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Report of a WHO Scientific Group

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Geneva, 23-29 September 1970

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HEALTH ASPECTS OF THE SUPPLY AND USE OF NON-HUMAN PRIMATES FOR BIOMEDICAL PURPOSES

Report of a WHO Scientific Group

A Scientific Group on Health Aspects of the Supply and Use of Non-Human Primates for Biomedical Purposes met in Geneva from 23 to 29 September 1970. Dr A. M.-M. Payne, Assistant Director-General, opened the meeting on behalf of the Director-General by welcoming the participants and the representatives of the International Committee on Laboratory Animals, the International Office of Epizootics, and the International Union for the Conservation of Nature and Natural Resources. He said that, until recently, neither the public health nor the veterinary authorities in most countries had been much concerned with the health aspects of international trade in, or use of, primates. In recent years, however, the greatly increased use of these animals for biomedical purposes had given rise to a number of public health problems, and it was now widely recognized that some control measures were necessary. Furthermore, most monkeys and apes reaching the laboratory fell far short of the present-day standards of health expected of animals used for producing and testing vaccines, and for the many other experimental purposes for which these animals had proved so valuable. A further problem created by the greatly increased use of monkeys and apes was the threatened shortage of supplies in the future, owing to deplation of wild stocks, which were the main source.

1. INTRODUCTION : NEED FOR INTERNATIONAL RECOMMENDATIONS

The Scientific Group discussed the need for recommendations concerning the health aspects of the handling, transport, and use of non-human primates for biomedical purposes. It was agreed that an important purpose would be served by the formulation of internationally acceptable recommendations for increasing the safety of personnel working with monkeys and apes, as well as for improving the quality and health of the

animals. A secondary purpose would be to reduce the wastage of animals from disease. The Group considered draft recommendations formulated by the WHO Secretariat with the assistance of consultants and experts from various parts of the world. After studying much additional material, the Group prepared an amended version of the recommendations which, they felt, would be useful as a guide to the development of appropriate measures and would contribute to the safer and more effective use of monkeys and apes for biomedical purposes. These recommendations are given in the Annex to this report.

Although the use of monkeys and apes in laboratories and elsewhere dates from perhaps a century ago, it has increased markedly in the last 15–30 years, owing largely to an upsurge in the demand for these animals for vaccine production and testing. The dangers involved in handling and using monkeys and apes were not fully realized until experience was obtained of the transmission of infectious disease from these animals to man, sometimes with fatal consequences. Such experience has been taken into consideration in formulating the recommendations for minimizing the hazards. These recommendations are particularly important in view of the increased use of these animals, but it should be emphasized that many problems still remain unsolved.

The recommendations adopted by the Group deal with the holding and exportation, transportation by air, importation, quarantine, and use of monkeys and apes. In addition, recommendations and suggestions are made for national control measures to minimize the danger to human health at all the above stages. Implementation of these recommendations would facilitate the production and supply of immunizing agents, and biomedical research of all kinds.

2. IMPLEMENTATION OF RECOMMENDATIONS

The Group considered a number of difficulties that may arise in the implementation of certain of its recommendations. The public health importance of the proposed measures cannot be over-emphasized; consideration should be given to using existing machinery, as well as other means that may be developed, for collaboration with international and national agencies, health administrations, professional groups, and other organizations. Other areas in which service could usefully be rendered would be in the furnishing of technical assistance, consultant services, and teaching and training. Suggestions for the training of various categories of personnel are given in this report. It is also important that all persons concerned with the handling or transportation of monkeys and apes should be aware of the occupational hazards involved, and should, where possible, receive instruction to protect them against such hazards.

Certain international organizations have recently been considering the formulation of rules for an international zoo-sanitary code.[1] It would be useful if such rules were to include provisions necessary for the international transportation of monkeys and apes and their tissues; the implementation of such rules by national agencies would be a valuable health measure.

Means of acquiring and disseminating reliable information on the availability of particular animals and the diseases they carry in certain areas would help in the implementation of these recommendations.

Where the manufacture and control of immunological products require the use of monkeys and apes or their tissues, the relevant requirements for biological substances should incorporate these recommendations to ensure that the animals are satisfactory.

3. SPECIAL PROBLEMS

3.1 Feeding of animals

Captured monkeys and apes must be given wholesome food and potable water daily. However, these animals are often given an inadequate supply of poor quality food in containers that may be heavily contaminated, occasionally with excreta from other groups of animals. It is important to appreciate that monkeys and apes are at least as susceptible to disease as man, and that food should be in clean containers.

It is impossible to be specific about diets, because different species of animals have different nutritional requirements. Animals held in the areas where they were captured are likely to be given food obtained locally, which would be their normal diet. While animals are being held in importing countries their feed, which may be in pelleted or other form different from their natural food, should have a high protein content and adequate minerals and vitamins. The routine use of antibiotics in the feed should be discouraged, because of the risk of inducing resistant bacterial strains.

It should be noted that nutritional requirements differ for different age groups and according to the purposes for which the animals may be used.

The Group felt there was insufficient information on the nutritional requirements of different species of monkeys and apes to make specific recommendations. It is important to collate the existing information and to encourage studies on the nutrition of these animals.

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[1] E.g., International Office of Epizootics (1968) *International zoo-sanitary code*, Paris.

3.2 Detection of tuberculosis in monkeys and apes

During the past five years, there has been a marked decrease in the prevalence of tuberculosis amongst recently imported monkeys and apes. This has been brought about by capturing animals away from human habitation, testing with tuberculin in the exporting country, and destroying positive reactors. Different species of monkeys and apes differ in their susceptibility to tuberculosis. Nevertheless, it is important to test all monkeys and apes repeatedly for tuberculosis (see Annex, p. 24). The only reliable way is by the intradermal inoculation of tuberculin. Either Old Tuberculin (OT) or Purified Protein Derivative (PPD) may be used, but it is important to use preparations that have been correctly standardized.[1] This is particularly important with regard to the movement of animals between countries. A dose of 100 IU of either OT or of mammalian PPD is required for the detection of tuberculosis in these animals. It is emphasized that this is a substantially larger dose than would be used for tuberculin testing in man. In addition, the procedure that has been shown to be satisfactory for a particular kind of animal should be strictly followed.

It is essential that the tuberculin be given intradermally and not subcutaneously. The upper eyelid has commonly been used as the injection site, but in an unanaesthetized animal this is a difficult site at which to give an intradermal injection correctly. A freshly shaved area of either the upper part of the abdomen or the forearm is a more convenient site, and when the animal is in a cage equipped with a squeeze barrier there is often no need to handle it in order to perform the inoculation. Reactions should be read between 24 and 48 hours after injection of the tuberculin. A zone of erythema 10 mm or more in diameter should be considered a positive reaction; a zone of erythema less than 10 mm in diameter should be considered of doubtful significance. When a doubtful reaction is obtained, the test should be repeated between 2 and 4 weeks later.

Experimental studies have shown that *Macaca mulatta* can be infected by as few as 1–10 viable organisms of *Mycobacterium tuberculosis* or *Myco. bovis*, whereas other species, particularly the New World monkeys, require 10^5–10^6 organisms to establish infection. In all monkeys the establishment of infection, as shown by a positive reaction to tuberculin, can be detected within 3 weeks of exposure to an infective dose. The Group considered that testing monkeys or apes on receipt and during the quarantine period, repeating the test each month, and destroying reactors is the only certain way of preventing tuberculosis from entering and spreading within a colony. Repeated testing does not give rise to sensitivity to tuberculin; one colony of animals that has been tested each month for 25 years has not become sensitive.

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[1] See *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 384, Annex 1.

The use of X-ray examination for the early detection of tuberculosis has certain drawbacks, which must be appreciated. Both radiography and the interpretation of the roentgenograms require specialist knowledge. Much of the lung fields are masked by other organs, while the confusion of lesions caused by pneumonia or lung mites (*Pneumonyssus* spp.) with early signs of tuberculosis has led to the unnecessary destruction of some animals. The Group agreed that X-ray examination alone cannot be relied upon for the detection of tuberculosis, and was doubtful about its value unless the films are examined by a specialist in this field.

The use of isoniazid to prevent the spread of tuberculosis should be discouraged when animals are held for relatively short periods such as during the quarantine period. Administration of this drug for a period of 2–3 months does not entirely clear up an infection, and the animal with residual disease is a danger to the colony when the drug is stopped. The use of ioniazid may be justified, however, if it is administered for many years, e.g., in a breeding programme, in which case the animals must be kept continuously on the drug through its incorporation into their diet. There are valid objections also to the use of BCG vaccine as a means of preventing tuberculosis. The degree of protection given to monkeys and apes by BCG vaccine is very variable, and the vaccine cannot be relied upon to give long-lasting protection.

3.3 Diagnosis of virus diseases contracted by man from monkeys and apes

Information on virus diseases contracted by man from monkeys and apes is not readily available, and thus knowledge of them is lacking among physicians to whom a sick person might report for treatment.

To facilitate the diagnosis of such an infection, blood samples should be obtained periodically, e.g., twice a year, from all persons working with monkeys and apes or their tissues, and the serum stored (preferably frozen) indefinitely. In the event of any such person having pyrexia of unknown origin or a disease of obscure etiology, further blood samples should be taken at the onset of the illness and either 3 weeks later or during convalescence. These sera should be compared with the earlier samples and examined for antibodies to simian infections. The necessary procedure for this has been described,[1] but many laboratories do not have all the viruses, antigens, or reference sera necessary to make a full examination. WHO has designated a reference centre for primate virology,[2] and examinations of the sera could be made by it.

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[1] See Kalter, S. S. & Heberling, R. L. (1969) *WHO Chronicle*, **23**, 112.

[2] Division of Microbiology and Infectious Diseases, Southwest Foundation for Research and Education, San Antonio, Tex., USA.

3.4 Action to be taken in case of injury

The Group considered the action to be taken in the case of bites or scratches caused either by handling monkeys or apes or by handling or contact with cages, glassware, etc., used for the animals or their tissues.

All cases of injury should be reported to the person in charge, and appropriate medical attention given immediately. First aid treatment should be given for the wound, such as washing with copious amounts of soap and water. The wound should be treated further with antiseptics.

If a monkey or ape has caused the injury, the animal should be identified, anaesthetized, and thoroughly examined for lesions, especially in the mouth. If lesions are found, the animal should be killed and attempts should be made to isolate virus from the lesions. The injured person should be kept under medical observation for some time, particularly to watch for the more dangerous infections, such as B virus infection.

A useful public health measure would be the familiarization of medical officers with diseases that are transmissible from monkeys and apes to man through injuries, particularly with regard to the diagnosis of B virus infection.

It would also be useful if personnel who come into contact with monkeys and apes were to carry a card, which could be shown to the doctor. This card should describe the nature of the holder's employment and state that he has been in close contact with monkeys or apes or their tissues. It could also suggest that a particular specialist (giving his name and address) should be contacted should symptoms appear that are suggestive of CNS disturbances.

4. CONSERVATION OF SUPPLIES OF MONKEYS AND APES

Hitherto, the main source of monkeys and apes used in the laboratory has been wild populations, but unless action is taken to conserve stocks this source of supply cannot be relied upon in the future. Some species are already in short supply and the populations of others are being reduced, but detailed statistics of natural populations are often lacking or inadequate.[1]

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[1] See International Union for the Conservation of Nature and Natural Resources (1966) *The red data book*, Vol. 1 : *mammalia*, Lausanne, Heliographia. This loose-leaf volume, which is brought up to date annually, lists all the taxa of mammals currently regarded as being threatened with extinction throughout their geographical range.

The principal causes of depletion of monkeys and apes are : modifications of their habitat; their capture for laboratory purposes and the pet trade (including wastage during trapping and transportation); and their destruction as agricultural pests. Some national authorities have been led to ban or restrict the exportation of monkeys and apes.

It is clearly important that the more commonly used species should continue to be available in adequate numbers, and that all species should be preserved for their economic and scientific value, including their potential use as laboratory animals. Thus, efforts by international organizations and national bodies to prevent their extinction and improve their management should be encouraged, as contributing indirectly to medical science in the future.

Supporting activities that would reduce depletion and maintain future supplies of these animals are :

(*a*) Measures to reduce the wastage of captured animals due to mortality and illness, and the wastage of tissues that have to be discarded because they carry infective agents. The recommendations in the Annex to this report have been formulated with such measures in view.

(*b*) Measures to discourage the use of monkeys and apes for research purposes for which other animals could be used.

(*c*) Limitation of the use of monkeys and apes for non-essential purposes, e.g., as pets. The hazard to human health from having a monkey or ape as a pet is considerable, and should be more widely appreciated by the public and by public health authorities.

(*d*) Breeding of monkeys and apes in captivity.

5. BREEDING IN CAPTIVITY

The only satisfactory solution for ensuring the future supply of adequate numbers of suitable monkeys and apes for laboratory use is to breed them in captivity. The Group agreed that breeding programmes should be started without delay. Such programmes would also help to decrease the health hazards to man from these animals.

An additional and important reason for the establishment of breeding colonies is the superior quality of animals bred in captivity. It was found some years ago that laboratory-bred dogs and cats were far superior to stray animals for experimental purposes.

Several types of breeding colonies can be set up, depending on the purpose for which the animals are to be used. Range breeding of animals, on an island supplied with good food and water and free from contact with humans or other disease carriers, provides a much better grade of animal than is available in the wild state. Breeding in groups consisting of a male and several females, either indoors or outdoors, produces satisfactory animals, provided that accurately timed pregnancies are not required. If, for the purposes of special studies, accurately timed pregnancies are essential, then breeding in cages, taking the female to the male, must be employed.

The cost of the animals differs according to the type of breeding system, but any captive-bred monkey or ape will be more expensive than one captured wild. Since, however, it can be expected that fewer laboratory-bred animals will be needed in order to obtain reliable data, the increased cost of laboratory-bred animals can be justified when the total cost of the research effort is estimated. This is especially true in comparing the cost of laboratory-bred animals with that of conditioned, rather than freshly captured, animals. The use of laboratory-bred animals may even effect a saving in cost, in view of the enormous wastage due to contaminant viruses, which are inherent in monkey-kidney tissue and may be present in as much as 50% of tissues from captured animals.

The setting up of breeding establishments would be a valuable measure. Information on the newer techniques of colony breeding should be collected and disseminated. Emphasis should be placed, whenever appropriate, on the fact that captive-bred animals, by virtue of their known history and greater freedom from disease, are superior to wild animals for most biomedical uses. It should be pointed out, however, that breeding colonies should be maintained with proper precautions to prevent the introduction of infective agents, to which the animals may be highly susceptible. The Group agreed that detailed recommendations for breeding programmes were outside the scope of the present report.

6. TRAINING OF PERSONNEL

There is an acute need for training personnel in the handling and general management of monkeys and apes. Although, in some countries, there are courses in laboratory animal husbandry, none is specifically designed to give instruction with regard to monkeys and apes, and most are postgraduate courses for persons already trained in veterinary medicine. WHO has had occasion to arrange training courses, but in general these have been for health laboratory personnel. Various fellowships have also been awarded by national and international bodies for similar purposes. The Group agreed that the best solution to this problem would be to arrange courses dealing specifically with monkeys and apes. This would be preferable to including the necessary subjects in undergraduate teaching programmes, which are already crowded, or adding to the training of health laboratory personnel, which already may be of many months' duration.

In considering the educational level of persons who may receive such training, it was thought that, in the first instance, professional staff and supervisors of the animal house should receive instruction. Thereafter, it would be their responsibility to train the less skilled personnel,

such as the animal attendants under their supervision. This would not only be an effective way of disseminating specialist knowledge but would also overcome the difficulty of language barriers, which might be great if courses for animal handlers were to be arranged at an international level. It would be better for such personnel to be instructed through the medium of national training courses or in the laboratory itself.

The Group felt that the most suitable training for personnel who already have either professional qualifications or relevant basic knowledge and experience would be an intensive course, of 2–4 weeks' duration, held at some primate centre. Suggested subjects for inclusion in such an intensive course are as follows :

Introduction

General biology of primates
Anatomy and physiology
Trapping, handling, and transporting
Quarantine
Use of primates in the laboratory

Management

Design of animal houses
Design of equipment, such as cages
Protective clothing
Cleansing and disinfection of animal rooms and cages
Disposal of carcasses
Nutrition
Methods of breeding different species

Diseases

Infectious disease:
prevention of spread : between animals
from animals to man
from man to animals
prevention of spread : within rooms
between rooms
Non-infectious disease
Precautions to be taken

Special techniques

General handling and recapture
Bleeding and collection of specimens
Administration of drugs, tuberculin testing
Care of sick animals, X-ray examinations
Anaesthetizing
Minor surgery
Handling of newborns
Principles of germ-free animals
Autopsy procedures
Diagnostic laboratory services

The extent and depth of training would have to be appropriate to the educational and professional level of the trainees. Such a course would do much to improve the efficiency of those concerned with the supply and use of monkeys and apes for biomedical purposes, as well as of those concerned with primate husbandry.

A problem of great concern is the shortage of suitable animal handlers, owing to the limited career prospects. This work calls for much more responsibility and skill and carries greater dangers than looking after many other laboratory animals. The creation of greater interest, for example by providing better career opportunities, would do much to relieve this shortage.

7. FUTURE ACTIVITIES

The Group considered that certain activities deserved particular attention and should be given priority in future.

7.1 Prevention of losses

(*a*) There is a need for improvement in communication all the way from the user back to the personnel concerned with trapping and transporting animals in the exporting countries. People at all stages in the supply of monkeys and apes should possess the appropriate knowledge for ensuring the health of personnel and improving the condition of the animals.

(*b*) There is a need to provide holding units in the exporting countries with data on adequate diets, since it is not generally appreciated what a significant part the nutrition of animals plays in their survival following capture.

(*c*) There is a need for advice on the housing and handling of monkeys and apes in holding units in the exporting countries. National authorities could play a significant role in improving conditions in these units.

(*d*) The collection and dissemination of data on the infectious diseases prevalent in monkey and ape populations in the wild state would provide a valuable service to laboratories using these animals. There is little or no information on the causes of loss of monkeys and apes in the wild state, or on corrective measures needed.

7.2 Ensuring future supplies

(*a*) The establishment of breeding colonies should be encouraged. The collection and dissemination of currently available data on colony breeding techniques would be helpful.

(*b*) Encouragement should be given to studies to obtain more accurate data on population size and dynamics among monkeys and apes in various parts of the world, so that undue demands need not be made on particular sources.

7.3 Public health measures

(*a*) National health authorities should be advised of the health hazards in handling and transporting monkeys and apes at all stages from capture to use.

(*b*) There is a need to train appropriate medical personnel in the detection of diseases of monkeys and apes, especially of infections that are transmissible to man.

(*c*) There is a need to develop methods of identifying monkeys and apes, or at least the area and country where they have been captured. This would facilitate tracking down the source of dangerous infectious diseases transmitted by these animals.

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Annex

RECOMMENDATIONS ON HEALTH ASPECTS OF THE SUPPLY AND USE OF NON-HUMAN PRIMATES FOR BIOMEDICAL PURPOSES [1]

General considerations

Monkeys and apes [2] have been used for biomedical purposes on an increasing scale during the last 30 years, but the greatest increase in recent years occurred as a result of the introduction of poliomyelitis vaccine, which requires monkeys and their tissues for production and testing. Such use of monkeys for vaccine production resulted in these animals being caught, transported, and handled in whatever way was most expedient. Today, monkeys and apes are being used in biomedical research programmes for a wide variety of other purposes also, and they will continue to be used, since for many of these purposes no other animal can be substituted. These animals are still mostly caught wild, and it is known that they frequently either carry or contract infections, which reduce their value in the laboratory and are sometimes a hazard to man. In recent years there have been a number of cases of human infection, some of which were fatal, and consequently attention has been focused on methods of handling monkeys and apes.

Many animals die, or are discarded, between trapping and receipt in the laboratory, and many animals and their tissues have to be discarded owing to illness or infection. It is evident that wasteful methods of capturing and holding monkeys and apes should be avoided, and that methods

[1] A preliminary document that formed the basis of these recommendations was prepared by : Dr W. I. B. Beveridge, Consultant, Veterinary Public Health, WHO, Geneva, Switzerland; Dr R. Murray, Director, Division of Biologics Standards, National Institutes of Health, US Department of Health, Education, and Welfare, Bethesda, Md., USA; Dr J. R. Napier, Unit of Primate Biology, Queen Elizabeth College, London, England; Dr F. T. Perkins, Head, Division of Immunological Products Control, National Institute for Medical Research, Holly Hill, London, England; Dr W. T. Roth, Roth Research-Animal Care Inc., Washington, D.C., USA.

[2] The term " monkeys and apes " is used in this document to mean all non-human primates. Although the recommendations have not been designed to include prosimians, many could be applied to them.

of transporting and handling should be used that reduce the risk of transmitting disease to man. Improvements have taken place mainly in the quarantining and handling of these animals in the importing countries; less improvement has taken place in the way in which the animals are caught and dealt with in exporting countries.

In many countries, monkeys and apes are caught from widely different areas at all seasons of the year, are collected in dealers' compounds, being intermingled without regard to source or species, and held often under insanitary and poor nutritional conditions. They are exposed to human diseases as well as to those of other animals, including birds. Since monkeys and apes may be heavily infected in some areas of a country but not in others, trapping should be carried out only in areas selected as being most likely to yield healthy animals. The advice of public health, veterinary, and wildlife experts should be used in selecting suitable areas, and it would be useful if the animals could be made identifiable, e.g., by suitable marking, with regard to the trapping site.

The effect of seasonal factors should be taken into consideration, since the health of the animals may vary, depending on the availability of food sources. It is generally accepted that animals caught prior to and during the rainy season are, for various reasons, commonly in poor condition when received in the laboratory. Users would be well advised, therefore, to avoid ordering animals that may be caught during the rainy season. This may necessitate planning in advance, in order to ensure a supply of healthy animals. Furthermore, those that, immediately after trapping, are placed in regularly cleaned transport boxes with individual compartments and are shipped without undue delay to the importing laboratory, thus avoiding exposure in a compound, are usually received in better physical condition.

The number of animals caught, their age and sex, and the methods employed should be such as not to lead to serious depletion of the species or damage to the animals. Only those methods that reduce to a minimum physical injury, stress, and the spread of disease should be used. Information on humane, efficient, and adequate trapping methods, based on experience, should be circulated to national authorities for dissemination to trappers and others concerned. Every effort should be made to avoid holding trapped animals in the traps themselves, unless arrangements can be made to provide them with food and water. The animals should be transported from the trapping site as quickly as possible, either for immediate shipment or to the quarantine premises. National authorities, such as those concerned with the conservation of wildlife as well as veterinary and public health authorities, should endeavour to induce trappers and transport personnel to follow these suggestions, and may find it useful to introduce a system of licensing of persons allowed to catch monkeys and apes. Further, if the animals are to be held in exporting

countries for any period, they should be housed in suitable quarantine premises and not exposed to unsatisfactory conditions. Alternatively, they should be taken as quickly as possible after capture to the point of shipment for immediate export.

National authorities should consider instituting measures for exercising control and supervision over quarantine premises.

In recent years, much information has been collected concerning simian infections and their treatment. Much less information is available, however, concerning simian infections in man. In general, the emphasis should be placed on the prevention of infection, especially viral infections since these are not amenable to treatment. Experience has shown that animals caught in areas where there is little contact with human beings, and shipped out rapidly after capture, have a low incidence of tuberculosis and other human infections. Tuberculosis infection is particularly important with *Macaca mulatta* and the great apes. It is commonly thought that simian diseases are not transmitted to man by contact with monkeys and apes in the wild state, but this belief may be due to lack of information and further studies would therefore be useful.

Many laboratories in importing countries already safeguard the health of their personnel by regular medical examinations and by supplying suitable protective clothing, including masks and visors to prevent contact with any part of the animal or its excreta, either directly or by aerosol. Such protection has been accompanied by the rigid enforcement of a satisfactory routine for handling and by improved standards for quarantine facilities. Facilities for the diagnosis and treatment of simian diseases in man are extremely valuable.

It is known that the handling of monkeys and apes, at any stage from capture to use, may be a health hazard; the relevant health authorities should be aware of this. There are several recent publications concerning these problems, as well as other aspects of the care of monkeys and apes,[1] and health authorities in both exporting and importing countries would do well to become acquainted with these publications. Unfortunately, there are available to health authorities too few veterinary or medical scientists familiar with simian pathology and medicine; training programmes for appropriate personnel would be useful.

The health standards of laboratory animals, especially rodents and dogs, have improved enormously as a result of breeding under controlled conditions. The same degree of improvement can be achieved for monkeys and apes with modern breeding methods. Further, the establishment of breeding programmes would have the dual purpose of helping to conserve these animals, thereby ensuring supplies of such species, and of decreasing the health hazards to man. It would be useful if existing information on

[1] See page 27.

breeding procedures could be collected and made widely available; also, efforts should be made as a matter of urgency to establish breeding colonies. By these means, supplies of monkeys and apes for biomedical purposes may eventually become independent of natural sources of these animals.

In the meantime, however, it is necessary to improve the conditions under which monkeys and apes are captured, transported, and quarantined before they reach the laboratory, as well as to apply safeguards for personnel concerned with their handling at all stages. WHO has already drawn attention to the health hazards inherent in the transportation of monkeys.[1]

The purposes of the present recommendations, therefore, are (*a*) to minimize the risk of infection to personnel handling monkeys and apes or their tissues, and (*b*) to improve the health status of monkeys and apes that are currently available for biomedical purposes, such as the production and testing of biological products and research. Adoption of these recommendations would, in addition, help to conserve supplies of useful animals by reducing wastage due to death, disease, and latent infections.

It would be unrealistic to suggest that all the necessary improvements in exporting countries, from trapping to the moment of shipment, could be achieved immediately. Nonetheless, any improvement, however small, would contribute towards reducing the risk of transmitting disease to man. Such measures could be applied progressively as they become feasible. It is evident that such improvements will depend largely on the extent to which governments of exporting and importing countries, acting independently or in collaboration, exercise supervision. It may be foreseen, in this connexion, that consideration would have to be given not only to public health aspects but also to economic factors, such as income from exports, on the one hand, and increased value of the animals to users, on the other. Implementation of the recommendations contained in this document would require, in each country concerned, the establishment of appropriate facilities and official machinery for controlling the export and import of monkeys and apes. Exporting countries may, however, be unwilling or unable to undertake such a task. It would then be the responsibility of the national authorities in the importing countries to ensure that only animals that conform to the provisions of these recommendations are used. If national authorities, or laboratories, in importing countries are not in a position to do this, reliance must be placed on (*a*) the rapid transportation of animals to importing countries, so that the total period from trapping

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[1] The Committee on International Quarantine, in its fourteenth report (adopted by the Twenty-first World Health Assembly), drew attention to the dangers of human infection inherent in the international transport of monkeys and recommended " that this subject should be studied by the relevant expert bodies of the Organization in order to obtain suitable advice, both as to the risk involved and what minimum requirements might be desirable for handling such transportation, and that this study should be undertaken in co-operation with other international organizations concerned ". (*Off. Rec. Wld Hlth Org.*, **168**, p. 73.)

to quarantining on import is reduced to a minimum, (*b*) the imposing of an adequate quarantine period in the importing country, and (*c*) constant vigilance for the appearance of disease of potential danger to man. If these conditions cannot be ensured, there is no alternative but to keep animals in the importing countries, before use, for far longer quarantine periods than are at present enforced in any country.

These recommendations have been formulated, essentially, for animals used for biomedical purposes. However, the handling of monkeys and apes is a potential hazard to human health, whatever the purpose for which the animals are intended. Quarantine alone will not ensure that these animals can be handled with safety. The keeping of monkeys and apes as pets should therefore be discouraged, and the hazards of public access to these animals in zoological gardens, circuses, etc., should be realized.

In formulating the recommendations that follow, the Group took into consideration the basic document prepared by those listed on p. 16, the opinions of consultants, regulations and recommendations that have been published in a number of countries, and information from both published and unpublished reports. In addition, opinions and data have been received from experts, whose assistance is acknowledged on p. 27.

1. Holding and exportation

1.1 In order to minimize the exposure of monkeys and apes to infection and stress, they should be taken as quickly as possible after capture either to the point of holding or to the point of shipment for immediate export.

1.2 At the point of holding in the exporting country, suitable quarantine premises should be available. Monkeys and apes may be deemed to have fulfilled the recommendations for quarantine only if they have (*a*) been held for the relevant periods in the exporting and importing countries in such quarantine premises, according to the procedures recommended in this Annex (see section 3.2), or (*b*) been exported immediately without prior holding (see section 1.1), in which case the entire quarantining would take place in the importing country.

1.3 Quarantine premises should consist of suitably constructed buildings, which should have an adequate number of separate rooms, be so designed as to exclude rodents, birds, and insects, and have impervious floors and proper drainage. There should be suitable metal cages that can be thoroughly cleaned and disinfected. The animals should not be crowded, and those of different species or from different trapping areas should not be housed in the same room. Periodically, each room should be emptied of animals and, together with the cages and utensils, thoroughly cleaned and disinfected. The room should preferably be re-stocked with fresh animals.

1.4 During the quarantine period, the animals should be observed daily for signs of ill health; any with minor ailments should receive proper treatment. Animals that die, fail to respond to treatment, or show signs of serious disease should be removed and disposed of in such a manner as not to cause a public health hazard. These procedures should preferably be carried out by qualified persons, e.g., veterinarians or medical personnel with experience of primates.

1.5 Until they are exported, the monkeys and apes should be supplied with an appropriate and nutritious diet (containing, in particular, adequate amounts of vitamin C and protein) and potable water. Antibiotics should not be included routinely in the feed.

1.6 Only animals that appear to be healthy on inspection should be shipped. Selection should preferably be made at the trapping site or, if this is not possible, at the quarantine premises or point of shipment. Reasons for rejection should include deformities, skin diseases, debility, pregnancy, and evident illness.

1.7 Access to the quarantine premises should be restricted to necessary personnel.

1.8 Records should be kept of the number of each species caught, the sites of capture, the numbers used and exported, the time for which each animal has been in quarantine, and the number of deaths (including animals killed), as well as laboratory reports, the results of treatment for infections, and information from autopsies. These records should be available to importers and the appropriate authorities in importing countries.

2. Transportation by air [1]

2.1 Transportation to the importing country should be by the most expeditious means—where possible, by jet aircraft. Every effort should be made to avoid changes of aircraft, and to avoid carrying animals of different species, or from different countries, in the same aircraft.

2.2 The animals should be transported in containers of such a design [2] as to prevent their escaping or injuring themselves and to permit easy and safe feeding and watering. Such containers should be labelled clearly as to the nature of the contents, and designated as " perishable cargo ". The label should carry instructions that the animals should not come into contact with other animals and should be maintained at between 15 and 30 °C.

[1] Surface transportation between countries is preferably avoided; these recommendations have been framed accordingly.

[2] The design of the cage should be one acceptable to the airlines; a guide to their requirements should be consulted, e.g., International Air Transport Association (1968) *IATA manual for the carriage of live animals by air*, Montreal.

2.3 Since extremes of temperature create stresses that may lead to the exacerbation of latent infections, care should be taken to ensure that the animals are maintained at a suitable temperature (15–30 °C) both at airports and in the aircraft. The aircraft compartment in which monkeys and apes are carried should be pressurized in the same way as compartments carrying human passengers.

2.4 If it becomes necessary to unload the animals *en route* e.g., for transhipment, or to hold them temporarily at the airport of destination, they should be housed in such a manner that they have no contact with other animals and are not exposed to temperatures outside the range of 15–30 °C. Every effort should be made to minimize such periods of holding, in view of the inadequacy of facilities for feeding and watering these animals and the lack of trained personnel for handling them.

3. Importation and quarantine

3.1 Suitable quarantine premises should be available to receive imported monkeys and apes. They should at least meet the recommendations made in section 1.3, while additional provisions may be needed for particular species.

3.2 On arrival in the importing country, in order that they should not be subjected to adverse conditions, the animals should be transferred to the quarantine premises as quickly as possible. This requires arrangements for expediting customs clearance and other formalities, and adequate advance notice from the shipper to the importer. The aircraft should be met by a suitable vehicle, and arrangements made for rapid transfer of the animals.

3.3 Monkeys and apes should be held in suitable quarantine premises for a total of not less than nine weeks, of which not less than six weeks should be in the importing country (see section 1.2), except when immediate use of the animals is specifically permitted. Animals, or their tissues, may be used for biomedical purposes without the full period of quarantine, provided that they are maintained in a state of quarantine from the time of import, but only with the agreement of the appropriate national authorities. Any animals that are so used and are not destroyed should be kept for the remainder of the quarantine period before being used for other purposes.

3.4 On arrival at the quarantine premises, any ill or dead animals should be removed for appropriate examination and disposal, and the cause of illness or death ascertained with regard to the possible hazard to man and to the remaining animals. The containers that held these animals should be regarded as potentially hazardous, and should immediately be incinerated or sterilized by heat.

3.5 It is preferable to cage animals in the quarantine premises singly, or at the most with two per cage, except in the case of certain New World monkeys where caging in small groups may be beneficial for their health and well-being.

3.6 Different species of monkeys and apes and different shipments, even of the same species, should be placed in different rooms and there should be no contact with other animals. All possible precautions should be taken to prevent cross infection between rooms.

3.7 The animals should be supplied with an adequate and appropriate diet, and with water fit for human consumption.

3.8 In order to safeguard personnel and to minimize stress to the animals, handling during the quarantine period should not exceed what is absolutely necessary. The use of cages fitted with squeeze barriers and of transfer boxes helps in this respect. It is advisable that, prior to handling, the monkeys and apes be anaesthetized or tranquillized, using an agent that suppresses the bite reflex. Special precautions should be taken by personnel working with animals suspected of being infected with potentially dangerous transmissible diseases.

3.9 During the quarantine period, animals should be observed daily for signs of ill health by qualified persons, e.g., veterinarians or medical personnel with experience of primates. Any sick or dead monkeys should be investigated for the presence of diseases transmissible to other monkeys or to man, and appropriate measures should be taken as necessary. Assistance, if available, should be sought to help in the diagnosis of these diseases.[1]

3.10 Should *Herpesvirus simiae* (B virus) infection, Marburg virus disease, or some other transmissible disease dangerous to man be suspected or discovered, the sick animals in the group should be removed to a special isolation area, suitable for work with infectious agents, and studied. Animals so isolated should be used for no other purpose than research into that infection. If facilities for such studies are not available, the sick animals should be destroyed and incinerated. The remaining animals in the group should remain in quarantine for a further relevant complete period (six or nine weeks) and be observed as described in section 4.9.

3.11 If, at any time during the quarantine period, the death rate of the shipment reaches 10% (excluding deaths from accidents or causes specifically found not to be due to infectious diseases), then from that time the entire shipment should remain in quarantine for a further relevant complete period (six or nine weeks). If, during this further quarantine period, the death rate reaches 5%, this should be regarded as indicating

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[1] See Kalter, S. S. & Heberling, R. L. (1969) *WHO Chronicle*, **23**, p. 112.

the presence of a significant infective agent in the group. These animals should not be used unless the cause of death has been satisfactorily established.

3.12 Animals should be tuberculin tested.[1] Exceptions may be made for some species of animals, e.g., the New World monkeys, which are known to be resistant to tuberculosis. The test should be carried out on entry into quarantine and on two further occasions at least three weeks apart; if, at any time during the quarantine period, a positive reactor is detected, it should be removed immediately. From that time, the rest of the group should be kept in quarantine for a further relevant complete period (six or nine weeks) and then be similarly tested until three successive negative reactions have been obtained.

3.13 All carcasses, excreta, and detritus should be packed in leakproof bags[2] until such time as the material is destroyed by incineration; this should preferably be done each day.

3.14 Access to the quarantine premises should be restricted to essential personnel. All the actions of personnel working there should be based on the assumption that there is a potential hazard at all times on the quarantine premises.

3.15 Prior to employment on quarantine premises, personnel should be medically examined, particularly for tuberculosis. Further medical examinations should be made periodically. A blood sample should be taken periodically and the serum stored, as an aid to the diagnosis of any illness of unexplained origin that may occur. The frequency and scope of the examination for tuberculosis should be those approved by the national health authority.[3]

3.16 Personnel should be provided with protective clothing, including gloves, footwear, and masks or visors. Adequate changing rooms should be provided between the clean and potentially infected areas. Working clothes should not be taken out of the quarantine premises without prior sterilization. In the animal rooms of the quarantine premises, street clothes should not be permitted and smoking, chewing of gum, eating, and drinking should be forbidden.

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[1] Appropriately standardized tuberculin should be used and appropriate methods carefully followed. See *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 384, Annex 1.

[2] Only polyethylene bags of 0.05 mm thickness are considered as leakproof; no paper bag can be regarded as satisfactory for this purpose.

[3] The frequency of radiological examination should be adequate for the detection of the disease, and yet insufficient to cause radiation complications. For recommendations for personnel working in BCG vaccine manufacturing establishments, see *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 329, p. 36; these may be used as a guide. Certain highly susceptible populations are liable to develop tuberculosis rapidly once infected. In such cases examinations should be made more frequently, but with due regard to the risks of radiation exposure.

3.17 Medical history records of all personnel should be maintained. Each person should carry a card that can be shown to a doctor in case of pyrexia of unknown origin, particularly when associated with symptoms suggestive of CNS disturbances. The card should describe the nature of the holder's employment, stating that he has been in close contact with monkeys or apes or their tissues.

3.18 Complete records should be maintained of all animals. These should contain their history and disposal, including details of illnesses, medication, the results of laboratory or other examinations, and any deaths that may occur.

4. Health aspects related to biomedical use

Monkeys and apes and their tissues may be infectious *at any time*; the purposes of the recommendations given in the previous sections are to lessen this possibility and to reduce the risk of spread of infection. It is important also that adequate precautions and proper procedures be adopted in the laboratories in which these animals are used. Good laboratory practice that has been found satisfactory and has been adopted in laboratories for the safe handling of any animals and tissues known to be infectious should be scrupulously followed, and personnel working in biomedical laboratories should have had adequate training in the handling of these materials. Particular attention should be paid to the fact that there are a number of simian viruses that may be carried into the laboratory in monkey tissues and that some of these viruses survive procedures such as trypsinization.

Certain recommandations relating to the production and control of biological substances can be found in the series *Requirements for biological substances* published by WHO.[1]

5. National control

The existence of adequate national control measures in exporting countries would be a valuable safeguard in helping to minimize the danger to human health at all stages. Such measures would also increase the value of the animals and the tissues derived from them. It is the responsibility of the public health authorities of the importing countries to ensure that the use is permitted only of animals that have been subjected, before and after importation, to the recommended procedures. National public health authorities in importing countries should ensure that adequate measures are taken for quarantining, and for the control of animals and their

[1] See *Wld Hlth Org. techn. Rep. Ser.*, 1970, No. 444, Annex 4, for a complete list.

tissues used in biomedical laboratories. The scope of such measures should be at the discretion of the national public health authorities, but should be based on the general principles outlined in these recommendations.

Public health authorities of exporting countries should be responsible for the health of persons engaged in trapping and exporting animals. In order to decide whether or not to establish adequate control facilities, or whether to develop more elaborate control measures than are already available, the governments of exporting countries must weigh the benefits of preserving natural resources in useful animals, and the economic advantages of exporting them, against the cost and feasibility of establishing suitable quarantine facilities and other national control measures. Therefore, in cases where the exporting country has not established quarantine facilities, users of monkeys and apes and their tissues in importing countries may need to consider establishing such facilities in the exporting countries. These facilities would have to satisfy the appropriate authorities in the importing countries, but they would have to be established and maintained under licence from, or with the approval of, the governments of the exporting countries.

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