

*This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.*

WORLD HEALTH ORGANIZATION

TECHNICAL REPORT SERIES

No. 248

# **RADIATION HAZARDS IN PERSPECTIVE**

**Third Report  
of the Expert Committee on  
Radiation**

WORLD HEALTH ORGANIZATION

GENEVA

1962

## EXPERT COMMITTEE ON RADIATION

Geneva, 24-30 October 1961

### *Members :*

- Lord Adrian, O.M., The Master's Lodge, Trinity College, Cambridge, England (*Chairman*)
- Dr A. M. Brues, Director, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Ill., USA (*Rapporteur*)
- Dr L. T. Friberg, Professor of Hygiene, Institute of Hygiene, Karolinska Institute, Stockholm, Sweden (*Rapporteur*)
- Dr M. Hašek, Czechoslovak Academy of Sciences, Biological Institute, Prague, Czechoslovakia (*Vice-Chairman*)
- Dr E. E. Pochin, Medical Research Council Department of Clinical Research, University College Hospital Medical School, London, England
- Dr M. N. Rao, Professor of Physiological and Industrial Hygiene, All-India Institute of Hygiene and Public Health, Calcutta, India
- Dr A. T. Shousha, Supervisor, Health Department, League of Arab States, Cairo, Province of Egypt, United Arab Republic
- Dr E. C. Vigliani, Professor of Occupational Medicine, Clinica del Lavoro, University of Milan, Italy

### *Representatives of other organizations :*

- Dr H. Cember, Occupational Safety and Health Division, International Labour Organization, Geneva, Switzerland
- Dr H. T. Daw, Division of Health, Safety and Waste Disposal, International Atomic Energy Agency, Vienna, Austria
- Dr F. Sella, Secretary, Scientific Committee on the Effects of Atomic Radiation, United Nations, New York, USA
- Dr A. H. Wolff, Consultant, Atomic Energy Branch, Food and Agriculture Organization of the United Nations, Rome, Italy

### *Secretariat :*

- Dr R. L. Dobson, Chief Medical Officer, Radiation and Isotopes, WHO (*Secretary*)
- Dr H. Hardy, Medical Department, Occupational Medical Service, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA (*Consultant*)
- Dr F. H. Sobels, Professor of Radiation Genetics, Department of Radiation Genetics, State University of Leiden, Leiden, Netherlands (*Consultant*)

## CONTENTS

	Page
1. Introduction . . . . .	5
2. Differences in approach to radiological and toxicological risks . . . . .	9
3. Chemical toxicity in comparison with radiation injury	11
3.1 Occupational exposure . . . . .	11
3.2 Residential risks . . . . .	13
4. Carcinogenesis . . . . .	16
4.1 Natural sources . . . . .	18
4.2 Occupational sources . . . . .	18
4.3 Conventional hazards of living . . . . .	20
4.4 Self-imposed hazards . . . . .	21
4.5 General remarks . . . . .	22
5. Genetic effects of radiation, chemicals and temperature	23
5.1 The hereditary burden in man . . . . .	24
5.2 Production of mutations by radiation . . . . .	25
5.3 Genetic effects of chemicals . . . . .	27
5.4 Potential mutagens in the environment of man .	31
5.5 Gonad temperature and mutation rate . . . . .	32
5.6 General remarks . . . . .	34
6. Shortening of life-span and the problem of aging . .	34
7. Summary . . . . .	35
8. Recommendations . . . . .	37



# **RADIATION HAZARDS IN PERSPECTIVE**

## **Third Report of the Expert Committee on Radiation**

The Expert Committee on Radiation met in Geneva from 24 to 30 October 1961. Dr F. Grundy, Assistant Director-General, opened the meeting on behalf of the Director-General and welcomed the participants and representatives of international organizations. He referred to the problems confronting public health authorities in determining how radiation protection should best be fitted into public health programmes. Radiation had received a great deal of attention in recent years from a number of points of view, and this made it sometimes difficult to view it in perspective against other hazards as a part of the larger health picture. Protection against radiation hazards was an important part of public health activities. It was also important that maximum use of the knowledge which had been gained from intensive studies carried out in the radiation field should be made in connexion with other comparable public health hazards.

The desired perspective might be achieved by comparing what is known of the somatic and genetic effects of ionizing radiation with information on other agents and substances in our environment having toxic, carcinogenic or mutagenic properties. Dr Grundy pointed out that an approach to this perspective required contributions from a wide variety of fields in the health sciences; for that reason, this committee was notably interdisciplinary, with biology, genetics, physiology, occupational medicine, public health, radiobiology and toxicology represented.

Lord Adrian was elected Chairman and Dr M. Hašek, Vice-Chairman; Dr A. M. Brues and Dr L. T. Friberg were elected rapporteurs.

### **1. INTRODUCTION**

Throughout history, mankind has been exposed to a wide variety of hazardous factors in his environment, to many of which, over thousands of years, he has been able to make successful adjustment. In recent years, the hazards of ionizing radiation have caused particular anxiety because of the variety of malignant and other changes that may follow irradiation—sometimes after prolonged latency or, in the case of genetic changes, in subsequent generations—and also because of the widespread and increasing exposure of people to radioactive fallout and other man-made sources of radiation.

A discussion of the hazards of ionizing radiation may be misleading if proper emphasis is not given also to the beneficial aspects of many procedures that involve radiation exposure. The fact is well established that the benefits of the appropriate medical use of radiation in diagnosis and therapy far outweigh the hazards and that, given adequate protective measures, the uses of radioactive materials and the peaceful employment of nuclear energy represent great technological advances.

It appears profitable to review radiation hazards in relation to other hazards to life and health, preferably on a global scale, with emphasis on those attributable to man-made causes. For much of the world, however, adequate vital statistics are not available: such statistics are believed to cover only about 40% of the world's population. The areas for which health statistics are most deficient are, in general, those that are relatively less developed. In such areas communicable diseases and malnutrition are at present the most pressing public health problems, although man-made hazards associated with industrialization, including the use of ionizing radiation and nuclear energy, are likely to increase. In these countries infant mortality is high. Malnutrition, malaria, leprosy, filariasis, bilharziasis and trachoma are commonly the leading causes of morbidity and death; the estimated prevalence of certain of these conditions is given in Table 1.

TABLE 1. ESTIMATED PREVALENCE OF CERTAIN DISEASES AFFECTING MAINLY DEVELOPING COUNTRIES<sup>1</sup>

Disease	Estimated number of persons suffering in the world (millions)
Trachoma	400
Filariasis	300
Malaria	200
Goitre	200
Bilharziasis	150
Yaws	50
Leprosy	10

In countries that are more highly developed industrially, cardiovascular diseases, malignant neoplasms and respiratory disorders account for about 60% of all deaths. Cardiovascular diseases appear in almost all of these countries as the first cause of death, comprising one fourth to more than

<sup>1</sup> Taken from Swaroop, S. (1960) The Health Aspects of World Population, *Roy. Soc. Hlth J.*, 80, 238.

one third of the total; malignant neoplasms are, in general, second in importance (Table 2). Deaths due to these causes, however, occur predominantly in the older age groups.

TABLE 2. DEATH RATES PER 100 000 FROM SELECTED CAUSES IN CERTAIN COUNTRIES (1959)<sup>1</sup>

	Austria	France	England & Wales	Switzerland	Guatemala	USA
All causes	1248	1121	1163	950	1725	942
Neoplasms	249	193	214	192	24	147
Cardiovascular diseases	469	347	535	403	38	471
Respiratory disorders	91	76	148	46	407	41

Man-made hazards to health—whether of recent origin or long-established importance—must thus be reviewed against the background of known or unknown causes of disease, co-extensive with the whole field of medicine. While man-made hazards account for only a small proportion of the illness occurring in less developed areas, they are responsible for a significant fraction of illness and death in highly developed countries. In many such countries accidents rank third as a cause of death, and constitute the leading cause of death in the younger and more productive age groups (Table 3).

TABLE 3. ESTIMATED MAN-YEARS LOST DUE TO DEATH OF PERSONS AGED 20-29 FROM THE FIVE LEADING CAUSES OF DEATH IN THIS AGE GROUP: UNITED STATES, 1955<sup>2</sup>

Cause of death	No. of deaths	Man-years lost
All accidents	12 646	634 498
Motor vehicle accidents	8 401	421 460
Malignant neoplasms	2 765	136 629
Diseases of heart	1 993	98 067
Homicide	1 883	93 452
Suicide	1 485	73 361
All other causes	8 761	434 489
Total, all causes	29 533	1 470 496

<sup>1</sup> United Nations Demographic Yearbook, 1960.

<sup>2</sup> Derived from: United States, Department of Health, Education and Welfare, Division of Special Health Services (1958) *Accident injury statistics*, Washington D. C.

It should be noted, however, that the introduction of new processes and the use of new materials, often giving rise to new hazards, have been concurrent with progressive and rapid improvement in the health and life expectation of populations (Table 4).

TABLE 4. EXPECTATION OF LIFE AT BIRTH IN SELECTED COUNTRIES<sup>1</sup>

	Males	Females
Japan		
1899-1903	44.0	44.9
1959	65.2	69.9
Sweden		
1901-1910	54.5	57.0
1957	70.8	74.3
USA		
1900-1902	47.9	50.7
1958	66.4	72.7

The problem under study is obviously a difficult one since it raises almost unlimited numbers of questions regarding man's relation to his environment. An accurate appraisal of relative risks is nearly impossible, since variations in such basic factors as social customs and even semantics may have far-reaching effects. However, the need for such an appraisal is great. A disproportionate fear of radiation should of course be avoided, but it is even more important that full use should be made of the knowledge that has come from intensive study of the radiation problem in order to appreciate the public health significance of other comparable hazards that may be of equal, or in some cases perhaps even greater, importance.

In any review of agents that have harmful effects on man's health, a proper appreciation of their relative importance must be based not only on the possibility of reducing these effects but also on quantitative evidence of the prevalence—now or in the future—of each agent, and the frequency of the harmful effects that it may produce. Ideally, decisions about the exposure of the individual and the population should depend on exact knowledge regarding the nature and frequency of the effects produced. This information is not, however, available for a great number of hazards; the scope, therefore, of this report has been confined to a consideration of a group of chemical and physical agents, including ionizing radiation, which appear to require a special examination of this type because of their recent introduction or increasing use.

<sup>1</sup> Based on data from: United Nations Demographic Yearbook 1948 and 1960.

## 2. DIFFERENCES IN APPROACH TO RADIOLOGICAL AND TOXICOLOGICAL RISKS

In considering the health and safety of people who may be exposed to toxic substances, the question to be answered is: "How dangerous is this material?". It was formerly assumed that in dealing with the multitude of toxic agents to which man is exposed occupationally and in his general environment there existed some level of exposure to each of these agents which produced no harmful effects,<sup>1</sup> so that it was customary to ask: "What is the smallest amount of this material that will be dangerous?". This level of exposure was called the threshold.

As knowledge of toxic hazards developed through clinical observations and through epidemiological and experimental studies, various national and international committees were established to formulate guide-lines and to present criteria and standards for safe exposure levels. In setting these limits, the assumptions made by committees were based on human data whenever clinical observations were available and were supplemented by results of animal experiments. In those cases where even animal data were lacking, estimates were based on comparison with toxic agents having similar or related chemical properties. The concept of safe or acceptable exposure levels rested initially on the assumption of thresholds for early effects. However, with the accumulation of data and experience with various toxic substances, delayed effects attributable to exposure to toxic agents have appeared long after exposure at levels previously thought to have been safe, for instance in the case of beryllium. This necessitated downward revision of many of the recommended maxima.

During recent years, the more cautious view has been taken in radiation protection that there may not be thresholds for certain biological effects such as genetic changes, and that the dose-effect relationship not only has no threshold, but is linear. Man, however, would not wish to dispense with the use of ionizing radiations and the potentialities of nuclear energy and therefore, in practice, the problem becomes one of limiting the risk to a level that is "acceptable" to the individual and to the population. This concept of "acceptable risk" is generally used in radiation protection.

In radiological practice, the permissible dose for an individual is described as:

"that dose, accumulated over a long period of time or resulting from a single exposure, which, in the light of present knowledge, carries a negligible probability of severe

---

<sup>1</sup> Some confusion arises over the use of the word "effect" in discussing the results of exposure either to radiation or to toxic materials. It should be made clear that an "effect" is not necessarily damaging. Even the words harmful, damaging, disabling used to describe the effect need not imply permanent loss of biological, social, occupational or other efficiency.

somatic or genetic injuries ; furthermore, it is such a dose that any effects that ensue more frequently are limited to those of a minor nature that would not be considered unacceptable by the exposed individual and by competent medical authorities." <sup>1</sup>

In radiation safety practice the principle is recognized that various groups in the population may be allowed different levels of exposure. A difference in the levels allowable for exposure of different population groups appears reasonable on several grounds, for instance, that those occupationally exposed are subject to special selection, monitoring and health surveillance.

There are no exactly comparable statements to these regarding the toxicological problem, but in industry a committee for studying maximum allowable concentration values under the Permanent Commission and International Association on Occupational Health has stated (1959) that : "The term maximum allowable concentration for any substance shall mean that average concentration in air which causes no signs or symptoms of illness or physical impairment in all but hypersensitive workers during their working day on a continuing basis, as judged by the most sensitive internationally accepted tests." A more recent trend in some countries is to refer to these as threshold limit values.

The maximum allowable concentrations for non-radioactive agents are usually based on the assumption of a threshold dose. The particularly cautious approach adopted in radiation protection has not yet been generally applied in setting so-called maximum allowable concentrations for non-radioactive toxic agents. In regard to these agents, there is, however, growing concern about the possibility of the induction of delayed carcinogenic and mutagenic effects resulting from even low level exposures.

The spectacular manner in which atomic energy was brought to public notice, as well as subsequent developments in this field, have resulted in world-wide reactions of fear and anxiety greater than have been associated with any other important technological advance. As a result, extensive scientific thought and work related to the biological effects of radiation have been stimulated. There has been much more investigation into the mechanism, nature and prevention of radiation injury than has been the case with any other toxic agents. However, as more is learned about the subtle effects of non-radioactive toxic materials, a new philosophy of risk must also be adopted for those agents as well.

---

<sup>1</sup> International Commission on Radiological Protection (1959) *Recommendations of the International Commission on Radiological Protection adopted September 9, 1958*, London, Pergamon Press, p. xix.

### 3. CHEMICAL TOXICITY IN COMPARISON WITH RADIATION INJURY

Severe damage and death have followed high-level exposures, both in the case of chemical toxins and in the case of radiation, but overwhelmingly more injuries have been described caused by toxic agents and accidents in general than by ionizing radiation. Injuries can occur as a result of exposure to a vast number of different substances, both organic and inorganic, in industry and in man's environment. Most of the reported injuries come from industrial exposure. Radiation injuries have been encountered as consequences of occupational exposures and of radiation therapy, but have become less frequent in recent years as the hazard has been recognized. Experience has shown that damage may result to various tissues, including the blood-forming organs, eyes, skin, lung, bone, etc., both from exposure to certain levels of radiation and from certain doses of a variety of industrially employed substances. Certain, although not all, lesions caused by toxic substances can be compared fairly easily with those caused by radiation. Examples of such injuries—and their toxic causes—are given in Table 5.

Unfortunately it is not possible to give reliable figures showing the extent of toxic risks in different countries. Out of many examples that may be given of the extent and variety of toxic hazards, only a very few are reported here to indicate the variety of situations that exists.

#### 3.1 Occupational exposure

In Germany, it has been reported that there are each year 3000-4000 new cases of silicosis in coal miners. In the region of the Ruhr alone there are 400 000 coal miners, and 40 000 receive compensation for coal worker's pneumoconiosis. In Italy, it is estimated that about 80 000 people are exposed to a real hazard of silicosis: in 18 years 16 000 people with silicosis received compensation. Taking into account all countries, hundreds of thousands of fatal cases of silicosis have occurred within the last century.

A survey made in northern Italy in 1939 showed 82 cases of asbestosis out of 400 workers exposed for more than five years to asbestos dust concentrations higher than 1000 particles per cm<sup>3</sup>. Approximately the same incidence of the disease was found in asbestos manufacturing plants in the USA at that time.

As far as metals are concerned, it is known that during the last fifty years lead has caused at least several thousand fatal cases of poisoning. About forty to fifty cases of lead poisoning are still seen every year at one clinic in Italy where control measures are employed. It is probable that

TABLE 5. INJURIES CAUSED BY CERTAIN TOXIC AGENTS SIMILAR TO THOSE CAUSED BY RADIATION

Organ	Disease	Cause
Eyes	Cataract	heat ultra-high-frequency radio waves
Skin	Erythema Hyperkeratosis Pre-cancerous lesions Cancer  Alopecia	a vast number of irritants arsenic tar polycyclic hydrocarbons high-boiling aliphatic hydrocarbons crude paraffin oil arsenic thallium
Lung	Fibrosis Cancer	fibrogenic dusts nickel, chromium, asbestos
Blood	Anaemia  Clotting defect Leukaemia	arsine lead benzol aromatic nitro and amino compounds rare earths (animals only) benzol
Bone	Osteitis  Sarcoma	phosphorus fluorides beryllium (animals only)

currently each year some thousand cases of lead poisoning occur all over the world from industrial exposure.

In a well-studied cotton industry, chronic bronchitis and emphysema due to inhalation of cotton dust—byssinosis—is very frequent among cardroom workers. In England about 100 disabled workers receive compensation every year for byssinosis. Documented cases of byssinosis occur, although to a lesser extent, in cotton mills in many other countries.

During and after the second world war several dozens of workers in dynamite plants died suddenly shortly after resuming work on Monday or after one or two day's absence. This so-called "Monday morning death" was attributed to the inhalation of vapours of nitro- and dinitro-glycol.

From 1940 to 1945 many hundred cases of carbon disulphide intoxication arose in viscose factories in Europe. Exposure to an air concentration of more than 1 mg/litre created symptoms of polyneuritis in a matter of weeks or a few months; concentrations from 0.2-1 mg/litre created symptoms

after several months or a couple of years. Concentrations below 0.1 mg/litre did not produce symptoms, but workers exposed to that concentration for 10-20 years showed an apparent increase in incidence of vascular encephalopathies and kidney damage.

### 3.2 Residential risks

For the purposes of this discussion, residential risks refer to those caused by pollution of air, food and water. Some of the substances to which people living in industrialized urban communities are exposed are man made; others occur in the "natural background" and are thus comparable with the background of natural radiation. For instance, lead is distributed in the earth's crust, but the fact that it is also used in many industrial operations and in fuel for combustion engines (from a few hundred thousand pounds in 1926 to over 4 million pounds in 1958) means that lead widely contaminates the air, food and water. The body burden in humans was investigated in a study by Tipton in 1959 in two cities of the USA; spectrographic studies were made of 17 different metals in various body tissues from 121 adults not occupationally exposed. An accumulation of several substances was found in different organs. As an example, Tipton found about 3000 µg of cadmium and about 100 µg of lead per g of ash in the kidneys. The aluminium content in the lungs rose from less than 100 µg/g of ash in infants to about 1000 µg in adults. Up till now there is no evidence, however, that accumulation of these metals to this extent with age causes disease.

#### 3.2.1 Air Pollution

The list of air contaminants is a long one in countries with heavy traffic and industry, and where carbonaceous fuels are used for domestic heating. In agricultural areas there may also be potential hazards because of widespread use of pesticides. Variation in procedures creates great differences in recorded concentrations and in damage to people, animals and plants.

Certain data are available for assessing these risks,<sup>1</sup> and evidence is still accumulating. For example, in London in 1952 the combination of smoke containing several chemical agents and a heavy fog led to 4000 more deaths in seven days than would have normally occurred at that time of year. The study of this episode forms a landmark in experience with air pollution. It is believed that the increase in deaths was largely due to the action of the pollutants on already ill or old people. The amount of pollutants found was very small, for most substances less than 1 particle

---

<sup>1</sup> World Health Organization (1961) *Air pollution*, Geneva (*Monograph Series*, No. 46).

of material per million particles of air. The pathogenesis of the illnesses is not known ; probably it was a combination of several agents. The present view is that the agents responsible may have been sulfur dioxide, sulfuric acid and nitrogen dioxide.

Ozone is considered to be of importance in connexion with air pollution in some areas, such as Los Angeles. Ozone arises both from the interaction of sunlight with combustion products and from ionization of air. It is a strong oxidant and is known to affect pulmonary function directly.

Perhaps the most severe consequence of long-term exposure to low-level air pollution in cities is the effect on the respiratory tract. The evidence of a connexion between such air pollution and lung cancer will be dealt with in section 4 and the possibility of genetic effects is discussed in section 5. Here it can be mentioned that there is evidence that the frequency of some diseases of the lung, specifically chronic bronchitis and emphysema, are greater in areas with heavier pollution. It has been claimed that in England thousands of cases of fatal chronic bronchitis have been caused by irritating substances in the air.

In a small Norwegian village the mortality rate for pneumonia increased fourfold when a plant producing iron-manganese alloy was put into operation. The village and the plant were located at the end of a fjord and the fumes from the stacks were spread over the village. A similar outbreak of pneumonia occurred in another community in a valley where the steel mill near the town started producing an iron-manganese alloy.

Exposure to varying concentrations of carbon monoxide in urban air for brief periods, as from traffic in a tunnel or in the use of imperfect heating equipment, offers a risk. Since haemoglobin has 300 times as great an affinity for carbon monoxide as for oxygen, the carbon monoxide content of the air may become critical, especially for people already ill. The number of accidental poisonings in the home probably outweighs by far the number of occupational poisonings ; the latter can be roughly estimated at some thousands every year throughout the world.

### 3.2.2 *Contamination and adulteration of food and water*

The increasing use of pesticides sprayed over agricultural areas has created a potential risk to health, the extent of which is unknown. The two main groups of these materials are the organic phosphates which act on the nervous system and the chlorinated hydrocarbons which act both on the nervous system and other organs.

Concerning food, the Joint FAO/WHO Expert Committee on Food Additives has published a review of the carcinogenic hazards of food additives.<sup>1</sup> There are in addition a number of reports of toxic materials

<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1961, 220.

in food giving rise to damage, disability or death. Well-documented reports are available of arsenic intoxication as a result of lead arsenates sprayed on fruit and vineyards. In the case of illness due to drinking wine from such contaminated grapes, the high incidence is thought to be due to the combination of alcoholic content with the toxic element arsenic.

Severe damage and disability has been produced by the use of tri-orthocresylphosphate in food. Less than four years ago 4000 people were affected in Morocco when oil intended for airplanes was used in the manufacture of oils for cooking. Such experience points to food adulteration as a toxic risk for people in all parts of the world. These reports are all of high level exposures. There might also be, however, important toxic effects of food contamination at much lower levels of exposure. For instance, a few years ago about thirty schoolboys in Sicily experienced abdominal colic in a period of a few weeks. Some of them were operated upon for appendicitis before the correct diagnosis of lead colic had been made. This lead poisoning was caused by the use of cooking pans coated with tin containing lead. In the same context, one may also mention numerous cases of intoxication of children eating lead-containing paint from toys, cribs and houses. The subject of lead poisoning in children deserves attention and it should be remembered that lead may be directly harmful to the cerebrum and may cause idiocy and blindness. These circumstances emphasize the need for also studying possible harm from lead at low doses.

Concerning water pollution, the problem of bacterial contamination has been and is constantly under study. Pollution by chemicals from industry and those used in water softening and purification are likewise receiving attention. It is, for example, important to exclude the possibility that the use of sodium ethylenediaminetetra-acetate (sodium edetate) in water softening may have a damaging effect on children and patients with kidney disease because its action through chelation may remove important amounts of certain essential heavy metals. In addition, calcium edetate has been shown to be toxic to the kidneys at certain doses. Although the amount of lead in water contributes only a small increment to the many other polluting materials, it is worthwhile to draw attention to the fact that this is a widespread finding. Where lead-lined pipes for delivering water are used the lead content of the water increases.

An important problem in certain places is the natural occurrence in water supplies of elements at levels shown to be toxic. In the geographical areas where such elements are found in water and in soil, they gain access to vegetation and to animals and thus reach local food supplies. Two striking examples may be quoted. Certain geological formations in some parts of the world have resulted in a high fluoride content of the soil. This may lead to a toxic level of fluoride in the drinking water and in food. In some areas, epidemiological studies have been made, and, for example

in Nellore, Andhra Pradesh, India, the human and animal population groups have shown pathological lesions in teeth and bones. In other areas, toxic effects have been shown to be due to an accumulation of selenium in the soil. Cattle grazing in areas where water and soil are high in selenium content may develop a disease known as "alkali disease". This occurs and has been studied in certain parts of the USA. Both the animal and the human populations in these areas were found to be excreting significant amounts of selenium in their urine, and there was evidence suggesting that the selenium had exercised a toxic effect.

From this it is clear that both in industry and in his environment in general, man may be exposed to toxic hazards causing well-defined diseases, and to a wider extent than is the case with radiation. This is understandable in view of the thousands of toxic agents that exist ; but it is clearly anomalous that so much less detailed attention has been paid to injuries due to these agents than to the study of radiation damage.

#### 4. CARCINOGENESIS

The hazard of malignant disease, cancer and leukaemia, occupies a very important place in any consideration of risks from exposure to toxic agents and radiations. Malignant disease may develop years after the application of the noxious agent, and in only a few of the exposed individuals. It is therefore often difficult to determine that an agent is carcinogenic or leukemogenic, especially since the malignant diseases also occur in individuals without known exposure to such agents, i.e. apparently "spontaneously".

In certain instances, particularly of some types of cancer in childhood, it appears that malignant disease may develop as a result of inherited factors and that carcinogenic agents are unimportant. Thus a simple genetic factor seems to determine retinoblastoma. Other cancers develop on the basis of inborn, abnormal, "precancerous" states, such as, for example, xeroderma pigmentosum and polyposis of the intestine. In certain African tribes, it has been found that youths develop certain types of cancer (e.g., chondrosarcoma and Kaposi's sarcoma) which are excessively rare elsewhere.

At the opposite extreme, some tumours are clearly induced as the result of exposure to carcinogenic agents. This is true of many types of human tumours associated with industrial exposures, and of tumours induced by certain physical agents and a great variety of chemical agents in experimental animals. Ionizing and ultra-violet radiations, and certain specific hydrocarbons, are the best known examples of the latter.

Between these extremes, the great majority of tumours arise without a detectable single cause. The general state of the tissue of origin seems to be important as a predisposing factor : this may involve such factors as

the endocrine balance, or some general condition of tissue derangement. The latter is illustrated by the fact that liver cancer, in man, is frequently preceded by cirrhosis induced by alcohol or carbon tetrachloride; and in experimental animals, a malignant state may be induced when a plastic barrier is introduced into a previously intact tissue. In a great many instances, it is obvious that multiple etiological factors must be at work. Some agents, such as urethane, may determine only a preliminary stage in the carcinogenic process, while others, such as croton oil, only determine the development of tumours after the preliminary stage has been reached. The more potent carcinogens, including radiation and certain hydrocarbons, seem able to act in both capacities.

The overall incidence of "spontaneous" cancer increases with age. It is not clear to what extent this is due to accumulation of the effects of external carcinogens, and to what extent to deterioration of tissue associated with aging.

Much interest has naturally been taken in the question of whether very small exposures to carcinogens (such as low doses of radiation, or small quantities of carcinogenic chemicals) can induce malignant disease in a very small proportion of individuals. Unfortunately, this question cannot be answered for man, even in a qualitative sense, by direct experimentation or by any clinical observations that have so far become "practicable". It is likely that only a more fundamental knowledge of the processes leading to malignant disease will provide a solution of this question.

To complicate the matter further, it is known that there are viruses, at least in some species, that may lead to tumour development, but often after a long period of latency. In some cases, the viruses are responsible only for the production of non-malignant states in which cancer is likely to develop. Also, many carcinogenic agents are capable of inducing genetic mutations, and it is not unlikely that similar mutations in somatic cells may be one of the necessary stages in the development of certain malignant changes in tissue. Various theories and models have recently been put forward; these result in very different predictions as to the doses required to produce a low incidence of malignant tumours (say one in a million). The assumptions used in the case of radiations have tended to be much more restrictive than in toxicology.

Much suggestive information has been gained from demographic observations on the relative frequency of various types of cancer in various milieus, indicating regional, social, racial, and cultural differences of considerable magnitude. With the development of more precise vital records, such observations may be expected to afford valuable clues to hereditary or environmental influences affecting the origin of malignant disease. It would be of special value if internationally co-ordinated studies in special areas of demography, as in studying monozygotic twins, could be facilitated.

The following survey of carcinogenic agents has been arranged according to a few general categories indicating the commonest sources of exposure. In certain instances—where information is available—the approximate relative magnitudes of the hazards is given.

#### 4.1 Natural sources

The only known natural source that is unequivocally carcinogenic is sunlight, largely or altogether in the ultraviolet wavelengths. Skin cancer has long been known to occur with greater frequency in persons, such as sailors and farmers, having high exposures to sunlight. The natural incidence of skin cancer is four times as high in the southern than in the northern parts of the USA (80/100 000 per year as compared to 20/100 000).

Ionizing radiation occurs from natural sources, and can be accurately measured. It consists of radiation of cosmic origin, gamma radiation from the earth and building materials, and naturally radioactive elements (potassium-40, carbon-14, radium) existing in the human body. Because of local conditions and altitude, this natural "background" to which peoples are exposed may easily be increased to double the usual amount, and in certain places (e.g., monazite areas in India and Brazil) it may be increased some ten to twenty or more times. There is a large area in the central USA in which the radium content of human bones is five to ten times that ordinarily encountered.

No evidence exists that this natural radiation, even when high, has any influence on the cancer rate in man; indeed, it is one-hundredth part or less of the lowest radiation dose rate that has so far been shown to induce malignant disease in man or experimental animals. However, in the light of the widespread use of radiation for medical and other purposes and of speculations that may be made on the possible carcinogenic effects of radioactive contamination from fallout and nuclear accidents, it is important to look for any small effects that might be detected in areas where the natural background is much above normal.

Among natural causes of cancer may be mentioned one that might be preventable, namely infection with bilharziasis. The effects of this disease may lead to cancer of the bladder, and in certain parts of the world it has been held responsible for a very high incidence of this condition.

Various non-radioactive metals vary greatly in concentration in the natural environment. No evidence has so far been found to show that these variations play a role in cancer frequency.

#### 4.2 Occupational sources

It is in this category that some of the clearest evidence pertaining to etiological factors in human cancer is available. The occupational agents comprise largely:

- (1) soot, tars, and shale and mineral oils, which on contact with the skin have given rise to some thousands of cases of industrial cancer ;
- (2) benzidine and beta-naphthylamine, which have been the cause of many cases of bladder cancer ;
- (3) agents giving rise to lung cancer, notably chromium and asbestos and some material involved in the process of refining nickel ;
- (4) radioactive substances and radiations.

In the case of the tars and oils, a large number of pure hydrocarbons (notably benzyrene and methylcholanthrene) have been isolated or synthesized which, in concentrated form, are highly carcinogenic to experimental animals. While no direct proof is available in man, it is likely that such compounds are responsible for the action of the tars and oils.

Radioactive substances have acted in various ways : lung cancer has for a very long time been encountered in some central European mines, and is now attributed to the radioactive decay products of radon gas, which are inhaled along with dust. Radium, absorbed through the alimentary tract in workers in the luminous watch-dial industry, has been retained in the skeleton and has given rise to malignant tumours of bone. Prolonged exposure to X-rays has caused a considerably increased frequency of leukaemia in radiologists.

Certain agents that cause degenerative changes and cirrhosis of the liver may lead, as an eventual result, to liver cancer. Of these, carbon tetrachloride is a well established carcinogen. It seems probable that such agents will lead to cancer development only after such quantities have been absorbed as to create widespread disturbance of the cellular architecture of the organ.

Exposure to benzol is commonly believed to cause leukaemia, perhaps again through widespread destructive and regenerative responses in the bone marrow. The relation between benzol exposure and leukaemia has not, however, been subject to the same rigorous type of study that has shown the relation between radiation exposures and leukaemia.

Where industrial carcinogenesis has been noted, it has been possible in all cases to eliminate or greatly reduce the hazard by appropriate measures. In the watch-dial industry, for example, absorption of radium fell by a factor of 100 following the simple expedient of avoiding direct contact of the material with the mouth. It seems probable, on general principles, that other industrial hazards exist unnoticed, in view of the great variety of carcinogens known experimentally and of the variety of new chemicals being developed.

### 4.3 Conventional hazards of living

While almost none of the agents chiefly associated with the increasing complexity of living—except those discussed under “self-imposed hazards” in section 4.4—has been demonstrated to be carcinogenic in man, many of them are carcinogenic in experimental animals and must therefore be given careful consideration.

As noted above, benzpyrene, a coal tar derivative, is highly carcinogenic in various experimental animals and has consistently induced skin or subcutaneous tumours, depending on the mode of application. It is produced in the combustion of coal and petroleum products and is found in measurable quantities in the air, being present in much higher concentration in urban localities. While its carcinogenicity to man has not been shown, it comes under suspicion because of the differences between urban and rural incidences of lung cancer, in circumstances when other known factors are not responsible.<sup>1</sup> The high incidence of gastric cancer among people consuming much smoked fish is of interest because of the high concentrations of benzpyrene present in smoked foods.

Experimental studies of various pesticides in common use have revealed that certain of them, e.g., aramite and thiourea, have carcinogenic properties. These and a number of others have been discussed in the fifth report of the Joint FAO/WHO Expert Committee on Food Additives, referred to in section 3.2.2. The use of pesticides with known carcinogenic potency has been discouraged.

Many food additives have been and are being introduced for a variety of purposes. It should be pointed out that the testing for carcinogenesis normally carried out on such substances is considerably less stringent than that which would be considered adequate to exclude the possible hazardousness of radioactive material; indeed, this is inevitable because of the large number of compounds that need to be tested. Within the scope of this report it is not possible to survey this complicated subject, but mention will be made of an instance that has attracted wide attention.

Domestic fowls have been treated, on a large scale, with oestrogenic hormone, which improves the quality of the meat in a way similar to caponization. Although oestrogens are synthesized in human beings of both sexes and their output varies from person to person and according to physiological conditions, they exert a carcinogenic influence in excessive quantities and the growth of certain tumours of the secondary sex organs is to some extent dependent on their presence. The amounts introduced through the ingestion of treated fowl cause relatively small increments to the amounts naturally present, but although oestrogens have been used

---

<sup>1</sup> The World Health Organization is currently assisting a study of this problem in Dublin and Belfast.

to produce regressions of certain types of cancer, the particular compound used for treating fowls (diethylstilbestrol) is not one of the naturally occurring ones and is classified as a carcinogen; its use has come under criticism and the possible hazard requires further examination.

#### 4.4 Self-imposed hazards

Among these it appears quite obvious that cigarette smoking, or something closely associated with it, is largely responsible for the high incidence of bronchiogenic carcinoma in certain countries. The incidence in heavy smokers (between 150 and 200 cases per 100 000 per year in many countries) is high compared with the incidence of skin cancer in northern countries (20 per 100 000 per year) and in the southern USA (80 per 100 000 per year), or with the total leukaemia incidence (not over 6 per 100 000 per year) and the total incidence of tumours arising in bone (about 1 per 100 000 per year). Some anomalies in the distribution of lung cancer strongly suggest that other agents play some part—the most substantial evidence appears to be the higher incidence in urban than in rural smokers. Another self-imposed hazard of a comparable type to cigarette smoking is the chewing of betel with other substances, a practice which, in certain localities, has been implicated in cancer of the mouth.

The medical use of radiation for the purposes of therapy of non-malignant conditions and of diagnosis has occasionally been shown to lead to malignant disease; in the earliest days of radiological practice this was more common than it is today. A series of patients treated by X-rays for a form of arthritis of the spine (ankylosing spondylitis) subsequently showed an abnormally high incidence of leukaemia. Children treated by X-ray therapy over the upper chest have developed thyroid cancer occasionally, as well as a few tumours of other types. From the results of some surveys it would appear that radiation doses of approximately 150 to 400 rads to this region may occasionally result in cancer of the thyroid. There are sporadic reports indicating that in the range of doses used in radiotherapy, malignant sequelae may be expected in a small proportion of cases. A number of patients who received radium burdens by injection or ingestion during the period (early 1930's) when this was considered a safe procedure, have shown bone tumours, as have some who were exposed industrially. Injections of thorium dioxide (thorotrast) for diagnostic purposes have given rise, after some years, to cancer in areas of the body where this radioactive material concentrates, particularly in the liver and at the site of the injection.

As regards the lower doses received in diagnostic radiation, certain studies have indicated the likelihood that irradiation of the foetus, such as may occur during pelvic irradiation of the mother, may increase the

frequency with which leukaemia and cancer occur within a few years after birth.

There are numerous instances in which thermal effects (from burns, pipe stems, charcoal-heated body warmers, and perhaps hot drinks) have been precursory to local cancer. Nonspecific trauma, "chronic irritation" (as from bad teeth) and the presence of foreign bodies have been linked to cancer development. Good experimental evidence has been obtained in animals that embedded sheets of plastic materials such as cellophane (without known chemical carcinogenic properties) or large doses of an injected iron compound can induce cancer.

#### 4.5 General remarks

As mentioned in the introduction to this section, demographic studies have shown quite remarkable differences in the incidence of cancer in various groups of persons. Some of these may be accounted for on a genetic basis, but for a number of reasons it appears likely that many if not most of the differences in incidence point to unsuspected external carcinogenic influences. Insofar as these differences change with migration and acculturation of population groups, this seems an inevitable conclusion.

It is worth noting that the recognition of a certain agent as a causal factor for the induction of cancer in a group of persons exposed to that agent depends on the frequency of the same type of cancer in individuals not so exposed. Thus, the first form so recognized (by Percival Pott in 1775) was chimney sweeps' cancer of the scrotum, since this condition was observed to be fairly common in chimney sweeps but excessively rare in persons not exposed to soot. Thus, while 100 cases of any very rare disease (not necessarily cancer) would probably attract much attention to a particular mode of exposure, an increment of 1000 cases of a common disease might escape notice. It has been suggested that fatal cardiovascular disease may be a commoner outcome of smoking than lung cancer in absolute terms, but the evidence would be much more difficult to establish.

Increases in the reported incidence of a disease with the passage of time may occur because of improved diagnosis, and for some years there was a tendency to assume that this was true of lung cancer. It seems to be true that the incidence of human leukaemia increased sharply for some years, certainly in many parts of the world. While various explanations of this have been suggested, including virus infection as well as medical or other radiations, none of them is fully satisfactory. The possibility that other agents, especially those having known effects on the blood-forming system, may bear some responsibility for the increase, deserves consideration.

The possibility that contamination by nuclear debris from fallout or nuclear accidents may have a carcinogenic effect is at present one that cannot be estimated directly, since present levels add only a fraction to the natural radiation background and because of the many other variables indicated in this discussion. It seems likely that much more will need to be learned about the complicated process of carcinogenesis, or that highly controlled, accurate, and widespread studies in areas of differing natural radioactivity will have to be pursued before semi-quantitative or even qualitative judgments in this matter can be more than speculative.

## 5. GENETIC EFFECTS OF RADIATION, CHEMICALS AND TEMPERATURE

It is a well-known fact that exposure of animals or plants to ionizing radiation produces changes in their genetic material. Two kinds of change can be distinguished: mutations and breaks in the chromosomes. The great majority of genetic changes have deleterious effects on the descendants in which they become manifest. The growing use of X-rays and other sources of ionizing radiation in medicine and industry, as well as recent nuclear energy developments tend to augment the level of radiation to which man is exposed. This raises the question of what consequences an increase in the mutation frequency in man may have for the health and well-being of future generations. During the past few years this problem has received ever-increasing attention. This is reflected both in the wide range of research projects and in the number of reports that have appeared since 1956.

It has been shown, however, that mutagenic effects can be caused not only by radiation but also by a number of chemical agents. Furthermore, it is known from experiments with the fruit fly that raising the temperature results in an increase in the frequency with which mutations arise.

With the aim of putting the genetic hazards of radiation into proper perspective, the effects that can be expected on the health of future generations from an artificial increase in the mutation frequency will be reviewed briefly, and the possible genetic consequences of the presence of mutagenic chemicals in man's environment and of the effect of clothing habits on the male gonad temperature will be discussed.

The practical method of assessment of genetic hazards consists of a synthesis of three independent estimates regarding:

- (a) the hereditary fraction of the total burden of morbidity and mortality;
- (b) the extent to which this fraction is maintained by mutation;
- (c) the relationship between radiation dose and dose-rate and the number of mutations produced.

Similar procedures might perhaps be used in the case of other mutagenic agents such as chemicals and increased temperature.

### 5.1 The hereditary burden in man

The total incidence of hereditary diseases and defects may be estimated at present at 6% of all live births. Of this about one-third consists of traits with a simple and known mode of inheritance, about one-fourth are serious constitutional diseases with a major genetic component in their causation, and the rest is composed of malformations with unknown heredity components.

Half the traits in the first category show simple autosomal dominant or sex-linked recessive inheritance. The other half are congenital defects associated with chromosome aberrations, such as Down's syndrome (mongolism), Klinefelter's syndrome, etc. The discovery that a surprisingly high frequency of defects in man are associated with anomalies of chromosome number or structural aberrations of the chromosomes came to light recently as a result of progress in the field of human cytology. Since such types of chromosome abnormalities can be produced by radiation, these findings suggest a radiation hazard more extensive than was suspected before.

In addition to the hereditary burden mentioned above there will be stillbirths, neonatal deaths and infant mortality due to recessive genes in the population which are detrimental if received from both parents. An estimate of the total disadvantage originating from such genes can be obtained by measuring inbreeding depression in consanguineous marriages. From these calculations it is concluded that each individual carries in the heterozygous state an average of 2.5 to 4 lethal equivalents (gene changes which, when combined in the homozygous state, would result in death before the age of 20 to 30), and possibly an equal number of detrimental equivalents resulting in malformation in homozygotes.

#### 5.1.1 *Role of mutation in maintaining the hereditary burden*

The role of mutation in maintaining the hereditary burden described above may be different for the various categories listed. In view of the considerable reduction in reproductive fitness in carriers of dominant and sex-linked traits (one-sixth of the total hereditary burden) it is assumed that they are almost entirely maintained by recurrent fresh mutation. Defects due to chromosomal aberrations (present in about 1% of all live-born children) are characterized by dominant transmission, and the reproductive fitness of their carriers is almost zero. In consequence, the frequency of gross chromosomal aberrations in the population is almost entirely maintained by their rate of fresh occurrence, and their effect is manifest mainly in the generation after their occurrence.

Experimental data have shown that apparently recessive genes, whose main disadvantageous effect is expressed in the homozygote, may also manifest an effect in the heterozygous condition. In man, a number of cases are known where genes with pronounced disadvantageous effects in the homozygotes nevertheless are maintained at high frequency in the population because of the better chances of survival they confer to their heterozygous carriers. An example is the gene for haemoglobin S, which in the homozygote produces sickle cell anaemia but which in the heterozygote apparently confers a degree of resistance to falciparum malaria. For such genes mutation plays only a minor role in maintaining their frequency in the population. If, on the other hand, a mutant gene is deleterious both in the heterozygote and the homozygote it can be maintained only by recurrent mutation. Since usually the number of homozygotes is extremely small in comparison with that of the heterozygous carriers, it is mainly the reproductive fitness of the heterozygote which determines in how many generations the mutant gene will be passed on to successive descendants. If, for example, an average reduction in fitness of 2% is experienced by the heterozygote, it will take, on the average, approximately fifty generations before the mutant gene has disappeared from the line of descendants.

The role of mutation in maintaining the hereditary burden in man is still under debate. To be on the safe side, the usual practice has been to assume that all of it is maintained by recurrent mutation. The field is very complex and an answer to this question, based on observations in man, is likely to be arrived at very slowly.

## 5.2 Production of mutations by radiation

Recent studies in the mouse have shown that the rate at which radiation is delivered may have a pronounced effect on the number of mutations produced. Thus it was found that prolonged exposure to radiation, given at a low dose rate, produces a significantly lower frequency of mutations than is observed after the same dose given at a high dose rate; in spermatogonia this value is  $2.1 \times 10^{-7}$  per roentgen for acute irradiation in the mouse, and  $0.96 \times 10^{-7}$  per roentgen for chronic irradiation. It is of particular significance that such an effect of dose rate is observed in spermatogonia in males and in oocytes in females, stages which are of greatest concern in an evaluation of genetic radiation hazards in man. Experiments with very low dose rates have given no evidence for a threshold dose rate.

These results have been interpreted on the assumption that in actively metabolising germ cells, part of the initial radiation damage can be repaired before the mutation process has become completed. Evidence favouring this idea has been recently obtained in studies with both micro-organisms and *Drosophila*. The practical consequence of these studies for man is

that in all probability, as in the mouse, a lower mutagenic effect of a given dose may be expected from prolonged low exposures than from brief high exposures.

For clarification it should be mentioned, however, that once a mutation is completed, repair is no longer possible, and that the mutagenic effect of radiation is additive: what counts is the total dose of radiation received from conception to the end of the reproductive age.

In the mutation experiments with mice it has been observed that after either chronic or acute exposure to radiation the number of mutations produced is proportional to the dose of radiation. For evaluating the radiation hazard to human populations it would be of particular importance to know whether this relation holds for low doses of chronic exposure in immature germ cells. At present there is no evidence suggesting that this is not so.

For the population at large this would mean that exposure of a large number of individuals to small doses of radiation may produce the same overall number of mutations as the exposure of a small group to larger doses, provided that in both cases the total dose delivered throughout the group has been the same and that the exposed individuals had the same child expectancy.

#### 5.2.2 Observations in man

Owing to the difficulties encountered in studying the mutagenic action of radiation in man, the relation between radiation dose and induced mutation frequency is unfortunately still not well known.

Information available so far on the production of mutations by radiation in man is limited to the observation of a lowered sex ratio (decreased percentage of male children) among the progeny of irradiated women. This effect has been observed in a number of independent surveys.

It is known that exposure to radiation produces chromosome aberration in the somatic cells of man, as it does in animal and plant material. Chromosome aberrations induced by *in vitro* irradiation of human tissue cultures have recently been studied by a number of workers. The reported frequencies of chromosome breaks range from 0.2 to 2 breaks per cell per 100 r. It is not certain, however, whether an equivalent response would be obtained in gametic cells irradiated *in vivo*.

In view of the hazards outlined before, arising from the induction of chromosome aberrations and because the effect of chronic radiation exposures is accumulated mainly in the gonads, it would be desirable to know to what extent gonadal irradiation contributes to an increase of chromosome aberrations in the functional germ cells. The available evidence from studies in the mouse suggests that the chances of finding chromosome aberrations after radiation exposure of spermatogonia are considerably

smaller than after irradiation of mature sperm. Moreover the production of chromosomal aberrations is a dose-rate dependent phenomenon. In view of these considerations it is not possible to state to what extent gonial irradiation may contribute to the frequency of chromosome aberrations. On the basis of the available experimental evidence one can assume that this hazard will be comparatively greater following exposure of mature sperm prior to or after fertilization.

### 5.3 Genetic effects of chemicals

Mutations occur naturally in all animals and plants. The causes of these spontaneous mutations are not well understood. It is estimated that only a small fraction of them could be due to the natural background radiation to which all living things are exposed.

There is however no *a priori* reason for believing that ionizing radiation is the only, or even the main, environmental factor that can produce an increased number of mutations in man or in other forms. Some hundreds of chemical agents are known to be mutagenic, but none has been studied in such detail as radiation.

The reasons for the special emphasis that has been given to the effects of radiation on heredity are easily understood. Muller's discovery in 1927 of the mutagenic action of X-rays provided a very powerful tool for research in genetics. Investigators in many countries pursued studies with this new method. Subsequently, with the advent of the atomic age, attention to radiation genetics was greatly intensified and led to research of a great magnitude, such as that of Russell and co-workers involving hundreds of thousands of mice. Thus, a good deal has come to be known about radiation as a mutagenic agent and as a cause of chromosome aberrations, but knowledge of chemical mutagenesis is at a much earlier stage.

Enhancement of the mutation frequency by means of chemical agents was not reported before the end of the last war. It was, however, shown as early as 1942 that mustard gas has strong mutagenic activity in *Drosophila*. In 1943 chromosome aberrations were produced in the evening primrose, *Oenothera*, by injecting urethane into the flower buds. Subsequent tests showed that in *Drosophila* also this substance acts as an effective mutagen. Almost simultaneously with these discoveries, the highly mutagenic activity of formaldehyde, when added to the food of *Drosophila* larvae, was reported. Moreover, in the years 1946-48 mutagenic activity was demonstrated for various substances, such as epoxides, dimethyl- and diethylsulphate, diazomethane, ethylene imine, phenol, acrolein and other unsaturated aldehydes. Since then a great variety of chemicals have been reported as capable of producing mutations or chromosome aberrations. Research in this field has received considerable impetus from the development of new carcinostatic compounds.

Thus far, most data have been obtained in work with *Drosophila*, *Neurospora*, bacteria and a number of higher plants. In contrast to the recent advancement in knowledge of the mutagenic effects of radiation in the mouse, practically nothing is known about mutagenic chemicals in mammals; such data are needed for an evaluation of the potential hazards of mutagenic chemicals in man. For chemicals this question is even more important because the mutagenic action will depend to a much greater extent than in the case of radiation on penetration, diffusion, metabolism and other variables, which differ specifically from one kind of organism to the other.

### 5.3.1 *The effects of mutagenic chemicals on Drosophila and lower organisms*

A number of active mutagens are listed in Table 6. These are substances that affect the genetic material at concentrations lower than those that would cause serious cellular damage. The list does not aim at completeness. Most of these chemicals have been reported to produce both mutations and chromosome aberrations although exceptions have been recorded in a few cases. A few mutagens show exceptional behaviour. Urethane, for example, proved non-mutagenic in the tests for reverse-mutation in *Neurospora*, but it produced mutations in *Drosophila* and in bacteria. The list shown in the Table would have been extended by a great number of substances if observed chromosome aberrations in *Vicia* or *Allium* root tips had been taken into consideration.

5.3.1.1 *Relation to radiation mutagenesis.* The overall spectrum of effects of a number of mutagenic chemicals resembles so much that produced by radiation that the term "radiomimetic chemicals" has now gained widespread use. In particular, a great number of alkylating agents belong to this group. It was, in fact, the striking correspondence in pharmacological effects between mustard gas and irradiation that led to the discovery of the first chemical mutagen. Biological effects common to radiation and radiomimetic chemicals include nausea and vomiting after moderate doses, thrombocytopenia, leucopenia, vesication, greying of hair, mitotic disturbance, mutagenesis, carcinostasis and carcinogenesis.

There are also substances that could be called radiomimetic in regard to their chemical action on the genetic material. It is known that, apart from the direct effects of ionizations and excitations, intermediary chemicals play a role in the genetic action of radiation. Although their exact chemical nature is still under debate, it seems probable that peroxides are involved. The finding, therefore, that a number of peroxides have a mutagenic action bridges the demarcation line between radiation and chemical mutagenesis.

There are a few characteristic differences between the effects of most mutagenic chemicals and those of X-rays. Firstly, many chemicals produce

TABLE 6. SOME EFFECTIVE MUTAGENS STUDIED IN DIFFERENT ORGANISMS \*

Mutagen	Droso- phila	Neuro- spora revers- ions	Higher plants	Bacteria	Source of exposure
<b>Mustard derivatives</b> nitrogen mustards	+	+	+	+	Therapy
<b>Epoxydes <sup>a</sup></b> epoxide diepoxybutane	+	+	+	+	Industry Domestic use
<b>Imines</b> triethylenemelamine (TEM)	+	+	+	+	Therapy
<b>Alkane-sulphonic esters</b> dimethylsulfonylbutane (Myleran)	+	+	+	+	Therapy
<b>Other alkylating agents</b> dimethylsulphate diethylsulphate	+	+	+	+	
<b>Peroxides <sup>a</sup></b> tert. butyl hydroperoxide dihydroxymethyl peroxide	+	+	?	?	Smog
<b>Aldehydes <sup>a</sup></b> formaldehyde propionaldehyde acrolein	+	+	=	+	Industry Smog Disinfectant
<b>Basic dyes <sup>a</sup></b> proflavine pyronine acridine orange	+	?	?	+	Industry
<b>Purines <sup>a</sup></b> caffeine 8-ethoxy caffeine	± —	? ?	? chroms <sup>b</sup>	+ ?	Beverages Widespread use
<b>Antimetabolites <sup>a</sup></b> 5-bromouracil 2-aminopurine	—	?	?	+	Therapy
<b>Pyrolizidine alkaloids</b>	+	?	?	?	Herbs
<b>Miscellaneous</b> nitrous acid phenol manganous chloride urethane diazomethane beta-propiolactone maleic hydrazide <sup>a</sup>	? + — + + ? —	? — ? — + + —	? chroms <sup>b</sup> ? chroms <sup>b</sup> ? + chroms <sup>b</sup>	+ ? + ? ? + —	Industry      Food and agriculture Widespread Widespread
ethyl alcohol <sup>a</sup> nicotine <sup>a</sup>	— —	— —	chroms <sup>b</sup> chroms <sup>b</sup>	— —	Widespread Widespread

\* One or more typical examples listed in each class of mutagen.

<sup>a</sup> of common occurrence, at least in certain human environments

<sup>b</sup> produces chromosome breaks in plants

+ mutagenic

— not mutagenic

± weakly mutagenic

? no reference to mutagenic activity available

delayed genetic effects, resulting in a much greater frequency of mutations affecting only part of the body (mosaic manifestations) than is observed after irradiation. Secondly, chromosome rearrangements are less frequent after chemical treatment than after irradiation.

In several organisms indications have been obtained that the distribution of mutations produced by chemicals is different from that induced by radiation and that also it may vary from chemical to chemical. No attempt is made to treat the question of mutagen specificity in this report.

5.3.1.2 *Stage-specific responses.* In *Drosophila* it has been shown that different stages of sperm development may react differently to the action of mutagens. These effects are analysed by comparing mutation frequencies in successive broods from treated males. Greatest sensitivity to the mutagenic effects of X-rays is found in spermatids and spermatocytes. Mustard gas, on the other hand, produces its maximum mutagenic effect in a slightly earlier stage. Formaldehyde given in the food acts only on the stage that precedes meiosis in male larvae. In adults, however, formaldehyde in the food is not mutagenically effective, although when given by injection into adult males it produces mutations mainly in mature sperm. *Drosophila* females are completely refractory to the mutagenic action of formaldehyde, except when the adults are exposed to cyanide before the formaldehyde is injected.

Still another substance, chlorethyl methane sulfonate, produces very few mutations in mature and nearly mature stages of sperm development, but in early gonial cells it acts as a very powerful mutagen.

These great differences in response of different cells within the same organism even to the same mutagen may serve to illustrate how careful one should be in extrapolating from *Drosophila* or micro-organisms to man.

5.3.1.3 *Dose-effect relationship.* A detailed knowledge of the relation between the concentration of a chemical and the degree of its mutagenic effect seems one of the most elementary prerequisites for any evaluation of genetic hazards due to chemical mutagens.

For a few chemical mutagens dose-effect curves have been obtained, mainly in *Drosophila*. Their interpretation is made difficult, however, by the fact that we do not know the roles played by penetration, diffusion, and other secondary factors. Of particular significance in this context seem data that were obtained on the quantitative relation between lethals (essentially one-hit events) and translocations (requiring two independent breaks for their production). After irradiation, the frequency of lethals varies in direct proportion to the dose, while that of translocations goes up as the square, or nearly the square, of the dose. In the case of mustard gas, translocations were found to increase exactly as the square of the lethal frequency. These results suggest, therefore, that mustard gas induces translocations by two independent events, each of which produces a lethal,

i.e., that mustard gas is radiomimetic in the sense of being a "hit" poison. Similar results were obtained with triethylenemelamine.

Altogether, however, the available information on dose-effect relations for chemical mutagenesis is still meagre.

### 5.3.2 *The effect of chemical mutagens in mammals*

5.3.2.1 *Cytological observations.* The first clear effect of a chemical mutagen on mammalian chromosomes was obtained by treating Walker-carcinoma of the rat with nitrogen mustard (HN-2). An analysis of the cell injuries showed that these were of two kinds. Injuries that appear not later than 48 hours after the application of the drug consist of chromosome breaks and bridges and parallel those produced by radiation. Those injuries that are found 72 hours after treatment consist of complete fragmentation of the chromosomes leading to an arrest of cell division. These effects are useful in explaining the basis for the use of these agents in tumour therapy.

An observation has been reported in mice that may be of particular significance for man: metabolic disturbances, brought about by a diet deficient in vitamin B, also resulted in chromosome abnormalities during spermatogenesis.

5.3.2.2 *Genetic observations.* The only data thus far available on the mutagenic action of chemicals in the mouse were obtained in Edinburgh by Auerbach and Falconer using nitrogen mustard (HN-2) and by Cattanaach using triethylenemelamine (TEM).

TEM proved exceedingly active: it produced as many dominant lethals and translocations as the highest tolerated X-ray dose, and two visible mutations. Nitrogen mustard also produced translocations in mice, but its effectiveness was less than that of TEM. Because of its great systemic toxicity, however, HN-2 could not be given in high doses.

A new and very elegant technique for studying the genetic effects of TEM in mammalian cells has been recently applied by Auerbach and Dhaliwal. It consists of studying induced changes at loci that determine histocompatibility in mouse tumours. For these experiments tumours are used that are hybrid for two antigens. In consequence, such tumours will not grow in strains that are homozygous for either one of the two specific antigens. Genetic change at one of the two histocompatibility loci results in growth of the tumour. Such changes have been induced by both TEM and X-rays. It is not yet possible to decide, however, whether the postulated event in the nucleus of the cell is mutation proper, chromosome loss, deficiency, or somatic crossing-over. Techniques such as this might be very useful in increasing the efficiency of the search for chemical mutagens.

Auerbach also points out the great value of mutation experiments with mutagenic chemicals on somatic cells *in vitro* for testing the hypothesis of whether cancer arises by somatic mutation.

#### 5.4 Potential mutagens in the environment of man

In Table 6, a number of chemicals, potentially mutagenic, to which man may be exposed are marked by an asterisk. It may be pointed out that some of the powerful mutagens, such as alkylating agents (mustards, TEM, myleran) only affect a small minority of the population treated for cancer. A far greater part of the population is exposed to other substances like caffeine, the aldehydes and peroxides. Whether these agents penetrate as effective mutagens into human germ cells is, however, uncertain. Since, as has been mentioned earlier in this report, chromosome aberrations and abnormal karyotypes contribute significantly to congenital defects in man, consideration should be given also to a few substances of widespread occurrence which are only known for their ability to produce chromosome aberrations. Ethyl alcohol, for example, has been reported to induce chromosome aberrations in root tips of plants. Maleic hydrazide, which is widely used to prevent sprouting of potatoes, is well known to produce chromosome aberrations. Chromosome aberrations have also been reported after treatment with nicotine.

The mutagenic activity of ozone has not been established beyond doubt, but it is probable that in cities covered by smog ozone takes part in the formation of mutagenic peroxides and epoxides.

Caffeine is one of the substances that might deserve special attention because of its worldwide use in a variety of beverages and because it has been reported to have a mutagenic action in bacteria and *Drosophila*, although this effect has not been found in the mouse. For theobromine, which is also widely used as a constituent of cocoa, no experimental data are available.

When dealing with chemicals that are potentially mutagenic it should be clearly borne in mind that until their pharmacology is understood any prediction regarding their actual effect is highly conjectural. Even the most powerful mutagenic agent will, in fact, be ineffective if it does not reach the germ cells. Straightforward extrapolation from animal data to man requires, therefore, the greatest caution. In this respect, chemical mutagenesis differs essentially from radiation mutagenesis, since energy will be released in the gonads of any species exposed to penetrating radiation. The action of a chemical mutagen is contingent on its absorption, distribution, and diffusion, and these in turn depend on a host of chemical and physiological factors.

These complications, however, should not deter one from seriously considering the possibility that at least some of the chemical contaminants

of the environment might be mutagenic to man. The inherent difficulties of studying mutagenesis directly, as well as the multiplicity of chemical contaminants, severely limit our understanding of this question at the present time. Yet the need to preserve the genetic endowment of human populations demands that such knowledge be gained, at least for the principal contaminants.

In particular, there is complete lack of information on the possible mutagenic effects of such widespread substances as lead, beryllium, carbon tetrachloride, the oxides of sulfur, ammonia, etc. While it seems senseless to embark on extensive and costly human investigations on agents which have not been shown to exert mutagenic effects in other organisms, in the case of widespread contaminants it would certainly be worth while to carry out extensive research in suitable organisms so as to obtain preliminary indications of the possible effects in man.

### 5.5 Gonad temperature and mutation rate

Some time before the discovery of the mutagenic action of radiation, pioneer studies by Muller had already shown that the natural mutation rate in *Drosophila* can be considerably increased by raising the temperature. These changes are most easily understood as energy fluctuations in the molecular configuration of the genes. According to Timoféeff-Ressovsky and Zimmer the temperature coefficient ( $Q_{10}$ ) of the mutation frequency in *Drosophila* is 6.5.

It is not known what role temperature may play in the origin of spontaneous mutations in man. Since, however, not more than a small fraction of the spontaneous mutations arising in man can be due to natural background radiation, the greatest proportion of such mutations must originate from either energy fluctuations or the production of mutagenic chemicals in normal cell metabolism. Consequently, changes of the gonad temperature brought about by environmental conditions, such as clothing and hot baths, may deserve consideration.

To investigate the possibility of whether clothing habits in man raise the gonad temperature in males, Ehrenberg, von Ehrenstein and Hedgran undertook a number of measurements. Their investigation showed that the mean scrotal temperature was 34.0°C in males clothed in European dress and 30.7°C in unclothed males. The temperature difference in the testis itself may, of course, be much smaller. If a  $Q_{10}$  of 6.5 is also valid for man, the observed difference of  $3.3 \pm 0.4^\circ\text{C}$  could be interpreted as corresponding to an increase of 85% in the mutation rate in males.

In this context it should be pointed out, however, that no experimental evidence is available to indicate that the effect of temperature on the mutation rate of *Drosophila* may be extrapolated to a warm-blooded species like man.

### 5.6 General remarks

From the foregoing it is clear that much further research is required before it will be possible to assess the genetic hazards due to mutagenic chemicals and temperature. One may hope that the specific locus studies that have yielded such significant results in the case of radiation will be expanded to include the effects of certain chemicals. Since mutation research in the mouse requires large numbers of animals it is expensive and can be carried out only in adequately equipped laboratories. It might therefore be useful to start simply by using recessive lethals in *Drosophila*. *Drosophila* still offers unrivalled opportunities for the study of mutation, and of the effects of various factors, such as oxygen and metabolic disturbances, on the mutation process.

In view of the risk associated with chromosome aberrations and aneuploid karyotypes in man, it seems of importance to study a number of chemicals for their ability to produce chromosome aberrations in human cells cultured *in vitro*. Even more valuable would be a system that would make it possible to study point mutations at the cellular level.

Since our present knowledge of the mutagenicity of chemicals in man is still so deficient, a quantitative evaluation of the potential genetic hazards as compared to those produced by radiations is impossible. In developing standards for protection against chemical pollutants in industry and the environment, however, the possibility of genetic hazards should certainly be taken into consideration.

## 6. SHORTENING OF LIFE-SPAN AND THE PROBLEM OF AGING

Animals exposed to radiation may show a reduction of life-span. This seems to be due not only to an increased incidence of such diseases as are known to be induced by radiation in the species under investigation, but also to an earlier incidence of all other causes of death. The age-specific death-rates in the irradiated populations are similar to those prevailing in control population at a later age. Both the overall shortening of life-span and the earlier occurrence of deaths appear to be quantitatively related to the cumulative dose of radiation received. However a number of animal experiments where low doses of radiation were given have shown a decreased rate of mortality in early and middle life but no evidence of greater longevity, perhaps owing to some effect that conditions the animals against infectious disease.

It has been thought that the effect of radiation on life-span might be caused by damage to the cellular genetic material. Some support for this hypothesis has been obtained recently from experiments with fruit

flies carrying chromosomes likely to be lost when broken ; these showed that such flies, when irradiated or treated with chemical mutagens, have a shorter life-span than similarly treated normal flies. Offspring of irradiated male mice have shown a decreased life expectancy.

The question is whether irradiation produces similar effects in man. Studies carried out on American and British radiologists have failed to show evidence that this is the case, although the incidence of malignancies is known to be raised. This was particularly true amongst the early radiologists. There is not yet any evidence either that the overall life-span of survivors of the explosions in Hiroshima and Nagasaki has been appreciably reduced. Before ruling out the possibility of an effect on life-span, however, investigations on larger exposed populations than radiologists should be carried out, and the survivor populations in Hiroshima and Nagasaki must be followed up for a longer time.

The experimental observation that radiation shortens the life-span and produces a mortality pattern characteristic of older age prompted the hypothesis that radiation accelerates the aging of exposed individuals. Unfortunately, the concepts of aging and of physiological age, although in common use, are extremely difficult to study, owing to the present lack of objective criteria to define them. There is some scanty experimental evidence, however, that such pathological phenomena as are known to be associated with aging (e.g., arteriolo-capillary alterations) occur earlier in irradiated animals. Such alterations have also been observed in men chronically poisoned with lead or with carbon bisulfide who sometimes show signs of premature aging. While it seems too early to make first statements on the aging effects of either radiation or other toxic materials, it is clear that, if such effects occur, they might be extremely important. More refined methods for studying this problem and their use on a statistically adequate basis seem to be highly desirable.

It will be appreciated, however, that this study must be seen against a background of medical progress that is resulting in an increasing life expectancy (see Table 4). This increase obviously outweighs any reduction that is likely to be caused by the agents that have been considered in this report.

## 7. SUMMARY

Consideration of radiation hazards in relation to other risks should be of value to health authorities in various countries in developing a balanced perspective. The Committee was concerned particularly with a group of chemical and physical agents, including ionizing radiation, which appear to require a special examination of this type both because of their recent introduction or increasing use and because decisions on the exposure of the individual and the population should depend on exact

knowledge regarding the nature and frequency of the effect produced by each.

Concerning both radiological and toxicological exposures, severe damage and death have followed *high-level exposures*. Many more early injuries have been described as resulting from a variety of toxic agents than from radiation. It is probable that this is due to more elaborate measures taken to protect workers against radiations hazards—even if correction is made for the numbers of persons at risk. This is true for both mortality and morbidity. The Committee attempted to subject these questions to a quantitative examination by referring to actual experiences in industrial practice and conditions existing in man's environment.

Exposure to *low doses* of radiation is generally regarded as resulting in hereditary effects, and possibly also cancer and leukaemia. In the case of toxic substances, mutagenic effects have hardly been investigated; cancer and leukaemia have been observed after long exposures, but the risk has been even less well estimated than for radiation. Instead, attention has tended to be focussed on more obvious forms of injury. The methods currently used in toxicology would hardly have revealed certain of the hazards of radiation that are now well recognized and considered to be of great importance.

There is a wide gap between the exposure levels resulting in consistent or unequivocally determined toxicological changes in organs, and the natural levels of certain toxic agents in the environment. In the case of radiation exposures, cancer, leukaemia, and genetic effects are presumed to occur in small proportions of individuals exposed to levels below those that regularly cause early pathological effects, and there is some reason to believe that there is no threshold dose for genetically determined changes. It should, however, be stressed that mutations due to the natural background radiation can only represent a small fraction of the total number of spontaneous mutations.

The Committee recognized that risks are an unavoidable accompaniment of developments in medicine and technology that bring comfort, security and prolongation of life. No sense of discouragement should be felt from the emphasis given in this report to hazards—not only the hazards of radiation, which have been widely discussed in recent years, but those of a similar nature that may ensue from exposure to toxic agents, the less subtle actions of which have for a long time been familiar. Human life has always involved efforts to estimate and compare risks, and to balance hazards against good to be gained. Drugs that save very large numbers of lives can, under certain circumstances, cause injury or death. In the same way, ionizing radiation used in therapy or diagnosis may occasionally lead to injury or malignant change. This idea of balance is essential to any attempt to visualize the hazards of radiation and of toxic materials in perspective.

## 8. RECOMMENDATIONS

A large section of the public finds difficulty in comprehending the nature of nuclear energy and of radiation hazards; this has tended to create not only anxiety but a sort of mysticism concerning these hazards. While attempting to view radiation hazards in perspective in relation to other hazards, the Committee desires to stress the importance of health education programmes in this field.

The Committee notes that protection procedures have been developed to a much greater extent against radiation hazards than against other toxic agents. The Committee therefore recommends that studies be undertaken to establish criteria for safe exposure levels to these agents, both for individuals (as in the case of occupational exposure) and for populations (as in the case of pollution of water, food and air). The Committee takes note that there are a number of established groups now working in this field, and recommends that WHO continue to encourage such efforts at the national level, and stimulate and co-ordinate them at the international level. The Committee also considers that such protection programmes should be encouraged to develop in the light of knowledge and experience gained in the field of radiation protection.

There are various lines of evidence suggesting that certain chemical agents may have deleterious somatic and genetic effects similar to those produced by ionizing radiation. Many of these chemical agents have so far received little attention, and the Committee recommends that investigations in this field be encouraged. Some of these studies will have to be very detailed and involve large numbers of test organisms if they are to provide statistically valid results. Priority should therefore be given to those chemical agents most widespread in man's environment that are thought to be toxic or possibly carcinogenic or mutagenic. The Committee would therefore recommend that international standards of statistical reporting of effects, damage, disability and death due to toxic materials be improved and their use extended to facilitate international comparison; epidemiological and genetic studies of the effects of toxic materials similar to those carried out in the radiation field be promoted; and intensive research be stimulated on the mechanism of action of these materials, including their carcinogenic and genetic effects.

---

**WORLD HEALTH ORGANIZATION  
TECHNICAL REPORT SERIES**

<i>Recent reports :</i>	Price		
	s.d.	\$	Sw. fr.
No.			
191	<b>(1960) Insecticide Resistance and Vector Control</b>		
	Tenth report of the Expert Committee on Insecticides (98 pages) . . . . .		
	5/-	1.00	3.—
192	<b>(1960) Epidemiology of Cancer of the Lung</b>		
	Report of a study group (13 pages) . . . . .		
	1/9	0.30	1.—
193	<b>(1960) Teacher Preparation for Health Education</b>		
	Report of a Joint WHO/UNESCO Expert Committee (19 pages) . . . . .		
	1/9	0.30	1.—
194	<b>(1960) Local Health Service</b>		
	Third report of the Expert Committee on Public Health Administration (49 pages) . . . . .		
	3/6	0.60	2.—
195	<b>(1960) Expert Committee on Tuberculosis</b>		
	Seventh report (19 pages) . . . . .		
	1/9	0.30	1.—
196	<b>(1960) Medical Supervision in Radiation Work</b>		
	Second report of the Expert Committee on Radiation (31 pages) . . . . .		
	1/9	0.30	1.—
197	<b>(1960) Joint FAO/WHO Expert Committee on Milk Hygiene</b>		
	Second report (55 pages) . . . . .		
	3/6	0.60	2.—
198	<b>(1960) European Technical Conference on the Control of Infectious Diseases through Vaccination Programmes</b>		
	Report (21 pages) . . . . .		
	1/9	0.30	1.—
199	<b>(1960) Post-Basic Nursing Education Programmes for Foreign Students</b>		
	Report of a Conference (47 pages) . . . . .		
	3/6	0.60	2.—
200	<b>(1960) Requirements for Biological Substances.</b>		
	6. General requirements for sterility Report of a Study Group (31 pages) . . . . .		
	1/9	0.30	1.—
201	<b>(1960) Expert Committee on Rabies</b>		
	Fourth report (28 pages) . . . . .		
	1/9	0.30	1.—
202	<b>(1960) Chagas' Disease</b>		
	Report of a Study Group (21 pages) . . . . .		
	1/9	0.30	1.—
203	<b>(1961) Expert Committee on Poliomyelitis</b>		
	Third report (53 pages) . . . . .		
	3/6	0.60	2.—
204	<b>(1960) Second African Conference on Bilharziasis (WHO/ CCTA)</b>		
	Report (37 pages) . . . . .		
	1/9	0.30	1.—
205	<b>(1961) Expert Committee on Malaria</b>		
	Eighth report (50 pages) . . . . .		
	3/6	0.60	2.—
206	<b>(1961) Aircraft Disinsection</b>		
	Eleventh report of the Expert Committee on Insecticides (26 pages) . . . . .		
	1/9	0.30	1.—
207	<b>(1961) Periodontal Disease</b>		
	Report of an Expert Committee on Dental Health (42 pages)		
	3/6	0.60	2.—
208	<b>(1961) The Undergraduate Teaching of Psychiatry and Mental Health Promotion</b>		
	Ninth report of the Expert Committee on Mental Health (36 pages) . . . . .		
	1/9	0.30	1.—

No.		Price		
		s.d.	\$	Sw. fr.
209	<b>(1961) The Teaching of the Basic Medical Sciences in the Light of Modern Medicine</b> Eighth report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel (31 pages) . . . . .	1/9	0.30	1.—
210	<b>(1961) Standardization of Methods for Conducting Microbic Sensitivity Tests</b> Second report of the Expert Committee on Antibiotics (23 pages) . . . . .	1/9	0.30	1.—
211	<b>(1961) Expert Committee on Addiction-Producing Drugs</b> Eleventh report (16 pages) . . . . .	1/9	0.30	1.—
212	<b>(1961) The Use and Training of Auxiliary Personnel in Medicine, Nursing, Midwifery and Sanitation</b> Ninth report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel (26 pages) . . . . .	1/9	0.30	1.—
213	<b>(1961) Chronic Cor Pulmonale</b> Report of an Expert Committee (35 pages) . . . . .	1/9	0.30	1.—
214	<b>(1961) Molluscicides</b> Second report of the Expert Committee on Bilharziasis (50 pages) . . . . .	3/6	0.60	2.—
215	<b>(1961) Planning of Public Health Services</b> Fourth report of the Expert Committee on Public Health Administration (48 pages) . . . . .	3/6	0.60	2.—
216	<b>(1961) Recommended Requirements for Schools of Public Health</b> Tenth report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel (24 pages) . . . . .	1/9	0.30	1.—
217	<b>(1961) Public Health Aspects of Low Birth Weight</b> Third report of the Expert Committee on Maternal and Child Health (16 pages) . . . . .	1/9	0.30	1.—
218	<b>(1961) Expert Committee on Health Statistics</b> Seventh report (28 pages) . . . . .	1/9	0.30	1.—
219	<b>(1961) Arthropod-Borne Viruses</b> Report of a Study Group (68 pages) . . . . .	5/-	1.00	3.—
220	<b>(1961) Evaluation of the Carcinogenic Hazards of Food Additives</b> Fifth report of the Joint FAO/WHO Expert Committee on Food Additives (33 pages) . . . . .	3/6	0.60	2.—
221	<b>(1961) Scientific Meeting on Rehabilitation in Leprosy</b> Report (37 pages) . . . . .	3/6	0.60	2.—
222	<b>(1961) Expert Committee on Biological Standardization</b> Fourteenth report (54 pages) . . . . .	3/6	0.60	2.—
223	<b>(1961) Programme Development in the Mental Health Field</b> Tenth report of the Expert Committee on Mental Health (55 pages) . . . . .	3/6	0.60	2.—
224	<b>(1961) Joint ILO/WHO Committee on the Hygiene of Seafarers</b> Third report (14 pages) . . . . .	1/9	0.30	1.—
225	<b>(1961) Expert Committee on the Public Health Aspects of Housing</b> First report (60 pages) . . . . .	3/6	0.60	2.—

No.		Price		
		s.d.	\$	Sw. fr.
226	<b>(1961) Chemotherapy of Malaria</b> Report of a Technical Meeting (92 pages) . . . . .	5/-	1.00	3.—
227	<b>(1962) Toxic Hazards of Pesticides to Man</b> Twelfth report of the Expert Committee on Insecticides (32 pages) . . . . .	1/9	0.30	1.—
228	<b>(1962) Evaluation of the Toxicity of a Number of Antimicro- bials and Anti-oxidants</b> Sixth report of the Joint FAO/WHO Expert Committee on Food Additives (104 pages) . . . . .	6/8	1.25	4.—
229	<b>(1962) Expert Committee on Addiction-Producing Drugs</b> Twelfth report (16 pages) . . . . .	1/9	0.30	1.—
230	<b>(1962) Calcium Requirements</b> Report of an FAO/WHO Expert Group (54 pages) . . . . .	3/6	0.60	2.—
231	<b>(1962) Arterial Hypertension and Ischaemic Heart Disease — Preventive Aspects</b> Report of an Expert Committee (28 pages) . . . . .	1/9	0.30	1.—
232	<b>(1962) Chemotherapy of Cancer</b> First report of an Expert Committee (52 pages) . . . . .	3/6	0.60	2.—
233	<b>(1962) Expert Committee on Filariasis (<i>Wuchereria</i> and <i>Brugia</i> Infections)</b> Report (49 pages) . . . . .	3/6	0.60	2.—
234	<b>(1962) Expert Committee on Trachoma</b> Third report (48 pages) . . . . .	3/6	0.60	2.—
235	<b>(1962) The Role of Public Health Officers and General Practitioners in Mental Health Care</b> Eleventh report of the Expert Committee on Mental Health (54 pages) . . . . .	3/6	0.60	2.—
236	<b>(1962) Planning, Organization and Administration of a National Health Laboratory Service</b> Third report of the Expert Committee on Health Laboratory Services (46 pages) . . . . .	3/6	0.60	2.—
237	<b>(1962) Requirements for Biological Substances</b> <b>7. Requirements for Poliomyelitis Vaccine (Oral)</b> Report of a Study Group (29 pages) . . . . .	1/9	0.30	1.—
238	<b>(1962) The Teaching of Genetics in the Undergraduate Medical Curriculum and in Postgraduate Training</b> First report of the Expert Committee on Human Genetics (19 pages) . . . . .	1/9	0.30	1.—
239	<b>(1962) Internationally Acceptable Minimum Standards of Medical Education</b> Report of a Study Group (59 pages) . . . . .	3/6	0.60	2.—
240	<b>(1962) Principles Governing Consumer Safety in relation to Pesticide Residues</b> Report of a meeting of a WHO Expert Committee on Pesticide Residues held jointly with the FAO Panel of Experts on the Use of Pesticides in Agriculture (18 pages) . . . . .	1/9	0.30	1.—
241	<b>(1962) Joint FAO/WHO Expert Committee on Meat Hygiene</b> Second report (87 pages) . . . . .	5/-	1.00	3.—
242	<b>(1962) Standardization of Reporting of Dental Diseases and Conditions</b> Report of an Expert Committee on Dental Health (23 pages) . . . . .	1/9	0.30	1.—
243	<b>(1962) Expert Committee on Malaria</b> Ninth report (43 pages) . . . . .	3/6	0.60	2.—