WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

EXECUTIVE BOARD

Nineteenth Session

Provisional agenda item 2.9.2

EB19/40
12 December 1956

ORIGINAL: ENGLISH

EFFECT OF RADIATION ON HUMAN HEREDITY

Report of a Study Group

The Director-General has the honour to submit to members of the Executive Board the Report of the Study Group on the Effect of Radiation on Human Heredity,[1] which is shortly to be published.

[1] Document MH/D/26.56

E M B A R G O

THE DISTRIBUTION OF THIS REPORT IS RESTRICTED AND NO REVIEW OF IT MAY BE PUBLISHED UNTIL GENERAL DISTRIBUTION IS AUTHORIZED BY THE DIRECTOR-GENERAL.

MH/24.56 Rev.1

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

5 December 1956

ORIGINAL: ENGLISH

EFFECT OF RADIATION ON HUMAN HEREDITY
REPORT OF A STUDY GROUP

Copenhagen, 7-11 August 1956

CONTENTS

MH/D/26.56

STUDY GROUP ON THE EFFECT OF RADIATION ON HUMAN HEREDITY

Copenhagen, 7-11 August 1956

Members:

Dr T. C. Carter, Radiobiological Research Unit (Medical Research Council of Great Britain), Atomic Energy Research Establishment, Harwell, Berks, England

Dr W. M. Court Brown, Group for Research into the General Effects of Radiation (Medical Research Council of Great Britain), Radiotherapy Department, Western General Hospital, Edinburgh, Scotland

Dr S. Emerson, Biology Branch, Division of Biology and Medicine, US Atomic Energy Commission, Washington, D.C., USA

Dr N. Freire-Maia, Laboratory of Genetics, University of Parana, Curitiba, Parana, Brazil

Dr A. R. Gopal-Ayengar, Biology Division, Department of Atomic Energy, Indian Cancer Research Centre, Bombay, India

Dr A. Hollaender, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn., USA (Chairman)

Mr G. H. Josie, Research and Statistics Division, Department of National Health and Welfare, Ottawa, Canada

Dr S. Kaae, Finseninstitutet og Radiumstationen, Copenhagen, Denmark

Professor T. Kemp, Universitetets Arvebiologiske Institut, Copenhagen, Denmark

Dr J. Lejeune, Centre National de la Recherche scientifique, Paris, France

Professor H. J. Muller, Department of Zoology, University of Indiana, Bloomington, Ind., USA

Professor J. V. Neel, Heredity Clinic, Institute of Human Biology, University of Michigan, Ann Arbor, Mich., USA

Dr H. B. Newcombe, Biology Branch, Atomic Energy of Canada Limited, Chalk River, Ont., Canada

Professor L. S. Penrose, The Galton Laboratory, University College, London, England

Professor R. M. Sievert, Institute of Radiophysics, Karolinska Hospital, Stockholm, Sweden

Dr C. A. B. Smith, The Galton Laboratory, University College, London, England

Professor A. C. Stevenson, Department of Social and Preventive Medicine, The Queen's University of Belfast, Institute of Clinical Science, Belfast, Northern Ireland (Rapporteur)

Professor O. Freiherr von Verschuer, Institut für Humangenetik der Universität Münster, Münster, Germany

Dr Bruce Wallace, Biological Laboratory, Long Island Biological Association, Cold Spring Harbor, Long Island, N.Y., USA

Professor M. Westergaard, Universitetets Genetiske Institut, Copenhagen, Denmark

Observers:

Dr R. K. Appleyard, Acting Secretary, Scientific Committee on the Effects of Atomic Radiation, United Nations, New York, USA

Dr R. A. Silow, Specialist in Atomic Energy, Agricultural Institutions and Services Branch, Agriculture Division, FAO, Rome, Italy

Dr R. L. Zwemer, Chief, Division of International Co-operation for Scientific Research, Department of Natural Sciences, UNESCO, Paris, France

Secretariat:

Dr P. Dorolle, Deputy Director-General, WHO

Dr M. Pizzi, Chief, Epidemiological Information and Morbidity Statistics Section, WHO

Dr I. S. Eve, Medical Officer in charge of Questions dealing with Atomic Energy and Health, WHO

Two national committees reported in 1956 on the effects of ionizing radiation on man.[1] Although difficult to compare in detail, these reports come to remarkably similar conclusions as to the probable effects on the descendants of populations exposed to increased amounts of such radiations.

The emphasis in both these reports was, however, on trying to set some quantitative limits to the risks in the light of existing knowledge.

The purpose of assembling the Study Group whose report is presented here was essentially twofold. The first aim was to obtain the opinions also of authorities on genetics from countries, other than those whose national committees have already stated their views. The second was to have the opinions of a number of experts on an aspect relatively little considered in the national reports - namely, the lines of research which are needed in the light of present knowledge, to increase our understanding of the genetic effects of ionizing radiations on man.

The Group met, by courtesy of the Rector of the University of Copenhagen, in the Council Room of the University, from 7 to 11 August 1956. The agenda adopted was intended to permit exploration of the views of the members on the theoretical and practical difficulties in closing present gaps in knowledge. The procedure adopted was for a number of members to open discussions either by short statements or by submission of invited papers. The opportunity was also taken to discuss a number of subjects not formally introduced.

The papers submitted[2] are reproduced as annexes to this report.

The proceedings were opened by Dr P. Dorolle, Deputy Director-General of the World Health Organization, and the Group elected Dr A. Hollaender as Chairman.

---

[1] United States of America, National Academy of Sciences (1956) Biological effects of atomic radiation; Great Britain, Medical Research Council (1956) The hazards to man of nuclear and allied radiations, London

[2] These papers are only reproduced in the published version.

1. INTRODUCTION

Man's most unique and precious possession is his heredity material which must determine the health and orderly development of future generations. The Group is of the opinion that the well-being of descendants of the present generation is threatened by developments in the use of nuclear energy and of sources of radiation. Both of these developments are inevitable and they should contribute much to man's social and cultural development. It would seem therefore that some risk must be accepted, but if the dangers are to be minimized every possible step must be taken to reduce the exposure of man and to understand the effects of exposure. Only in the light of more knowledge can decisions be taken to define more accurately the maximum amount of exposure which may be accepted by individuals and populations without risk of serious harm.

Radiation has been demonstrated to be one of the agents which produces mutation in a wide range of organisms from bacteria to mammals. The Group is agreed that additional mutation produced in man will be harmful to individuals and to their descendants. While there may be inherent and environmental mechanisms which modify the impact of these mutations over periods of many generations, the effectiveness of such mechanisms in man is not known. In essence then, all man-made radiation must be regarded as harmful to man from the genetic point of view.

In recent years, considerable quantitative knowledge has been accumulated on the basic mechanisms of genetics. There are strong grounds for believing that most genetic effects are very closely additive so that a small amount of radiation received by each of a large number of individuals can do an appreciable amount of damage to the population as a whole. There are, however, many gaps in knowledge particularly concerning these effects in man. These gaps will only be closed after a great expansion of general and ad hoc research in genetics and other fields of biology.

The Group has received the following resolution passed by the First International Congress of Human Genetics in Copenhagen and it notes and agrees (while at the same time recognizing that WHO's work is only concerned with the peaceful use of atomic energy)

> "The damage produced by ionizing radiation on the hereditary material is real and should be taken seriously into consideration in both the peaceful and military uses of nuclear energy as well as in all medical, commercial

and industrial practices in which X-rays or other ionizing radiation is omitted. It is recommended that the investigation of the amount and type of damage and of related genetic questions, be greatly extended and intensified with a view to safe-guarding the well-being of future generations."

The Group agrees with the memorandum, entitled "Human and Medical Genetics", which was submitted in 1955 by the Government of Denmark to the World Health Organization.[1]

This Group takes note of the report of the National Academy of Sciences of the United States of America and that of the Medical Research Council of Great Britain. It is not intended to reproduce any of the material in these reports but the Group notes the substantial similarity of the findings and recommendations of these reports and is in essential agreement with them.

2. NATURAL AND MAN-MADE SOURCES OF IONIZING RADIATION

The present sources of ionizing radiations of interest for the treatment of problems related to the genetic effects in man include the following:

Natural sources

1. Cosmic radiation.

2. Naturally occurring amounts of radium, thorium and potassium in the earth crust.

3. Content of natural radioactive elements in living tissues.

Man-made sources

4. Radioactive material and technical arrangements producing ionizing radiation (such as X-ray tubes and other particle accelerators, nuclear reactors, etc.) used in education, science, medicine, industry and commerce.

5. Sources used by the population for other purposes than those mentioned in 4 (radioactive luminous compounds on watches and other articles for common use, television sets, etc.), although such sources are much less significant than those mentioned in 4 and 6. It is important, however, that their existence be recognized.

---

[1] Off. Rec. Wld Hlth Org., 68, 147

6. Artificial radioactive elements distributed by man in nature.

Information as to the contributions to the doses received by individuals and by large population groups from the various sources listed above is summarized in Professor R. M. Sievert's paper, from which it is obvious that as regards the average dose to the gonads the most important contributions are at present those from the natural radiation (normal level: between 2 and 5 r per individual in 30 years) and from the radiation received by patients undergoing medical X-ray examination (probable average between 1 and 3 r per individual in 30 years). If therapeutic exposures are also considered, the "total" exposure to a population might be greater. It is, however, difficult to get sound data for estimating how much exposure is received in therapeutic exposures to persons before the age at which procreation may be expected to be ended.

It may be noted that at the present time the highest dose to the gonads caused by natural radiation in areas with a large population seems to exist in parts of Travancore, India, on ground containing monazite sand (possibly of the order of between 10 and 20 r per individual in 30 years).

3. IMPORTANCE OF RECORDING RADIATION EXPOSURE IN INDIVIDUALS AND POPULATIONS

From a genetic point of view the total accumulated dose is the important one and for this reason the measurement of exposure to ionizing radiations is an essential preliminary to attempts to relate dosage received to effects in man. For such measurements to be useful, the information must be recorded systematically. Unless the information is available in the form of the dose received by individuals, records of exposure would be unsuitable for many purposes and therefore some system of registration is essential. The effect of recording would almost certainly be to cut down the exposures given in medical diagnosis and treatment, since it would impress radiologists and technicians with the magnitude of such exposures. In one hospital where such recording was started there has been a 30 per cent. reduction in the total exposure of the staff. Doubtless a similar system of recording in diagnostic practice would reduce the exposure to the patients. This in itself would be a sufficient justification for introducing the procedure. It seems likely that the two national reports will already have done much to overcome the hesitation to

record the dose on the part of those who would be concerned in making such records but that a recommendation from this Group would also be helpful.

The Group is conscious that the adoption of any system of recording dosage will give rise to difficulties because it will increase the burden of work of radiologists and their staffs. Nevertheless, it feels that the importance of these procedures is such, and is so well recognized by radiologists that both those in charge of radiological departments and other physicians who use X-rays will be co-operative.

Whatever system adopted should take into account three desirable requirements:

1. That the individual will not, through lack of information, accumulate excessive exposure.

2. That information becomes available as to how much exposure to the gonads is received at each age in individuals and on an average per head of population.

3. That it should be possible to recognize the amount of exposure received by the parents of a given child. (Eventually, the information would be available for several generations.) This information is particularly valuable for purposes of genetic analysis.

The Group suspects that exposures in some industries and in scientific work are unnecessarily high. Exposures from these sources should be recorded in such a way that the dosage received can be related in individuals and populations to that received from other sources.

It seems unlikely that all countries would favour or indeed would be able to introduce the same standards of registration. Although it is expected that recommendations on mechanisms of recording will shortly be available from the International Commission on Radiological Protection, there should not be any delay in improving the standard of recording of exposures.

Whatever procedures of recording and registration are adopted will entail a large expenditure of money and effort. The need, however, is urgent. Further, the present is the appropriate time to initiate such procedures, since the introduction of atomic energy for industrial use and the extension of the use of radiation tools in biology and medicine make it possible to start with such procedures at an early stage of a period of rapid development.

4. RESEARCH

General

Additions to the understanding of the effects of radiation in man come from a very wide field of research. It is impossible to forecast what work in biology or genetics will contribute information relative to the problems. Accordingly, the Group is strongly of the opinion not only that as much experimental work as possible should be done on radiation effects on suitable organisms and such controlled observation studies as offer in man, but that there should be an intensification of all human and experimental genetic research. The Group feels that there should be the closest possible collaboration between those working in the experimental and human fields: their work is complementary. Each should be stimulating the other's research projects. This need for intensification of research in man and in other organisms raises problems of finance and of shortages of trained research workers. Both these difficulties are likely to be intensified if new areas of work, such as that on tissue cultures, chemical mutagenesis, serology, biochemical genetics and epidemiological problems of genetic disease are to develop as rapidly as is desirable. The problem of manpower shortages, in regard to both biologists and physicians, tends to be perpetuated by lack of career opportunity for those working on genetics. There is also an insufficient number of institutions where an adequate training in genetics, particularly in human genetics, can be given.

It is possible that the results of much effort in these fields will prove disappointing. Nevertheless, research workers and those supporting their work must have the courage to face the possibilities of such disappointments and still go forward.

The developments of nuclear energy would never have been made unless enormous risks of failure had been accepted. These innovations have extremely important implications among which the possible effects on man's genetic composition are outstanding. If there is to be a climate of public opinion favourable to the development of nuclear energy the peoples must be assured that investigations essential for their future health and welfare and that of their children will be undertaken on an adequate scale. This will require recognition by governments that very substantial financial provision must be made for genetic and other biological

investigations essential to an understanding of the effects of radiation on man. Biological research in the past has suffered severely from lack of funds.

Specific

The Group does not feel that it should attempt to recommend specific research projects. Nevertheless, it seems desirable to recognize the larger gaps in knowledge as they appear at the present time. Among the fields in which the need for further work is urgent, if the genetic hazards of the irradiation of human populations are to be understood, the following appear outstanding. It should be emphasized that the rapid developments in genetics and other sciences must determine that recommendations for lines of research should only be accepted as tentative and should be revised periodically.

(a) Further study of spontaneous and artificially-induced mutation. There is need for further study of the number and kinds of mutations produced by various doses and types of irradiation applied at different stages of the life-cycle under a variety of conditions and utilizing different kinds of organisms. The relatively limited opportunities to study irradiated human beings and their offspring should be exploited to the fullest extent possible. The appreciation of radiation-produced mutations is intimately related to a similar extension of knowledge concerning mutations that appear to arise spontaneously or as the result of the action of chemicals and of physical agents other than ionizing radiation.

(b) Mutational component in the somatic changes produced by radiation and other means. The role of changes in the hereditary material of somatic cells in the genesis of leukaemia, in other forms of neoplasms, and in alterations in the life span, is at present a controversial field which needs clarification. The effects of low doses of radiation, including those from radioisotopes, require special study. An important method of attack on this problem is opened by recent developments in tissue culture techniques.

(c) Means of protection against mutagenic agents. The pioneer studies which indicate the possibility that the production of radiation-induced mutations can be modified by various means have important implications for man and require extension in many directions.

(d) Development of new and improved techniques for the identification of mutants. Efforts directed at developing more exact methods for the recognition of mutant individuals, and the distinction between the latter and phenocopies, should be intensified. It is important to prosecute studies of the frequency of a wide range of types of mutations including those with extremely small effects, recognizable only through special statistical or breeding techniques.

(e) Manner of gene action. The phenomena of dominance, synergism and other forms of gene interaction, the multiple effects of a single gene and the role of environmental factors in the determination of traits require a great deal of elucidation, since they are highly important in appraising the effects of radiations. They should be studied both in man and in other organisms. In this connexion, the prospects raised by the rapid advances being made on human biochemical specificities are of particular interest.

(f) Selective factors in populations, with particular reference to the special conditions in man. Very little is known concerning the detailed effects of natural selection on the frequency of specific genes, constellations of genes, or cytological alterations. Such information is basic to attempts to understand the genetic composition of present and past human communities and to predict future trends consequent upon changes in radiation levels, medical practices, and social and economic conditions. These gaps in knowledge can in part be filled by the collection of relevant demographic and experimental data.

(g) Patterns of mating in human populations and their genetic implications A standard type of information always required in understanding the genetic composition of human populations and the effect on it of various amounts of radiation is the recording and interpretation of data on the consequences of inbreeding, assortative mating, geographical and cultural isolation and random genetic fluctuations.

(h) Twin studies in man. These are recognized as being helpful in understanding many problems of human heredity. Such studies have already been extensively used but could be advanced by standardized registration of twins in various countries. They give useful information concerning the relative importance of hereditary and environmental influences.

(i) Determination of the frequency of diseases with a significant genetic component, with particular reference to their epidemiology. This is fundamental for investigations on the significance of mutation as a cause of disease in man. In this connexion central registration of human inbreeding, hereditary disease and variation is of the utmost importance. It is also of importance to know the number of people who on account of hereditary lesions have to be treated in hospitals or institutions or given social aid.

(j) Study of populations of special genetic interest. Important information is to be obtained from the study of relatively stable, primitive communities, long isolated by geography or culture. Studies of this type require for their execution teams of persons from a variety of disciplines, such as cultural anthropologists, physicians and geneticists. It should be emphasized that the understanding of the genetic structure of contemporary populations will be greatly aided through these studies, which should be maintained continuously over a considerable period of time. The opportunity for these studies diminishes with each passing year. Among special communities to be studied are those receiving unusually large amounts of radiation, those in which the degree of inbreeding has long been very high or low, and those in which special conditions of selection have prevailed. In some investigations radiation physicists would be essential members of the teams.

(k) Genetic mapping of human chromosomes. This is a highly specialized field in which encouraging advances are now being made. Among the possibilities to be exploited is the use of these data to aid in the identification of independently occurring mutant genes and in the study of chromosome rearrangements.

(l) Cytochemistry and human cytology. Direct cytological observations should be conducted both on normal individuals and on those with suspected chromosomal abnormalities. Material from the individuals themselves as well as mutant cells of tissue cultures may be used in such work. Basic information concerning the ultramicroscopic structure and chemical composition of the hereditary material, and the manner in which this is altered by irradiation and other mutagens, is essential and should include information on lower organisms as well as man. The new developments in biochemistry, the emerging immuno-biochemical investigation of tissue proteins, bone marrow and other tissues, the metabolic investigations which may elucidate

both physical and mental pathology, the new developments in electronmicroscopy which advanced our knowledge of the structure of human sperm all indicate the development of new tools for the study of human genetics.

(m) Development of further statistical methods. New mathematical methods have continually to be developed to deal analytically with problems which arise as the result of researches in human and in experimental population genetics. This is particularly so in relation to observations on the genetic structure of and intensity of selection in populations with regard both to traits due to single gene and those due to multiple gene effects. Special techniques requiring electronic computers will also be required for analysing data on genetic linkage in man.

5. SOME CONCLUSIONS

(a) The Group is of the opinion that there are too few institutions or large university departments devoted to general genetics and even fewer concerned with human genetics. It recommends the establishment of such institutions and departments and suggests that there could be no one ideal pattern. One of the benefits of such institutions would be to accustom people of different scientific disciplines having implications for genetics to work together. Physicians, general biologists, geneticists, biochemists, cytologists, serologists and statisticians are examples of the kind of workers who may be needed. When such institutions are concerned with human genetics their location should have regard to the adequacy of existing medical services, to the kind and size of human populations available for field studies and to the adequacy of background vital statistics and general demographic information of the population concerned. For many purposes a population of about two million is optimal particularly for intensive epidemiological investigations. Such institutions, in addition to their research functions, could eventually serve as centres of elementary and advanced training in genetics.

(b) Such research departments and institutions should contribute much to teaching in general and human genetics. Medical undergraduates should all receive training in genetics and the teaching should be co-ordinated with that in radiology and in the use of radioactive substances in medicine, so that the genetic hazards of diagnostic and therapeutic procedures are thoroughly understood. Medical men training

as radiologists should have specific, more advanced instruction in genetics. Health physicists, radiological physicists and radiological technicians should also receive instruction in genetics as part of their technical training.

It seems essential that instruction in genetics should be given to all scientists, particularly those whose work is likely to involve the use of radiation and radioactive materials in research. The principles of human genetics could with advantage be conveyed to those training in the social sciences by means of formal instruction. Finally, the Group is of the opinion that public education in genetics should be more common and adequate than it is at present.

(c) In the future it will be necessary from the point of view of preventive medicine and genetic hygiene to register serious hereditary diseases and defects in various populations or countries in the same way as, for instance, epidemic diseases. For that purpose, genetic hygienic ascertainment or registration will be an indispensable and necessary step. The recording of hereditary diseases and defects in various countries and regions is to be highly recommended.

(d) In many countries there are very few biologists or physicians properly trained in genetics. This situation will only be solved by producing more career opportunities in genetics, but may be alleviated by granting fellowships or subsidizing training at approved institutions in countries which can offer training facilities. It is possible, also, that advice and technical assistance could be given in connexion with research projects in countries with insufficient resources in trained manpower to carry them out.

(e) It might be possible for a United Nations Agency to assist on request in administration or supervision of studies of specific populations over a period of years or by strengthening a research team or by giving advice on organization.

(f) In the past, United Nations Agencies have done useful service in contributing to the collection and standardization of vital and health statistics. It is recommended that such agencies continue their efforts and stimulate the efforts of others in the collection and publication of specific data such as fertility, consanguineous marriages and parental ages, which are so essential as background information in many studies in human biology.

(g) The Group wishes to call attention to the evidence that damage to body tissues produced by radiation after relatively small doses is, at least in part, mediated through effects on genes and chromosomes. There is also some evidence that the life-span may be reduced in mammals even by relatively small doses. Ad hoc investigations are urgently needed.

(h) The Group is particularly impressed with the genetic hazards of man-made radiation from sources used in medicine, industry, commerce and experimental science, etc. Both as an approach to control and as providing basic background information for relating quantitatively radiation exposure and effects on man, it is essential that methods be found of recording exposures to individuals and populations, however difficult this may prove.

There is reason to believe that radiation exposure can be much reduced, therefore, those in charge of sources of ionizing radiations should always ensure that there is adequate justification for exposing individulas to doses however small. On account of the danger to offspring resulting from irradiation of the gonads by X-rays, consideration should be given to determining what efficient means of shielding the gonads could be devised and brought into general use. In addition, in every exposure the X-ray beam ought as far as practicable to be directed so that a minimum of radiation reaches the gonads.