



WORLD HEALTH ORGANIZATION
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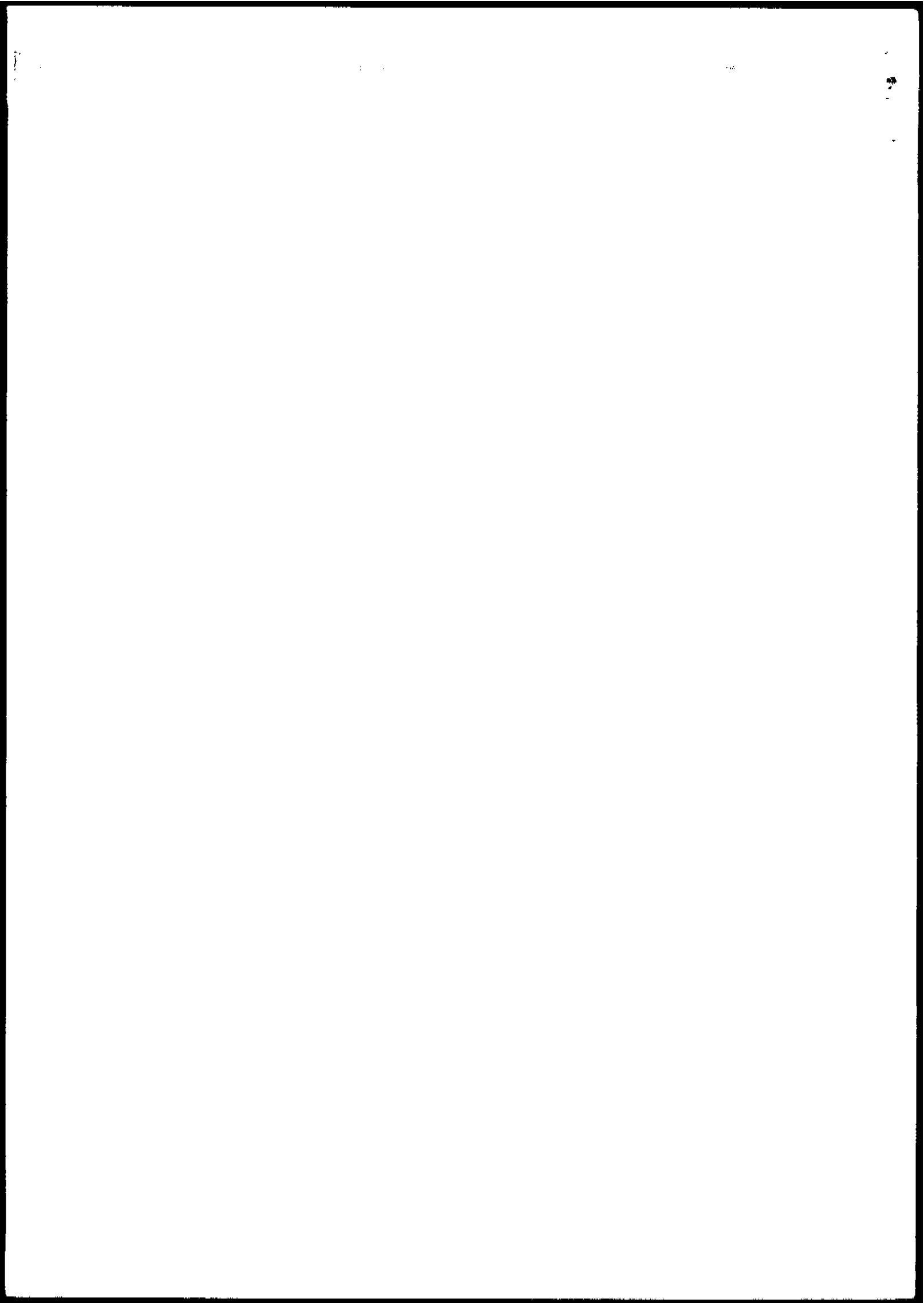
Report of a Scientific Meeting
on
Perspectives for
Immunological and Neurobiological Research
in Aging

Geneva
13-16 May 1985



IRP/HEE 114 s23
ENGLISH ONLY
Unedited

Copenhagen
September 1986

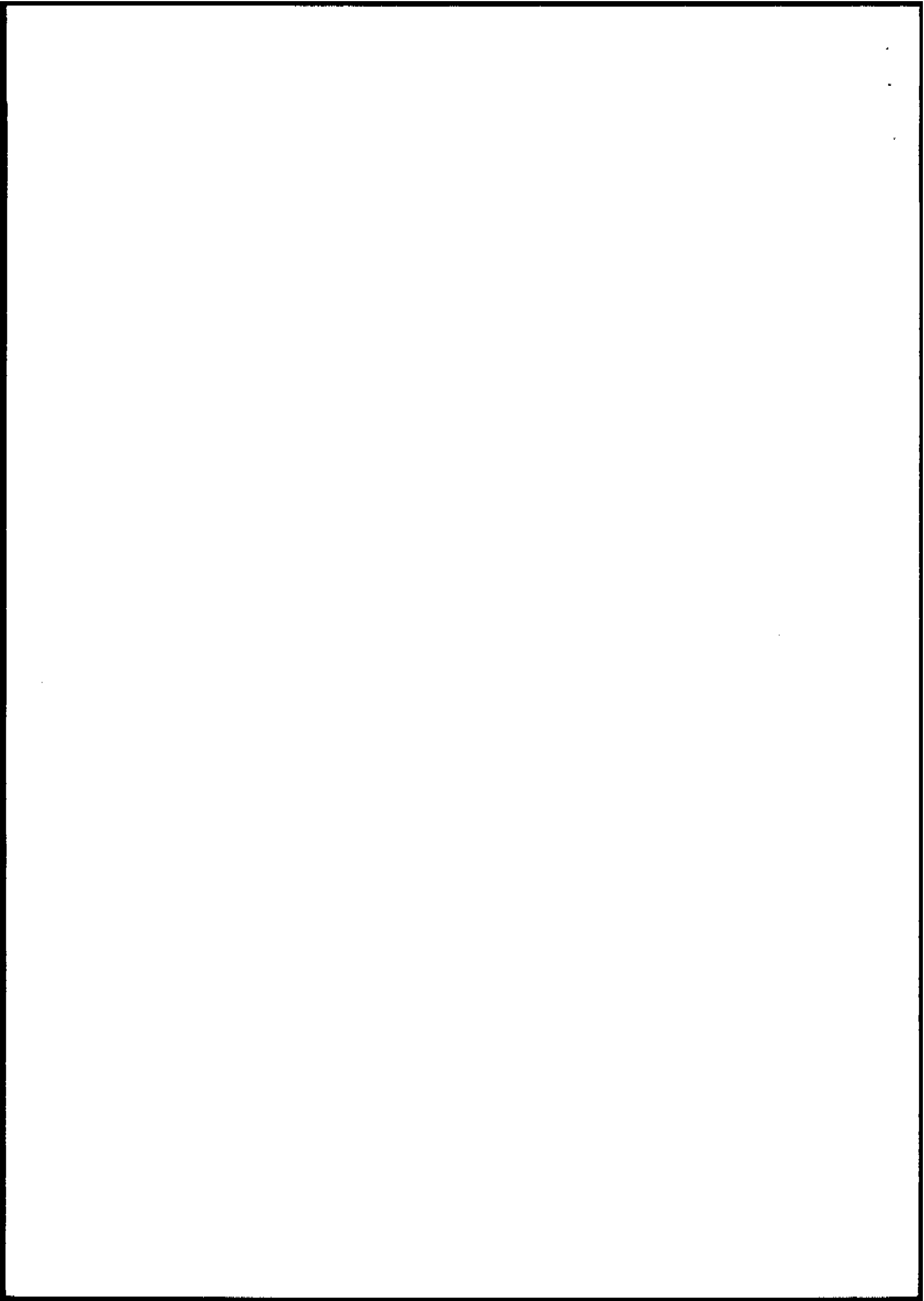


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1 Introduction

1.1 The World's Elderly: A Population Exploding

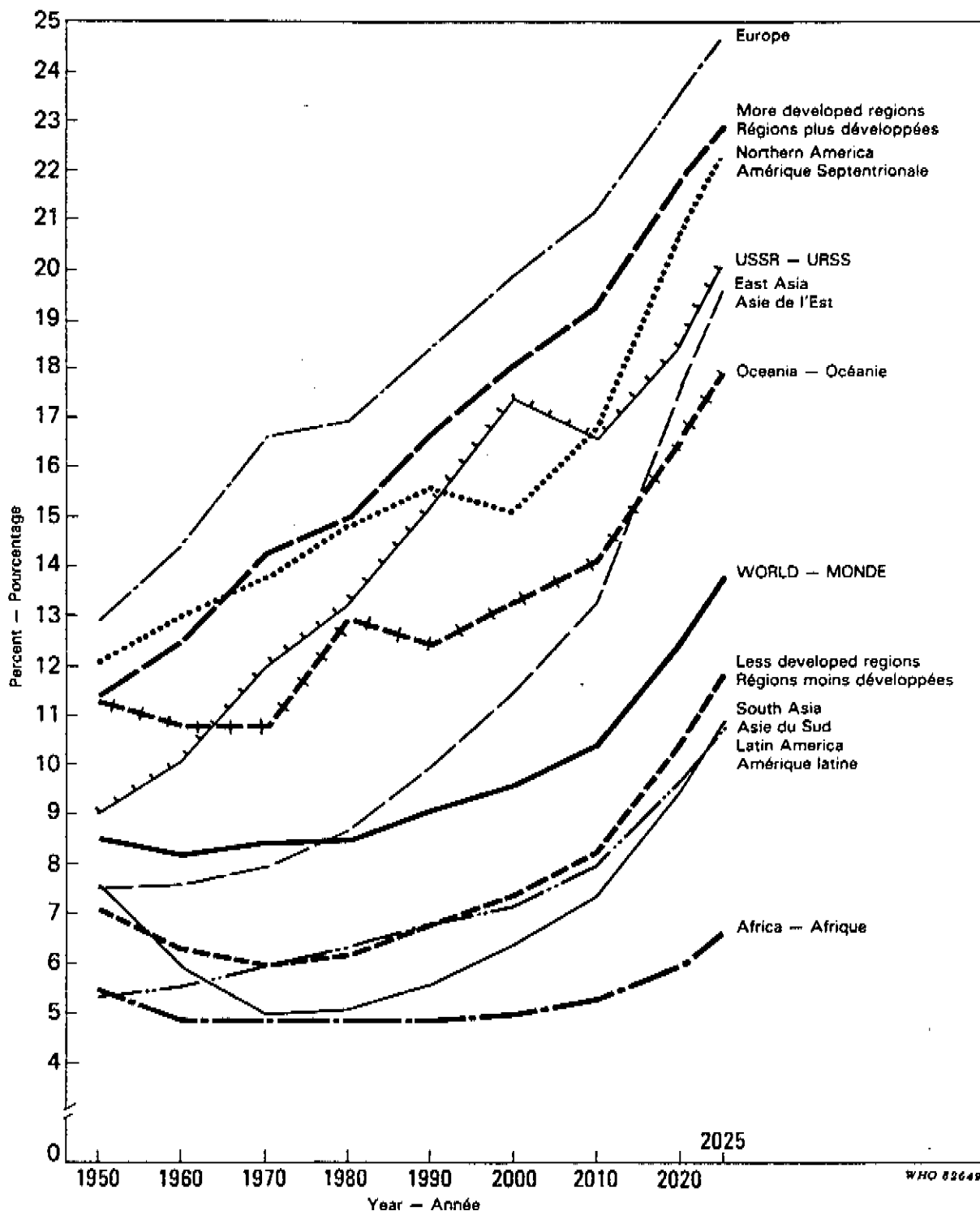
Since the beginning of this century, the industrialized nations have witnessed a remarkable increase in the number of people over 65 years of age. Today, persons over 65 in these countries constitute at least 10-12% of the population while the segment of the population over 75 years of age is expanding most rapidly. A number of factors have contributed to this increase in older individuals: decreasing birth rate, improved sanitation, diminished infant mortality, better nutrition, and advances in medical care. These events have altered the balances between young and old in society resulting in an increase in the average age of the population.

Fig 1 The spectrum of disease has also changed dramatically. Acute diseases that at the turn of the century caused the majority of deaths have given way to chronic disabling and debilitating diseases which demand extraordinary medical and social resources. The cost of caring for the elderly now threatens economic advance in many countries.

Fig 2 The health problems of the elderly are not confined to industrialized nations. It is now clear that the advances in medical technology now being applied throughout the world will produce an increasing number of elderly in all countries. In fact, the rate of change with respect to numbers of elderly persons will be far greater in the coming years in the economically less developed nations than in the economically developed nations. Thus, the

FIGURE 1

PERCENTAGE OF THE TOTAL POPULATION 60 YEARS AND OVER, FOR REGIONS: 1950 TO 2025
POURCENTAGE DE POPULATION DE 60 ANS ET PLUS, PAR RÉGION: 1950 À 2025

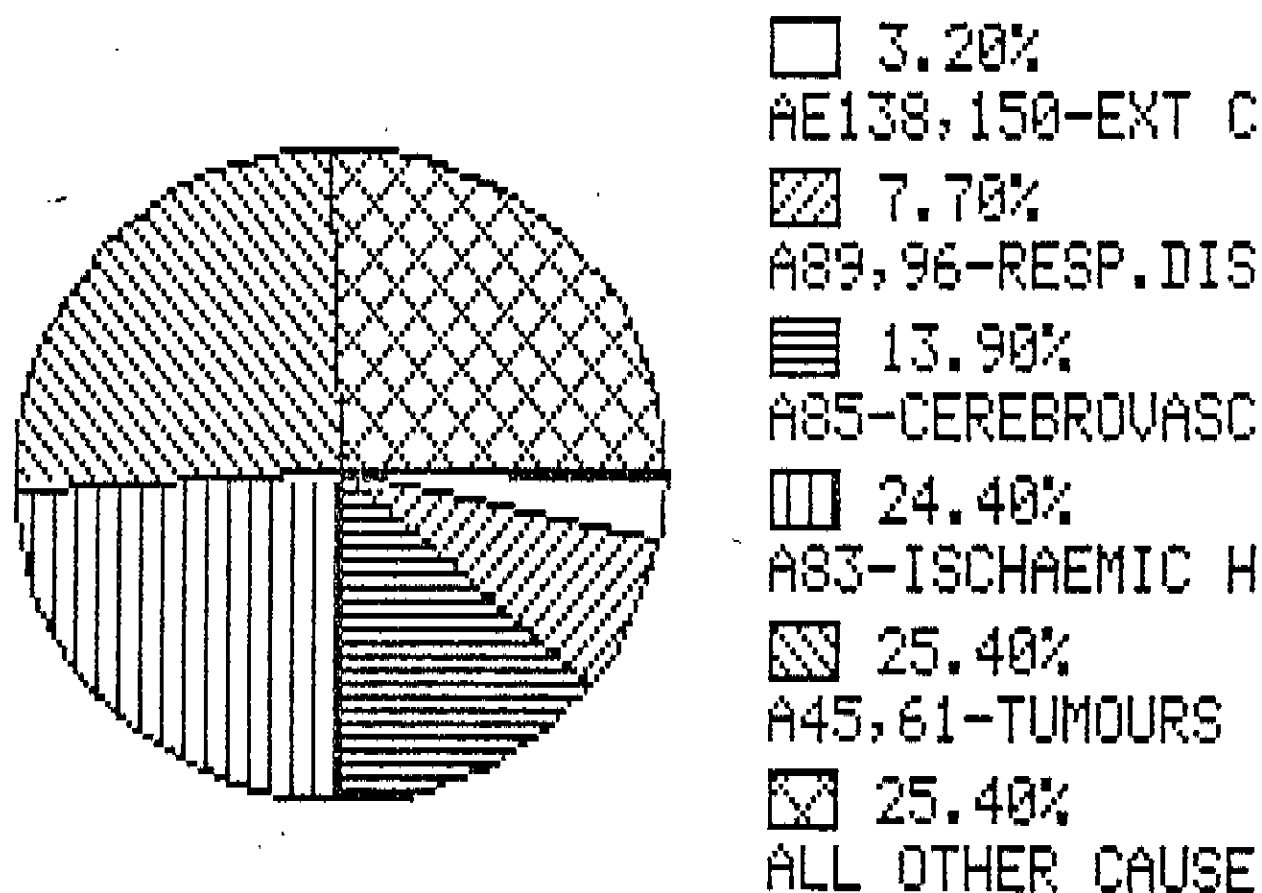


WHO 82649

Source: World Health Statistics Quarterly, Vol.35, 3/4 1982, p.196

FIGURE 2

DEATHS 65-74 29 COUNTRIES
DISTRIBUTED BY ICD CODE



average lifespan which has increased 50% in the past 80 years in industrialized states, has doubled in less than 40 years in some developing countries such as India and China.

By the year 2000 and beyond, the developing countries will have more dependent elderly in terms of absolute number than the developed countries. Although, at present the bulk of elderly people in developing countries may still be taken care of by their children or grandchildren, it is to be feared that industrialization and changing social and economic conditions might cause similar, if not even more acute, problems than those already burdening the economies of the populations in developed countries. The consequences of these changes will be severe economic strain as the resources needed for economic development are directed toward sustaining the quality of life for an increasing number of elderly citizens. The so-called blessing of longer life will become a burden to the elderly and to society if healthspan does not grow as rapidly as lifespan.

1.2 Ageing Research: A Timely Opportunity and a Socio-economic Necessity

Fig 3

The purpose of the WHO initiative in Gerontology is to plan concerted action to increase our understanding of the aging process and its influence on diseases which threaten the health and well being of the elderly population. Certain diseases, such as cardiovascular and neurovascular disease and cancer, are already seen as major problems in the health of the population. Such diseases, as Alzheimer's disease, osteoporosis and recurrent

FIGURE 3

Growth of the very old population



Source: Health Policy Aspects of Aging: Report of World Health Organization, United Nations, 1982, A/Conf. 113/19 p.30

chronic infectious disease, are just now being recognized as further major threats. There is the unpleasant prospect that the quality of life enjoyed by many persons will decline as a longer life span is achieved. Furthermore, the costs of care for the elderly may severely compromise economic advance as measured in terms of the standard of living of the population as a whole. It is clear that the world wide increase in the number of the elderly warrants international concern. Toward this end, it is recommended that the WHO programme in aging serve as the focus for new international health initiatives.

In developed countries, the advent of focused measures in research on aging has come too late for preventive programmes to be applied at the early stages of the demographic shift in age distribution. Developing countries however, which at present are aiming to increase the lifespan of their citizens, may be able to deal with the shift in an earlier stage of development. To this end we must establish policies for health care and for preventive medicine of age related diseases. We cannot afford to wait until the aging problem reaches crisis proportions before initiating international research efforts. The potential economic and social impact of such research may represent the best and most cost effective means of preparing for the future, and providing directions for a better quality of life with reduced chronic and debilitating illness for the elderly. Indeed, prevention appears to be the only approach able to lower the enormous economic burden of the cost of geriatric medicine. There

are many precedents in medical research (such as immunization against poliomyelitis instead of developing improved models of iron lungs, and prevention of renal dysfunction instead of more and better dialysis machines) in which preventive measures proved to be much more cost effective than therapeutic means. Some immediately practicable initiatives, such as optimization of vaccinations for the elderly, may bear sizeable fruits within the next decade; however it must be stressed that major advances in the prevention of age-related diseases can only be expected from the application of basic research to this complex problem.

Support for research on aging provides a unique opportunity for global efforts toward the identification of specific problems in different societies. The elucidation of mechanisms underlying the aging process and the rapid communication and application of scientific information to practical purposes will yield important benefits to mankind.

1.3 Aging: A Complex Phenomenon

Age-related physiological changes affect most cells, tissues and organs, although not to the same extent, at the same time, or at the same rate. These alterations however result in the loss of adaptability which makes the elderly more susceptible to a variety of diseases. In short, old age is a composite of different individual manifestations. Some of these may be due to diseases that are more easily contracted and more severe in the elderly and others are due to alterations in cells and tissues that are attributable to "normal aging" without overt

pathological manifestations. It is not known how or to what extent these two processes interact with one another. Take for example the appearance of a carcinoma in a 60 year old. Did it take 60 years for the carcinoma to develop, or did physiological "aging" changes in the individual allow a carcinoma to develop at that time? We need to know (1) what alterations in cells, tissues, organs and systems are due to a failure to maintain functional integrity as time passes, and might be considered as "normal" aging and (2) what are the cumulative deteriorations secondarily caused by diseases.

The first achievements of scientific medicine were based on the specific etiology concept of disease, perhaps best illustrated by the success of vaccination in the control of infectious diseases. This single cause approach also provides the definition of a disease entity itself. We would suggest that, in this context, aging is not an adequately defined entity and the search for a unique central biochemical or cellular reaction responsible for senescence is a pursuit of folly. In fact, there is every indication that aging occurs in different cell types at different rates. Thus, aging should be analyzed as a multicentric progression which shows considerable individual differences. It is highly polymorphic and should be viewed as a temporal component of lifelong processes of continuous differentiation.

Multicentric and individually different control mechanisms regulate cellular systems which retain the capacity for self-renewal as well as systems of cells that are established early

in life and cannot be replaced. Health and survival are the outcome of an interplay between environmental stimuli and the inherited individual controls which affect the function and capacity of cells, tissues, and organs. Detailed knowledge of inherited controls, identification of relevant genes and consequent identification of populations at risk from particular organ failures and stress are an important goal of this proposal. One could expect that some genes which code for deleterious products manifest themselves late in life, possibly as a consequence of natural selection against those genes being transcribed early in life. Senescence should be seen as resulting from age-related events which have most profound consequences on the capacity of a cell line or of an organ to adapt to environmental stress. Failure to adapt may entail degenerative diseases of old age and may be responsible for high tumor incidence and central nervous system deterioration. Evaluation of these multicentric controls can be achieved by studying inbred animals of relatively short lifespan and by identifying groups of changes which seem to occur at the same rate. On this basis, corresponding human changes can be readily identified and analyzed.

1.4 Aging Research in Immunology and Neurobiology: A Special Challenge

We have chosen, in the first instance, to study age-related changes in the immune and neurobiological systems, in receptors, factors and hormone production and in the response of cells to these vehicles of biological communication.

The immune and neural systems are very important targets for assessment in gerontology and geriatrics in that they (a) have the major task of monitoring the environment and "self", (b) possess persisting homeostasis when subjected to potentially harmful stimuli; and (c) may become suitable targets for preventive or therapeutic intervention.

Immunologic dysregulation commonly observed in the elderly is associated with the emergence of several diseases; however the cause-and-effect relationship between immunologic changes and some specific illness is not yet firmly established. Studies of the immune system can yield important information on the process of aging in general. Because of the close linkage with neuroendocrine and other systems, the results achieved with these studies will have wide implications. Immunologic assays can give information at the chromosomal, subcellular, tissue and organ levels as well as for the whole organism. From a practical point of view, the ready accessibility of serum and immunocompetent cells makes the immune system relatively easy to monitor. For these reasons, recent work has led to detailed characterization of functional, genetic and molecular markers, of both murine and human cells involved in immunologic processes. These basic data provide a useful base on which to plan immunologic studies in aging and in the management and prevention of age-related disease.

Research initiatives with immediate practical value would be aimed at protection of the elderly from various infectious diseases, in particular influenza and pneumococcal pneumonia.

Protection of individuals from infectious diseases by immunization has been the greatest contribution of immunology in public health. This strategy, developed by Jenner for smallpox almost 200 years ago, has been applied throughout the world by WHO and has led to the elimination of smallpox. In this century, useful vaccines have been developed for the viral diseases, mumps, measles, polio influenza, Rubella as well as bacterial disease caused by diphtheria, tetanus and the pneumococcus. The development of new vaccines are underway for the protection of humans from hepatitis, herpes and other viral diseases as well as from malaria and other parasitic diseases. Many of these advances have already contributed to improved health in children but have had less impact on the health of the elderly. This may be due, in part, to the age-related immunologic dysregulation which must be overcome. Therefore, it is suggested that there is a need to systematically study the effects and possible benefits of concomittant immunologic manipulations and immunization of the elderly. Reasons for promoting close parallel studies in neurobiology and neuroimmunobiology are equally compelling.

The dimension of the health problems posed by age-related changes in the central nervous system is vast. Basic research into the neurobiology of aging as a route to resolving these problems has been demonstrably successful in advancing knowledge of the human brain and providing the first real insights into some of the more complex neurological disorders. The treatment of Parkinson's disease patients with L-DOPA to replace the loss

of a vital brain chemical, dopamine, and the discovery of the enkephalins and endorphins- the brain's own "opiate" drugs are important examples. The finding that Alzheimer disease involves specific deficits of neurotransmitters is a further example of ongoing advances in this field.

Research findings during recent years have made it possible to start formulating a coherent scientific basis for the pathogenesis of some degenerative disorders of the ageing brain and to identify promising scientific opportunities that are ready to be exploited. It is now possible to propose verifiable hypotheses that provide a framework for interrelating the observations reported by scientists working in this area of research. Recent evidence indicates that studies concerning the interactions between stress, the immune system, neuroendocrine factors and neural functions might provide unusual scientific opportunities for research leading to practical applications in geriatric medicine.

Despite the compelling socio-economic pressures for advances in the preventive aspects of gerontology, this research has not been adequately supported. The reasons for this are related to several unique problems associated with aging research, which are:

- (a) The aging process and its effects on health and the development of age-related disease is a multifaceted phenomenon, requiring a complex interdisciplinary approach.
- (b) Prospective and long-term longitudinal studies carried out under well-defined and standardized conditions are the major tools

by which questions pertaining to the identification of factors influencing age related diseases and the possibilities to prevent them may ultimately be answered. Such studies require careful planning and long term commitment, as well as measures to maintain the scientific quality and manpower during the course of the investigation. Such studies are obviously beyond the scope of a single investigator and will usually not be supported by the classical research funding mechanisms through investigator initiated individual grants of limited duration.

(c) Since nutritional, socio-economic and genetic factors markedly influence health and longevity, comparative studies in various parts of the world using comparable scientific criteria are needed for the evaluation of regional differences and to study the effects of intervention or therapy.

(d) International coordination of multidisciplinary aging research is needed for results which can form the basis of effective health care policies. To do this it is necessary to establish a coordinating body under WHO sponsorship. This body should be provided with the financial means to ensure standardization and coordination of research protocols to provide joint evaluation of study results and to directly support projects in those parts of the world where other support for research projects is not available.

(e) In addition to financial support for international cooperation, there is an increasing need for grant support of aging research at the national level. In many countries this support is not at

a level commensurate with the socio-economic size of the problem or the potential for practical applications.

2 Decline in Immune Function with Age

There are well documented age related patterns of illness and a general appreciation of those diseases which have an increased incidence, morbidity and mortality with age. Strong arguments can be made for a central causative role of an age related immunodeficiency in the pathogenesis of infectious diseases and in the serious consequences of these diseases in the elderly. A less compelling but equally interesting hypothesis can be proposed to link immunodeficiency with the increased incidence of malignant tumours seen with age. Furthermore, the immune system forms a buffer between the individual and his environment and it is logical to assume that dysequilibrium will result with the failure of this important buffer system. The results of that dysequilibrium may manifest themselves in many forms. The changes in human immune function with ageing are many. Those in which there is general agreement amongst the various laboratories are:

1. Decreased numbers of peripheral blood lymphocytes occurring during a 3 year period prior to death.
2. Decreased T-cell DNA synthesis in response to mitogenic stimulation.
3. Decreased helper T-cell activity.
4. Decreased levels of specific antibody such as anti-tetanus toxoid.
5. Increased diversity and number of autoantibodies.

6. No change in numbers of peripheral blood B cells.
7. Increased incidence of homogeneous monoclonal immunoproteins.
8. Decreased heterogeneity of the antibody response and decreased specificity of the antibody molecules produced.
9. No change in NK cell function.
10. Increased production of anti-idiotypic antibodies.
11. Decreased numbers of circulating suppressor T-cells.
12. Increased numbers of autorosette-forming cells.
13. No clinically significant change in serum immunoglobulin levels.
14. Enhanced cellular sensitivity to prostaglandin E₂.
15. Diminished intracellular synthesis of mediators such as interleukin 2 (IL-2, formerly T-cell growth factor, or TCGF).
16. Diminished in vivo delayed hypersensitivity

The studies of human immune function have been approached from two standpoints, cross-sectional and longitudinal studies. The results of both approaches are complementary and it is important to have interaction between them.

In cross-sectional studies efforts have been directed towards determination of age-related differences which are not the result of associated disease. These studies have highlighted the problems of subject selection. In an attempt to solve this problem, the SENIEUR protocol was developed by a working party within the framework of the EURAGE Concerted Action Programme on Aging of the European Community. The usefulness of this approach for subject selection has already been validated in several studies in individual research groups, but problems still exist at the level of

laboratory investigation. For example, there are no generally agreed parameters for the assessment of humoral or cellular immune function. There is an urgent need for identification and validation of standardized assay systems to be used by all participating groups of investigators.

Longitudinal studies provide opportunities both for cross sectional and for long-term data analysis. As such they are able to provide data on the underlying physiological changes which can be the cause of age-related diseases. These studies allow a multidisciplinary approach to the study of aging and become more cost effective when so structured.

Model systems based on inbred mammals need to be developed in order to determine the controls which influence the rate and incidence of these changes and the methods for arresting them. The ultimate goal of the gerontologist is to contribute to the quality of life of the elderly human. This involves long-term studies, which can be partly replaced by studies in animals, especially rodents. Close contacts between experimental and medical gerontologists are essential for an optimal use of resources.

Animal studies provide a necessary model to study the immunodeficiency of aging. The areas of study in which the animal model is particularly relevant and valuable are several. Since inbred strains of mice are available many manifestations of genetically based diseases found in both man and rodent are more easily approached analytically and therapeutically in the

animal model. Experimental manipulation and therapeutic regimens are more easily performed in animal models. Animals provide a model with shorter life spans than humans and with age related diseases whose appearance is similar to those seen in man. Therefore, the results of preventive measures or therapeutic interventions can be evaluated more quickly and extensively in animal models. Animal model systems allow the examination of tissues and organs in addition to peripheral blood cells which is the major source of information in clinical research. The animal research therefore helps to identify the changes in the function and representation of peripheral blood cells as they relate to changes seen in central lymphoid organs which are not easily accessible in humans.

3 Neurobiological-Aging and the Immune System

A growing body of experimental evidence in many fields is pointing towards the existence of interactions and modulatory communication between the nervous and immune systems, establishing for the first time a scientific link between psychosocial and environmental phenomena. These interactions effect the well being of the ageing population, the functioning of the immune system, and as such influence the levels of morbidity and mortality in the elderly. The socio-economic impact of the health consequences resulting from stressful life events is enormous.

Many diseases in which there are modulating psychosocial influences are now known to have a major immunologic component, including infections, cancer and autoimmune disorders. Bereavement, depression, change in living conditions, or other culturally significant stressful events may impact adversely on the elderly. Many animal studies over the past decade have shown that a broad array of "stressors", including psychological factors, can significantly influence the morbidity and mortality from infectious agents and tumours. Furthermore, the results of experiments in which immuneresponses were measured directly support the contention that stress can alter immunocompetence.

Recent work has clarified further the presence of communication channels between the nervous and immune system. Neuro-endocrine outflow from the hypothalamo-pituitary axis can influence immune function through a variety of hormonal agents, such as the glucocorticoids. The autonomic nervous system has

direct fiber connections that innervate precise regions of primary lymphoid organs (bone marrow, thymus) as well as secondary lymphoid organs (spleen, lymph nodes, gut-associated lymphoid tissue, accessory lymphoid structures) providing direct channels for neurotransmitter influences. Patterns of innervation changes with aging, showing diminution with age in the parenchyma of lymphoid organs.

In addition to pathways of communication from the nervous system directed towards the immune system, pathways in the other direction has also been demonstrated. Secreted products of lymphocytes during in vivo antibody responses and from cultures of activated lymphocytes in vitro can alter electrical activity in some hypothalamic neurons, induce deep-wave sleep, alter catecholamine metabolism in circuits related to immune function, both peripherally and centrally, and can provide feedback to regions of the brain concerned directly with neuroendocrine and autonomic outflow to lymphoid organs. The demonstration of conditioned immunosuppression points towards "sensory" channels, either hormonal or anatomical or both, that can provide information to the brain concerning immune function. Indeed, this input to the brain may have a profound impact on CNS functioning, providing a route for afferent immune signals to impact adversely on neural function.

4 Perspectives in Aging Research: Immunological and Neurobiological Research

4.1 Recommendations for Studies in Human Immunogerontology

4.1.1 Epidemiology Programmes

Epidemiological studies should be established to cover genetic, geographic (environment, altitude, climate, temperature, isolation), diet, and socio-economic-psychologic factors such as forced retirement, overcrowding, bereavement, institutionalization all of which can influence aging and health. This would be an important international step in the definition and resolution of some of the problems in aging research. Factors that contribute to health and longevity would be able to be identified and may provide insights into the complicated process of aging and the interaction of immune and neurologic function.

4.1.2 Human Populations for Research Protocols

Unified criteria for the admission of volunteers to immunogerontological studies should be detailed along the lines of the SENIEUR protocol. This protocol assures a well characterized study population and should be periodically revised and updated by all participating centres. This will promote standardization of methods, the availability of reference values, and should uncover any significant differences between national groups.

4.1.3 Types of Studies

Long-term follow-up and longitudinal studies with information on morbidity and mortality are essential to uncover prognostic indices in these population samples, and will help to define the

risk factors for the development of age-related illness or early mortality.

4.1.4 Nutrition

The role of dietary factors, particularly specific nutrients, in the regulation of immunocompetence and susceptibility to infection is recognized but there are few data on this relationship in the elderly. This is due to the considerable problems in the objective evaluation of dietary intake and nutritional status, particularly in the elderly. Although these problems make it difficult to conceive of multicentre collaborative studies of nutritional effects on immunity, because of the potential significance of this topic makes a strong case for the support of pilot studies to examine selective aspects of the role of nutrition in the immunodeficiency of aging and the development of age-related illnesses. Epidemiological studies on an international basis could be a useful research tool in this regard.

4.1.5 Molecular Genetics

Careful differentiation between high and low responders in response to immunization in the elderly will help to identify genetic markers of the immune response which will be the subject for molecular biologic research and also indicate the role of environmental factors such as nutrition lifestyle and stress factors. (See also Section 4.3.1)

4.2 Optimization of Immunization in the Elderly

An important area requiring both animal and human models is

the study of immunization procedures. The development of new or modified vaccines specifically designed to be used in the elderly will provide primary preventive measure with direct benefit to the elderly population.

Until recently the development of vaccines has been directed toward the protection of children and young adults usually in military service. Because of the increasing number of elderly in society and the realization of their problems with infectious illness there is now an interest in the development of vaccines for use in the elderly population. The two best known vaccines in this category are the pneumococcal vaccine and the various influenza vaccines. However, there are other vaccines that could be used or developed for use in this age group, such as salmonella, hepatitis, tetanus and varicella-zoster vaccines. In spite of the perceived need for protection from these illnesses, very little is known about the efficacy and side effects of most vaccine preparations in the elderly age group. The route of immunization, the age for instituting an immunization programme, the need for booster injections, the dosage and the type of immunogen needed are all open questions with little or no information available for the formulation of policy recommendations or decisions. The testing of vaccine preparations in the elderly will not only offer opportunities to prevent disease but also offer an opportunity to correlate in vivo responses with in vitro assay systems to facilitate the diagnosis of the age related immunodeficiency and to find the cause of that deficiency. The determination of

humoral, cellular, and local mucosal and pulmonary cellular immune mechanisms should be the subject of immunization research programmes in this field. Along with the investigation of immune function, it will also be important to know the function of non-specific host defense mechanisms which also determine the eventual outcome of the interaction of individual immune responses against pathogens in the environment.

4.3 Projects Related to Neurobiological Sciences and Immunology

4.3.1 Mechanisms of Brain Aging at the Molecular and Genetic Levels

There should be an intensification of studies to probe the basic mechanism of aging of the normal and diseased human and animal brain at the level of the gene using the techniques of genetic engineering and molecular biology. Particular emphasis should be directed toward the study of genes relevant to the interaction between the brain, and the neuro-endocrine and immune systems. These projects should be integrated with these international organisations devoted to brain research such as IBRO.

4.3.2 Studies on Neurobiology in Animal Models

Longitudinal studies are needed in animal models so as to understanding the effects of altered hormonal and neurotransmitter systems on immune responses, and the effects of altered immune responses on brain function and neurotransmitter metabolism. Several animal models are available in which specific neurotransmitter systems (e.g. noradrenergic postganglionic sympathetic, cholinergic vagal, and specific peptide systems) can be manipulated with neurotoxins, degenerative genetic deficits, pharmacologic

agents, denervation, and other methods to understand on a causal basis (as opposed to a correlative basis, which usually is the best human studies can reveal) how the functioning of the immune system can be altered by changes in the nervous system, and vice versa.

4.3.3 Studies on the Effect of Human Neuro-degenerative Disorders on Immune and Neuro-endocrine Functions

Studies are needed on the effects of specific neuro-degenerative disorders (e.g. Alzheimer's disease, Parkinson's disease) on immune function, and on the interaction of autonomic and hormonal function with immune function. Neuro-degenerative disorders are accompanied by specific depletion of chemically-identifiable neuroendocrine and autonomic outflow. Patients with these disorders may be an excellent study group in which to investigate the relationship between the nervous and immune systems. They represent an extreme example of the degeneration of chemically specific systems that undergo a progressive degree of deterioration as part of the normal aging process.

4.3.4 Identification of Specific Stress-induced Neuroendocrine Changes

In studies devoted to aging of the immune system, attention should be paid to the possible effect of psychologic and physical stress. Immunological evaluations should include studies to identify potential selective stress-induced modifications of cellular subsets and functions. When possible, neuroendocrinological assays should be extended to produce stress-hormone profiles which can be correlated with immune function profiles.

5 Means Needed to Support the Immunology/neurobiology Aging Research Programme (INARP)

As indicated in section 1.4, research in the immunology and neurobiology of aging has been impeded by a lack of long-term financial and logistic support, without which meaningful results in this complex field can not be determined. Analysis of the problems involved in projects described in section 4 suggests that support will be needed in the following areas:

5.1 Establishment of Intergovernmental Coordinating Structures for the INARP Programme

5.1.1 Creation of a WHO-sponsored Special Programme (INARP)

Of primary consideration is the creation under WHO sponsorship and guidance a Special Programme devoted to Immunological and Neurobiological Aging Research (INARP).

This Programme would be supported by a WHO-based Executive Secretariat and a Steering Committee composed of scientists active in the field and representative of major national and international groups. The Steering Committee would be responsible for scientific assessment of projects and decisions concerning disbursement of funds.

Funds to support this programme would be solicited from governmental agencies, private institutions, and foundations.

5.1.2 Linkages to Existing ("EURAGE") or Potential ("WORLDAGE") Intergovernmental Organizations

The proposed aging research in immunology, and the interaction with neurobiology requires longterm support and inter-

national cooperation. It is not possible for any nation alone to implement such a programme in sufficient depth and with the speed dictated by the problems discussed above. It is proposed that a WHO initiative establishing a coordinating structure for interdisciplinary research and the identification of reference laboratories.

The existing European network on aging research (EURAGE) might be extended to facilitate international cooperation among research groups (WORLDAGE). This could be implemented by providing means for the exchange of scientists, biological materials (animals, tissues, cells, sera) and information.

5.1.3 Reference and Standardization Facilities

One method of facilitating international research is to establish reference laboratories and provide standardization of methodology and research protocols.

The SENIEUR protocol for the study of human immune function establishes strict admission criteria for immunogerontological studies in man based on clinical information and laboratory data, and it sets limits to pharmacological interference. The use of this protocol would lead to standardization between centres and to a closer study of the influence of age on the immune system. The results of research using this protocol can serve as reference values for immunogerontological studies in subjects who do not meet the SENIEUR criteria. In this way, the use of this protocol can contribute to the dissection of the influence of disease versus aging on the immune system.

The SENIEUR protocol could be usefully applied in different regions of the world to test its validity and provide a vehicle to obtain acceptable reference values for a large number of different parameters of human immune function in aging. This data may make it possible to define the metabolic defect in the decline of immune function in relation to age. Indices for survival would then be available and this would lead to attempts to modulate the immune response so that age related illness could be avoided.

Reference protocols and laboratories with standardized methodology would permit integration of research programmes in all areas of the world and would encourage research initiatives at the international level. This would facilitate prospective investigations on the prevalence of age-related diseases and the design of national control programmes.

The availability of standardized protocols for both assay procedures and for the tissue and biologic freezing and storage sample is a necessity. This point can not be stressed too strongly. The ability to evaluate changes, differences in function and the effects of age demand standardization. For example, depending on how lymphoid cells are frozen, the results obtained in subsequent assays will vary. This is especially true in the case of cells from old animals and perhaps elderly humans in which resistance to freezing damage is much less and consequently the freezing procedures can be more detrimental to the function of the cells.

The exchange of information is also an important feature of an international approach to this problem. This can be accomplished through newsletters, abstracts of relevant articles, construction of appropriate bibliographies, sharing of computer software which has been developed to provide data collection, organization and analysis and provision for consultative services for the initiation and integration of international research programmes.

5.2 Logistics for Longitudinal Studies

Longitudinal studies in which research subjects are well characterized and are studied at intervals throughout life provide data which can answer specific questions. These questions are (1) the relevance of age related changes in immune function in the pathogenesis of age related illness and (2) the interactions of physiologic systems. By their nature, longitudinal studies are able to be best utilized by a multidisciplinary approach to research in human ageing. The individual entering this type of study as a research subject can supply useful information to a wide spectrum of research activity. These studies also allow the development of interventionist programmes in the therapy of age related illness or in procedures to augment or bypass areas of dysfunction or poor function.

5.3 Training in Immunology/Neurobiology Research

In order to be effective and to recruit gifted young investigators in the field, it is essential that the INAR Programme be able to distribute post-doctoral research fellowships

and training grants. In this way, knowledge available at major research institutions devoted to immunological/neurobiological aging research could be disseminated to benefit long-term prospective studies.

The multidisciplinary nature of aging research makes it desirable that this work should not be conducted exclusively in Institutes of Gerontology but should be conducted in institutions in which a wide range of biomedical research is being pursued. This offers opportunities for cooperation with experts in many different disciplines. The fruitful execution of this cooperation is dependent on linkage personnel who can work between the cooperating groups and with individuals in relatively isolated circumstances. Grants must be available to support linkage personnel consisting of postdoctoral fellows and technicians.

An international research and training programme would have a considerable effect in disseminating technical knowledge and improving medical skills in the assessment of and care for aging populations.

5.4 Research and Travel Grants and Support of International Meetings

As assessment of the current haphazard patterns of support in immunological/neurobiological ageing research demonstrates that many opportunities are not seized because of lack of direct research support at the local or national level. It will be essential if INARP is to have an impact, that not only will there be a coordination of existing activities but also the generation of initiatives to implement and select grant proposals most

relevant and useful to the goals of the programme. Such proposals would be reviewed and assessed for scientific values by the Steering Committee, helped when needed by recognized outside experts (peer review).

Investigators need opportunities to spend time in centres other than those in which they normally work. Travel funds would be needed for this purpose. In addition, support for salaries will be needed for technicians and research associates as well as for graduate, postgraduate and postdoctoral personnel in some of the centres participating in the programme and in some cases involved in long-term prospective studies.

Standardization of investigative techniques and protocols will be fostered by the organization of "wet" workshops, as needs arise. INARP should also have the opportunity to organize and support specialized meetings, particularly in conjunction with more general meetings in the scientific immunological and neurobiological areas.

5.5 Animal Resources

The cost of immunological and neurobiological animal research is usually covered by conventional fundings. However, gerontologic aspects of such studies are not usually covered by conventional sources and are markedly more costly as a consequence of the need for sizeable cohorts of animals that must be maintained for 2-3 years to provide a supply of old animals and also to provide enough animals in order to allow longitudinal studies to be performed.

Special funding needs arise because of two special aspects of research: long-term maintenance of animals and multidisciplinary research. Since most existing facilities are designed for short-term maintenance, special measures will need to be financed to provide for the supply of old animals. In particular, long-term maintenance requires protection against even mild diseases which are often endemic in short care facilities. The measures often described as "ultra-clean" necessitate additional expenses in terms of special equipment and labour.

To enable investigators in smaller and possibly remote centres to use animals of the same genetic and environmental background as those kept in the larger centres, there would be need for the common inbred strains to be maintained in at least two different locations. It would be advisable to take the opportunity to use and complement existing breeding and animal facilities for the special purposes of aging research.

5.6 Organization of Tissue, Cell, and Serum Banks and Repositories

The discussion of prospective immunological and neurobiological studies described in section 4 shows that the conservation and distribution to investigators of various biologic materials adequately preserved and stored is an important prerequisite for many of the planned studies. Lack of facilities for central storage and distribution of biologic material has been a major impediment to aging research. In addition, the preservation of tissue, cells, and serum samples from old animals or individuals

permits optimal use of these materials by investigators and considerably diminishes the overall research costs in these areas.

To this end, specimen banks need to be developed with supporting computer facilities for documentation and organization, utilizing standardized procedures, and the assignment of equipment and staff to carry out the mission. These banks would need to be integrated with existing facilities and ongoing research groups, in order to provide additional storage facilities, staff and shipping funds required for an expanded operation of the bank. Since the operation of biologic sample repositories represents an essential logistic prerequisite for progress in gerontologic research, the proposal is more fully described in Annex I.

6.0 Conclusions

Aging does not follow a single path but instead a sequence of inherited and acquired traits, which over a lifetime ultimately determine the quality of life enjoyed by the elderly. The analysis of these processes is a social and economic imperative.

From time to time, a belief in rejuvenation emerges, and intuitive "treatments" that claim either to stop the process of ageing or to cause rejuvenation are widely publicised. It is important to replace these nonscientific wishful hopes with a coherent research policy for scientific analysis and for the development of preventive medicine in geriatrics. It is essential at this time to lay foundations for a future in which there is an improved quality of life for the elderly.

This goal, as the history of preventive medicine shows us, will only be achieved by intensifying basic research on the aging process and by applying the resultant newly gained knowledge to the prevention of age-related diseases. The complexity of the problem, and the needs for an interdisciplinary approach and long-term commitment lead to the premise with that support of an international agency such as WHO and with adequate funding for establishment of a multicentric, multinational programme in ageing, immunology and neurobiology research are prerequisites for eventual success.

It is the conviction of this group that the interactions between the immunological, neurobiological and neuroendocrine fields in aging research hold the promise of significant advances

in our understanding of the role of immune dysregulation and neurobiological changes in the genesis of age-related diseases, thereby opening new approaches in preventive medicine. Although short term benefits are not the primary goal of this programme, the optimization of immunization in the elderly would undoubtedly contribute to immediate improvements in health and a resulting decrease in medical costs.

The scientific background and technology required for major advances at the molecular and genetic levels, are at hand and need to be applied to the investigation of the process and age-related diseases. It has, however, become clear that such advances will only be possible with a coordinated and interdisciplinary programme, on a multinational scale.

An international programme is therefore being proposed using common models and bringing together scientists from different countries and different areas of competence and orientation. The effect of this programme will not only be to pave the way for new approaches in preventive medicine and geriatrics, but will also disseminate research and medical capacity and technical know-how in developing countries, where problems of health in the elderly may soon become even more acute than in developed countries.

ANNEX I

Proposal for the Establishment of WHO Sponsored Tissue, Cell, and Serum Banks for Aging Research

It is proposed that WHO establishes one or more international collection and storage centers devoted to the acquisition and storage of lymphocytes and sera from living patients and brains from autopsy cases, that could then be available for distribution to laboratories conducting aging research.

This proposal would have the following benefits:

- (a) establish uniform standards for tissue and data collection, storage and dissemination;
- (b) improve the uniform quality of research in different laboratories (for comparative purposes);
- (c) identify valuable patient donors who are at present contributing to research;
- (d) make specimens available to those research centers without the means to have their own collection facilities;
- (e) eliminate a major obstacle to current efforts which is the lack of a sufficient supply of well-characterized normal control tissues from aged individuals. This problem is most severe in neuroscience research.
- (f) increase the usefulness of Restriction Fragment Length Polymorphism (RFLP) studies on characterized lymphocytes, since diagnoses would be confirmed by autopsy.

The proposed centre(s) would particularly benefit studies of age-related neuronal degeneration, e.g. Alzheimer's diseases. The availability of rapidly collected (e.g. with post-mortem intervals of 3 hours or less)

human brain autopsy specimens are crucial in importance because they are required for molecular studies at the cellular level. These data could be complemented by immunocytological analysis of the same brain tissue. Criteria would need to be established to determine the types of research for which the tissues would be available. However, priority would be given to aging studies.

A significant aspect of these proposals is that normal, non-diseased control specimens would be banked with the same enthusiasm as pathological specimens. At present a number of methods have been used to ascertain the health status of patients: imaging (PET, CT, NMI), and medical, neurologic, psychiatric, and psychometric evaluations. In the proposed collection system, postmortem examinations will be used to establish accurate diagnosis, thus we would not have to rely solely on premortem evaluations. This is important for neurodegenerative diseases, such as Alzheimer's disease which requires a neuropathologic diagnosis.