NAHRES-14
Vienna, 1993

COMPARATIVE INTERNATIONAL STUDIES OF OSTEOPOROSIS USING ISOTOPE TECHNIQUES

Report of an IAEA Advisory Group Meeting

28 - 30 October 1992

IAEA, Vienna, Austria

INTERNATIONAL ATOMIC ENERGY AGENCY

Summary

An Advisory Group Meeting convened by the IAEA in October 1992 made recommendations on the setting up of a Co-ordinated Research Programme (CRP) using nuclear and isotopic techniques for international comparative studies of osteoporosis. The proposed CRP will be implemented by the IAEA during the period 1993-1997. The main purpose of this programme is to undertake pilot studies of bone density in selected developing country populations for the purposes of (i) determining the age of peak bone mass in each study group, and (ii) quantifying differences in bone density as functions of the age and sex of persons in the study groups, as well as quantifying differences between the study groups in different countries. The preferred technique for bone density measurements in this study is DEXA (dual energy X-ray absorptiometry). Additional measurements of trace elements in bone (and possibly also teeth) are also foreseen using neutron activation analysis and other appropriate techniques.

NAHRES--14.

CONTENTS

ANNEXES

1. INTRODUCTION

Osteoporosis is an important bone disease of the elderly (particularly post-menopausal women) which severely limits their quality of life and is placing an increasing burden on the health-care systems in many countries. Much still remains to be learned about the aetiology of the disease, about differences in incidence and severity between population groups living in different countries, as well as about how to prevent the disease and optimize diagnosis and therapy when it occurs. More work is needed on these and other factors, and in this work there are potentially many possibilities for usefully applying nuclear and isotopic techniques.

An Advisory Group Meeting (AGM) was convened by the IAEA in October 1992 to throw more light on some of these issues. In particular, the Group was requested to advise the IAEA on the purpose and scope of future actions that could be organized within the framework of a Co-ordinated Research Programme (CRP). The meeting was attended by the experts listed in Annex 1. The Agenda is given in Annex 2. A background document prepared by the IAEA, which was provided to the experts prior to the meeting, is reproduced in Annex 3.

2. OVERVIEW OF CURRENT KNOWLEDGE OF OSTEOPOROSIS AND RELATED ISSUES OF BONE METABOLISM, AND OF CURRENT INTERNATIONAL RESEARCH PROGRAMMES IN THIS AREA

2.1. Definition of osteoporosis

It was agreed to use the most recent definition proposed by the European Foundation for Osteoporosis [1], namely that osteoporosis is a disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced fragility and a subsequent increase in fracture risk.

2.2. Epidemiology of osteoporosis

The incidence of osteoporosis, as indicated by markers such as the frequency of occurrence of hip and vertebral fractures, varies significantly from one country to another. In general, developing countries have a much lower incidence than developed ones. Within Europe there appears to be a gradient of incidence from south (lower incidence) to north. Although some of these differences may be due to under-reporting (particularly in developing countries), the general trends are considered to be real. There are also secular trends; in many countries there appears to be a real increase in the age specific incidence of the disease.

It is difficult to compare bone mass measurements between one country and another due to methodological problems. Nevertheless, there appear to be some real differences. In developing country populations, bone mass at comparable ages generally appears to be

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1. EUROPEAN FOUNDATION FOR OSTEOPOROSIS. Consensus Development Conference: Prophylaxis and Treatment of Osteoporosis. Osteoporosis Int. 1 (1991) 114-117.

TABLE I. RISK FACTORS FOR OSTEOPOROSIS

Well established

Age - elderly
Sex - female
Race - caucasian or asian

Gonadal deficiency
- Post menopausal women
- Early menopause
- Hypogonadal men

Probable

Low body mass
Excessive smoking
Excessive alcohol
Sedentary life style
Malabsorption of calcium in elderly

Possible

Low calcium intake
High Caffeine intake
High protein intake (developed countries)
Low protein intake (developing countries)
Vitamin K deficiency
Minor & trace element deficiency: B, Ca, Cu, Ga, Mg, Mn, Sr and Zn
Minor & trace element excess: Al, Cd, F, heavy metals, Na

Secondary osteoporosis

Corticosteroid excess
Excess thyroxine (thyrotoxicosis or replacement)
Multiple myeloma

This list is not exhaustive and other factors could be added if desired. The placement of some of the factors in the various categories is a little controversial. It should be noted that this is a list of risk factors for osteoporosis not fractures.

greater than in developed countries; in blacks ***peak bone mass*** is achieved at a later age (around 50 years, instead of around 30 years or earlier).

2.3. Aetiology of osteoporosis; risk factors

It is now generally agreed that osteoporosis is a multifactorial disease. Many different risk factors have been suggested, but a quantitative apportionment of risk among them is not yet feasible.

Metabolic processes involving calcium and phosphorus are felt to be of fundamental importance. These and other aspects of bone turnover are regulated by a great number of biochemical and cellular factors which are not yet fully understood. Some of the known factors include systemically acting hormones, e.g. parathyroid hormone, 1,25-dihydroxy-cholecalciferol (vitamin D), estrogens and thyroid hormones, as well as local mediators at the skeletal level such as prostaglandins, growth factors (IGF-1, TGF-β etc.) and cytokines (IL-1, IL-4, IL-6, and gamma-interferon).

The main risk factors for osteoporosis are listed in Table 1.

2.4. Diagnosis of osteoporosis (including screening)

Osteoporosis is usually diagnosed by a combination of two or more indicators, of which the most conclusive is the occurrence of a fracture (usually hip or vertebral) associated with only a minor or no traumatic event. Low bone density is also an important indicator of osteoporosis, however, only in terms of estimating the probability of a subsequent fracture. Such measurements are usually compared with locally-obtained reference values. No generally-agreed guidelines or cutoffs for bone density have yet been developed which can be applied globally.

At the present stage of knowledge, screening for osteoporosis in the general population is not considered to be cost-effective, but may be advisable in specific risk groups.

2.5. Therapy and prevention of osteoporosis

A number of different preventive strategies and therapies for osteoporosis have been developed, or are still being tested. These include physical exercise, HRT (hormone replacement therapy, usually with estrogens), calcium, calcitonin, anabolic steroids, bisphosphonates, vitamin-D, fluoride, parathyroid hormone, and the ADFR protocol (activation-depression-free-and-repeat). Many of these therapies have been shown to lead to transient, or even long term increases in bone mass. However, no consensus yet exists as to their long term benefits in relation to reducing fracture risk. Many different therapeutic trials are now in progress to try to settle this issue.

2.6. Animal and other models

No generally acceptable animal models for osteoporosis have yet been developed, though some workers have proposed using the dog or ovariectomized ewe. *In vitro* methods have useful applications for studies of biochemical and cellular processes.

2.7. Costs involved (e.g. burden to public health)

Osteoporosis is placing a heavy burden on the health care systems in many countries. According to some estimates, as many as 200 million people may be affected world-wide. In developed countries, the extra costs associated with osteoporosis have been estimated to be of the order of 2% of the total health-care budget, or in the range of US$ 4,000 - $ 8,000 per case. In developing countries, cost are expected to rise rapidly above present levels due (i) to increased incidence associated with greater affluence, and (ii) a higher proportion of older people in the population (note: by the year 2020 it is estimated than more than two-thirds of all people over the age of 60 will be living in developing countries).

2.8. Current international research programmes on osteoporosis

The WHO osteoporosis project is a cross-national study coordinated at Stanford University, USA. Candidate participating countries are Barbados, Brazil, China, Hong Kong, Hungary, Iceland and Nigeria. The principal research goals are (1) validation of cross-national data on osteoporotic fractures (based on hospital discharge records and population surveys); (2) cross-national assessment of risk factors for bone loss and fractures; and (3) determination of the age of peak bone mass and the distribution of bone mass in different populations by race, age and sex (cross-sectional and longitudinal components). Population and hospital discharge surveys are expected to begin in 1993.

The WHO Collaborating Centre for Epidemiology of Rheumatic Diseases at Huddinge University Hospital, Karolinska Institute, Sweden, has had the responsibility for design, coordination, data collection and processing for a multicentre study on hip fracture in 14 centres in 6 Mediterranean countries (Portugal, Spain, France, Italy, Greece and Turkey).

The project that started in 1987 includes a register study based on information provided by ministries of health in Europe. Major inconsistencies in data collection were found to exist, which hampers interpretation. A second part is a study of hip fracture incidence, where major differences between countries were found both within centres and between centres. Results of this are under publication. The major part of the study is a case-control study with 2,816 cases and 5,369 age and sex-matched controls to study risk factors. In the analysis phase the WHO Collaborating Centre for Metabolic Diseases at Sheffield and others have been actively involved.

A major project of the Sheffield centre is the EVOS study (sponsored by the EC), which is investigating the prevalence of vertebral fracture in 18 countries (9 EC and 9 non-EC); this study will involve 14,000 subjects and will be extended to provide information regarding fracture incidence and baseline data including non-invasive measurements of bone mass.

3. POSSIBILITIES FOR APPLYING ISOTOPIC & NUCLEAR-RELATED TECHNIQUES IN STUDIES OF OSTEOPOROSIS AND RELATED ISSUES OF BONE METABOLISM

3.1. Bone density measurement

A variety of techniques have been developed during the past few years for determining bone density. These include SPA (single photon absorptiometry, usually with

an ^{125}I isotope source), DPA (dual photon absorptiometry, usually with a ^{153}Gd isotope source), DEXA (dual energy X-ray absorptiometry) and QCT (quantitative computed tomography). Other techniques such as ultrasound and magnetic resonance are in development.

At the present time, DEXA is the preferred measurement technique. There are more than 3,000 units now installed world-wide, mostly in developed countries. Some units have almost certainly also been installed in developing countries and, in principle, information on the whereabouts of these units is available from the manufacturers.

DEXA units are presently available from four manufacturers and cost around US$ 100,000. They provide results in units of grams hydroxyapatite per cm^2. The *in vivo* precision is around 1% CV for anterior-posterior measurements of the spine, and around 2% for lateral measurements. The latter measurements are useful, despite the lower precision, since they give a better measure of trabecular bone (which is a more sensitive measure of bone loss). The radiation dose is low ($<$ 5 mrem).

Problems with DEXA include (i) uncertainties caused by body fat, (ii) difficulties in comparing results from one instrument to another, (iii) the fact that results are obtained in terms of surface density (g cm^{-2}) rather than true density (g cm^{-3}). As regards using already-existing instruments for research purposes, there is also the problem that most of them are already being fully utilized for routine clinical investigations. Quality assurance is an important issue, but is manageable with the use of phantoms and provided that the operator is sufficiently well trained.

Although DEXA is generally to be preferred to SPA, the latter still has useful applications, e.g. for measurements of the wrist. In view of the large number of units already installed world-wide, their use in any possible future IAEA programme should be considered seriously.

QCT is generally not considered to be a very appropriate technique for use in any future IAEA programme because, in comparison with DEXA, it is less available, less accurate, more expensive, and delivers a higher radiation dose to the subject.

3.2. Calcium metabolic studies using radioactive and stable isotopes

Techniques for studying calcium uptake and metabolism with radio- and stable-isotopes were developed and have been in use since the 1960s. However, up to the present time their application has been limited either by safety considerations or by the complex methodology required. Thus, detailed information on calcium transfer between body compartments has not yet been obtained. With respect to osteoporosis research, data on the efficiency of calcium absorption from the intestinal lumen via paracellular versus transcellular pathways, and on the relation of fractional intestinal absorption to urinary excretion and deposition of calcium in bone tissue at different ages would be particularly useful.

3.3. *In vivo* neutron activation analysis (e.g. for whole- or partial body calcium)

In vivo neutron activation analysis (IVNAA) is a much older technique than DEXA, and has been successfully applied in osteoporosis research for more than 20 years. It

gives a direct measure of skeletal calcium, either in the whole body, or in parts of the body, such as a limb. Other elements in bone, such as P and non-exchangeable Na can be determined simultaneously.

In comparison with DEXA, the radiation dose is significantly higher (~300 mrem), and the precision somewhat lower (~5% CV). The cost per examination is roughly comparable. At present, only a very small number of specialized research centres have access to the technique. However, in principle, it is relatively easy and cheap to assemble a suitable system, and this fact may make it attractive to some developing countries.

3.4. *In vitro* neutron activation analysis (e.g. for trace elements in bone and diets)

In vitro NAA is a highly appropriate analytical technique for the determination of trace elements in specimens of the kind that may be of interest in osteoporosis research, e.g. bone and diets. This has already been demonstrated successfully in a number of IAEA research programmes. The application of this technique in osteoporosis studies has so far not attracted much attention, but may be of interest in view of the possible role that many different trace elements may play in bone metabolism.

3.5. Stable isotope applications (energy expenditure; protein turnover)

In recent years there have been important developments in techniques using stable isotopes of hydrogen, oxygen, and nitrogen for studies in humans of energy expenditure, protein turnover and metabolism, and protein-energy interactions.

In osteoporosis research, there is some interest in being able to quantify physical activity, which is thought to play a role in the disease. The DLW (doubly-labelled water) method is, in principle, applicable in such research. However, the high cost (at present) of the ^{18}O isotope that is needed is likely to impair the widespread application of this technique.

Protein turnover and metabolism are also thought to be related in some way to the probability of developing osteoporosis. Protein forms a significant part of the organic matrix of bone. Therefore, there may be scope for applying ^{15}N- or ^{13}C-labelled proteins and amino acids in research on these factors. However, the Group was not able to identify any specific topics that are of high priority at the present time.

3.6. Radioimmunoassay (RIA)

Several of the hormones involved in osteoporosis (e.g. PTH, estrogens), biochemical markers of bone formation (e.g. osteocalcin), and other biochemical substances possibly related to the disease (e.g. interleukins), are amenable to study by RIA. Commercial kits are available for several of them.

The Group did not identify any particular problems requiring co-ordinated research to further develop or to improve these techniques. However, it was agreed that, in any future research programme on osteoporosis supported by the IAEA, RIA should be regarded as an appropriate isotope technique justifying support by the IAEA.

3.7. Other nuclear-related techniques

The only other nuclear-related technique discussed by the Group was SIMS (secondary ion mass spectrometry). This is a surface analysis technique which, in recent years, has undergone significant improvements in spatial resolution. It permits the determination of a large number of elements at concentration levels exceeding 1 ppm (mg/kg) with a spatial resolution of around 20 nm. As such it is potentially able to reveal the microdistribution of elements in bone sections. Since many of the elements of possible interest in osteoporosis research can be determined with high sensitivity, SIMS may be a useful tool to include in any future IAEA programme on osteoporosis. Although the investment costs are very high (~ US$ 1 million), many instruments are already available in institutes engaged in materials science. (Other principles, such as laser ablation mass spectrometry are also potentially applicable in such work.)

4. ORGANIZATION OF THE IAEA'S NEW CO-ORDINATED RESEARCH PROGRAMME (CRP) ON OSTEOPOROSIS

After discussing various options and priorities, the Group decided to recommend to the IAEA the setting up of a CRP comprising a core programme and various supplementary programmes. This CRP should, as far as possible, be organized in collaboration with WHO's Osteoporosis Project, and in such a way that these programmes (WHO's and the IAEA's) would be mutually supportive of each other.

4.1. The core programme

Purpose and scope

The main purpose of the core programme is to undertake pilot studies of bone density in selected developing country populations for the purposes of (i) determining the age of peak bone mass in each study group, and (ii) quantifying differences in bone density as functions of the age and sex of persons in the study group, as well as quantifying differences between the study groups in different countries. Study groups selected for inclusion in the IAEA's programme should be chosen so as to be complementary to those included in WHO's programme.

Measurements are recommended in subjects of both sexes across the age range 15-50. At least 15 subjects are required in each 5-year age range (i.e. altogether 105 subjects of each sex). As far as possible, these subjects should be representative urban residents. The time frame for the project, which should be specified, should take account of possible seasonal differences in bone density. Guidance will be provided later on techniques for the selection of representative subjects, and on the information to be collected from each subject (by questionnaire).

Measurements of bone density are required (i) in the lumbar spine region (anterior/posterior), and (ii) at the femoral neck. Whole body measurements should also be included, if possible, and retained for later evaluation, together with measurements of an appropriate phantom.

Nuclear and isotopic techniques to be supported

The preferred technique for bone density measurements in this study is DEXA, and its use should be made obligatory except in special circumstances. Other methods for studying age of peak bone mass should be accepted only if the study group is of special interest, and if there is otherwise no access to DEXA. Suitable techniques to use in these circumstances include SPA, DPA and IVNAA.

Quality assurance and quality control

An important purpose of the CRP is to obtain data which are comparable from one study group to another. To this end, an appropriate quality assurance (QA) programme should be developed and implemented. In addition to requiring the development and use of common QA protocols, there will be a need to use a single bone phantom to standardize the measurements made at different centres. This phantom should be circulated to all participants, and the results should be evaluated by a reference laboratory. It is important for the measurement techniques to be validated at an early stage of the research programme.

4.2. The supplementary programme

Trace elements are supposed to play a role in bone metabolism; alternatively, bone is thought to serve as a storage organ for many of them. However, there is very little reliable data on the trace element composition of bone or on differences in composition between persons living in different parts of the world. In view of the possible importance of this topic in relation to osteoporosis, and recognizing the IAEA's unique analytical competence in this area, the Group agreed to recommend the inclusion of a supplementary programme designed to obtain reliable data on trace elements in bone.

Purpose and scope

All participants in the core programme are recommended, where possible, to undertake studies of the trace element composition of bone, or to provide suitable bone samples to the IAEA.

In order to study cross-national differences in bone composition, study centres are recommended to obtain autopsy samples of rib bone from healthy accident victims. These may be persons of either sex, but should preferably be in the age range 20-50 years. Guidance will be provided later regarding procedures for the selection of these subjects in order to be reasonably confident that they are representative of the population. The amount of bone to be taken (which should be sufficient to permit other kinds of study, e.g. of biomechanical strength), and the sampling procedure, will also be specified later. At least 8 subject should be included in each study group.

For the study of possible differences in trace element composition between osteoporosis patients and controls, 2 or 3 study centres should be identified that can arrange to collect suitable biopsy specimens (ileac crest). These study centres should be chosen to include countries with respectively high and low incidences of osteoporosis. Prior to initiating this phase of the programme, the IAEA should explore the feasibility of analysing such samples.

In view of the difficulty, in some countries, of obtaining autopsy samples, the use of tooth samples should be considered as an alternative. To this end, it would be useful if one or more centres could undertake studies to validate the use of tooth samples as indicators of skeletal composition (with respect to minerals and trace elements).

The elements of potential interest include Al, B, Ca, Cd, Cu, F, Mg, Mn, Na, Sr, Zn and other heavy metals. Any appropriate analytical method may be used provided that it has been properly validated. NAA has already been demonstrated to be an appropriate method for many of these elements in centres that have access to this technique.

A quality assurance programme should be developed and instituted by the IAEA's Seibersdorf Laboratory (see section 5).

Participants in the CRP should also be encouraged to develop their own supplementary programmes. The appropriate use of any of the nuclear-related techniques discussed in section 3 would help to justify the IAEA' support for such work.

4.3. Selection of participants

The main criterion for selection of CRP participants in developing countries is access to DEXA. One member of the Group (Dr.Pommet) had access to information according to which DEXA units already exist in the following developing countries (among others): Argentina, Brazil, Chile, China, Columbia, CSFR, Ecuador, Greece, Hungary, Korea (Republic of), Lebanon, Mexico, Philippines, Poland, Saudi Arabia, Singapore, Tunisia, Turkey and Venezuela. The final selection of participants should be made in consultation with the technical officer responsible for WHO's osteoporosis programme.

Another important criterion in selecting CRP participants is that the countries included in the programme should cover a wide range of incidence of osteoporosis. On various grounds, Turkey has already been identified as an interesting country to include in such studies. Therefore the IAEA should make a special effort to find a suitable Turkish participant in the CRP. Other countries may also merit priority for inclusion in the CRP, e.g. India on account of the wide variability in the intake of fluoride, with consequential effects on bone density.

5. OTHER KINDS OF IAEA SUPPORT REQUIRED

The proposed supplementary study of the trace element composition of bone requires a reference analytical laboratory with competence in this area. The Group recommended that the IAEA's Seibersdorf Laboratory should serve in this function. In addition to a limited number of "backup" measurements, this implies the provision of appropriate analytical quality control services, including the supply of suitable analytical reference materials.

The Group recommended the IAEA to give favourable consideration to suitable requests from institutes in developing countries for technical co-operation (training, experts, equipment) in support of the kinds of applications discussed in this report.

In addition, it was recommended that the IAEA should organize a suitable meeting of experts to review present knowledge of the role of trace elements in relation to bone metabolism, composition and structure, and to suggest testable hypotheses. In preparation for this meeting it would be useful to compile information on the trace element composition of bone as reported in the literature, as well as by users of the IAEA's former bone reference material, H-5 (and similar reference materials from other suppliers).

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Annex 2

AGENDA

WEDNESDAY, 28 OCTOBER 1992

9:00 - 9:15 REGISTRATION

9:15 - 9:30 OPENING: *Welcome & Introductions*

9:30 - 12:30 SESSION 1: *Chair:* S.S. Krishnan

Background and purpose of the meeting (Scientific Secretary)

Adoption of the agenda

Discussion topics 1.1 - 1.3 *

14:00 - 17:30 SESSION 2: *Chair:* E.V. McCloskey

Discussion topics 1.4 - 2.4 *

THURSDAY, 29 OCTOBER 1992

9:00 - 12:30 SESSION 3: *Chair:* R. Pommet

Discussion topics 2.5 - 3.4 *

14:00 - 17:30 SESSION 4: *Chair:* S. Maggi

Discussion topics 3.5 - 4.6 *

FRIDAY, 30 OCTOBER 1992

9:00 - 12:30 SESSION 5: *Chair:* E. Allander

Remaining discussions

Report of the meeting

14:00 - 15:00 SESSION 6:

Report of the meeting

CLOSING OF THE MEETING

* See discussion topics listed overleaf

DISCUSSION TOPICS

1. Overview of current knowledge of osteoporosis and related issues of bone metabolism, and of current international research programmes in this area

    1.1. Definition of osteoporosis
    1.2. Epidemiology of osteoporosis (nationally and internationally)
    1.3. Aetiology and prevention of osteoporosis; risk factors
        life-style and environmental factors
        genetics
        nutrition
            macro-nutrients - energy, protein, etc.
            micro-nutrients - vitamins, trace elements, etc.
        other risk factors?
    1.4. Diagnosis of osteoporosis (including screening)
    1.5. Therapy of osteoporosis
    1.6. Other relevant human studies (e.g. effects of weightlessness)
    1.7. Animal models
    1.8. Costs involved (e.g. burden to public health & costs of screening)

2. Possibilities for applying nuclear and isotopic techniques in studies of osteoporosis and related issues of bone metabolism

    2.1. Bone density by dual photon absorptiometry
    2.2. Calcium metabolic studies using radioactive and stable isotopes
    2.3. In vivo neutron activation analysis (e.g. for whole- or partial body calcium)
    2.4. In vitro neutron activation analysis (e.g. for trace elements in bone and diets)
    2.5. Stable isotope applications (energy expenditure; protein turnover)
    2.6. Radioimmunoassay (e.g. for hormones related to bone metabolism)
    2.7. Other techniques

3. Organization of the Agency's new Co-ordinated Research Programme (CRP) on osteoporosis

    3.1. Purpose and scope:
        narrow or broad scope (core/supplementary programmes)
        related to aetiology or therapy (or both)
    3.2. Nuclear and isotopic techniques to be supported
    3.3. Equipment needed
    3.4. Possible participants
        in developed countries
        in developing countries
    3.5. Protocols required for implementation of the CRP
    3.6. Collaboration with other organizations
    3.7. Possible sources of additional funding
    3.8. Other matters

4. Other kinds of Agency support required
    4.1. Laboratory services
    4.2. Quality assurance and reference materials
    4.3. Training
    4.4. Publications and information services
    4.5. Meetings
    4.6. Other matters

Annex 3

BACKGROUND DOCUMENT

INTERNATIONAL COLLABORATIVE RESEARCH PROGRAMME ON OSTEOPOROSIS WITH SPECIAL REFERENCE TO THE USE OF ISOTOPE TECHNIQUES

1. INTRODUCTION

Osteoporosis is an important disease of the elderly (particularly post-menopausal women) which severely limits their quality of life and is placing an increasing burden on the health-care systems in many countries. The incidence of the disease shows wide variability among different population groups and appears to be increasing in many of them, not only due to increasing life expectancy but also, apparently, to an age specific increase in incidence. Physical activity, diet (particularly, but not only, calcium intake) and other environmental factors are assumed to play an important role in this, but the available data do not permit the drawing of final conclusions. Because the incidence varies so much from one population group to another, it is reasonable to assume that international comparative studies will throw important new light on the aetiology of this disease. The programme proposed here will, in the first place, be co-ordinated by IAEA and will run for a 5 year period from 1993-1997.

2. PURPOSE AND SCOPE OF THE PROPOSED PROGRAMME

The detailed purpose and scope of the proposed programme will be defined later by an Advisory Group (see section 4). However, some or all of the following topics are expected to be included:

- comparative studies of the incidence and severity of osteoporosis in different population groups, e.g. by measurements of bone density in selected subjects;

- comparative measurements of calcium intake, uptake, turnover and body-content in affected individuals and in normal subjects;

- studies of other elements known to be important in bone metabolism or suspected of playing a role in the development of the disease (e.g. Al, B, Cd, F, Mg, Mn, Na, Sr and Zn), including measurements of their concentrations in diets and in autopsy samples of bone;

- comparative studies of physical activity as determined, for example, by measurements of energy expenditure;

- comparative studies of different therapies;

- development and validation of protocols, techniques and quality control materials for use in making the above mentioned measurements.

3. JUSTIFICATION FOR AN IAEA ROLE IN THIS PROGRAMME

IAEA is interested in promoting the use of isotope techniques in human nutrition research - particularly in developing countries - and already has many years of experience in organizing co-ordinated research and providing technical assistance in this field. Relevant isotope and/or radiation techniques that may be included in the research programme are:

- measurements of bone density by dual photon absorptiometry (using photons from isotopes or X-rays);
- isotope studies of calcium uptake and turnover (using either radioactive or stable isotopes);
- in vivo neutron activation analysis of whole-body or partial-body calcium in affected persons (and possibly also in normal controls);
- measurements of other elements (e.g. Al, B, Cd, F, Mg, Mn, Na, Sr and Zn) in diets and bone samples by nuclear related techniques (e.g. neutron activation analysis);
- determination of energy expenditure in selected subjects by the doubly-labelled water technique and of protein turnover using ^{15}N-tracer;
- determination of hormones related to bone metabolism using radioimmunoassay.

Important note: It is not intended to restrict IAEA support solely to the use of these techniques. From IAEA's point of view eligibility for support depends only on the inclusion of some aspect of the use of isotope techniques (even if only as a rather minor component of the programme), and the simultaneous use of other complementary techniques will indeed be actively encouraged.

4. IAEA SUPPORT TO THE PROPOSED PROGRAMME

IAEA is planning to organize an Advisory Group Meeting (in October 1992) to help define the purpose, scope and administrative arrangements for this programme, and to draw up a tentative list of participants. Thereafter, some funding will be available for a 5 year co-ordinated research programme with up to 15 participants (of which more than half are expected to be institutes in developing countries; the rest in developed countries). Additional support is also, in principle, available under the IAEA's Technical Co-operation Programme.

5. COLLABORATION WITH OTHER ORGANIZATIONS

It is anticipated that this programme with be planned and implemented in co-operation with WHO. Suggestions for collaboration with other interested organizations would also be welcomed.

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