INTERNATIONAL GUIDING PRINCIPLES FOR BIOMEDICAL RESEARCH INVOLVING ANIMALS (1985)

INTRODUCTION

The International Guiding Principles for Biomedical Research Involving Animals were developed by the Council for International Organizations of Medical Sciences (CIOMS) as a result of extensive international and interdisciplinary consultations spanning the three-year period 1982-1984.

Animal experimentation is fundamental to the biomedical sciences, not only for the advancement of man's understanding of the nature of life and the mechanisms of specific vital processes, but also for the improvement of methods of prevention, diagnosis, and treatment of disease both in man and in animals. The use of animals is also indispensable for testing the potency and safety of biological substances used in human and veterinary medicine, and for determining the toxicity of the rapidly growing number of synthetic substances that never existed before in nature and which may represent a hazard to health. This extensive exploitation by man of animals implies philosophical and moral problems that are not peculiar to their use for scientific purposes, and there are no objective ethical criteria by which to judge claims and counterclaims in such matters. However, there is a consensus that deliberate cruelty is repugnant.

Suggestions had been received from several quarters that CIOMS, as an international nongovernmental organization representative of the biomedical community, would be ideally placed to propose a broadly based statement, acceptable worldwide in different cultural and legal backgrounds, and designed to create a greater understanding on the subject of biomedical research involving animals. Moreover, in several countries political action was being taken to stop or severely limit animal experimentation, and the Council of Europe had for some time been engaged in the elaboration of a convention to regulate the use of vertebrate animals for experiments or toxicity tests.

While many countries have general laws or regulations imposing penalties for ill-treatment of animals, relatively few make specific provision for their use for scientific purposes. In the few that have done so, the measures adopted vary widely, the extremes being: on the one hand, legally enforceable detailed regulations with licensing of experimenters and their premises together with an official inspectorate; on the other, entirely voluntary self-regulation by the biomedical community, with lay participation. Many variations are possible between these extremes, one intermediate situation being a legal requirement that experiments or other procedures involving the use of animals should be subject to the approval of ethical committees of specified composition.

In elaborating and publishing the International Guiding Principles the objective of CIOMS is not to duplicate such national regulations or voluntary codes as already exist but to provide a conceptual and ethical framework, acceptable both to the international biomedical community and to moderate animal welfare groups, for whatever regulatory measure each country or scientific body chooses to adopt in respect of the used animals for scientific purposes. The Principles strongly emphasize that there should not be such restrictions as would unduly hamper the advance of biomedical science or the performance of necessary biological tests, but that, at the same time, biomedical scientists should not lose sight of their moral obligation to have a humane regard for their animal subjects, to prevent as far as possible pain and discomfort, and to be constantly alert to any possibility of achieving the same result without resort to living animals.

The International Guiding Principles are the product of the collaboration of a large and representative sample of the international biomedical community, including experts of the World Health Organization, and of consultations with responsible animal welfare groups. They have constituted the agenda for three international meetings, the first of these being a Working Group that met in March 1983 to consider a preliminary draft prepared by CIOMS with consultant aid and the collaboration of the WHO Secretariat. The next meeting was the XVIIth CIOMS Round Table Conference, held in December 1983, to give the draft International Guiding Principles, as amended by the Working Group, a much wider exposure to criticism and suggestions. The third and last meeting, which took place in June 1984, was of a CIOMS Expert Committee which met for a final review of the International Guiding Principles as revised in the light of comments made during the Round Table Conference and subsequently by correspondence.

The International Guiding Principles have already gained a considerable measure of acceptance internationally. European Medical Research Councils (EMRC), an international association that includes all the West European medical research councils, fully endorsed the Guiding Principles in 1984. Proposed U.S. Government Principles for the Utilization and Care of Vertebrate Animals used in Testing, Research and Training formulated in 1984 by the U.S. Interagency Research Animal Committee, were to a considerable extent based on the CIOMS Guiding Principles. In the same year, the Guiding Principles were endorsed by the WHO Advisory Committee on Medical Research at its 26th Session.

It is the hope of CIOMS that these Guiding Principles will provide useful criteria to which academic, governmental and industrial bodies may refer in framing their own codes of practice or legislation regarding the use of laboratory animals for scientific purposes.

Zbigniew Bankowski, M.D.
Executive Secretary, CIOMS

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PREAMBLE

Experimentation with animals has made possible major contributions to biological knowledge and to the welfare of man and animals, particularly in the treatment and prevention of diseases. Many important advances in medical science have had their origins in basic biological research not primarily directed to practical ends as well as from applied research designed to investigate specific medical problems. There is still an urgent need for basic and applied research that will lead to the discovery of methods for the prevention and treatment of diseases for which adequate control methods are not yet available - notably the noncommunicable diseases and the endemic communicable diseases of warm climates.

Past progress has depended, and further progress in the foreseeable future will depend, largely on animal experimentation which, in the broad field of human medicine, is the prelude to experimental trials on human beings of, for example, new therapeutic, prophylactic, or diagnostic substances, devices, or procedures.

There are two international ethical codes intended principally for the guidance of countries or institutions that have not yet formulated their own ethical requirements for human experimentation: The Tokyo revision of *the Declaration of Helsinki* of the World Medical Association (1975); and *the Proposed International Guidelines for Biomedical Research Involving Human Subjects* of the Council for International Organizations of Medical Sciences and the World Health Organization (1982). These codes recognize that while experiments involving human subjects are a *sine qua non of* medical progress, they must be subject to strict ethical requirements. In order to ensure that such ethical requirements are observed, national and institutional ethical codes have also been elaborated with a view to the protection of human subjects involved in biomedical (including behavioural) research.

A major requirement both of national and international ethical codes for human experimentation, and of national legislation in many cases, is that new substances or devices should not be used for the first time on human beings unless previous tests on animals have provided a reasonable presumption of their safety.

The use of animals for predicting the probable effects of procedures on human beings entails responsibility for their welfare. In both human and veterinary medicine animals are used for behavioural, physiological, pathological, toxicological, and therapeutic research and for experimental surgery or surgical training and for testing drugs and biological preparations. The same responsibility toward the experimental animals prevails in all of these cases.

Because of differing legal systems and cultural backgrounds there are varying approaches to the use of animals for research, testing, or training in different countries. Nonetheless, their use should be always in accord with humane practices. The varying approaches in different countries to the use of animals for biomedical purposes, and the lack of relevant legislation or of formal self-regulatory mechanisms in some, point to the need for international guiding principles elaborated as a result of international and interdisciplinary consultations.

The guiding principles proposed here provide a framework for more specific national or institutional provisions. They apply, not only to biomedical research but also to all uses of vertebrate animals for other biomedical purposes, including the production and testing of therapeutic, prophylactic, and diagnostic substances, the diagnosis of infections and intoxications in man and animals, and to any other procedures involving the use of intact live vertebrates.

1. *BASIC PRINCIPLES*

I. The advancement of biological knowledge and the development of improved means for the protection of the health and well-being both of man and of animals require recourse to experimentation on intact live animals of a wide variety of species.

II. Methods such as mathematical models, computer simulation and *in vitro* biological systems should be used wherever appropriate.

III. Animal experiments should be undertaken only after due consideration of their relevance for human or animal health and the advancement of biological knowledge.

IV. The animals selected for an experiment should be of an appropriate species and quality, and the minimum number required to obtain scientifically valid results.

V. Investigators and other personnel should never fail to treat animals as sentient, and should regard their proper care and use and the avoidance or minimization of discomfort, distress, or pain as ethical imperatives.

VI. Investigators should assume that procedures that would cause pain in human beings cause pain in other vertebrate species, although more needs to be known about the perception of pain in animals.

VII. Procedures with animals that may cause more than momentary or minimal pain or distress should be performed with appropriate sedation, analgesia, or anesthesia in accordance with accepted veterinary practice. Surgical or other painful procedures should not be performed on unanesthetized animals paralysed by chemical agents.

VIII. Where waivers are required in relation to the provisions of article VII, the decisions should not rest solely with the investigators directly concerned but should be made, with due regard to the provisions of articles IV, V, and VI, by a suitably constituted review body. Such waivers should not be made solely for the purposes of teaching or demonstration.

IX. At the end of, or, when appropriate, during an experiment, animals that would otherwise suffer severe or chronic pain, distress, discomfort, or disablement that cannot be relieved should be painlessly killed.

X. The best possible living conditions should be maintained for animals kept for biomedical purposes. Normally the care of animals should be under the supervision of veterinarians having experience in laboratory animal science. In any case, veterinary care should be available as required.

XI. It is the responsibility of the director of an institute or department using animals to ensure that investigators and personnel have appropriate qualifications or experience for conducting procedures on animals. Adequate opportunities shall be provided for in-service training, including the proper and humane concern for the animals under their care.

2. SPECIAL PROVISIONS

Where they are quantifiable, norms for the following provisions should be established by a national authority, national advisory council, or other competent body.

2.1 Acquisition

Specialized breeding establishments are the best source of the most commonly used experimental animals. Nonspecifically bred animals may be used only if they meet the

research requirements, particularly for health and quality, and their acquisition is not in contradiction with national legislation and conservation policies.

2.2 Transportation

Where there are no regulations or statutory requirements governing the transport of animals, it is the duty of the director of an institute or department using animals to emphasize to the supplier and the carrier that the animals should be transported under humane and hygienic conditions.

2.3 Housing

Animal housing should be such as to ensure that the general health of the animals is safeguarded and that undue stress is avoided. Special attention should be given to the space allocation for each animal, according to species, and adequate standards of hygiene should be maintained as well as protection against predators, vermin, and other pests. Facilities for quarantine and isolation should be provided. Entry should normally be restricted to authorized persons.

2.4 Environmental Conditions

Environmental needs such as temperature, humidity, ventilation, lighting, and social interaction should be consistent with the needs of the species concerned. Noise and odour levels should be minimal. Proper facilities should be provided for the disposal of animals and animal waste.

2.5 Nutrition

Animals should receive a supply of foodstuffs appropriate to their requirements and of a quality and quantity adequate to preserve their health, and they should have free access to potable water, unless the object of the experiment is to study the effects of variations of these nutritional requirements.

2.6 Veterinary Care

Veterinary care, including a programme of health surveillance and disease prevention, should be available to breeding establishments and to institutions or departments using animals for biomedical purposes. Sick or injured animals should, according to circumstances, either receive appropriate veterinary care or be painlessly killed.

2.7 Records

Records should be kept of all experiments with animals and should be available for inspection. Information should be included regarding the various procedures which were carried out and the results of post mortem examinations if conducted.

3. MONITORING OF THE CARE AND USE OF ANIMALS FOR EXPERIMENTATION

3.1 Wherever animals are used for biomedical purposes, their care and use should be subject to the general principles and criteria set out above as well as to existing

national policies. The observance of such principles and criteria should be encouraged by procedures for independent monitoring.

3.2 Principles and criteria and monitoring procedures should have as their objectives the avoidance of excessive or inappropriate use of experimental animals and encourage appropriate care and use before, during, or after experimentation. They may be established by: specific legislation laying down standards and providing for enforcement by an official inspectorate; by more general legislation requiring biomedical research institutions to provide for peer review in accordance with defined principles and criteria, sometimes with informed lay participation; or by voluntary self-regulation by the biomedical community. There are many possible variants of monitoring systems, according to the stress laid upon legislation on the one hand, and voluntary self-regulation on the other.

4. METHODS NOT INVOLVING ANIMALS: "ALTERNATIVES"

4.1 There remain many areas in biomedical research which, at least for the foreseeable future, will require animal experimentation. An intact live animal is more than the sum of the responses of isolated cells, tissues or organs; there are complex interactions in the whole animal that cannot be reproduced by biological or nonbiological "alternative" methods. The term "alternative" has come to be used by some to refer to a replacement of the use of living animals by other procedures, as well as methods which lead to a reduction in the numbers of animals required or to the refinement of experimental procedures.

4.2 The experimental procedures that are considered to be "alternatives" include non-biological and biological methods. The nonbiological methods include mathematical modelling of structure-activity relationships based on the physico-chemical properties of drugs and other chemicals, and computer modelling of other biological processes. The biological methods include the use of micro-organisms, *in vitro* preparations (subcellular fractions, short-term cellular systems, whole organ perfusion, and cell and organ culture) and under some circumstances, invertebrates and vertebrate embryos. In addition to experimental procedures, retrospective and prospective epidemiological investigations on human and animal populations represent other approaches of major importance.

4.3 The adoption of "alternative" approaches is viewed as being complementary to the use of intact animals and their development and use should be actively encouraged for both scientific and humane reasons.