees regardless of the source of funds.

The characteristics of the types of research that should be reviewed were discussed and although, again, there appeared to be major emphasis on research related to drug trials, it was recognized both implicitly and explicity that consideration should be given to research not only on clinical pharmacology and drug trials, but to other forms of clinical research which might be in the area of therapy, or in the area of diagnosis, or in the area of prevention or. finally and importantly, in the area of behavioural research.

One of the interesting and instructive issues raised related to the qualifications of a review committee member that made for expertise in judging ethical questions. Although it was opined that physicians are inherently inclined to act in an ethical manner, many of the conference participants expressed humility, particularly those who had served on an ethical review committee. Many of the issues that come up are extraordinarily complex, requiring judgement coming from experience and knowledge of local attitudes and customs. It was suggested that it was important that there be an increased emphasis on the training of all of us with regard to ethical issues in medicine. To this end, syllabi and texts are now available, beginning with the medical student, carrying on to the period of house officer training and into the area of continuing education in which all of us are personally involved. Some of these are in the form of simulated cases in which a group, whether they be of medical students or others, address themselves to a particular issue and attempt to come to a conclusion which can then be checked against the conclusion that has been reached by the ethical review committee. I was interested to learn from Sir Douglas Black that, in the United Kingdom, an annual event is a meeting of the chairmen of review committees throughout the UK who get together to discuss their common problems. These may include general questions such as types of research carried out on children or the chronically ill, but they may be very specific cases that are brought to the attention of the assembled chairmen of the review committees for their consideration. It would seem to me that this is a useful type of group education which could be extended.

The next issue that was considered by the symposium related to the selection of subjects. This one was fraught with a number of problems, for here involved were healthy subjects, patients, institutionalized subjects and children. It seemed to me again a useful educational experience for all of us to find out that there is considerable diversity of opinion with regard to the utilization of such subjects. I was particularly interested and amused by the fact that we need some new definitions of normal subjects or healthy subjects who now, it seems to me, we shall have to define as those who are sound of mind having also successfully passed a complete physical examination and medical history and are, in addition, consenting. These constitute perhaps the healthy subjects and volunteers, but the fact that they say they are healthy is not enough.

It was pointed out by a delegate from an epidemiological society that we must be aware of the fact that those who volunteer to participate are self-selected and therefore the issue of having an appropriate sample of the population is enormously important. Dr. Robbins further stressed that in the vaccine trials the complete spectrum of the community that is to be affected is important in the selection of the subjects.

With regard to patients it seems to me that the major issue that came up related to the controls in therapeutic trials of drugs. The question was whether the control group should receive a placebo as one possibility or whether the control group must receive the best available known treatment of the time. It appeared from the discussion that to attempt any generalizations on this would be difficult, for in each specific issue that may come before the review committee, the appropriateness of one or the other must be considered.

Dr. Neki presented to us the issues regarding clinical research using institutionalized patients, and again the fact that emerged there is no final answer on the appropriateness of whether one utilizes patients in psychiatric institutions or those for the mentally retarded, or those with chronic diseases, but rather that the conditions of the particular experiment must be reviewed by a competent and thoughtful body before a final decision is made. In some instances, as was pointed out, measures have been taken to provide protection to individuals, and this has constituted a deterrent to effective research that was designed to benefit patients in one or another type of institution. This reemphasizes that one of the values of having an ethical review mechanism, widely known among the profession and equally widely known among the members of the community, is that this will reduce the frequency with which regulations are set up in an attempt to control research. Regulations present the difficulty of being not only constraining but having a static quality, whereas in this area it seems to me that dynamism is of importance.

The definition of informed consent also proved to be one of the difficult issues, but the fact that it is difficult does not diminish its importance. It has been said that the whole area of informed consent is like weaving a strand out of sand. That is so because it is an area of ambiguity and it is difficult to set down final answers in this area. It was pointed out that a signed consent document has little legal weight. Far more important is a description of the process whereby the experimental subject is informed before he signs the consent form. I can recall that when I received the swine flu vaccine I was one in a very long line of people. Just before reaching the place where I was to receive the vaccine, I was given a slip of paper and told: 'Sign, it's a consent paper.' In the meantime I was being pushed from behind and in front they were ready to make the injection. The degree of informed consent on that was fairly limited and if I had come down with the Guillain Barré syndrome I would have been back at the US Government as fast as the next person. So the informed consent really constitutes, if properly obtained, evidence that a transaction has taken place. It was suggested in this discussion that it would be valuable for journals that report clinical research to require that authors provide a description of the process of obtaining informed consent from their subjects. This would be an educational process for younger clinical investigators and would also indicate the importance of the process.

As is, I am sure, the case with all of us, we come to a meeting with high expectations that by the time we leave we will be thoroughly informed and expert, and be able immediately to translate the results of the meeting into some practical aspects. I don't think that this meeting achieved that. I believe that it has formed a mechanism for sensitization of all of us to the issues, not only in our own countries, but throughout the world. It has provided an opportunity to learn something about what is being done in the rest of the world and, to the surprise of many, there was a remarkable consensus with regard to the characteristics of review committees in those countries that have it, because we had known so little of what was going on. I would now like to indicate to you the intentions of CIOMS and at the same time solicit your comments. CIOMS is a non-governmental organization. It is closely related to the World Health Organization and to UNESCO both physically by virtue of office space in these organizations and, more importantly, by having a community of interest for many of the programmes of WHO and UNESCO. CIOMS is, however, non-partisan and non-political. It represents sixty-six of the international organizations of the medical sciences and there are twenty-seven national members. It is the belief of CIOMS that further investigation and collection of information with regard to the mechanisms for ethical review throughout the world should be our purpose, with the ultimate objective, in association with WHO, to establish general guidelines which, however, can be adapted to the specific needs of a country. It is our hope that through the Round Table Conference we

have just enjoyed together with the aforementioned activities, CIOMS can serve a catalytic purpose to create such mechanisms for ethical review of research where such do not exist. The information regarding existing ethical control of clinical research will be obtained through our member organizations and through those facilities that are made available to us by the World Health Organization. Finally, it is proposed to establish regional meetings where the particular problems of a region can be thoroughly considered.

PARTICIPANTS

Chairman/Président	
Prof. Alfred GELLHORN	President, Council for International Organizations of Medical Sciences
Secretary/Secrétaire	
Dr. Zbigniew BANKOWSKI	Executive Secretary, Council for International Organizations of Medical Sciences
Invited Speakers	
Prof. B.K. ADADEVOH	Director of Medical Research, National Institute for Medical Research, Nigeria
Sir Douglas BLACK	President, Royal College of Physicians, UK
Prof. N. BOCHKOV	Director, Institute of Medical Genetics Academy of Medical Sciences, USSR
Prof. H. BREUER	German Research Society, Federal Republic of Germany
Dr. C. D. BURRELL	Vice-President, Sandoz Foundation, USA
Prof. J. CHEYMOL	Ancien président, Académie Nationale de Médecine, France
Prof. R.E. COOKE	President, Medical College of Pennsylvania, USA
Prof. W.J. CURRAN	Professor of Legal Medicine, Harvard University, USA
Dr. E.S.H. DAOUD	Director-General. Laboratories and Medical Research. Ministry of Health, Democratic Republic of the Sudan
Prof. B.M. DICKENS	Faculty of Law, University of Toronto, Canada
Prof. C.C. DOWNIE	Technical Services Director, Imperial Chemical Industries Limited, UK
Dr. H.B. DULL	Assistant Director for Program, Assistant Surgeon General, Department of Health, Education, and Welfare, USA
Dr. J.F. DUNNE	Medical Officer, Pharmaceuticals, Secretary of Secretariat Committee on Research Involving Human Subjects, World Health Organization, Switzerland

Dr. F.W. FISCHER	German Research Society, Federal Republic of Germany
Prof. K. GIBINSKI	Chairman, Committee of Experimental Therapy, Polish Academy of Sciences
Prof. G. GIERTZ	Swedish Society of Medical Sciences
Dr. F. JOHNSON-ROMUALD	Ancien directeur de la Division de la Pharmacie, Ministère de la Santé, Togo
Dr. T.A. LAMBO	Deputy Director-General, World Health Organization, Switzerland
Prof. L. LASAGNA	Department of Pharmacology and Toxicology, University of Rochester, USA
Prof. R.S. MACH	Président de l'Académie Suisse des Sciences médicales
Prof. G.E. MILLER	Coordinator of International Activities, University of Illinois at the Medical Center, USA
Prof. J. MILLER	Professor of Medical Genetics, University of British Columbia, Canada
Prof. J.S. NEKI	Postgraduate Institute of Medical Education and Research, India
Prof. I. NIR	Hebrew University Schools of Medicine and Pharmacy, Israel
Prof. H.H. PHILLIPS	Dean, University of Ghana Medical School
Prof. S. M. RAPOPORT	Ministry of Health, German Democratic Republic
Sir William REFSHAUGE	Former Secretary-General, World Medical Association
Prof. P. RIIS	Department of Medical Gastroenterology, University of Copenhagen, Denmark
Prof. F.C. ROBBINS	Dean, School of Medicine, and Professor of Pediatrics and Community Health, Case Western Reserve University, USA
Prof. A. A. SAMPAIO	Former Director-General of Health, Portugal
Dr. M. SONDERVORST	Director, Clinical Investigation, A.H. Robins Company, USA
Prof. D.W. VERE	Professor of Therapeutics, London Hospital Medical College, UK
Dr. M. WEATHERALL	Director of Establishment, Wellcome Research Laboratories, UK
Mr. R. N. WILLIAMS	Head of Medicines Division, Department of Health and Social Security, UK

REPRESENTATIVES OF CIOMS MEMBER ORGANIZATIONS/ REPRESENTANTS DES ORGANISATIONS MEMBRES DU CIOMS

International Union of ANGIOLOGY	Prof. F. PRATESI
International Society of AUDIOLOGY	Prof. R. HINCHCLIFFE
National Health & Medical Research Council, AUSTRALIA	Dr. T. HURLEY
Académie Royale de Médecine de BELGIQUE	Prof. P.G. JANSSENS Prof. A. de SCOVILLE
Federal Council of Medicine, BRAZIL	Dr. M. BELCHIOR
Union of the Scientific Medical Societies in BULGARIA	Prof. G. GALABOV
Medical Research Council of CANADA	Prof. J. MILLER
International Society & Federation of CARDIOLOGY	Prof. J. GOODWIN
Royal Danish Academy of Sciences and Letters, Denmark	Prof. P. RIIS
CZECHOSLOVAK Medical Society	Prof. B. SPACER
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International EPIDEMIOLOGICAL Association	Prof. L.A.C.R. CAYOLLA da MOTTA
Academie Nationale de Médecine FRANCE	Prof. J. CHEYMOL
World Organization of GASTRO-ENTEROLOGY	Prof. F. VILARDELL
GERMAN Research Society, Federal Republic of Germany	Prof. H. BREUER Dr. F.W. FISCHER Prof. T.M. FLIEDNER
International Society of HISTORY of MEDICINE	Dr. L.DULIEU Dr. R. JORIS
Federation of HUNGARIAN Medical Societies	Prof. K. MAGYAR
International Society of INTERNAL Medicine	Prof. D.T.D. HUGHES
ISRAEL Academy of Sciences & Humanities	Prof. I. NIR
Science Council of JAPAN	Prof. S. YAMAGATA

International LEPROSY Association	Dr. S.G. BROWNE
International Association for the Study of the LIVER	Prof. N. TYGSTRUP
International Society of LYMPH-OLOGY	Dr. P.E. PETERS
Royal NETHERLANDS Academy of Arts and Sciences	Prof. J.H.P. JONXIS
International Society of NEURO-PATHOLOGY	Dr. J. ESCALONA-ZAPATA
National Institute for Medical Research, NIGERIA	Prof. B.K. ADADEVOH
International Federation of OPHTHALMOLOGICAL Societies	Dr. M. SILVA PINTO
International PEDIATRIC Association	Prof. N.O.B. HALLMAN
World Federation of Associations of PEDIATRIC Surgeons	Prof. A. GENTIL MARTINS
International Union of PHYSIOLOGICAL Sciences	Prof. A.G.B. KOVACH Prof. K. THURAU
POLISH Academy of Sciences	Prof. K. GIBINSKI
World PSYCHIATRIC Association	Prof. M. PAES de SOUSA
REHABILITATION International	Prof. F. SANTANA CARLOS
International REHABILITATION Medicine Association	Dr. H.J. HACHEN Dr. W.M. ZINN
International League Against RHEUMATISM	Sir William REFSHAUGE
SWEDISH Medical Research Council	Prof. B. CRONHOLM
SWISS Academy of Medical Sciences	Prof. O. GSELL Prof. R.S. MACH
SOUTH AFRICAN Medical Research Council	Miss C.M. HAYWARD
International Congress on TROPICAL MEDICINE & MALARIA	Prof. J. PAPAVASSILIOU
Medical WOMEN'S International Association	Dr. H. THIEME
WORLD Medical Association	Dr. J. DAUGAARD

REPRESENTATIVES OF THE UNITED NATIONS AND ITS SPECIALIZED AGENCIES / REPRESENTANTS DES NATIONS UNIES ET DE LEURS INSTITUTIONS SPECIALISEES

United Nations Fund for Drug Abuse Control	Dr. B. REXED
United Nations Research, Studies and Prevention of Discrimination Section, Division of Human Rights	Mr. G. BRAND
United Nations Educational, Scientific and Cultural Organization, Division of Human Rights and Peace	Mr. V. SHELOPOUTOV
World Health Organization, Division of Prophylactic, Diagnostic and Therapeutic Substances	Dr. S. BUTERA
World Health Organization, Pharmaceuticals, Secretary of Secretariat Committee on Research Involving Human Subjects	Dr. J. F. DUNNE
World Health Organization, International Digest of Health Legislation	Mr. S. S. FLUSS
World Health Organization, South-East Asia Regional Office	Dr. B.A. JAYAWEERA
World Health Organization, Resource Group	Dr. B. KLECZKOWSKI
World Health Organization, News Media Relations Division of Public Information	Mr. G. LEVI
World Health Organization	Mr. S. SHUBBER
World Health Organization, Regional Office for Europe	Dr. A. WAHBA

OTHER PARTICIPANTS / AUTRES PARTICIPANTS

Dr. A. AKCASH	Head, Department of Pharmacology, Cerrahpasa Faculty of Medicine, Turkey
Dr. A. ALBINO	Director, Department of Gynaecology, Hospital Geral de Santo Antonio, Portugal
Prof. F. ANTONI	Rector, Semmelweis Medical University, Hungarian Academy of Sciences

Dr. S.R. BERNHARD	Director, Dahlem Konference, Federal Republic of Germany
Dr. T.B. BINNS	Senior Lecturer, London Hospital Medical College, UK
Dr. G. BOELCKE	Erster Abteilungsleiter, Institut für medizinische und pharmazeutische Prüfungsfragen, Bundesrepublik Deutschland
Dr. E. BOERI	Délégué Gouvernmentale Permanent aux Institutions Sanitaires Internationales, Monaco
Prof. C.F. BORCHGREVINK	Institutt for Almenmedisin, Norway
Mr. C. BORGNA	Presidente, Confederazione Industriale Firenze, Italy
Prof. C. BOURAMOUE	Doyen, Ecole de Médecine de Brazzaville, Congo
Mr. F. BRIDEL	Director, Pharma Information, Switzerland
Dr. D. BURLEY	Association of British Pharmaceutical Industries, UK
Mr. G. BURTON	SCRIP, World Pharmaceutical News, UK
Dr. J. CALDEIRA da SILVA	International Hospital Federation, Portugal
Prof. A. CORDERIO	Professor of Internal Medicine, Lisbon University, Portugal
Prof. R.J. DALY	Medical Research Council of Ireland
Dr. E.S.H. DAOUD	Director-General. Laboratories & Medical Research, Ministry of Health, Democratic Republic of the Sudan
Dr. J. DELGADO	Director of Research, R. Casal Center, Ministry of Health, Spain
Dr. G. DELTOUR	Director, International Medical Relations, Roussel-Uclaf, France
Dr. D. DOSE	Director, Pharmaceutical Department, Hoechst-Portuguesa, Portugal
Dr. A. DURAO	Docente de Faculdade de Medicina de Coimbra, Portugal
Prof. J.C. FERREIRA de ALMEIDA	Escola Nacional de Saude Publica, Portugal

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