



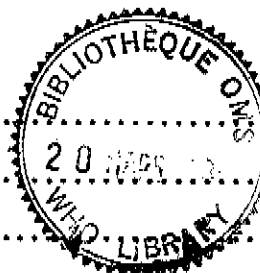
Report of the

JOINT WHO/EOPF/NIAMS(NIH) CONSULTATION
ON OSTEOPOROSIS

Geneva, 13-15 July 1988

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1. INTRODUCTION

The meeting was opened by Dr E.N. Chigan, Director of the Division of Noncommunicable Diseases. The importance of developing an improved strategy for health promotion, education and research into osteoporosis was stressed. Effective methods of prevention and treatment are urgently required because osteoporosis is now a major challenge to world health, and will make ever increasing demands on resources. The WHO welcomed the initiatives and interests of the European Foundation for Osteoporosis and Bone Disease (EOPF) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (NIAMS) in formulating these strategies.

This Consultation recognizes the importance of involutional bone loss in both sexes. Whereas post-menopausal osteoporosis is the major concern of this report, it wishes to emphasize the increasing importance of osteoporosis in men as well as women. Increased longevity of the male population will have a major negative impact on skeletal health. In some studies the age-specific incidence of osteoporotic fracture appears to be rising, a further reason for concern in both sexes. In addition, secondary causes of osteoporosis such as the use of corticosteroids are also of increasing importance to both sexes in various Member States.

Background to Joint Consultation

This Consultation arises from the working relationship between WHO and EOPF and the contacts between these organizations with NIAMS and the National Osteoporosis Foundation (USA).

The objectives of the meeting and this report are to review present knowledge and clinical practice of relevance to osteoporosis in order to:

- (a) identify deficiencies in our knowledge which require further study or research initiatives, particularly on an international scale;
- (b) identify areas of knowledge where meetings of experts should provide detailed information to assist Member States and international health organizations in formulating health policies and establishing standards for the prevention and management of osteoporosis;
- (c) identify and agree upon common knowledge which should be made known to Member States.

These aims are in accord with WHA Resolution 28.82 (1975): (a) to support studies on the biology, epidemiology and prevention of rickets, osteoporosis and osteomalacia; and (b) to consider the possibility of reviewing calcium requirements. These objectives are also in line with the more recent WHA Resolution 38.31 on collaboration with Nongovernmental Organizations in implementing the Global Strategy for Health for All.

2. REVIEW OF WHO ACTION

The meeting discussed the Special Programme for Research on Aging convened jointly last year between NIA (NIH) and WHO at Bethesda. This programme has developed a Scientific Programme for Research on Aging (SPRA), a component which is concerned with age-related nutritional changes and osteoporosis. Specific research proposals have been formulated, but have not yet been implemented. These include cross-national studies of age-specific fracture rates, bone density, nutrient intake, bone turnover, calcium absorption and obligatory losses. Objectives rather than mechanisms have been outlined and a further meeting is scheduled. It was recognized that although there had been limited consultation with WHO headquarters, improved communication in the future would enhance research opportunities on an international scale.

The meeting then reviewed the MEDOS Study (Mediterranean Osteoporosis Study), sponsored jointly by the EOPF and WHO and funded by Sandoz Pharmaceutical Company. The Study has two components. The first is to acquire accurate information from Ministries of Health (or equivalents) in all European countries on the incidence of hip fracture. The second part of

the Study presently in progress is concerned with demographic and other factors surrounding hip fracture in six nations (14 centres) throughout Southern Europe. From this prospective case control study, it is hoped to identify putative risk factors and to determine their relative importance in different communities recognizing the disparate age-specific incidence rates throughout Europe for hip fracture. Similar studies are in progress in the USA. The questionnaire and the methodology used in the USA will be made available to WHO headquarters.

3. REVIEW OF EPIDEMIOLOGY

Osteoporotic fractures are most common among women in Northern Europe and North America. Hip fractures are the most important type and result in 5-20% excess mortality and 2-5 weeks of hospitalization in Europe and North America. They are also important causes of morbidity, resulting in impaired mobility and the need for sheltered accommodation. The age-specific incidence of hip fractures is highest among women in Northern Europe and the United States, somewhat lower in Central Europe, and lowest in South African blacks and Malaysians and Chinese in Singapore. Racial differences within countries suggest that some of this variation is due to genetic factors. The age-specific incidence of hip and other fractures has been increasing throughout the European countries in which this has been studied, but this trend has not yet been confirmed in the United States and has not been studied outside of these regions. Some studies suggest that the rise has been greatest in women over age 75, but the reasons for this increase is not known and may not be related solely to changes in bone mass. They are most likely to be due to changes in a combination of factors such as mobility, nutrition and additional skeletal factors. Further research is needed to determine their individual and combined importance.

There are also large gaps in our knowledge of the incidence and burden of osteoporosis in many regions, particularly outside of North Europe and the United States. In particular, there are scant data about rates of hip, vertebral and other fractures in Asia, Latin America, Africa and the Middle East. In order to help differentiate between genetic and environmental influences such studies will require complete ascertainment of fractures in populations from within the same country but from different regions. The Mediterranean Osteoporosis Study (MEDOS) is in the process of describing the incidence of and risk factors for hip fractures in countries along Northern rim of the Mediterranean.

Several types of data are necessary to understand the differences in incidence rates between countries, and over time. In particular, information is required on bone mass and the relationship between bone mass and fracture in different regions; the prevalence of risk factors in populations, and the relative risk of specific types of osteoporotic fractures due to these risk factors. To be comparable, these data must be collected in a standardized fashion.

Several problems previously encountered in obtaining epidemiological information from some developing countries were reviewed. These included inaccuracies of age estimates, diagnosis and reporting and inadequate sampling due to homelessness, variable clinical facilities and cultural habits.

4. REVIEW OF SCREENING

The general principles of screening of individuals and populations at risk from osteoporosis were discussed with respect to the available methodology, the populations to be screened, the gains to be made from screening (which would depend upon national resources), the power of interventions and the specificity and sensitivity of the instruments used for screening. It is recognized that the approach to screening of an individual will differ from the approach of health care agencies where the care of populations is the priority. Screening techniques in the USA are more geared to their predictive value in individuals rather than to populations, whereas the needs of many Member States are to develop cohesive national policies for populations. The Consultation is not aware of national strategies being developed for populations and felt that this is an important area for further development. In developing such strategies, the crucial dependence upon good epidemiological information as well as the health care needs of individual nations was emphasized.

Important factors for the risk of developing osteoporosis in later life are the peak bone mass or density at maturity and the rate of bone loss thereafter. Screening techniques to assess the risk of osteoporosis might include, therefore, the measurement of peak bone mass and an estimation or measurement of the subsequent rate of bone loss. Such estimates might be made by direct measurement or inferred indirectly from demographic features or by biochemical tests. The age of attainment of peak bone mass is uncertain, but in women is likely to be between the ages of 30 and 40. After peak bone mass has been reached, both men and women lose bone. In men, small losses occur throughout later life, whereas accelerated bone loss occurs in women in the years around and after the menopause, so that the age-adjusted risk of fracture is much greater in older women than in men. Measurements of bone mass and rates of bone loss are now both possible. Physical techniques with sufficient accuracy include single and dual photon absorptiometry, x-ray based absorptiometry, computed tomography, and gamma camera based absorptiometry.

For this reason screening for risk of osteoporosis might include the determination of peak bone mass, and in women the measurement also of the subsequent rate of bone loss after the menopause. The advantages and disadvantages of the different physical methods have not yet been completely resolved. There is also no agreement as to whether peripheral measurements (e.g. at the forearm) are as specific or sensitive as measurements at the spine or the hip. In addition, repeated measurements to measure rates of loss require very precise techniques or long periods of observation due to the small inherent changes observed with time. Rates of bone loss can be estimated by measuring biochemical indices of bone turnover from urine and serum samples. Whereas such methods can identify 'fast bone losers' from 'slow bone losers' precisely and sensitively, their long-term predictive value is not known.

A number of risk factors have been identified which are associated with hip fracture (e.g. race, sex, family history, smoking, use of certain medicines, premature menopause etc.). These may variously provide indices of peak bone mass, duration and rates of bone loss, and liability to falls. Their value in screening programmes is not well established, nor too is their power in other types of osteoporotic fracture.

The potential of demographic, biochemical and physical methods to predict bone strength were discussed in relation to clinical and epidemiological work. It is recognized that the applicability, sensitivity and specificity of these methods require much more research which should include the development of new techniques, particularly markers of skeletal disease. Several prospective studies have been completed utilizing some of the potential methods of screening and others are underway in the United States, Australia and Europe. Despite the limitations of the current screening tools, it is recognized that in view of the pressing problems of osteoporosis, particularly in the Western World, health care policies need to be developed and applied using the information available today rather than to wait for prospective studies which may require many years to complete. Prospective studies of the value of screening techniques are, nevertheless, important both for primary and secondary prevention, and appropriate measures should be taken for their initiation.

5. REVIEW OF FACTORS OTHER THAN BONE MASS

Whereas bone mass/density was recognized as the single most important determinant of skeletal fragility, it was noted that cumulative trabecular discontinuities and alterations in bone tissue composition (e.g. fatigue damage) may contribute to skeletal weakening in osteoporosis. These causes of fragility are well recognized as causes of failure in man-made structures and are known to occur in bone as well. They are thought to be important to the world osteoporosis problem because:

- a) they may explain ethnic and national differences in fracture rates if such exist that cannot be accounted for by differences in bone mass alone; and
- b) at least one of them - fatigue damage - may be more amenable to intervention and reversal than would mass loss.

For countries with large populations of older women who already have low bone mass, repair of fatigue damage (if this can be achieved) could produce a greater reduction in fracture incidence and thus morbidity and medical costs than would any known means for increasing bone mass. Finally, the role of such factors is likely to assume greater importance with progressive bone loss and could have, therefore, a variable impact on screening techniques and programmes aimed at populations of different age and bone fragility.

Extraskeletal factors also contribute to osteoporotic fracture. These factors include falls, the circumstances producing falls, and the nature and efficiency of protective reflexes. The role of extraskeletal factors is likely to be greater in the case of hip fracture than in vertebral fracture, but few studies have investigated this important area. Available evidence suggests that extraskeletal factors assume increasing importance with advancing age.

6. REVIEW OF NUTRITIONAL ASPECTS OF RELEVANCE TO OSTEOPOROSIS

Calcium

The Consultation reviewed the difficulties of assessing the amount of calcium that was optimal for skeletal health at various stages of life, and the uncertain relationship of nutrient intake to subsequent fracture risk. These problems arose because of the indirect nature by which these questions could be addressed. Irrespective of the absolute requirement, requirements for calcium are increased in infancy and adolescence and may determine whether the skeleton achieves its full genetic potential. It is also important to determine whether intake in mid-life can be insufficient and can then aggravate age-related bone loss in later life (i.e. that due to oestrogen deficiency and the irreversible changes of aging). Intake requirements for each stage of life may vary from nation to nation, and might depend upon such factors as the intake of sodium, caffeine and protein, and on vitamin D status.

In North America and Northern Europe the apparent requirement for optimal skeletal growth average 1100-1300 mg during adolescence, and are roughly the same at the time of menopause. Part of the reason for this seemingly high requirement is the high obligatory calcium loss at all ages coupled with poor intestinal absorption of calcium in middle-aged and older women. The reasons for the disparate views on the RDA for calcium of the FAO/WHO and of the USA were discussed. Different views arose largely because of the national differences in apparent obligatory excretory losses of calcium and uncertainties concerning long-term adaptation to changes in calcium nutrition, as well as the uncertain influence of other dietary factors on adaptation. It was recognized, however, that the dietary intake of calcium of many women in various Member States was below that of all previous RDA's.

Vitamin D

There is a world-wide decline in vitamin D status with age, as assessed by serum values of 25-hydroxyvitamin D, and many studies show clear improvement in various indices of the calcium economy when vitamin D supplementation is used in the apparently well elderly. The precise contribution of this apparent insufficiency of vitamin D to the world osteoporosis problem is not clear. These difficulties arise because of the uncertain definition of vitamin D deficiency. It is recognized that extreme deficiency impairs the mineralization of bone, but milder deficiency states may have an important effect on bone remodelling in the elderly (e.g. by inducing parathyroid-mediated bone resorption) and by impairing the differentiation or performance of skeletal tissues. In addition, there is evidence that aging and osteoporosis may be associated with target organ resistance to the effects of active vitamin D metabolites which might impair the ability of the aged to adapt to low intakes of calcium. It is possible, therefore, that vitamin D nutrition is suboptimal in the elderly.

7. REVIEW OF CURRENT POSSIBILITIES FOR PREVENTION OF OSTEOPOROSIS

There is general understanding that prevention of osteoporosis is likely to be a significantly more effective mechanism for reducing fracture frequency than treatment of the established disorder. The major determinants of bone fragility in old age are the bone mass

and strength at maturity, and the losses of bone which occur thereafter. Whereas much work has focused on loss of bone tissue, much more research is required to identify factors determining peak skeletal mass and strength to improve the prospects for prevention.

In conjunction with nutritional and life-style factors, hormonal and pharmacological approaches to prevention of bone loss are available. Of the agents known, oestrogens are those for which there is greatest documentation. Data have demonstrated that prolonged (>10 years) prevention of bone loss occurs when oestrogens are given to oestrogen deficient women, and such preventive effects are evident at all skeletal sites. Epidemiological and other data indicate that this is translated into a significant reduction of fracture frequency. However, we recognize that oestrogens are potent metabolic agents with wide reaching effects on the risk of disorders other than osteoporosis, and that their benefits must be carefully weighted against their problems. As more data become available, particularly with respect to prevention of ischaemic heart disease, the patterns of oestrogen use may change and they may be more widely prescribed. However, not all women can or will take oestrogens and other agents are required as alternatives for prevention. Calcitonins and diphosphonates are recognized to be important agents that have been shown to prevent or delay bone loss and which require further investigation.

The real prospect for effective prevention requires that we develop the ability to identify those most at risk in order that they can be targeted for treatment. In addition, a major obstacle to the wider use of preventive measures arises from misconceptions about the effects of intervention. The Consultation recognized the need for increasing educational activities at many levels. It was agreed that a component of this report should serve this need.

8. REVIEW OF CURRENT POSSIBILITIES AND PRACTICE FOR THE TREATMENT AND REHABILITATION OF THE ESTABLISHED DISORDER

The Consultation reviewed all the medical modalities of intervention in the osteoporotic population, including those tested in men and in secondary causes of osteoporosis. Established osteoporosis is a heterogeneous syndrome characterized by differences in bone mass at different anatomical sites, and differences in rate of bone remodelling. Therapeutic strategy and research do not usually take these differences into account. Many therapeutic studies have been performed in patients with vertebral crush fractures, and similar studies on femoral neck fractures are also needed. For a number of bone active agents, including calcium, oestrogens, anabolic steroids, calcitonin, arrest or attenuation of further cortical and/or trabecular bone loss has been established, but a reduction of refracture rate is not well documented with the possible exception of fluoride.

The discussion emphasized the need for education in this area and to distinguish between measures which were practically feasible and those still at the stage of development and experimentation. As in the case of prophylaxis, it was felt that information had been unevenly and inadequately propagated throughout the world, as reflected by the very disparate prescribing habits for the treatment of bone disease in the many Member States where this information was available. For the most part, these differences are not based on scientific fact, but on local experience. It was agreed that components of this report should emphasize what is known and what is not known concerning such intervention.

It was also recognized that the successful national development of intervention policies throughout the world depended upon consistent attitudes of the public, physicians and health care agencies in various Member States. Many claims for efficacy (in distinction to phase II studies) had resulted from studies of inappropriate populations with insufficient power and with variable end-points not considered to be appropriate in different countries. The Consultation felt it important to include recommendations which would aim to strengthen the international approaches to prevention of and intervention in osteoporosis.

It was further recognized that there was a dearth of research information concerning the non-skeletal factors of relevance to primary and secondary prevention such as the epidemiology of falls and the putative interventions which might decrease falls. Further studies of the relationship between falls, medications, alcohol, life-style and environmental factors may lead to more effective intervention.

9. REVIEW OF FUTURE THERAPEUTIC POTENTIAL FROM CURRENT RESEARCH DEVELOPMENTS

The Consultation reviewed the modalities currently being tested for prevention and treatment. In addition, the Consultation reviewed the many new factors and agents which had been identified as influencing skeletal metabolism and which would merit clinical studies.

A major impediment to the development of this general area was the inadequate world-wide facilities for the assessment of putative treatments for the prevention and treatment of osteoporosis. The Consultation discussed the ways in which national and international activities might strengthen this deficit, and agreed that this should form a component of further recommendations on a national and international scale.

10. CONCLUSIONS AND RECOMMENDATIONS

Having reviewed the field of osteoporosis, the participants of the Consultation acknowledged the increasing problems of osteoporosis to world health. They recognized areas of common knowledge, and identified a need for this to be disseminated more uniformly to Member States. They identified areas of uncertainty where further research is required, and particularly areas of research where international approaches would yield worthwhile dividends. In order to stimulate transition from concept to action, the following conclusions and recommendations are being made with the unanimous agreement of the Consultation:

A. General

1. The report of this Consultation should be sent to the responsible agencies of WHO Member States to convey areas of common knowledge and to emphasize the need for, and the rationale and potential feasibility of, integrated community health programmes.
2. There has been an increase in public awareness of osteoporosis particularly in the Western World. This comes at a time when the scientific and medical knowledge of bone metabolism and osteoporosis has increased markedly, but is not matched by comparable increases in facilities for its prevention and treatment in all countries, even where the costs and morbidity are well recognized. Early detection, diagnosis, prevention and treatment of osteoporosis are now feasible and all of these techniques are constantly being improved. Member States, in which osteoporosis is an important problem, should consider ways to implement, coordinate and further refine public health strategies to prevent osteoporotic fractures.
3. Although integrated community action can be effected through education and research, it is recognized that the instruments to be used in such programmes require more research (e.g. detection, nutrition, and treatments) and need to be improved. To this end, meetings of experts should be convened by the WHO on a number of subjects to be specified in greater detail below.
4. There is a great need for a strong and continuing commitment of the WHO in collaboration with Member States and other national and international agencies to coordinate activities and to provide exchange of information. This is particularly acute in the case of large-scale epidemiological studies where independent research activities currently in progress could have been strengthened by common designs from cross-consultation. It is recommended that a close link be maintained between the components of SPRA dealing with osteoporosis and WHO headquarters. It is further recommended that the WHO consider mechanisms for coordinating WHO activities in osteoporosis research and its prevention including the appointment of medical officers and the use of collaborating centres.
5. There is a need for a great deal of research into the epidemiology, assessment, prevention and treatment of osteoporosis. It is recognized that much work in the field can be effected by Member States, but the WHO has an important role in helping to standardize the methodology so that cross-national comparisons can be made.

6. Osteoporosis and its clinical and public health consequences are underrecognized in many parts of the world. In some Member States facilities for surgical and medical treatment, including rehabilitation of patients, are inadequate. In view of the major morbidity and costs of osteoporosis and its increasing prevalence, Member States should where appropriate re-examine and, as necessary, expand the medical and surgical provisions for dealing with osteoporosis.
7. In view of the wide scope of activities recommended above and detailed below, it is recommended that a separate programme of WHO on osteoporosis should be developed.

B. Epidemiology

The joint Consultation recognizes the incompleteness of current epidemiological data concerning the incidence of osteoporotic fracture around the world particularly in view of the secular trends and the imperfect and unstandardized methods of data capture. It is recommended that more accurate information be acquired from the developing and developed world to investigate the size of the problem in more detail. Moreover it is further recommended that mechanisms be established whereby continued data acquisition can provide information on secular trends from specific geographical areas.

1. There is a paucity of data concerning the prevalence, incidence and morbidity from vertebral and other osteoporotic fractures throughout the world. It is recommended that such information be acquired in selected geographical areas utilizing standard methods of comparison and measurements.
2. More information is required on racial and geographic differences in the incidence of hip fractures to determine the relationship of fracture to bone mass and density, and to other factors.
3. Further information is required concerning the costs and consequences of osteoporosis in selected but different communities.
4. It is recognized that the rising prevalence of osteoporosis is in part due to the increasing number of women at risk as well as to an increase in the age-specific incidence of hip and wrist fracture particularly in Europe in elderly women. This may be true of other osteoporotic fractures. Data about secular trends are available from the United States and Northern Europe, but no information is available elsewhere. The cause of this increase is conjectural and it is recommended therefore that this be urgently investigated. In particular, longitudinal studies are needed to describe a change in the prevalence of putative risk factors in populations, utilizing standardized methods of data acquisition and methods of assessment of risk factors, bone mass and various osteoporotic fractures.
5. It is recognized that studies sponsored by the WHO/EOPF and the NIH/National Centre for Health Statistics may aid in the identification of risk factors. It is recommended that longitudinal studies should be developed specifically to study reasons for secular trends.
6. In implementing the research activities outlined above (B 1-5), a working group should be convened to offer guidelines for standardizing and coordinating these types of studies. The Consultation wishes to stress the importance of obtaining accurate data from many countries to describe the cost effectiveness of various intervention strategies and programmes. It is recommended that a study group be set up to acquire these data and to examine the impact of different interventions on public health, including cost-effectiveness which may be of benefit to Member States.

C. Screening

The Consultation recognized the potential importance of screening, particularly at the time of the menopause, but considered that currently available techniques were not being widely applied.

1. The application of currently available techniques for identifying patients at risk at or soon after the menopause should be further researched together with estimates of cost-effectiveness and possible methods of implementation. It is recommended that this activity form a component of the remit of the study group outlined above (B6).
2. Major prospective studies on the role of screening for individuals at risk are underway in Europe, United States and Australia. Such longitudinal studies should be organized in several other regions of the world. Screening techniques which should be evaluated include demographic, biochemical and physical methods of measuring bone mass and strength. These studies should be coordinated by global and interregional programmes of the WHO.
3. Whereas the risk of osteoporotic fracture is in part determined by peak bone density and rates of bone loss after skeletal maturity, the Consultation considered that the importance of additional skeletal factors (trabecular connectivity and fatigue damage) and extraskeletal factors (falls and their causes and consequences) should be further investigated by examining the relationship between bone mass and fracture in different communities. The interaction of skeletal and extraskeletal factors is particularly important for the development of screening techniques in the elderly and in secondary prevention.

D. Nutrition and life-style

(a) Nutritional aspects

It was recognized that there is still much uncertainty concerning the nutritional requirements for calcium and other nutrients not only at different stages of skeletal development, but also across cultural and racial boundaries. It is clear that man is capable of adaptation to large variations in dietary intake for calcium, but it is uncertain whether all people, particularly the elderly and adolescent population, are capable of efficient adaptation without detriment to skeletal mass and competence. Data on the role of other nutritional, environmental and racial factors are also incomplete, particularly the nutritional factors which determine peak skeletal mass and strength.

It was recognized that coexisting vitamin D deficiency could contribute to impaired skeletal integrity at all stages of skeletal development. It is desirable that the general community be placed at minimum risk of privational deficiency. Increased knowledge of the role of vitamin D suggests that the effects of deficiency and what constitutes deficiency should be redefined.

It is recommended that a study group be convened to examine all nutritional requirements for skeletal health particularly at adolescence and senescence.

(b) Exercise

Immobilization leads to bone loss which can be reversed, at least in young adults, by the resumption of weight bearing activity. The extent of reversibility of this process in the elderly is likely to be incomplete. There is now good evidence that an increased level of activity in the elderly can decrease the rate of bone loss, and this supports the view that men and women should be encouraged to maintain a reasonable level of physical activity. Exercise can reduce the rate of bone loss in the elderly and improve agility, but there is insufficient information available to recommend the type and duration of exercise and whether this modulates the risk of fracture. Notwithstanding, exercise and rehabilitation programmes improve quality of life and may prevent further falls. Excessive exercise without a commensurate increase in nutritional intake can lead to amenorrhoea and loss of bone.

(c) Smoking and alcohol

Smoking and excessive alcohol intake are important risk factors for the development of osteoporotic fractures. This provides yet one more reason to discourage smoking and excessive alcohol intake.

(d) Trauma

There has been relatively little research about falling and its role in fractures. Such research, including the epidemiology of falls, causes of falls and practical ways to prevent falls, deserves a high priority.

E. Pharmacological intervention

In order to have an important impact on the incidence of fractures, an intervention must not only be effective but it must also reach a substantial portion of those who are at risk of fracture. A powerful intervention that reaches only a few people may have less impact on fracture rates than a weak intervention that can be applied universally. Thus, there needs to be research documenting the efficacy of widely applicable interventions, such as nutritional changes, and research about how to increase the applicability of effective interventions, such as postmenopausal oestrogen therapy. This requires further research in Member States. Our knowledge of medical interventions is incomplete and will require continual research investments. Nevertheless, there are several areas of common knowledge which have been imperfectly applied in many Member States and are outlined below.

a. Oestrogen in the prevention of osteoporosis

- i. Oestrogen therapy prevents bone loss in postmenopausal women. It is currently the only well established prophylactic measure that has been shown to reduce the frequency of osteoporotic fracture. The minimum effective daily dose depends on the oestrogen and has been determined for several oral agents. The optimal dose of non-oral oestrogens needs to be defined.
- ii. Oestrogens have other effects both favourable and unfavourable: there is evidence that oestrogen therapy might reduce the incidence of cardiovascular disease, and that this is the most important potential benefit of oestrogen. It is well documented that the risk of endometrial cancer increases during and after oestrogen monotherapy.
- iii. Cyclical or continuous administration of progestogens prevents endometrial hyperplasia and reduces the risk of endometrial cancer. Their effects on breast cancer are less secure, but the majority of epidemiological studies do not suggest an overall increase in risk in oestrogen treated postmenopausal women. The risks and benefits of oestrogens and progestogens warrant further study, especially in regard to ischaemic heart disease.
- iv. Available evidence indicates that postmenopausal women at risk of developing osteoporosis should receive oestrogen therapy, provided that there are no contraindications. In a women with an intact uterus the concomitant use of progestogen therapy should be seriously considered. Therapy should be instituted as soon as possible after the menopause. The ideal duration of oestrogen treatment is unknown, but 10-15 years have generally been considered appropriate.

b. Calcium in the prevention of osteoporosis

Nutritional intake of calcium is an absolute requirement for bone health, but the threshold of calcium intake below which this is jeopardized at various stages of life is uncertain. Calcium in the diet does not substitute for oestrogen in preventing bone loss at the menopause. In contrast, randomized clinical trials in elderly women well past the menopause have found that high calcium intakes reduce the rate of loss of cortical bone, but its efficacy in preventing fractures is uncertain. Control trials are underway to examine this directly. In the meantime, it seems prudent to recommend a high intake of calcium (e.g. 1500 mg daily) in patients with established osteoporosis.

c. Fluoride

Fluoride with calcium supplements and an adequate intake of vitamin D may be used to increase trabecular bone mass in patients with severe vertebral osteoporosis. Fluoride is the only agent which has been shown to have a sustained anabolic effect on trabecular bone both at

appendicular and axial sites. The effect and its rate of onset is dose dependent as too are unwanted effects. Its effects on cortical bone mass are much less secure. It does not have an established role in the prevention of bone loss. Its use is best restricted to centres with an expertise in skeletal metabolism.

d. Vitamin D, its metabolites and analogues

Vitamin D, its analogues and metabolites have been assessed both in the prevention of bone loss and in the treatment of established osteoporosis. In the early postmenopausal period there is no evidence that vitamin D, its analogues or metabolites decrease the rate of bone loss or fracture. There are conflicting and unresolved observations concerning the effects of vitamin D metabolites to decrease the rate of bone loss and fracture in patients with established osteoporosis. A major recognized effect of vitamin D derivatives is to increase the availability of intestinal calcium for absorption, but the risks of vitamin D toxicity with 1 alpha-hydroxylated derivatives are much higher than the use of high dietary intakes of calcium. Apart from the prevention and treatment of coexisting vitamin D deficiency, the use of vitamin D derivatives is not recommended in postmenopausal osteoporosis.

e. Anabolic steroids

Currently available anabolic steroids do not have a place in preventing osteoporosis in women. They do increase bone mass in women with established osteoporosis but some concerns remain about their side-effects, particularly following oral administration. Apart from their effect on bone, they may also have a positive effect on muscle mass, which might further beneficially affect bone mass. There is currently no available evidence to suggest that the continued use of anabolic steroids results in the continual accrual of bone, and no data available on their effects on subsequent fracture rates.

f. Calcitonin

Calcitonin has been shown to prevent bone loss for periods of up to three years and may be considered as a treatment in men and those women at high risk, but who are not candidates for oestrogen therapy. Although minor side-effects are common, calcitonin is free from major side-effects. Apart from the high cost, its current use is limited by the necessity for parenteral administration. New formulations are now being tested in long-term studies and may avoid some of the problems of parenteral administration.

g. Experimental regimens

A number of drugs hold promise either as inhibitors of bone resorption or as anabolic agents. These include parathyroid hormone, the diphosphonates, progestogens and drugs utilized in cyclic and coherence therapies. These represent promising potential approaches to the prevention and treatment of osteoporosis which require further evaluation. Many other bone active compounds have been identified which may have potential benefit in modulating skeletal metabolism in osteoporosis.

The Consultation considered that clinical research facilities throughout the world are inadequate to cope with the scientific innovations. It is, therefore, recommended that urgent consideration be given to improving the efficiency of available resources for the clinical evaluation of experimental treatment regimens. In implementing this recommendation three practical further recommendations are suggested.

- i. That Member States provide the facilities for clinical investigators in bone disease.
- ii. In recognition of the disparate attitudes of Ministries of Health to drug registration of bone active compounds throughout the world, the Consultation further recommends that a Study Group be convened to consider the development of guidelines for Member States for studies of prevention of bone loss and treatment of established osteoporosis. The Study Group should consider guidelines for the

randomization of patients, blinding measurements of outcome, sample size and power calculations and the nature of the criteria for efficacy recognizing that the outcome criteria may differ for therapeutic, primary and secondary preventative measures.

- iii It is recognized that in many Member States clinical expertise in bone disease is not recognized for specialty training and this omission has significantly hampered the development of this field. Member States are recommended where appropriate to evaluate the ways in which this deficit can be remedied according to local priorities.

11. SUMMARY OF RECOMMENDATIONS AND PRIORITIES FOR WHO

This Consultation has agreed on the following recommendations outlining research activities and methods of implementation:

Research Priorities

1. To improve information on the world-wide epidemiology of osteoporosis. This will require:
 - a) standardized methods of measurement of epidemiological data;
 - b) acquisition of the incidence of various types of fracture;
 - c) bone mass measurements in various areas of the world;
 - d) continued research on the identification of risk factors;
 - e) information on the costs and consequences of fracture;
 - f) a review of current data bases and the consideration of new bases.
2. To develop improved methods for predicting the risks of osteoporosis and fractures.
3. To optimize the dissemination of knowledge to Member States with particular emphasis on:
 - a) the application of screening;
 - b) the nutritional requirements for skeletal health.

Methods of implementation

1. It is recommended that the WHO develop a separate programme on osteoporosis. In achieving this the WHO should consider the appointment of a medical officer responsible for this area and the use of collaborating centres.
2. It is recommended that the WHO convene a Scientific Advisory Committee to coordinate its future activities, with particular responsibilities to:
 - a) Establish guidelines for epidemiological research including:
 - i. methods for complete ascertainment and reporting of fracture rates;
 - ii. standards for assessing vertebral fractures;
 - iii. guidelines for measurement and reporting bone mass;
 - iv. practical and culturally-appropriate instruments for assessing potential risk factors.

- b) Acquire information on the prevalence and incidence of all fractures. The following areas of investigation are given high priority.
 - i. the prevalence of vertebral fractures in various regions, including Asia, Africa, Latin America and the Middle East, using full radiographs in representative populations;
 - ii. the incidence of hip fractures in Asia, the Middle East and Africa;
 - iii. a description of the economic consequences and morbidity due to fracture in all regions;
 - iv. the relationship between bone mass to fracture in the various regions of the world.
- c) Investigate secular trends. The group should examine methods of:
 - i. examining the relative risk of fracture for common potential risk factors, like dietary intake and physical activity;
 - ii. acquiring longitudinal data about changes in prevalence of risk factors, including bone mass, risk factors for osteopenia, falls, and risk factors for falls.
- 3. It is recommended that WHO, the EOPF and NIH establish study groups to consider:
 - (a) The nutritional requirements for skeletal health.
 - (b) Guidelines for studies of prevention of bone loss and treatment of osteoporosis.
 - (c) Application of screening and intervention in osteoporosis.



JOINT WHO/EOPF/NIAMS(NIH)
CONSULTATION ON OSTEOPOROSIS

13-15 July 1988, Geneva

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LIST OF WORKING PAPERS

1. MEDOS-88 Questionnaire
2. International epidemiology of osteoporosis, Steven R. Cummings
3. Is it possible to predict the fast bone loser just after the menopause? Claus Christiansen and Bente Juel Riis
4. Current possibilities and practice for the treatment of established osteoporosis and rehabilitation, J. Dequeker and P. Geusens
5. Non-mass factors in osteoporotic bone fragility, Robert P. Heaney
6. Nutrition and bone health, Robert P. Heaney
7. New approaches to the prevention and treatment of osteoporosis, William A. Peck
8. Consensus Development Conference Statement on Prophylaxis and Treatment of Osteoporosis

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