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1. Introduction

A WHO Scientific Group on Research on the Menopause in the 1990s met in Geneva from 14 to 17 June 1994. The meeting was opened by Dr Hu Ching-Li, Assistant Director-General, on behalf of the Director-General.

The menopause is the time of a woman's life when reproductive capacity ceases. The ovaries stop functioning and their production of steroid and peptide hormones falls. A variety of physiological changes take place in the body; some of these are the result of cessation of ovarian function and related menopausal events, others are a function of the ageing process. Many women experience symptoms around the time of menopause, most of which are self-limiting and not life-threatening, but are none the less unpleasant and sometimes disabling. The prevalence of menopause-related symptoms among women in developing countries is not well known.

More important than the immediate symptoms of the menopause are the effects of hormonal changes on many organ systems of the body. The most extensively studied of these are the cardiovascular and the skeletal systems. Both are adversely affected by the inevitable ageing process as well as by postmenopausal hormonal changes. The effects on the cardiovascular and skeletal systems have been documented in developed societies, but little research has been carried out in developing countries.

To ameliorate the immediate and long-term consequences of menopause, hormonal therapies have been recommended and are being used extensively in some societies. The therapies themselves have created new concerns about the increased risk of neoplasia of the endometrium and possibly the breast. Hormonal interventions raise complex issues with respect to health benefits achieved relative to their cost in both health and monetary terms.

The age at which natural menopause occurs is between the ages of 45 and 55 for women worldwide. Women spend a significant part of their lives in the postmenopausal state. In 1990 there were an estimated 467 million women aged 50 years and over in the world (*1*). This number is expected to increase to 1200 million by the year 2030. Although life expectancy at birth varies significantly across countries, for women who reach the age of 50 years, life expectancy is remarkably similar throughout the world (*2*). This apparent discrepancy occurs because infant and child mortality are the primary determinants of life expectancy at birth, whereas by middle age these factors are no longer operative. Table 1 shows life expectancy at birth and at the age of 50 for women in selected countries in different regions for which data are available (*2, 3*). Once women have reached 50 years of age, life expectancy is between 27 and 32 years except in the Islamic Republic of Iran, where it is only 22.5 years. The data from the Islamic Republic of Iran are from 1972, the most recent year for which reliable data are available.

Table 1
Life expectancy at birth and at 50 years of age for females in selected countries in the 1970s and 1980s[a]

Country and year	Life expectancy (years)	
	At birth	At age 50
Argentina, 1975-1980	72.1	28.4
Canada, 1980-1982	79.0	31.5
France, 1980-1982	78.4	31.1
Iran (Islamic Republic of), 1972	55.6	22.5
Japan, 1984	80.2	32.0
Mali, 1976	49.7	27.0
Mexico, 1975-1980	66.3	27.0

[a] Data from references *2* and *3*.

In 1980, WHO convened a Scientific Group to review the existing information on the menopause, and to make recommendations for future research and clinical practice (*4*). In response to the recommendations made in that report, attention has been given to population-based studies of the normal menopause, age at menopause and the transition to the postmenopause. Symptoms of the menopause have been evaluated from the perspective of normal populations and not just selected clinic groups. The importance of contraception for women approaching the menopause (i.e. in the late premenopause) has been recognized by researchers, clinicians and governmental regulatory bodies. Numerous studies have been conducted on the benefits of hormone therapy in reducing the risks of cardiovascular diseases and osteoporotic fractures in postmenopausal women. This research has also necessitated the continued study of the effects of hormone therapy on the risks of endometrial cancer and breast cancer. These studies have produced few conclusive answers. Despite the previous recommendations little is known about issues relating to the menopause in the developing world: almost all the research to date has been devoted to women in developed countries. The little cross-cultural research that has been done suggests that findings from developed countries about the menopause, its problems and their treatment, may not be generalized to women living in other parts of the world. Even within developed countries the data on risks and benefits of hormonal therapy are inconclusive and other therapies have received inadequate attention.

The present Scientific Group addressed emerging issues related to the menopause and updated information on topics covered by the Scientific Group that met in 1980. In some areas knowledge is now sufficient to

allow recommendations to be made on clinical practice, public health and health policy. The present Group also identified and described the areas where research needs are greatest, and emphasized the necessity for gaining information on women in the developing world.

2. Types of studies

As in all research, the methods used in the design, measurement and analysis of studies of the menopause are primary determinants of the validity of their findings. In menopause research, the most highly regarded studies use descriptive and analytical epidemiological methods and controlled clinical trials. Qualitative methods of data collection and presentation are also sometimes needed.

2.1 Descriptive observational studies

Descriptive studies include retrospective, cross-sectional and prospective research designs. The problems of determining age at menopause will be used to illustrate the advantages and disadvantages of each design.

Retrospective designs are the simplest and may be the only approach possible in small populations. The average age at menopause is determined by asking postmenopausal women to recall the date of their last menses. The reliability of the final estimate will depend on the accuracy of their recollection and will be partly determined by the length of time that has elapsed since they last menstruated. The longer the time since the last menstrual period, the more likely it is that women will have rounded the figure to the nearest 5 or 10 years (*5*).

Cross-sectional studies usually include both premenopausal and postmenopausal women and set upper and lower age boundaries roughly equidistant from the expected mean age at menopause. Hence they require a large total population from which to select their age-defined sample. The problems found with retrospective data still occur, but by narrowing the age range of the population surveyed, these studies have greater control over the length of the recall period and thus over the quality of the data obtained. Under- or overestimation of age at menopause may occur: underestimation because late premenopausal women in the sample will have, on average, a later age at menopause than the women who are already postmenopausal, and overestimation because the skewed distribution of age at natural menopause may result in exclusion of women who are very young when they reach the menopause.

In *prospective designs*, a group of late premenopausal women are recruited to the study and followed at regular intervals until they stop menstruating. Although more complex and expensive to implement, this design is the preferred method of establishing age at menopause.

Although the above examples are based on establishing age at menopause, the same three designs have been used to collect data on many other aspects of the menopause. Regardless of the area of study, many of the same qualifications on the reliability of the data apply.

2.2 Analytical epidemiological studies

Analytical epidemiological studies include both cohort and case-control designs. In cohort studies, women are defined in terms of their exposure or non-exposure to a particular factor (such as hormone therapy). In case-control studies, women are selected for the presence or absence of the outcome of interest (such as coronary heart disease).

Particular problems associated with these studies include:

- failure to use appropriate control groups that are representative of the source population from which the cases arise (case-control studies);
- failure to define appropriate comparison groups with equivalent opportunity to be exposed to the factor of interest (cohort studies) (for example, ensuring that women in the hormone-user and non-hormone-user groups have equivalent access to medical care);
- failure to analyse women with very different risk profiles separately (for example, separating women who had a surgically or medically induced menopause from those who had a natural menopause).

Good research design can be used to avoid some of these problems; for example, by the use of appropriate analytical techniques or the careful choice of control groups. The fundamental problem with analytical observational studies, however, is that they can be used to identify associations (such as an association between coronary heart disease and the use or non-use of hormone therapy), but they cannot definitively identify cause-and-effect relationships.

2.3 Interpretation of risk estimates from analytical epidemiological studies

Relative risk is an index of association. In cohort studies it is calculated directly as the ratio of the incidence rate of disease in a population exposed to the factor of interest (e.g. users of hormones) to the incidence rate in a population not exposed. The calculation for case-control studies is indirect, resulting in an "odds ratio", which, under most circumstances, is a good estimate of the relative risk. Other evidence is required before a cause-and-effect relationship can be established between a factor (such as postmenopausal hormone therapy (PHT)) and the development of a disease (such as coronary heart disease). If an increased (or decreased) relative risk is observed in an epidemiological study, the three most likely explanations are:

- chance
- bias, including confounding
- a causal relationship.

The first two possibilities must be ruled out before a cause-and-effect relationship can be considered plausible.

Five questions also need to be addressed before deciding whether an association is likely to be causal. These are:

- Is the relative risk large? (A causal hypothesis cannot be dismissed on the grounds that the observed association appears to be weak, but it is difficult to exclude bias as an explanation for relative risks close to 1.0.)
- Have similar results been obtained in other studies, including those using different study designs?
- Is the risk of disease related to the level of exposure (e.g. the dosage or duration of use of hormones)?
- Is the time sequence between exposure (e.g. use of hormones) and the development of disease consistent with a causal explanation?
- Do the results of experiments in appropriate animals and of other laboratory research support the association, and is the association consistent with known facts about the disease?

The strongest evidence for a cause-and-effect relationship in an observational study would come from a positive answer to all five questions. At the same time, the interpretation of risk estimates from observational studies (such as case-control and cohort studies) is often very difficult, and careful judgement is required.

If a causal link can be considered plausible, a measure of the absolute (rather than relative) risk is required in order to assess the public health importance of the finding. This absolute risk will depend on both the magnitude of the relative risk and the underlying incidence of the disease in the population being considered.

2.4 Controlled clinical trials

Clinical trials should be based on the principle of random assignment; for example, women should be randomly assigned to treatment with either a pharmaceutical agent or placebo. The placebo alternative, which is identical in appearance to the active agent, is necessary in order to avoid subjective assessment of disease outcome between groups. In a double-blind trial, neither the women nor the investigator should know to which group a woman was assigned until the end of the trial.

There have been relatively few well-designed trials of PHT or other methods of treatment for problems of the menopause (such as calcium or physical exercise to minimize bone loss). Although clinical trials are the preferred design, the difficulties involved in their use can be illustrated from trials of PHT. Side-effects (especially the bleeding associated with combined therapies) are likely to reveal whether a woman has been assigned to the hormone-user group or to the placebo group. If the women recruited to a trial have already used PHT, they are more likely than new users to be aware of the side-effects of the therapy, but are also more likely to tolerate these effects since they would otherwise be

unlikely to volunteer for such trials. Therefore, if new users are recruited, the risk of drop-out from the study may be higher among these women than among those who have already used PHT.

The design of randomized trials should incorporate the key elements listed below.

- Careful attention should be paid to the adequacy of placebo controls, the impact of placebo "run-in" periods (during which it becomes clear whether or not patients are likely to comply with treatment), and monitoring of the extent to which "blinding" is maintained throughout the treatment period, so that this can be used as a co-variable adjustment in the analysis, if necessary.
- The findings should be analysed according to the "intention to treat" principle, with comparable follow-up of all subjects whose therapy (active or placebo) is discontinued.
- The women recruited should not have been recent users of any form of PHT (or any other therapies under study), so that valid estimates of adverse effects can be made.
- Women should be classified by type of menopause (natural or induced) so that separate estimates of effect can be obtained for these separately randomized groups.

2.5 Qualitative and multidisciplinary research

2.5.1 *Qualitative research*

The main types of qualitative method used in research on the menopause are in-depth interviews, ethnographic studies and policy analysis. The first of these methods is used primarily to elicit women's attitudes and beliefs about ageing and reaching the menopause. Women are usually interviewed individually, but the use of focus groups is increasing. While the questions asked by the interviewer may be structured, the responses are not. This approach is quite different from the predetermined, closed-category question-and-answer format used in epidemiological research, but is the appropriate method when the objective is to determine the meaning of the menopause from a woman's perspective.

An ethnographic study will include interviews, but also presumes that the researcher spends time observing and participating in the daily activities of the community in which the study is located. A study of Mayan women, for example, included close observation of what women ate, how women carried loads, their physical work in agriculture and how they were treated as they grew older (*6*). Ethnographic research is time-consuming, but necessary to understand the sociocultural context of the menopause for women.

Policy analysis tends to rely on documents and published material, although interviews with policy-makers may also be used. A review of changes in medical policy relative to the prescription of hormone therapy, for example, was based on an analysis of all the articles on the

menopause published in two leading medical journals over a period of 10 years (*7*).

Each of the above methods produces different forms of data, which are rarely in numerical form and cannot be analysed using standard statistical techniques. The use of computers, however, is transforming analytical techniques in qualitative research.

2.5.2 *Multidisciplinary research*

The choice between qualitative and quantitative research designs depends on the nature of the research problem, but some problems are best investigated using two or more methods. A study of Mayan women, for example, combined ethnographic data with measures of bone density (*6*). A questionnaire-based survey of attitudes towards the menopause held by Japanese women was combined with a series of in-depth interviews with both women and physicians on the changing roles of women in Japanese society (*8*). Such designs are unusual, but as these examples suggest, they are particularly valuable when research is being done in settings where little is known about the social and cultural context of the menopause.

3. Demography of the menopause

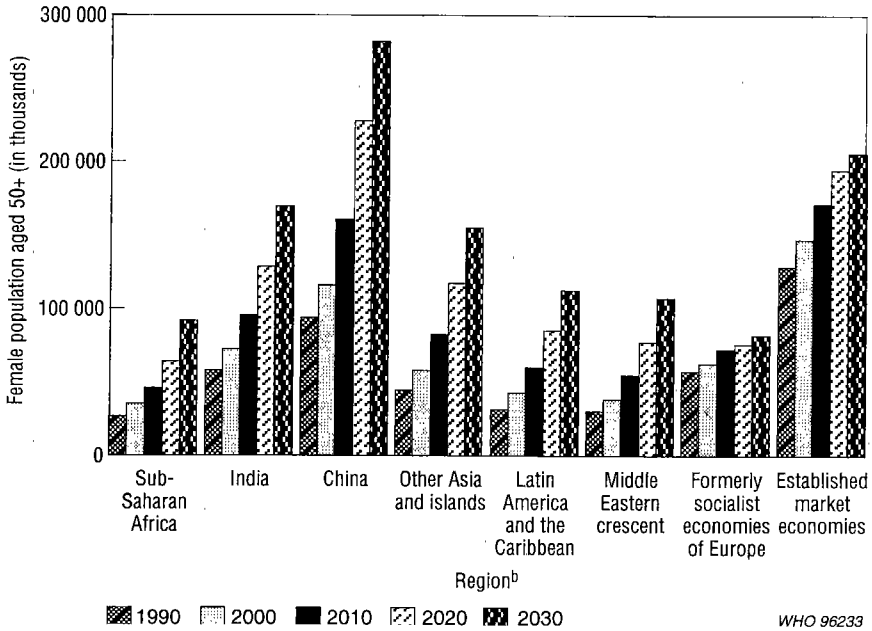
3.1 Population growth

The average age at which menopause occurs is approximately 50 years; it is possible that some variability exists between developed and developing countries. This figure is generally used in estimates of the number of postmenopausal women living in various parts of the world. Projections of the world population to the year 2030, available from the World Bank's 1993 *World development report* (*1*), have been used to describe the size and distribution of the population of postmenopausal women. These population projections divide the world into eight geographical regions[1] designed to be homogeneous with respect to their economies, social structures and epidemiological characteristics.

[1] The regions are as follows:

1. Sub-Saharan Africa (SSA): Africa, excluding countries of the Mediterranean littoral, and the islands of Mauritius, Réunion and the Seychelles.
2. India.
3. China.
4. Other Asia and islands (OAI): Asia, excluding China, India, Japan, the republics of the former USSR, and the Middle East as far east as Pakistan, and Oceania, excluding Australia and New Zealand.
5. Latin America and the Caribbean (LAC): the Americas and the Caribbean, excluding Canada and the United States of America.
6. Middle Eastern crescent (MEC): the Middle East as far east as Pakistan, North Africa and the predominantly Islamic republics of the former USSR.
7. Formerly socialist economies of Europe (FSE): the countries of eastern Europe including Belarus, Russian Federation and Ukraine.
8. Established market economies (EME): Australia, Canada, Japan, New Zealand, the United States and western Europe.

Figure 1
Population of postmenopausal women by region, 1990–2030[a]



[a] Reprinted from reference 9, with kind permission from Elsevier Science Ireland Ltd, Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.

[b] See footnote on page 7.

These population projections indicate that in 1990, there were approximately 467 million women in the world aged 50 years and over. This number is expected to increase to 1200 million by the year 2030 (9). Fig. 1 shows the projected population of postmenopausal women by region for each decade from 1990 to 2030. In 1990 40% of postmenopausal women lived in industrialized regions and 60% lived in developing countries. By 2030, the proportion of postmenopausal women living in industrialized regions will have declined to 24%, and 76% will be living in developing regions (China alone will account for 23% of the total). In 1990, about 25 million women worldwide reached the menopause; this number is expected to double by the late 2020s.

Postmenopausal women make up a relatively small proportion of the population in developing countries (ranging from 5% to 8%), whereas in industrialized countries they make up over 15% of the total population. By 2030, the proportion of postmenopausal women in the total population will have increased everywhere, most dramatic increases being from 8% to 17% in China, and from 15% to 23% in the industrialized world.

An average annual growth rate of 2–3.5% in the number of women aged over 50 is projected for the developing regions between 1990 and 2030. A growth rate of 1.5% is predicted for the industrialized regions and is expected to fall to below 1% by the 2020s. The primary factor

determining this rate of growth is the relative size of the cohorts born 50 years earlier, rather than any large changes in mortality patterns.

The average median age of postmenopausal women is around 62 years, varying from 60 years in sub-Saharan Africa to 65 years in the industrialized world. By 2030 it is predicted that these median ages will have increased to 64 years globally, and to 68 years in the industrialized world.

3.2 Menopause and mortality

Depletion of steroid hormones at the menopause may influence cause-specific morbidity and mortality in later life. The groups of diseases most likely to be affected are cardiovascular disease and malignant neoplasms. In industrialized countries, women of all ages have lower age-specific cardiovascular mortality rates than men in the same age group. This advantage for women diminishes during middle age, so that by the age of 75 cardiovascular disease mortality rates for women are almost as high as for men. Data on disease-specific mortality rates in the developing world are generally poor, but the patterns observed in the industrialized world appear to be followed in the developing world as well.

Age-standardized cancer mortality rates are lower for women than for men in most populations for which adequate data are available. On an age-specific basis, however, the mortality rates increase rapidly for women in the early and mid-reproductive years, but the rate of increase decreases towards the end of the reproductive period and after the menopause. In the industrialized world, cancer mortality rates are often higher for women than for men in the mid-reproductive years, after which the mortality rates for men rise much faster than those for women. For the few developing countries for which adequate data are available, the patterns appear to be similar, with perhaps even higher mortality rates for women than for men in the mid-reproductive years. Much of the higher mortality rate among women in the mid-reproductive years is accounted for by cancers of the breast and cervix that have no male counterpart, but mortality rates from cancers of other sites are also often higher among women than among men in this age group.

In an attempt to evaluate possible effects of the menopause on mortality, age-specific mortality rates were extracted from the *World health statistics annual* (*10*). Countries were grouped in such a way as to be consistent with the classification established in the *World development report* (*1*). The number of geographical regions and the number of countries within each region are reduced, primarily because countries from which data were inadequate were excluded. Within the four regions considered,[1] countries with large populations were selected so that

[1] The regions and countries were as follows:

1. Established market economies (EME): Italy, Japan, the United Kingdom and the United States.
2. Formerly socialist economies of Europe (FSE): Kazakstan and the Russian Federation.
3. Latin America and the Caribbean (LAC): Argentina and Mexico.
4. China (includes data from both urban and rural areas).

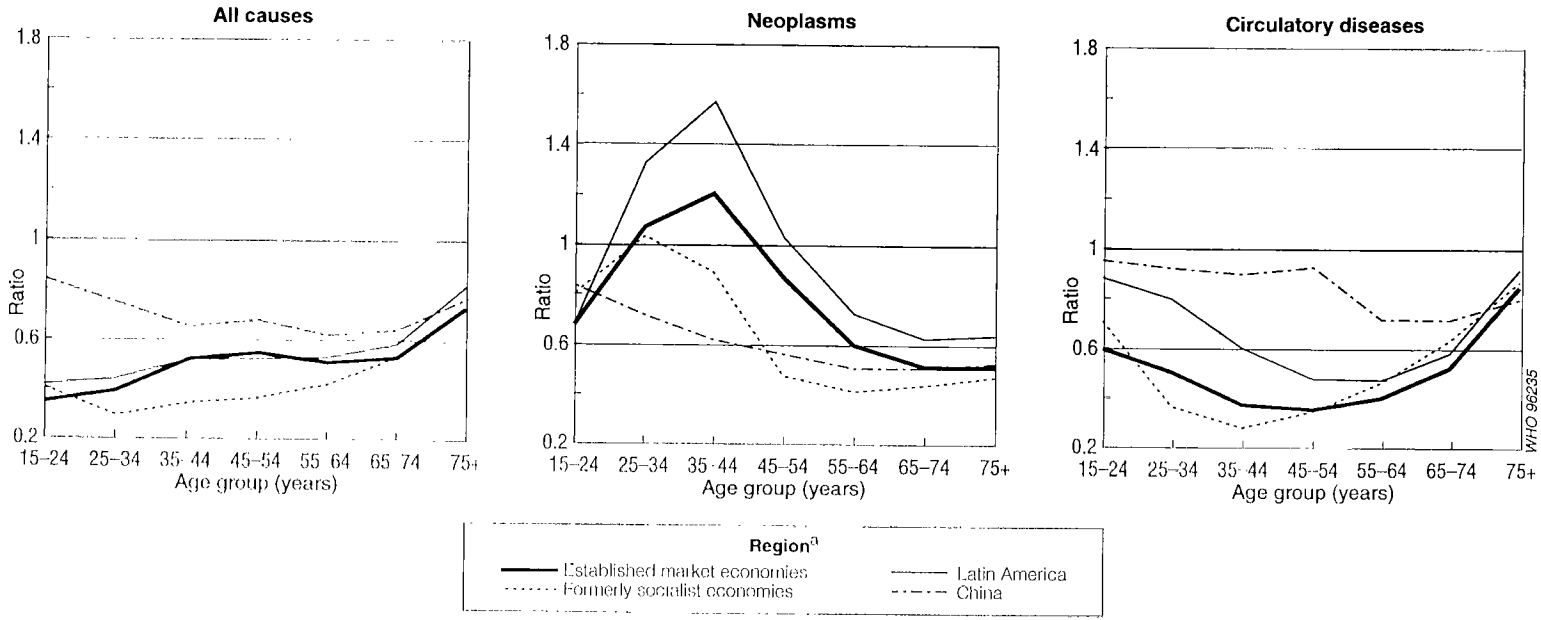
precise mortality estimates could be generated. The most recent data available from each country were used (from 1990, 1991 or 1992). For each region, the means of the country-specific mortality rates for different age groups were calculated for all causes and for malignant neoplasms and diseases of the circulatory system identified, respectively, by the codes 08-14 and 25-30 from the *International Classification of Diseases, ninth revision* (Basic Tabulation List, ICD-9) (*11*).

The ratios of female to male mortality rates by age and broad cause (Fig. 2) show quite different patterns for malignant neoplasms and for circulatory diseases. For malignant neoplasms these ratios are high for the reproductive years and then fall through the menopausal transition and remain low. Thus, in terms of mortality from malignant neoplasms, the menopause may have a beneficial effect on women. In contrast, for circulatory diseases, the ratios are consistently less than unity and reach a minimum between the ages of 40 and 50. Hence, the overall mortality rates among women are lower than those among men throughout the reproductive years and then increase after the menopause. This increase could be interpreted as an adverse health impact of the menopause, though other interpretations are clearly possible.

3.3 Conclusions

1. In 1990, it was estimated that there were 467 million postmenopausal women worldwide. This figure is expected to increase sharply over the next 40 years to a total of 1200 million by 2030.
2. The rate of increase in the number of postmenopausal women is substantially faster in the developing world than in the industrialized world. In 1990 40% of postmenopausal women lived in the industrialized world and 60% in the developing world. By 2030 the proportion living in the industrialized world is expected to fall to 24% while the proportion living in the developing world will increase to 76%.
3. Age-specific mortality rates, and the ratio of mortality rates in women to those in men at different ages, may provide some indication of the health consequences of the menopause. The diseases most likely to be affected by the hormonal changes at the time of the menopause are circulatory diseases and cancers.
4. Aggregate data on cancer mortality suggest some health benefits associated with the menopausal transition. On the other hand, data on circulatory disease mortality are broadly consistent with a protective effect of the reproductive period that diminishes gradually after menopause. In both cases the observed patterns could be explained in many other ways.

Figure 2
Ratio of female to male age-specific death rates



[a] See footnote on page 9.

3.4 Recommendation

National health authorities should examine the implications of the projected rapid growth in the number of postmenopausal women between 1990 and 2030 and should anticipate the provision of relevant health services, education and promotional activities to cope with the health needs of women in their postmenopausal years.

4. Endocrinology of the normal menopause

4.1 Background

Cessation of ovarian function and monthly menstruation is a normal concomitant of ageing in all women and is associated with the end of reproductive capability. The biological basis for these events is well established, being dependent on changes in ovarian structure and function. During the menopause, there is a reciprocal relationship between ovarian hormone levels, which decline, and pituitary gonadotrophins, which increase.

The ovarian hormones are divided into two classes: the steroids, primarily estradiol and progesterone, and the peptides, primarily inhibins and activins. Estradiol and the peptide hormones are secretory products of the ovarian granulosa cells, the major cell type of the ovarian follicle, whereas progesterone is a product of the corpus luteum. The primary biological properties of the peptide hormones are implied by their names; inhibin suppresses synthesis and secretion of pituitary follicle-stimulating hormone (FSH) whereas activin stimulates FSH secretion.

In addition to FSH, the other relevant pituitary hormone is luteinizing hormone (LH). Secretion of LH is controlled primarily by the steroid hormones, whereas FSH is regulated by both the steroids and the peptide hormones (*12*).

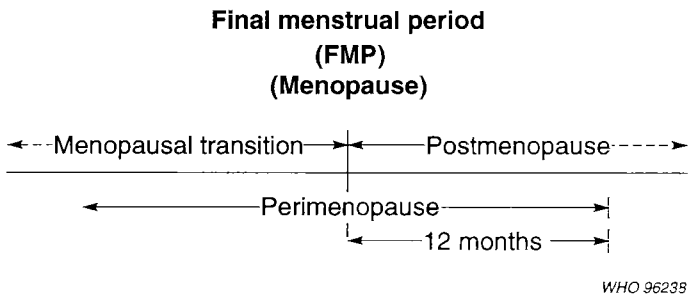
4.2 Terminology

The terms used to describe the various nodal points surrounding the menopause have not been consistently defined and applied, despite the recommendations made in 1980 by a WHO Scientific Group on Research on the Menopause (*4*). Reports on the menopause published since then have continued to use a variety of definitions, which has made it difficult to compare their findings. The definitions proposed in 1980 (*4*) are retained in this report and have been further clarified as described below and in Fig. 3.

1. The term *natural menopause* is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.

   Natural menopause is recognized to have occurred after 12

Figure 3
Relationship between different time periods surrounding the menopause



consecutive months of amenorrhoea, for which there is no other obvious pathological or physiological cause. Menopause occurs with the final menstrual period (FMP) which is known with certainty only in retrospect a year or more after the event. An adequate independent biological marker for the event does not exist.

2. The term *perimenopause* should include the period immediately prior to the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the first year after menopause. The term "climacteric" should be abandoned to avoid confusion.

3. The term *menopausal transition* should be reserved for that period of time before the FMP when variability in the menstrual cycle is usually increased (*13, 14*).

4. The term *premenopause* is often used ambiguously either to refer to the one or two years immediately before the menopause or to refer to the whole of the reproductive period prior to the menopause. The Group recommended that the term be used consistently in the latter sense to encompass the entire reproductive period up to the FMP.

5. The term *induced menopause* is defined as the cessation of menstruation which follows *either* surgical removal of both ovaries (with or without hysterectomy) *or* iatrogenic ablation of ovarian function (e.g. by chemotherapy or radiation).

6. *Simple hysterectomy*, where at least one ovary is conserved, is used to define a distinct group of women in whom ovarian function may persist for a variable period after surgery.

7. The term *postmenopause* is defined as dating from the FMP, regardless of whether the menopause was induced or spontaneous.

8. Ideally, *premature menopause* should be defined as menopause that occurs at an age less than two standard deviations below the mean estimated for the reference population. In practice, in the absence of

reliable estimates of the distribution of age at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cut-off point, below which menopause is said to be premature.

4.3 Ovarian morphology

The number of ovarian follicles present in the ovary, and thus the number of ovarian granulosa cells available for hormone secretion, appear to be the critical determinants of age at the menopause, steroid hormone secretion and gonadotrophin levels. Counts of ovarian follicles have shown the number to be greatest in the fetus at about 7 months of age with a subsequent decline to about 700 000 at birth (*15, 16*). The rate of decline in the number of ovarian follicles is approximately linear on a semi-logarithmic scale until about the age of 40 (*15, 17*). The decline is then more rapid until after the menopause when essentially no follicles remain (*18*). The relationship between age, menopausal status and number of remaining follicles is shown in Fig. 4, which combines data from three studies (*12*).

4.4 Menstrual cycle patterns

The regularity and length of the menstrual cycle vary throughout the reproductive life span. They also vary within and between individuals, and among cultural groups. Asian women, for example, have been reported to have menstrual cycle lengths averaging 32 days (*20*). A unique prospective study, initiated in 1934, documented menstrual cycle patterns in over 2700 women aged over 13 until either 1961 or one year following their FMP, whichever was the earliest. The median length of the menstrual cycle fell from 28 days at age 20, to 26 days at age 40, resulting primarily from a shortening of the follicular phase of the cycle (*20*). As women come closer to the menopause, menses frequently become irregular and are in general less frequent. Bleeding which recurs after 12 months of amenorrhoea in the perimenopausal years may be due to renewed follicular activity, but the possibility of pathological conditions requires diagnostic evaluation.

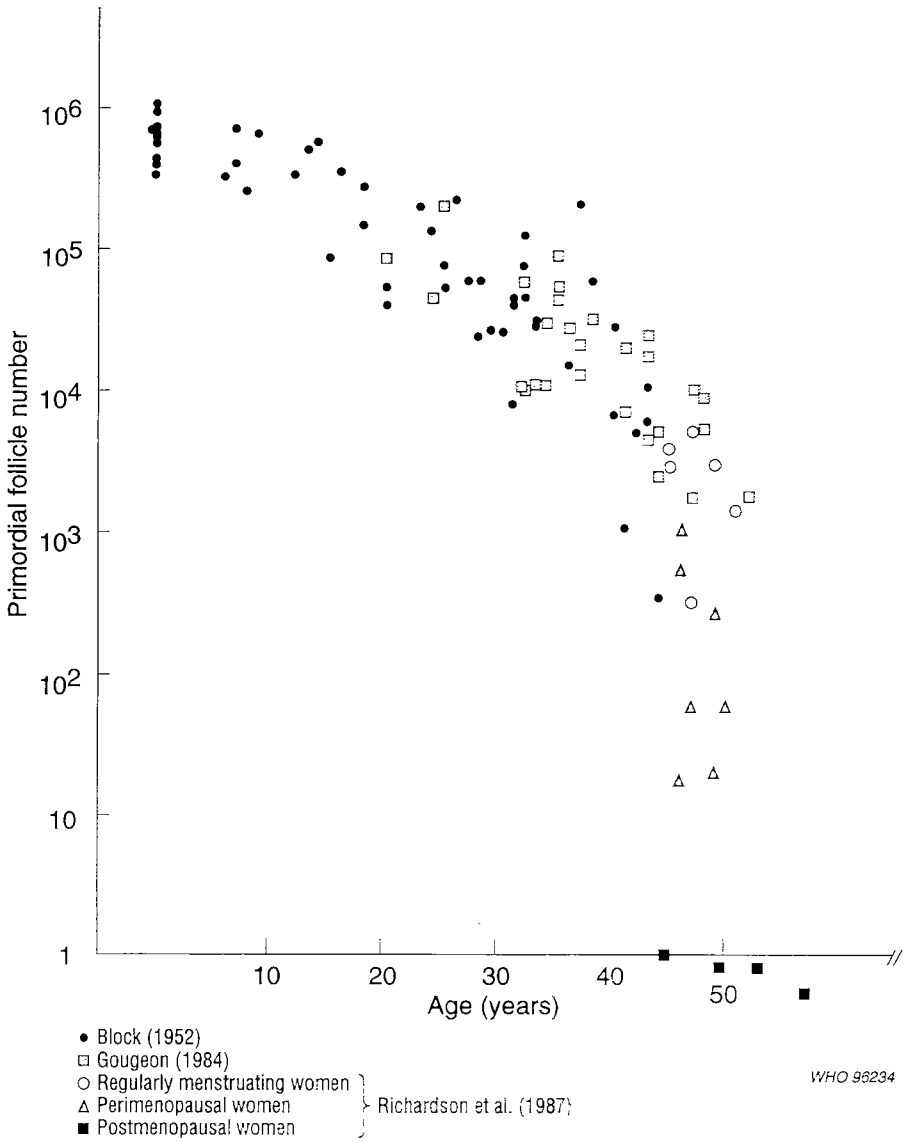
A recent prospective study from Massachusetts, USA, in which 2570 women aged 44-55 were followed for 5 years clarified the concept of the menopausal transition. Its lower limit is the onset of menstrual cycle irregularity, occurring at an average age of 47.5 years, and the upper limit is the FMP. The average duration of the menopausal transition is 3.8 years (*13*).

4.5 Age at menopause

In industrialized societies the average age at menopause is about 51 years (*21-23*). The age at menopause is lowered by smoking (the most significant factor), by nulliparity and possibly by low socioeconomic

Figure 4

The relationship between age and primordial follicle number is compared using data from the studies of Block (1952), Gougeon (1984) and Richardson et al. (1987)[a]



[a] Reprinted from reference 12, based on data from references 17–19, with kind permission from Elsevier Science Ireland Ltd, Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.

status (*21*, *22*). A recent analysis of data (*20*) showed that women with an average cycle length of less than 26 days reached the menopause 1.4 years earlier than those with longer cycles (*23*). The concept is also emerging that age at menopause may be a potent biological marker

of ageing and a later menopausal age could be associated with greater longevity (*24, 25*).

In most reports, women from developing countries are found to be older at menarche and younger at menopause than women in industrialized countries (*22, 26*). However, this difference was not observed in a cross-cultural survey of 400 women in each of seven Asian countries reported in 1991 (*27*). Little variation was observed between countries; the mean age at menopause was slightly over 51 years. This age is almost identical to that reported from industrialized countries (*13, 21-23*). Smaller studies, some restricted to isolated populations in Papua New Guinea (*28*) and the Philippines (*29*), or in various parts of Africa (*30, 31*), India and Pakistan (*32, 33*) and Thailand (*34, 35*) have reported younger ages at menopause (late forties). However, it is not clear whether these reports reflect true menopausal ages or spuriously low estimates because of methodological problems (*36*).

4.6 Hormone concentrations, age and menstrual status

Although many women continue to have regular menstrual cycles well after the age of 40, serum FSH levels rise throughout the fifth decade of life despite the apparent lack of variability in cycle pattern (*37-41*). Luteinizing hormone levels have also been reported to increase, but only in women close to the age of 50 (*40*). Although both serum inhibin and estradiol levels have been shown to correlate negatively with FSH (*41*), the relationship between these two hormones and approaching menopause is not as consistent as that with FSH (*42*).

During the menopausal transition when menstrual cycles become irregular in frequency and length, hormonal levels are unpredictable and variable. Periods during which levels of FSH and LH are high may occur; these may be followed by intervals when gonadotrophin levels are characteristic of those in young women and urinary pregnanediol levels are consistent with ovulation (*43, 44*). Overall, the menopausal transition is a period of marked variability in hormonal levels and endocrine assessments of ovarian function are of little use in predicting potential fertility or timing of the menopause (*45*).

By 2-3 years after the last menstrual period, serum FSH levels have increased to values 10-15 times higher than follicular phase levels in young women, and LH levels are about three times higher (*46, 47*). The levels of both gonadotrophins subsequently decrease with age and are negatively correlated with body mass index. This is in contrast to estrone and estradiol levels, which are positively correlated with body mass index (*48*). LH pulse amplitudes and frequencies, and FSH pulse amplitudes are decreased in older postmenopausal women, as are the gonadotrophin responses to gonadotrophin-releasing hormone (GnRH) stimulation (*49*). Serum immunoreactive inhibin levels are rarely detectable after the menopause (*50*).

A major change in the source and nature of circulating estrogens occurs after the menopause. Quantitatively, the most important circulating estrogen is estrone, with serum levels averaging about 100 pmol/l. Most of the estrone is derived from the extraglandular conversion of adrenal androgen precursors, particularly androstenedione (*51*).

Serum estradiol levels after the menopause are generally less than 80 pmol/l compared with a late premenopausal mean value of approximately 550 pmol/l. The low estradiol values after the menopause make its assay difficult. Cauley et al. (*52*), using radioimmunoassay following extraction and chromatography, noted that about 50% of samples from postmenopausal women had estradiol values below the sensitivity of the assay. To assess the reliability of the assay, short-term (4-week) and long-term (2-year) estimates of hormone levels were undertaken. A low intra-class correlation for both estradiol and androstenedione was found. Since estrone can be measured more reliably than estradiol, the authors suggested that estrone might be useful as an indicator of the total estrogenic status of postmenopausal women.

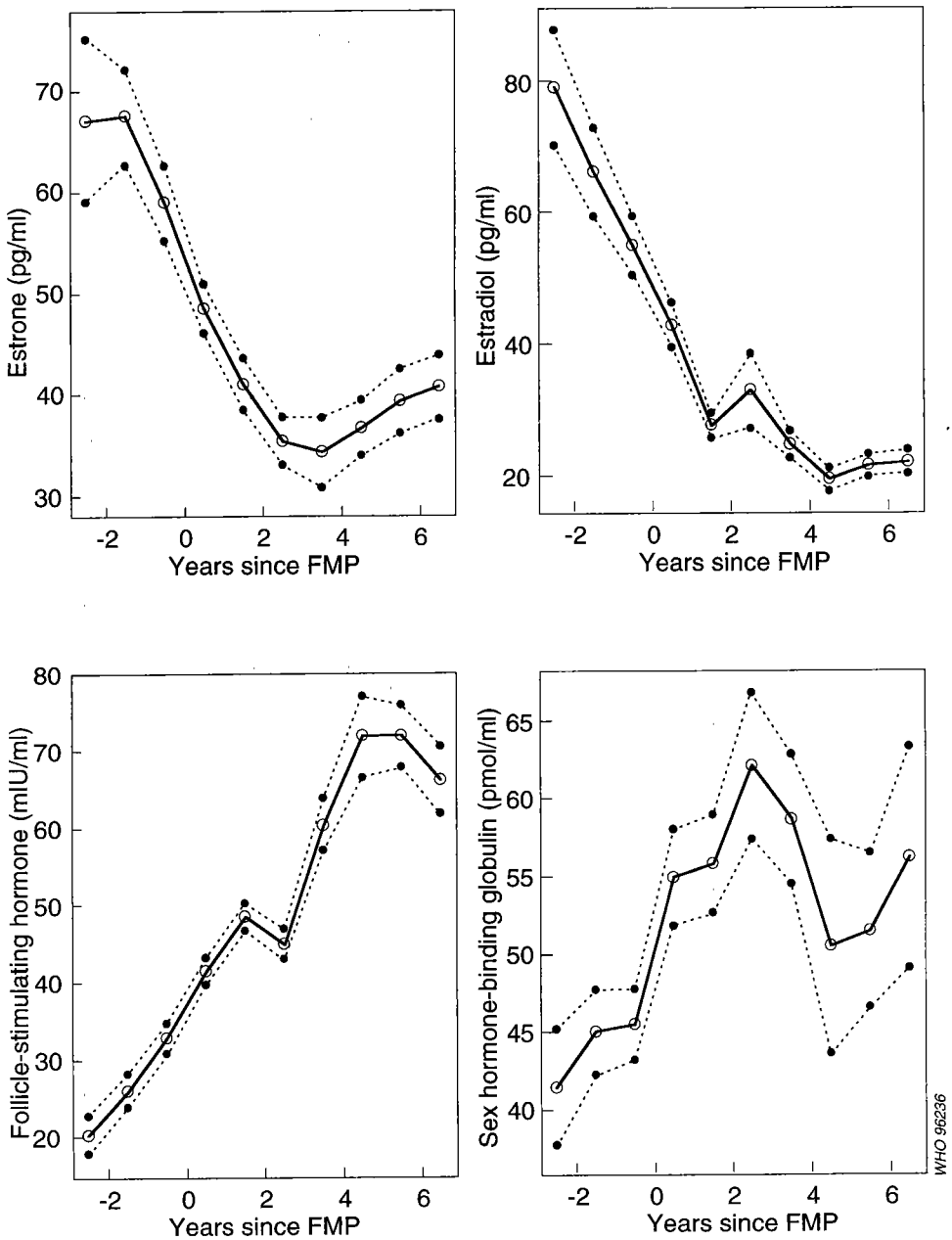
Serum androgen levels also change after the menopause. Testosterone concentrations decline by about 20% and androstenedione by about 50%. Following oophorectomy, the decrease in serum levels of both steroids is about 50% (*53*). After natural menopause, the ovaries of some women have been observed to undergo stromal hypertrophy and hyperplasia which gives them the capacity for production of up to 50% of postmenopausal androstenedione and testosterone (*54, 55*). In other women the ovaries become fibrotic and are then a poor source of steroids. The adrenal androgen, dehydroepiandrosterone sulfate (DHEAS), decreases linearly with age and is not specifically affected by the menopause (*56*).

The possible influence of diurnal variation on estimates of serum levels of testosterone and estradiol in postmenopausal women has been examined. Although testosterone and estradiol show some diurnal variation (*57*), the changes reported have been of only moderate magnitude. In a small study, serum levels of testosterone and estradiol showed a 29% coefficient of variation in samples taken between 08:00 and 24:00 (*58*). Repeated measurements of serum androgens have shown relatively good stability (*59*).

Both serum testosterone and estrogen are largely bound to sex hormone-binding globulin (SHBG) (*60, 61*); only 1–3% is unbound or free. Levels of this protein are increased by endogenous and exogenous estrogens and by thyroid hormone, and are decreased by androgens (*62*) and obesity. Levels of SHBG have been reported to be negatively correlated with bone mineral density in normal postmenopausal women (*63*). They have been variously found to be decreased, unchanged or increased, after the menopause. One longitudinal study (*64*) reported a small decline in SHBG levels after the menopause. In a larger, longitudinal study, SHBG levels were reported to increase during the perimenopause at the same

Figure 5

Selected serum hormone levels versus years since final menstrual period (FMP)[a, b]



[a] Reprinted from reference *14*, with kind permission from Elsevier Science Ireland Ltd, Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.

[b] The dotted lines indicate the mean levels ± the standard error.

time as endogenous estradiol levels fell (*14*). Characterization of biologically active testosterone or estradiol requires direct measurement of their free levels or the derivation of a calculated value determined from the total serum hormone level and the concentration of SHBG.

Fig. 5 shows the changes in serum estrone, estradiol, SHBG and FSH that occur in the 2 years before and the 6 years after the menopause (*14*). These data were obtained from serum samples drawn periodically from a sample of women being followed prospectively in the Massachusetts Women's Health Study. Samples from women who still had menstrual periods were collected between the second and tenth day of the cycle. Of particular note is the dramatic decline in estrogen levels that occurs before the FMP with a continuing more modest drop in the subsequent 2-4 years. The increase in FSH levels starts before the FMP and continues at a fairly constant rate for about 4 years afterwards. SHBG levels also increase after the FMP, but the amount of elevation is variable during the first 6 postmenopausal years (*14*).

Comparisons have been made of hormone levels between different ethnic groups. Mayan women have hormone levels similar to those of Caucasians, despite their lack of vasomotor symptoms (*6*), while Nigerians have hormone and symptom levels similar to those of Caucasians (*65*). In contrast the levels of estradiol and testosterone found in pooled sera from 3250 rural Chinese women aged 35-64 were lower than those for 300 British women in the same age range (*66*). Postmenopausal British women had significantly lower SHBG levels than their postmenopausal Chinese counterparts.

Predictors of sex steroid hormone levels in blood have been examined in postmenopausal American women (*67*). Neither age nor time since menopause was a significant predictor. There was a negative correlation between physical activity and levels of estrone. Estrone and estradiol levels were higher among obese women than among those who were lean. Androstenedione levels were higher in smokers than in non-smokers, but estrone and estradiol levels were not.

4.7 Conclusions

1. Age at menopause is determined by the number of follicles present in the ovary. The number of ovarian follicles decreases from late fetal life onward and few, if any, remain in the ovary after the menopause.
2. Granulosa cells in the ovarian follicle are the source of estrogens and inhibins which have a reciprocal relationship through feedback mechanisms with FSH secretion and serum concentrations.
3. The menopausal transition, starting with irregularities in the menstrual cycle during the fifth decade of life and ending with the FMP, spans an interval which on average is nearly 4 years.
4. During the menopausal transition, estrogen levels decline and FSH

levels rise. Estrogen levels reach their minimum and FSH levels reach their maximum some 3-4 years after the FMP.

5. For individual women levels of steroid and peptide hormones and of gonadotrophins are unpredictable and variable during the menopausal transition. They cannot be used to predict fertility or timing of the menopause.
6. In developed countries the age at menopause is approximately 51 years. In developing countries the reported age at menopause exhibits more variability, but is most often reported to be in the late forties.
7. Serum levels of testosterone and androstenedione fall at the time of the menopause as ovarian function declines, while dehydroepiandrosterone sulfate levels decline linearly with increasing age.

4.8 Recommendations

1. Laboratory standardization for hormonal assays is essential. Studies are necessary to identify sources of inter- and intra-laboratory variability and to devise means to minimize this variability.
2. Sufficiently sensitive assays should be developed to measure serum estradiol levels in peri- and postmenopausal women.
3. Studies are needed of levels of ovarian steroid and peptide hormones and gonadotrophins during the menopausal transition and the early postmenopausal years. These should be made in different populations from developing and developed countries, and in women in the same populations experiencing varying durations of transition. Follow-up of individual subjects would provide information on changes with age and menopausal status; cross-sectional studies can also provide estimates of means and variability for groups with similar characteristics.
4. Additional studies should be carried out to establish whether perimenopausal levels of endogenous estrogens and/or androgens can be used to predict future adverse health effects, and to identify those women who would benefit most from hormone therapy.
5. Age at menopause should be evaluated for its usefulness as a predictive marker for risk of a variety of ageing-related diseases and also as a correlate of other indicators of biological age.
6. The role of both adrenal and ovarian androgens in the health, well-being and sexuality of postmenopausal women and in possible complications of the menopause should be evaluated.
7. The relative contributions of inhibin and sex steroids to the feedback control of FSH during the menopausal transition should be determined together with the potential predictive value of changes in levels of these hormones for when the menopause will occur.
8. The Scientific Group recommends that standard definitions of terms

characterizing the menopause be used by researchers in their contributions to the scientific literature.

5. Symptoms of the menopause and their treatment

5.1 Background

A multiplicity of symptoms have been attributed to the menopause. Little distinction has been made between symptoms that result from a loss of ovarian function, from the ageing process or from the socioenvironmental stresses of the mid-life years. It is particularly difficult to distinguish the effects of ageing from those of the menopause. McKinlay (*36*) has proposed a model requiring prospective observations (a cohort study) on a large number of subjects followed during the pre-, peri- and postmenopausal periods to estimate the shape of the curve of data points on the variable of interest in order to distinguish better between the effects of ageing and those of the menopause. Another possibility is that cross-sectional studies include large numbers of women aged 45-55 in order to distinguish the differences in symptom frequency by menopausal status, while controlling for age.

Since 1985, several population-based studies of middle-aged women have been reported (*13, 68-71*). Their protocols have included sound methodological features:

- probability sampling methods from community-based populations;
- standardized definitions of different menopausal groups;
- distinction between women who have a natural menopause and those in whom menopause is induced;
- use of validated and reliable questionnaires which include questions pertaining to menopausal experiences within other health-related questions.

However, further assessment is needed of the reliability and validity of symptom-reporting in questionnaires and interviews, and to ensure the elimination of social stereotyping of the responses to symptom checklists of complaints attributed to the menopause. The distinction between having experienced a symptom and being disturbed or functionally incapacitated by it is important both to the well-being of the respondent and for the interpretation of the data. This distinction is also important because of the different implications for health care utilization and potential management strategies.

The establishment of population-based cross-sectional studies has provided the initial step in developing cohorts of women who can be followed prospectively. Cohort studies are particularly suitable for investigating the menopausal transition and the sequence in which the

symptoms occur. Several studies (*68-71*) have recently reported on menopausal symptoms in prospective additions to their earlier cross-sectional surveys (*13, 72-75*).

5.2 Symptoms of the menopause

5.2.1 *Vasomotor symptoms*

Hot flushes and night sweats are thermoregulatory disturbances which are characteristic of the menopause (*72, 76–79*). Night sweats are the night-time manifestation of hot flushes experienced during the waking hours. Insomnia is often cited as a menopausal complaint, but usually occurs secondarily to the disruption caused by the night sweats. Erlik et al. (80) observed a significant correlation between hot flushes and waking episodes, both of which were reduced by estrogen therapy.

Hot flushes arise as a sudden feeling of heat in the face, neck and chest; this is associated with diffuse or patchy flushing of the skin, profuse perspiration and frequently with palpitations. The feeling of heat, initially centred in the upper part of the body, spreads upwards and downwards throughout the body. The flush is associated with an acute feeling of physical discomfort and lasts about 3 minutes. Flushes may be induced by tension or nervousness and their frequency, duration and intensity can be reduced in some subjects with placebo interventions although estrogen therapy is the mainstay of treatment (*81*).

Vasodilatation occurs with the onset of the hot flush and continues for at least 5 minutes after symptoms have subsided (*82*). Vasodilatation and perspiration are heat-loss mechanisms, and shivering may be necessary after the flush to raise the core temperature back to normal. Vasodilatation is measured by an increase in peripheral blood flow and skin temperature and a decrease in skin resistance. Both the onset of the flush and vasodilatation precede the change in skin temperature and the pulsatile release of LH. LH release is not the triggering event. Although flushes occur during periods of estrogen withdrawal, estrogen levels do not correlate with the occurrence of flushes (*83-85*).

The prevalence of hot flushes associated with the menopause varies in different cultures. For example, the prevalence has been reported to be 0% in Mayan women, 10-22% in Hong Kong women, around 17% in Japanese women, 23% in Thai women, 45% in North American women and up to 80% in Dutch women (*6, 35, 70, 86-88*). Inconsistencies have been reported, e.g. one report from Thailand gives the prevalence of hot flushes as 69% (*34*). The American study noted that the peak flush rate occurred during the menopausal transition (*13*), while the Dutch study reported that the highest prevalence of hot flushes occurred in the 6-12 months after the FMP (*70*). A survey in south-east England noted that 15-25% of premenopausal women had flushes, rising to 54% at the time of the menopause (*74*). In a cross-sectional study in Australia, 31% of perimenopausal women had been troubled by hot flushes in the 2 weeks

preceding the survey, compared with 39% of those who were postmenopausal (*89*). In general, flushes and sweats are more common in European and North American women than in other populations.

Hot flushes may be more severe in women who undergo bilateral oophorectomy than in those who have a natural menopause (*90*). Ethnic differences in the prevalence of hot flushes after surgical oophorectomy have been observed. In a prospective study in Hong Kong (*91*) only 24% of women who had undergone surgical oophorectomy reported hot flushes as compared with 70% of similarly treated Caucasian women (*92*).

Hot flushes are not unique to menopausal women. A similar or equivalent phenomenon has been reported to occur in 10% of women before the menopausal transition (*13*) and in men (*93*). Lack of symptoms as found in the Mayan women can not be explained by a difference in endocrinology; these women had typical postmenopausal levels of FSH, estrone and estradiol, and experienced age-related bone demineralization (but not a high incidence of osteoporotic fracture) (*6*).

A high intake of dietary phytoestrogens has been suggested as a possible explanation of the lower frequency of menopausal symptoms in Japanese as compared with Caucasian women. Urinary phytoestrogens are about 100-fold higher in Japanese than in Finnish postmenopausal women (*94*). The addition of phytoestrogens to a Western diet can produce estrogenic changes in the vaginal epithelium (*95*).

Factors associated with the frequency of vasomotor symptoms at menopause include prior occurrence of premenstrual or menstrual symptoms (*74, 77*), and prior health status (*89, 96*). Ambient temperature affects the frequency of hot flushes; cool ambient temperatures alleviate flushes and warm temperatures exacerbate them (*97, 98*).

Treatment with estrogens and/or progestogens reduces the frequency and severity of hot flushes (*99-106*). Estrogens are effective whether administered orally, transdermally (*107*) or as implants and can be used with sequential progestogens, or both progestogens and estrogens can be given continuously (*108*). Hot flushes may be partially alleviated by a placebo, but in double-blind studies estrogens are significantly more effective than placebos (*101, 102*).

Estrogens may be given orally or parenterally. The most widely used oral preparation is "conjugated equine estrogen", a product prepared from the urine of pregnant mares and containing a number of biologically active components of which estrone sulfate predominates. A common dose is 0.625 mg daily, which is usually sufficient for symptomatic relief. Other compounds administered orally include piperazine estrone sulfate (1.25 mg daily) and estradiol valerate (2.0 mg daily). The regimens currently favoured involve continuous daily administration, although cyclical patterns are also effective. Parenteral modes of estrogen administration include transdermal preparations (e.g. gels 3 mg daily, patches 50 μg

daily), subcutaneous implants (25–50 mg every 4–6 months), vaginal rings and injectable preparations.

For women with an intact uterus, progestogens are given in addition to estrogens to prevent estrogen-induced proliferation of the endometrium. The most widely used oral progestogens are 19-acetoxyprogestogens and 19-nortestosterone derivatives. Equivalent doses of two commonly used preparations are 10 mg of medroxyprogesterone acetate and 0.7–1.0 mg of norethisterone. Such preparations are used cyclically for 10–14 days per month with continuous estrogen. If the progestogen is used continuously, a lower dose is adequate, e.g. 2.5 mg of medroxyprogesterone acetate or 0.35 mg of norethisterone.

Early reports on non-pharmacological therapies justify further investigation. In Sweden, a controlled study of over 1600 women aged 52–54 years found that moderate and severe hot flushes and night sweats were only half as common among the physically active postmenopausal women as in the control group (*109*). Behavioural treatment including muscle relaxation, paced respiration and biofeedback (the technique of using the feedback of a normally automatic bodily response to a stimulus, in order to gain voluntary control of that response) was investigated, but only paced respiration produced significant reductions in the frequency of hot flushes (*110*). Special diets, including those high in phytoestrogens could be of benefit, but controlled trials to assess their effectiveness have yet to be conducted (*95*).

5.2.2 *Urogenital atrophy*

After the menopause the vaginal mucosa becomes thinner. Basal and parabasal cells predominate over superficial estrogenized cells. However, estrogen effects can be identified even in old age. A study of vaginal cytology in 148 postmenopausal women aged from 40 to 78 years showed completely atrophic smears in only 20% of the women (*111*).

The frequency of postmenopausal dyspareunia associated with vaginal atrophy has not been well established from population-based studies. An estimate based on women attending menopause clinics is 10% (*112*). Estrogens administered by any route are effective in enhancing the thickness and secretions of the vaginal mucosa and thereby reducing dyspareunia (*113*). A double-blind placebo-controlled trial of conjugated equine estrogens showed a significant increase in the percentage of estrogenized vaginal cells in women taking estrogens as compared with women taking a placebo (*101, 114*). Alternatively vaginal lubricants offer reasonably effective, non-hormonal treatment for dyspareunia (*115*).

Continuing sexual activity may protect women against vaginal atrophy. This was demonstrated in a study of vaginal cytology which showed significantly less vaginal atrophy in a group of sexually active women than in a sexually inactive group (*116*).

Sexual interest may decline after the menopause (*71, 117*). It is not clear,

however, what component of that decline is attributable to the menopause, to ageing in general or to the declining sexual potency of the male partner. Most studies have found no improvement of libido in response to estrogen administration, but testosterone may be beneficial (*118-120*). A subcutaneous implant of 50 mg of testosterone every 6 months may be efficacious.

Urinary problems are common in ageing women and may occur in the perimenopause. The relative contributions of the menopause, obstetric history and tissue ageing to these problems have yet to be assessed. Symptoms of urgency of micturition, dysuria, nocturia or stress incontinence are reported to affect 25-50% of postmenopausal women (*121-124*). Estrogen therapy may improve some symptoms (*125, 126*), but it is not helpful in urodynamically proven stress incontinence (*127*). Recurrent urinary tract infections may respond to intravaginal administration of estriol succinate which probably modifies the vaginal flora (*128*).

5.2.3 *Irregular menstruation in the perimenopause*

Changing menstrual patterns and irregular bleeding occur during the menopausal transition (*37, 43, 44, 129, 130*). One study has estimated that 10% of women stop menstruating abruptly, but the majority experience months or years of irregular bleeding and variable cycle length before menses cease (*13*). This transitional pattern should be distinguished from bleeding due to a potentially serious condition.

5.2.4 *Other complaints*

A variety of symptoms, occurring either singly or together, are frequently reported as being part of a menopausal syndrome. Those already mentioned in sections 5.2.1-5.2.3 have distinct manifestations, but the remainder are not specific to the menopause and are presumed to be psychological or sociocultural in origin. Some frequently mentioned symptoms are depression, nervous tension, palpitations, headaches, insomnia, lack of energy, fluid retention, backache, difficulty in concentrating and dizzy spells. In most studies, occurrence of these symptoms is not highly correlated with menopausal status, but they are strongly correlated with each other (*72, 76, 77, 99, 131, 132*). They are also more common among women who experience severe flushing (*13, 131-133*). Most of the placebo-controlled trials that have used estrogens to suppress individual symptoms (other than hot flushes) have demonstrated no statistically significant benefits of this treatment (*112*). In a recent report from the Dutch National Survey of General Practice, health interviews were conducted on a random sample of the practice population including 8679 women and men aged 25-75 years. With the exception of vasomotor symptoms, none of the other complaints usually attributed to the menopause were more common among women than among men in the subjects aged between 45 and 54 years (*93*).

Depressive episodes are not disproportionally increased at the menopause (*75, 134*). The main predictors of depression in the menopause are the same as for other stages of life; these are prior depressive episodes and poor current or past health status (*75*). Stressful life events frequently precipitate depressed moods and such events are numerous in the mid-life period (*134*). Estrogen therapy may be effective for mood elevation in women who have had bilateral oophorectomy (*135, 136*). Estradiol implants or combined estradiol and testosterone implants may have some effect in naturally perimenopausal women; however, such therapies do not appear to be effective in postmenopausal women (*137*). Progestogens may have adverse effects on mood (*138*).

5.3 Relevance of existing data to developing countries

Most of the information on symptoms of the menopause has been obtained from populations in industrialized countries. The sparse data available from developing countries suggest that the symptoms reported to occur in Caucasian populations in developed countries are not universal, but rather that the intermixing of biology and culture produces different effects in different parts of the world. The data from Japanese studies show marked differences in the frequency and type of complaint and in the perception of menopause compared to those reported from Europe and North America (*139*).

Until there are adequate data on the magnitude and extent of a "menopause problem" in most parts of the world it is not possible to recommend appropriate interventions or treatments. The few comments on treatment noted in this report apply only to specific indications and conditions. Data are needed that describe and explain the nature of the menopause in many parts of the world where such studies have not yet been done. Such information will clarify whether specific interventions, and of what types, might be useful.

5.4 Conclusions

1. Vasomotor symptoms of hot flushes and night sweats are characteristic of the menopause.
2. Vasomotor symptoms can be relieved with an estrogen or an estrogen plus a progestogen. Non-pharmacological therapies such as exercise or special diets may be beneficial.
3. Other symptoms are not specific to the menopause, but may occur as a secondary phenomenon among women who experience severe hot flushes.
4. The frequency and severity of hot flushes differ in different countries and cultures. They are experienced by only 17% of Japanese menopausal women compared to a majority of European and North American women.

5. Vaginal atrophy with resulting dyspareunia can be relieved by estrogen therapy.
6. Some of the urinary problems experienced by postmenopausal women may also respond to estrogens.

5.5 Recommendations

1. Scientific data are needed from different countries and cultures on the nature of the menopause, the manifestation of its symptoms and its psychological importance. Such studies should use culturally sensitive and appropriate methods.
2. Studies should be designed that can differentiate the concurrent and long-term health effects of the menopause from the ageing process itself.
3. Studies should be designed that consider not only the presence or absence of symptoms of the menopause, but also their severity, the extent to which they interfere with daily activities, and any disability caused by them.
4. The possible relationship between the reported frequency of hot flushes and long-term health effects, such as osteoporosis and cardiovascular disease, requires comparative analyses between ethnic groups in which the reported frequency of hot flushes is high and those in which the reported frequency is low.
5. Research on the menopause should involve interdisciplinary research teams, and the findings should be communicated through journals and other media that reach health care providers and consumers as well as the scientific community.

6. Cultural context of the menopause

6.1 Background

The menopause is a normal physiological event that occurs in all women who live to middle age. However, as mentioned previously, most of the information on the menopause comes from research done in the industrialized world. This research has been the model for the relatively few studies carried out in developing countries and therefore these studies have tended to use the same research methods and to ask the same research questions, such as the age at menopause and frequency of symptoms. Further inquiry has been made about the incidence of cardiovascular disease, malignant neoplasms and osteoporosis following the menopause. While there are advantages to testing familiar hypotheses in different populations, these may not be the only questions of concern or relevance to the health of menopausal women in other parts of the world. These questions also omit to take into account the very different

factors which will have conditioned the health of women prior to their reaching the menopause and which will determine the implications of the menopause for their future well-being.

6.2 Cultural and economic context of the menopause in developing countries

The lives of women outside Europe and North America are framed within a very different set of social, economic and cultural parameters from those of the women who have been the usual subjects of menopause research. The implications of reaching the menopause vary from one society to another, depending on the political and economic structure of each society, and the conditions of life it provides for women of all ages, including their access to health care.

A report on middle-aged women in the Caribbean and Latin America presented a generally bleak social and economic picture characterized by poverty, family break-up, responsibility for ageing parents, and lack of opportunities for paid employment (*140*). The environment plays a significant role in the health of all women, but is particularly important in developing countries. By the time women in developing countries reach the menopause, their health may already have been undermined by the environmental conditions in which they live. Infectious diseases which are associated with poor public health measures remain common. Pollution, chemical toxins and hazardous working conditions compromise the health of urban women working in the industrial sectors of these countries (*141*).

Women's health is also undermined by chronic malnourishment. According to one estimate, half of all African women, two-thirds of Asian women and one-sixth of Latin American women suffer from nutritional anaemia as a result of insufficient food (*142*). The reasons are economic, social and cultural. When food is limited, the extent to which women are malnourished depends on their status within the family and society (*141*).

A woman's health at mid-life will have been affected not only by the number of children she has had, but also by the number of pregnancies, their spacing, her age at the last pregnancy, the number of unsafe abortions she has had and whether or not she has had access to contraception. Effective contraception can minimize the number of reproductive adversities, but contraceptive use varies greatly from country to country (*143*). A report of the Pan American Health Organization provides estimates of the lifetime fertility of women in the Caribbean and Latin America when they have reached the age of 45–59; these range from a mean of 6.6 children for rural women to 2.6 for urban women (*140*).

Access to health care in developing countries is limited for both women and men. The primary focus of existing health care and expenditure of

governmental resources is on maternal and child health. The use of scarce resources for the treatment of non-life-threatening conditions, such as the menopause, has low priority. In settings where private medical services exist, medical care for menopause-related complaints may be available, but at a cost which few women can afford.

6.3 Health effects of the menopause in developing countries

The incidence of menopausal symptoms among women in developing countries has been reported to be far lower than among women in Europe and North America. However, the majority of studies in developing countries have used the same symptom checklists as studies in developed countries. Therefore they could not determine whether women in developing countries experienced different symptoms at menopause nor how these symptoms were managed. A different methodological approach was used by Lock (*8*), who asked Japanese women and their physicians what symptoms they associated with the menopause and which methods they used to deal with these symptoms.

There are few data available on the incidence of osteoporosis and hip fractures among women in developing countries, but they do suggest that these rates may be lower than in the industrialized countries. The conclusion that there are differences in the risk of hip fracture between different ethnic groups is supported by data showing that the risk of hip fracture among Mexican American women is only 35% of that among Caucasian American women (*144*) and that Caucasian American women experience twice the fracture rate of Japanese women living in Okinawa or Hawaii (*145*). A study of Mayan women reported age-related bone demineralization, but a low incidence of osteoporotic fractures (*6*). These data came from a project which combined clinical data (bone measurements), a nutritional survey and careful observation of the daily activities of Mayan women (*86*).

The rates of coronary heart disease and breast cancer also appear to be lower among postmenopausal women in developing countries and Japan than among those in Europe and North America. Statistics are well kept in Japan, but in many other countries mortality and morbidity data on middle-aged women are either unreliable or unavailable.

Whereas researchers in North America tend to focus on the negative aspects of the menopause, descriptions of the menopause in women in developing countries tend to emphasize the positive aspects, such as freeing women from the burdens of childbirth and from cultural restrictions imposed on the social and religious life of younger women who still menstruate (*146*). In some societies women are said to relish the renewed freedom and influence in their families and communities that come with menopause and not to regret reduced sexual activity (*147-149*). These reports suggest that the psychological reaction of women to the menopause reflects the values of the society and the social status assigned to the ageing woman.

6.4 Conclusions

1. The health and well-being of all menopausal women are strongly influenced by the cultural and economic settings in which they live.
2. Health status at the menopause is largely determined by prior life experiences including the physical demands of work and home life, environmental exposures to infectious and chemical agents, reproductive experiences and their management, adequacy of diet and availability of health care services.
3. The model of menopause research developed in Europe and North America may not have addressed the issues relevant to the health of women in developing countries during the peri- and postmenopausal transition.

6.5 Recommendations

1. Studies are needed to determine how women from different societies and cultures perceive the menopause. Women in different age groups should be questioned both before and after the menopause and they should be given the opportunity to express perceived benefits as well as negative aspects of the menopause.
2. Studies of complaints associated with the menopause in different societies are needed. Such studies should allow for the occurrence of specific symptoms as well as symptoms that are not traditionally associated with the menopause in developed countries.
3. Research is needed on the long-term health and menopausal symptoms of women in developing countries. This should take into account all the factors that affect their health and well-being, including diet, use of indigenous therapies and levels of physical activity.
4. The research methods and their design should be adapted to reflect the multifaceted nature of the menopause. This means that multidisciplinary research projects should be encouraged in all settings.
5. Research priorities should be determined by the characteristics of peri- and postmenopause in each society and by the priorities of women in that society.

7. Contraception and the late premenopause

7.1 Background

For contraceptive purposes, the late premenopausal period is arbitrarily defined as starting at the age of 35–40 years and ending with the menopause. The rationale for this age span derives both from the

potential risks of childbearing and from the distinctive need for and requirements of contraception at this time. In most parts of the world, childbearing by women in this age group is not desired or is actively discouraged although in some developed countries a trend towards late childbearing has emerged as a concomitant of socioeconomic change. The median age at FMP is 50-52 in industrialized countries (*21*), and 1-2 years younger in women from developing countries (although the reported ages are more variable in these women). Thus, the late premenopause encompasses a period ranging from the mid-thirties to at least 50 years of age.

7.1.1 *Probability of pregnancy*

From the perspective of contraception, the fifth decade of life is a time of special needs and circumstances (*150*). Although the frequency of intercourse declines as couples age (*151*) and fecundity is also reduced the probability of pregnancy, in the absence of contraception, is high. Gray (*152*) reported that 50% of women over 40 are still potentially fertile; without contraception the annual risk of pregnancy is approximately 10% for women aged 40-44 and 2-3% for women aged 45-49, and the risk may not be zero for women over the age of 50. It has been estimated that, in women over the age of 45 who have been amenorrhoeic for one year, the probability of subsequent menstruation (which could be ovulatory) is in the range of 2% (*21*) to 10% (*153*). These data emphasize the need for contraception until menopause is established.

7.1.2 *Reduced fecundity*

The decline in the number of ovarian follicles and the accompanying hormonal changes that occur as the menopause approaches have been described in section 4. Factors contributing to the decline in fecundity include the increasing frequency of anovulatory cycles (*154, 155*) and the decreasing fertilizability of the oocytes which are released (*156*). Reduced fertility after the age of 35 has been confirmed by the sharp reduction observed in success rates of various methods of assisted reproduction in women above this age. In a study of nulliparous women undergoing artificial insemination, the probability of success was 74% for women under 30 years but dropped to 54% above the age of 35 (*157*). Finally, smoking may exacerbate these trends by independently reducing fertility in women attempting to become pregnant (*158*).

7.1.3 *Risks of pregnancy*

Pregnancy in late premenopausal women is sometimes an unwelcome occurrence. Pregnancy in women over the age of 35 carries increased health risks for both mother and fetus. There is a sharp increase in the maternal mortality rate which is four times as high in the fifth decade as in the third (*159*). Spontaneous abortion rates double between the third

and fifth decades and reach 26% in the fifth decade (*160*). Perinatal mortality rates also double between the third and fifth decades (*161*). These rates have been reported from developed countries and are expected to be much higher in developing countries where high parity and poor maternity care add to the risk of late pregnancy. In a community-based study in Upper Egypt, the maternal mortality ratio was found to be 368 per 100 000 live births, and 707 per 100 000 live births for women who had had five or more previous deliveries (*162*).

The risk of chromosomal anomalies in the fetus increases with the age of the mother. Tests for prenatal diagnosis of these anomalies are rarely available to women in developing countries. Even when tests are available, women frequently choose to have an abortion where this is legal, rather than undergo prenatal testing. Statistics from the Office of Population Censuses and Surveys in the United Kingdom show that up to 45% of pregnancies among women over the age of 40 are terminated by legal abortion (*161*); this is very much higher than the rate for other age groups and is out of proportion to the real risk of fetal anomalies.

Both psychological and physiological status in the late premenopausal period are deterrents to late pregnancy. Social pressure may also be exerted against late pregnancy; for example it may be considered socially unacceptable for a mother to become pregnant after the arrival of her grandchild (*151*).

7.2 Contraceptive options

7.2.1 *Combined oral contraceptives*

The formulation of oral contraceptives containing a combination of an estrogen and a progestogen has changed markedly over the past 30 years. The products currently marketed contain 20–35 μg of ethinylestradiol, which is 4–5-fold less than in the products that were available in the 1960s. Total progestogen content has decreased proportionately, but exact equivalency is more difficult to specify because of the diversity of progestogens used in oral contraceptives. New progestogens have recently been introduced (desogestrel, gestodene and norgestimate) with the aim of improving the blood lipid profiles. Triphasic preparations, which vary the amounts of hormones during the cycle, also lower the total steroid dose by about one-third (*163*). All these preparations are highly effective contraceptives and their use-effectiveness in most populations is high.

The dosage of hormones in combined oral contraceptives was reduced following studies in the 1970s and 1980s which showed that high-dose preparations had adverse health effects, most notably on the cardiovascular system. Considering that oral contraceptives were being used by more than 60 million women around the world by the late 1980s, there was an urgent need to quantify the risk of effects on the cardiovascular system and to specify who might be affected (*164*).

Most of the information available on the cardiovascular effects of oral contraceptives is based on studies in which the participants were using the older high-dose preparations. In these studies use of oral contraceptives increased the risk of venous thromboembolic disease, thrombotic stroke and myocardial infarction: the risk estimates were in the range of 3–5 times those among non-users, depending on the specific diagnosis and the subgroup studied (*165, 166*). In 1988 a review of oral contraceptive use by women aged over 35 years noted that the risk of adverse cardiovascular events was particularly high among women who smoked and those who had pre-existing cardiovascular diagnoses and risk factors for cardiovascular disease (*167*). There was no evidence of an increased risk among healthy non-smoking women aged 35–45 compared with women who were not using the pill.

Recent reports are generally reassuring regarding the risk of myocardial infarction in healthy non-smoking women who use oral contraceptives. The large prospective Nurses' Health Study from the United States reported no increased risk of myocardial infarction associated with current or past use of oral contraceptives (*168*). A case-control study of fatal myocardial infarction in women from England and Wales reported a statistically non-significant relative risk of 1.9 for both current and past use of oral contraceptives, mostly of low estrogen dosage (*169*). It is not certain how much of the increased risk was due to smoking because of difficulty in assessing smoking history. No evidence of an increased risk of myocardial infarction among current users of oral contraceptives was found in studies by Porter et al. (*170*) and Mant et al. (*171*).

The association of thrombotic stroke with use of oral contraceptives, however, still gives some cause for concern. In a case–control study from Denmark, the risks associated with current use of oral contraceptives containing 50 μg of an estrogen, 30–40 μg of an estrogen and a progestogen only were 2.9 (95% CI 1.6–5.4), 1.8 (95% CI 0.1–2.9) and 0.9 (95% CI 0.4–2.4), respectively. There was no change in risk with age (*172*). Similar results have been noted by Thorogood et al. (*173*). Few data are available on the risk of venous thromboembolism. In a British study, the relative risk of fatal venous thromboembolism in current users was estimated to be 2.0, but was not statistically significant compared to the risk among non-users (*174*).

Since data from developing countries are sparse, the pilot study reported in 1989 from WHO (*175*) is of particular note. This case–control study of venous thromboembolism and pulmonary embolism, ischaemic heart disease and stroke was conducted in the then German Democratic Republic, Hong Kong and Mexico. Few elevated risks related to current or former use of oral contraceptives were recorded in any country or in any age group. The only suggestion of an increased risk was for pulmonary embolism or venous thrombosis in current users (all estrogen doses combined) in all the countries studied. The pooled relative risk estimate across the three centres was 2.9 (95% CI 1.4–6.1) (*175*). WHO

is currently conducting a large multicentre case-control study of oral contraceptive use and cardiovascular diseases in developing and developed countries, the results of which are expected to be available in the near future.

Pharmacological and metabolic studies have contributed to our understanding of how the steroid hormones may function to produce cardiovascular effects. Estrogens absorbed from the gastrointestinal tract stimulate protein production in the liver. Among these proteins is angiotensin, which is elevated in estrogen users (*176*). This may be one of the factors that causes the increase in blood pressure that can occur in oral contraceptive users (*177*). High-dose levonorgestrel, a 19-nortestosterone derivative, reduces serum levels of high-density lipoprotein 2 (HDL2) cholesterol, an effect which is less evident with other progestogens. A WHO multicentre study on coagulation parameters and oral contraceptive use found an acceleration of prothrombin time and an increase in the levels of factor X and fibrinogen in users (*178*).

The other major concern that has inhibited the prescription of oral contraceptives is the possible effect on the risk of breast cancer. A large prospective study recently reported an increased risk of fatal breast cancer among current users of oral contraceptives (*168*). However, in most studies, there is no evidence of an increased risk of fatal breast cancer associated with oral contraceptive use in women diagnosed after the age of 45 (*179, 180*). The findings have been inconsistent, and where elevated risks have appeared they have been modest in size (*181-185*). As noted in the report of the WHO Scientific Group on Oral Contraceptives and Neoplasia (*186*) "the results showed no consistent evidence of an increased risk of breast cancer among women using oral contraceptives near the age of the menopause".

The scientific literature and the media may have given a disproportionately large amount of publicity to the possible adverse effects of oral contraceptives without paying equivalent attention to their beneficial health effects. The beneficial effects are in addition to their primary benefit as highly efficacious contraceptives. For example, use of combined oral contraceptives for 5 or more years reduces the risk of both ovarian and endometrial cancer by approximately 50%; this reduction in risk persists for at least 10 years after use is discontinued (*186*). In developed countries where these types of cancer are common, the impact of hormonal contraception is evident in some national databases, which show reduced morbidity and mortality rates for these diseases. For ovarian cancer for which the likelihood of survival is extremely poor, oral contraceptives are the only recognized measure to reduce the risk.

Other benefits attributed to oral contraceptives include reducing premenstrual tension, dysmenorrhoea and excessive menstrual blood loss, and the risk of anaemia, pelvic infection, extrauterine pregnancy, benign breast lumps and functional ovarian cysts. They may also reduce the risk of endometriosis and uterine fibroids. Each of these conditions

causes suffering and ill-health in large numbers of women throughout the world (*187*).

7.2.2 *Progestogen-only contraceptives*

Contraceptive progestogens may be administered in several different forms; these include progestogen-only pills, levonorgestrel implants (e.g. Norplant), injectable depot forms (e.g. depot medroxyprogesterone acetate (DMPA)) and levonorgestrel-releasing intrauterine devices (IUDs). In general, women at risk of cardiovascular complications, for whom use of combined oral contraceptives is not recommended, e.g. smokers, may choose to use progestogen-only compounds. These compounds provide lower doses of progestogen than those available from combined oral contraceptives, and their efficacy may be somewhat lower. Pregnancy rates of 1.4–4.3 per 100 woman-years for oral progestogen-only contraceptives have been reported (*188*). The acceptability of progestogen-only contraceptives is also reduced by bleeding irregularities.

Cardiovascular complications, including thrombotic events, have not been associated with use of progestogen-only contraceptives. However, data on this topic are sparse, reflecting the low frequency of use of these products and the resulting limited size of studies. The market share of progestogen-only pills, among all oral contraceptives, is only 0.2% in the USA, 3% in England and 4% in Australia, but it is 35% in Finland (*188*).

Norplant, the subdermal implant system consisting of silicone rubber capsules containing levonorgestrel, has a contraceptive effect that is essentially as good as sterilization and lasts for at least 5 years. The contraceptive effect is reversible; the capsules can be removed if bleeding irregularities become a problem. To date there has been no suggestion of an increased risk of breast cancer, but scientific data on this topic are scarce.

The injectable forms of progestogen, such as DMPA, provide sustained protection against conception for several months. The possible disadvantages are the need for re-injection of DMPA every 3 months and the impossibility of removing the hormone source in the event of complications. One study has provided evidence for a decrease in bone density associated with DMPA use (*189*).

Among the progestogen-only contraceptives, DMPA has received the most research attention with respect to the risk of breast cancer. At a recent WHO meeting (*190*), it was concluded that the risks from DMPA were similar to those observed with combined oral contraceptives. No increased risk of breast cancer was noted in women using DMPA after the age of 35 and there was no trend towards increased risk with longer duration of use.

A disadvantage of all forms of progestogen-only contraceptives is their tendency to disrupt the menstrual cycle and cause irregular bleeding. This could be a cause of concern in women aged over 40, when pathological

causes of bleeding become more common. Irregular bleeding is more of a problem during the first few months of progestogen use and decreases over time. Enlargement of the ovarian follicles with attendant symptoms can also occur (*191*).

7.2.3 *Intrauterine devices (IUDs)*

Copper-bearing IUDs

Copper-bearing IUDs are used extensively in many parts of the world. Their long-lasting efficacy suits the needs of women over the age of 35, who are usually more interested in limiting the size of their families than spacing pregnancies. In late premenopausal women use of IUDs may be extended until the menopause is established (*192*).

There are few studies reporting on the long-term use of copper-bearing IUDs in women above the age of 35 years. A randomized clinical trial from Denmark, Finland and Sweden involved 288 women over the age of 35 years using a copper-bearing IUD, who were followed up for a minimum of 5 years. The copper-bearing IUD was associated with a low incidence of side-effects, including bleeding and a low infection rate (*193*). In another study in the former Yugoslavia which involved women aged over 35 years at the time of insertion of the IUD (mostly copper-bearing IUD), there were fewer IUD removals during the 9 years of observation and fewer side-effects in these women than in women under the age of 35 years at the time of insertion (*194*).

The main problem with the use of the IUD by women over 35 years of age is that it accentuates the already increased incidence of uterine bleeding. A policy of removal in cases of bleeding and pain has been advised (*176*). This protects women from anaemia and infection and will avoid delay in diagnosis of organic causes of bleeding.

Levonorgestrel-releasing IUD

The levonorgestrel-releasing IUD (LNG-IUD) combines high efficacy with a reduction in the amount and duration of menstrual bleeding (*195*). The latter effect is due to a local suppressive action on the endometrium arising from the constant release of low levels of progestogen. The levonorgestrel has low systemic absorption. In a multicentre, randomized trial performed in Europe, 456 women aged over 35 years at the time of insertion were studied (*150, 176*). After 5 years of use the LNG-IUD users (306 women) had had significantly fewer IUD removals because of bleeding than the comparative group (150 women) using copper-bearing IUDs. The cumulative removal rate because of bleeding was 25.4 per 100 women using the copper-bearing IUD, and 9.0 per 100 women using the LNG-IUD. Another study has shown that, compared to the copper-bearing IUD, the LNG-IUD is associated with a lower incidence of pelvic inflammatory disease and higher levels of plasma ferritin and haemoglobin (*196*).

The LNG-IUD appears to be a suitable contraceptive for the late

premenopausal years, because it has a high acceptability and causes minimal bleeding problems. It can also be used as a therapeutic agent for menorrhagia. It should be especially useful in developing countries, because it is effective and long-lasting, but currently its availability in many parts of the world is limited. This device may also prove valuable in providing continued protection against endometrial cancer in postmenopausal women receiving systemic estrogens.

7.2.4 *Barrier methods*

The most commonly used barrier methods of contraception are diaphragms and condoms. The efficacy of these methods is less than that of IUDs and oral contraceptives. Reported pregnancy rates for women aged 35–39 years are at best 1.1 per 100 women-years (*197*). The advantage of the condom is that it offers protection against sexually transmitted diseases (*198, 199*) including human immunodeficiency virus (HIV) infection (*200*). The relative risk of HIV infection among condom users compared to non-users is reported to be 0.4 (*201*).

Coitus-related methods of contraception are preferred by some couples because they are under user control. However, this may create a difficulty for middle-aged men (50–70 years) who are the likely partners of late premenopausal women. If their sexual potency is already reduced, self-administered contraceptive methods may make the problem worse.

Diaphragms and condoms are suitable contraceptive methods for women nearing the menopause when both fecundity and the frequency of coitus are low. However, contraceptive failures may occur and these methods will be more useful if abortion back-up services are available.

7.2.5 *Sterilization*

Surgical methods for female sterilization include tubal resection, cautery, and tubal occlusion using bands and clips. These are listed in order of reversibility from the least to the most reversible. Tubal occlusion using bands and clips requires laparoscopic equipment, but can be performed as an outpatient procedure, thereby eliminating the need for an overnight stay in hospital.

When desired family size has been achieved, male or female sterilization is a good contraceptive choice. The need for reversibility should be low, but potentially reversible methods are still preferable when available. In the United Kingdom, over 40% of couples over 40 years of age have chosen sterilization as their preferred method of birth control (*160*). A similar situation exists in many developed countries. There has been suspicion that female sterilization by tubal occlusion causes premenopausal dysfunctional bleeding. However, the evidence suggests that any association of tubal occlusion using clips or rings with menstrual bleeding problems is coincidental rather than causal (*202*). Recent research suggests that sterilization may protect against ovarian cancer

(*203*). The cultural and political acceptability of sterilization varies among different countries. Surgical sterilization requires an adequate health care delivery system to minimize the risk of infection and other possible surgical complications.

7.2.6 *Natural methods*

Data on the applicability of natural methods of fertility regulation in the late premenopausal years are sparse. However, the available data indicate that the irregular menses and periods of amenorrhoea that occur in a large proportion of perimenopausal women make the use of, for example, safe periods impractical (*204, 205*).

7.3 Relevance of existing data to developing countries

Most of the available data on risks and benefits of contraceptives in the late premenopause have come from developed countries, mainly the United Kingdom and the USA. Working out the risk-benefit ratio for women in developing countries needs solid scientific data. WHO has undertaken a multicentre case-control study involving developed and developing countries to evaluate the risk of cardiovascular diseases, including myocardial infarction, thrombotic and haemorrhagic strokes, and venous thrombosis and embolism for contraceptive pill users. When completed, this study will provide information about any associations between modern oral contraceptives and cardiovascular diseases, and whether the risks demonstrated in American and British women apply to women in developing countries.

WHO has already completed a similar multicentre study on the risk of neoplasia in relation to use of hormonal contraceptives. The risks of neoplasia, or lack of them, were similar in both developed and developing countries (*186*). These data give confidence about the safety of hormonal contraceptives both to those who develop health policies and to those who provide contraceptive services.

The risk-benefit ratio of contraception in the late premenopause is greatly influenced by the risk of maternal mortality (*206*). In countries where maternal mortality rates are high the effectiveness of contraceptives in preventing pregnancy will be of overwhelming importance. For women in developing countries contraception protects against the high rates of morbidity and mortality associated with high parity (*150*).

7.4 Conclusions

1. The majority of women in their forties are potentially fertile, yet almost all have achieved their desired family size. Safe, efficacious and acceptable contraception is a high priority for older premenopausal women throughout the world.
2. Pregnancy in women aged over 35 causes health risks to both the mother and the fetus. Maternal mortality, spontaneous abortion,

perinatal mortality and fetal anomalies all increase with increasing maternal age.

3. Combined oral contraceptives containing low doses of an estrogen and a progestogen are suitable for healthy, non-smoking women over the age of 35.
4. Progestogen-only contraceptives (oral preparations, implants, depot injectables or IUDs) may be suitable for late premenopausal women. They have a distinctive role for women in whom estrogens are contraindicated.
5. Both copper-bearing and progestogen-releasing IUDs are effective, long-lasting and safe contraceptives for late premenopausal women. Copper-bearing IUDs are also inexpensive.
6. Although barrier methods are not the most efficacious of contraceptive methods, they may be the method of choice for late premenopausal women whose fertility and frequency of coitus are low.
7. Condoms can reduce transmission of HIV infection; this is an important consideration in areas of high HIV prevalence.
8. Male or female sterilization is an excellent contraceptive option, provided that this approach is culturally acceptable and available at reasonable cost and low risk.

7.5 Recommendations

1. Studies in different cultures of women aged over 35 (and their partners) are needed to clarify their perceptions of their contraceptive needs, their attitudes towards contraceptive use and the methods they currently use. Patterns of sexual behaviour and relationships should also be explored.
2. Studies are needed of the providers of contraceptive services to gain information on their perceptions of the contraceptive needs of late premenopausal women and on the methods they prescribe.
3. Descriptive studies as recommended in 1 and 2 above should be followed by educational interventions directed at providers of contraceptive services and potential users, to ensure that misinformation about contraception is eliminated and effective methods are used.
4. Research is needed to evaluate the availability, accessibility and acceptability of contraceptive services for late premenopausal women.
5. Further studies are required on the side-effects of combined oral contraceptives in late premenopausal women, with particular reference to their effects on bone-mineral density and on the cardiovascular system.

6. The possible adverse effects of progestogen-only contraceptives on bone-mineral density should be investigated.
7. The effects of sterilization by tubal occlusion on ovarian function should be established.
8. When studies of the safety and efficacy of contraceptives are undertaken, women aged over 35 should be included in sufficient numbers to enable a separate analysis to be made of this age group. In some instances this may require studies targeted exclusively at women aged over 35.
9. Studies are needed of the protective effect of progestogens administered by the intrauterine or vaginal route on the risk of uterine neoplasia in postmenopausal women treated with estrogens.
10. The above-mentioned studies should include a smoking history in individual women and educational efforts should aim at preventing or stopping tobacco consumption.

8. Osteoporosis and fractures

8.1 Background

A definition adopted at a consensus development conference in 1991 and reaffirmed by a WHO Study Group (*207*) states that osteoporosis is "a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk". Osteoporotic bone is characterized by excessive loss of mineral content with a reduction in the density per unit volume of bone. Additional structural alterations occur that reduce the mechanical strength of osteoporotic bone (*208, 209*). Although it has traditionally been stated that the biochemical composition of osteoporotic bone is normal, molecular studies of defects in a collagen gene suggest the possibility of bone matrix alterations (*210*).

The major health consequence of osteoporosis is fracture as osteoporotic bone is easily broken. The primary fracture sites are the long bones and vertebrae. Fractures of the vertebrae are painful and cause spinal deformity, but fractures of the long bones, especially the neck of the femur, cause the greatest morbidity and mortality.

8.1.1 *Magnitude of the problem*

Osteoporosis and associated fractures are a major cause of mortality, morbidity and medical expense worldwide. Osteoporosis affects an estimated 75 million people in Europe, Japan and the United States combined, including one in three postmenopausal women and most elderly people (*211*). Estimates of its prevalence are complicated, however, by the definitions used, the ranges of bone-mineral density

selected to define the normal population and the techniques and sites of measurement (*207*). Approximately 1.3 million osteoporotic fractures occur annually in the United States alone with an annual cost approaching US$ 10 000 million per year (*212*). As the world population ages, osteoporosis will become an ever greater public health problem.

Hip fracture is responsible for much of the mortality and morbidity due to osteoporosis and is a leading cause of disability in elderly people. Between 12% and 20% of patients with hip fracture will die within one year of the event and mortality rises progressively with advancing age (*213, 214*). Moreover, the majority of those who survive a hip fracture are unable to perform the activities of daily living unaided and a small but significant percentage require permanent care in an institution or nursing care (*215*).

8.1.2 *Geographical variation*

The prevalence of both osteoporosis and hip fracture varies by country and by population group within countries. Osteoporosis is rare in African countries (*216*), frequent in India (*217*), and is most common in Europe and North America. In the USA, black Americans have greater bone mass in both cortical bone and vertebrae than Caucasian Americans (*218, 219*), whereas Asian Americans have less cortical bone than Caucasians of similar age (*220, 221*).

Age-adjusted incidence rates for hip fracture for several countries are shown in Table 2. Rates for both women and men vary greatly by country; the highest rates are found in the USA and the lowest occur in the South African Bantu population (*224*). The ratio of the rates for women to men also varies from about 2.0–2.7 in countries that have a high rate of hip fracture to one or less for countries that have a low rate. The reasons for the geographical differences in the incidence of hip fracture are not fully understood, but bone density does not explain all of the difference. For example, bone density is low in Japan as well as in other developed countries, but fracture rates in Japan are significantly lower (*225;* BE Nordin, personal communication, 1991). It is noteworthy that age-specific hip fracture rates have risen considerably in some Asian countries in recent decades (*226*). An increasing incidence of hip fracture has also been recognized in many of the established market economies (*207, 227*).

In European and North American populations, women have greater vertebral fracture rates than men. Over a lifetime this amounts to a 2–5-fold greater risk of vertebral fracture (*228–230*); this is consistent with the greater bone loss experienced by ageing women as compared with ageing men. Similar data are not available for other populations.

8.2 Pathogenesis of osteoporosis and fractures

The probability of developing osteoporosis in later life is dependent on

Table 2
Incidence rates[a] of hip fracture by country and sex[b]

Country or area	Women	Men	Female: male ratio
United States (Rochester, MN)	101.6	50.5	2.0
New Zealand	96.8	35.2	2.7
Sweden	87.2	38.2	2.3
Israel (Jerusalem)	69.9	42.8	1.6
United Kingdom	63.1	29.3	2.2
Netherlands	51.1	28.5	1.8
Finland	49.9	27.4	1.8
Former Yugoslavia[c]	39.2	37.9	1.0
Hong Kong	31.3	27.2	1.2
Former Yugoslavia[d]	17.3	18.2	1.0
Singapore	15.3	26.5	0.6
South Africa (Bantu)	5.3	5.6	0.9

[a] Per 100 000, age-adjusted to US population, 1970.
[b] Based on data from reference *222*, with the permission of the publisher. Reproduced, with minor editorial amendments, from reference *223*, with the permission of the publisher.
[c] Low-calcium diet.
[d] High-calcium diet.

both the peak bone mass achieved at maturity and the rate of bone loss over the subsequent years. Although previous cross-sectional studies had suggested that peak bone mass in women is achieved at about 30 years of age (*231*), more recent cross-sectional (*232, 233*) and longitudinal data (*234*) indicate that bone accretion is essentially complete by the late teenage years. Although bone mass in women is less than in men at all ages and at all body sites (*235*), after correction is made for body size, the peak bone density achieved by women at maturity is equivalent to that in men (*236*). In the subsequent years bone is lost at a rate of about 0.5–1% per year at most bony sites in both sexes (*231, 237*). In women, the rate of bone loss increases in the 5–10 years after the menopause, resulting in an average total loss of approximately 15% in the first few postmenopausal years (*231, 238*). After several years of accelerated bone loss the rate of loss decreases to a much slower pace (*239*).

The adverse effect of menopause on bone is attributed to the loss of ovarian steroids and of estrogen in particular (*238*). Several reports have examined the relationship between endogenous sex hormones and bone mineral density in perimenopausal and postmenopausal women. Murphy et al. (*240*) described a community-based cross-sectional study of 90 postmenopausal women. They found significant positive correlations

between indices (calculated from hormone concentration and level of sex hormone-binding globulin) of free estradiol and testosterone and bone mineral density at all sites, an observation also reported by Steinberg et al. (*241*). Slemenda et al. (*242*) reported that mean serum estrogen concentrations were strongly predictive of the rate of loss of bone mass in perimenopausal and postmenopausal women. In contrast, Spector (*243*) found no correlation between sex hormones and bone mineral content of the spine in 136 healthy white women with a mean age of 52 who were investigated within 30 months of their last menstrual period.

During the early postmenopausal years, bone loss is predominantly trabecular. This may be a function of the more rapid rate of bone turnover or remodelling that occurs in trabecular bone as compared to cortical bone. Remodelling is a process that couples bone resorption with bone formation and bone loss occurs when the amount resorbed is not fully replaced. An imbalance of formation and resorption occurs in the early postmenopausal years (*238*). Trabecular bone predominates in the vertebral body, which accounts for the vertebral osteoporosis and compression fractures that appear in many women in the 10-20 years following the menopause.

A number of factors that increase the likelihood of developing osteopenia (low bone mass) have been identified. Some of these affect the peak bone density achieved at maturity and others affect the subsequent rate of loss. The greater risks associated with increasing age, female gender and white or Asian racial group have been described in section 8.1. Postmenopausal women are at an increased risk of osteopenia, particularly those who have had an early natural menopause or a bilateral oophorectomy. Family history has long been recognized as an important indicator of risk of osteopenia, and more recently evidence for a specific marker of genetic susceptibility has been reported. Many of the differences in bone density between healthy individuals may be accounted for by allelic variations in the gene encoding the vitamin D receptor (*244*), but the absolute importance of this parameter is not yet known. Endocrine disorders including excess glucocorticoid (endogenous and exogenous), hyperthyroidism and hyperparathyroidism accelerate bone loss. The risk of bone loss also appears to be increased by lifestyle factors such as smoking, excess alcohol intake, lack of physical exercise, low calcium intake and inadequate acquisition of vitamin D through either exposure to sunlight or dietary consumption (*213, 223*). The extent to which lifestyle factors can modify genetic predisposition is not clear, particularly in later life when fractures are more likely to occur (*225, 238*).

Osteopenia is one of the important determinants of the likelihood of fracture occurrence. Therefore, the risk factors noted for osteopenia also increase the risk of fractures. In addition to bone density, other skeletal characteristics contribute to the risk of fracture. Bone fragility is increased by architectural abnormalities in cancellous (trabecular) bone (*208*) and by fatigue damage (micro-damage) (*245*). Since there are no

in vivo techniques for measurement of these alterations, the magnitude of their contribution to fracture risks is uncertain (*246*). Length of the femoral neck appears to influence fracture risk independently of bone mass in the hip (*247*). A long femoral neck presumably creates a mechanical disadvantage at the time of falls or other stresses (*246*). With vertebral fractures, prior fracture is predictive of subsequent fracture (*248*).

Falls and the tendency to fall are the other major considerations that affect fracture risk. Hip fractures are predominantly a condition of the elderly (median age 80 years) (*223*) and both the physiological condition of the individual and the status of the immediate living environment affect the risk of falls. Lack of exercise, muscular weakness, neurosensory disturbances, chronic illnesses and disability all contribute to the propensity to fall (*249*). Drugs that impair locomotor function appear to convey a particular risk (*250*) and lack of attention to hazards in the living environment adds to the problem.

8.3 Methods of measuring bone density and predicting fracture risk

8.3.1 *Bone mineral densitometry*

A WHO Study Group (*207*) has recently provided a detailed account of methods for the assessment of fracture risk and their application to screening for postmenopausal osteoporosis. New techniques for measuring bone density, applicable to both research and clinical settings, have made it possible to quantify accurately and precisely current bone density and to measure the rate of bone loss over time. The principle employed in all these techniques is that ionizing radiation is absorbed in proportion to the amount of bone mineral in its path. All are photon absorptiometric techniques that measure the mineral content of bone; they provide no information about bone micro-architecture or other characteristics. With the exception of quantitative computed tomography (QCT), all methods provide an integrated measurement of cortical and trabecular bone combined (*238*).

The choice of a technique for measurement of bone density depends largely on the research goals of a study, or the clinical decisions to be made on the basis of the test result. The characteristics of these techniques have been recently reviewed in detail by WHO (*207*). Clearly cost and feasibility are important. Accuracy and repeatability (precision) of the technique must be known and be suitable for the purposes for which the procedure is undertaken. Radiation exposure and safety of the subject must be considered; for a diagnostic test with important therapeutic implications, exposure to a higher level of radiation may be tolerable than would be acceptable for a screening procedure in healthy people.

Single-photon absorptiometry (SPA) is the technique that has been used for longest; it has a number of desirable features as noted in Table 3.

Table 3
A comparison of techniques for measuring bone density[a]

	Single-photon absorptiometry (SPA)	Dual-photon absorptiometry (DPA)	Quantitative computed tomography (QCT)		Dual energy X-ray absorptiometry (DEXA)
			Single energy	Dual energy	
Site(s) measured	Distal radius, os calcis	Spine, femur, total body	Spine (trabecular bone)	Spine (trabecular bone)	Spine, femur, total body, radius
Precision	Very good	Good	Good	Fair	Excellent
Accuracy	Very good	Good	Fair	Good	Good/very good
Radiation dose	Low	Low	Moderate	Moderate	Low
Typical time per study (minutes)	10	20–30	10–20	10–20	5–10
Relative cost	Low	Intermediate	High	High	Intermediate

[a] Based on data from reference 238, with the permission of the publisher.

Very good precision and accuracy at low cost are important characteristics of this technique and are essential when large numbers of individuals are to be evaluated. SPA has been used extensively for studies of bone mass at the distal radius and other peripheral sites, but it is unsuitable for measuring bone density at the spine and hip because of the characteristics of the radioactive source and the soft tissues surrounding the bone (*238*). SPA values at the forearm and calcaneus can be used to predict the risk of fracture at certain vulnerable sites (*251, 252*), but recent data indicate that site-specific fracture risk is better predicted by measurement at that site (*253, 254*).

Dual-photon absorptiometry (DPA) was developed to overcome the problem of measuring bone density at sites where bone is surrounded by soft tissue. Photons are emitted from a radioisotope at two energy levels with different absorbance constants for soft and mineralized tissue, thus allowing for measurement of absorbance due to each tissue component. Although DPA has been superseded by dual-energy X-ray absorptiometry (DEXA), it remains an acceptable technique for measurement of bone density at central sites including the spine and hip (*238*).

DEXA is currently the method of choice for bone density measurement in situations in which the high-cost equipment, the technical expertise to maintain the equipment, and the professional personnel to interpret the results are all available. For most countries these requirements are met only at selected research institutions or in tertiary care hospitals that specialize in orthopaedics and bone metabolism. The measurements made with DEXA use the same principle as for DPA, but the source of photons is an X-ray tube emitting X-rays at two major peaks of energy. The use of X-rays has several technical advantages over the radioisotope used in DPA (*238*). The excellent precision (1% or better for the lumbar spine) of DEXA (*255*) makes it the best technique for measuring small changes in vertebral bone density (*255, 256*). The detection of changes is worth while if patient management will be altered as a result. For epidemiological studies and large surveys, or when peripheral bone density is the main concern, SPA is the most cost-effective technique. As with DEXA, the radiation dose for SPA is low. For a DEXA scan of a specific skeletal region, the radiation dose is appreciably less than for a standard chest X-ray and is approximately one-hundredth of the annual background radiation (*238*).

Quantitative computed tomography (QCT) is the only technique that can measure the true density of trabecular bone in the vertebral body; it also provides an image that includes information about the trabecular structure (*238*). These features may be useful for patient care. The radiation dose is significantly higher with QCT than with the other techniques, which inhibits its use in situations where repeated bone density measurements are being considered.

Although bone densitometry can be used to predict the likelihood of

fracture, currently there is insufficient evidence to justify population screening programmes (*207*).

8.3.2 *Ultrasound of bone*

The velocity, attenuation or reflection of ultrasound in bone can be measured by several methods. The potentially attractive features of using ultrasound include the avoidance of ionizing radiation, the portability of the equipment, the potential for reducing capital and operating costs, and the possibility that ultrasound may provide some information concerning the structural organization of bone in addition to bone mass (*207*). Early evidence suggests that ultrasound of the calcaneus may be used to predict fracture risk (*257, 258*).

8.3.3 *Biochemical markers*

Markers that can be used to predict whether or not an individual woman is at risk of rapid bone loss and of incurring fractures could help to determine who might receive most benefit from preventive interventions. Such a policy would maximize benefits of interventions, while minimizing the risks and costs. The characteristics required of biochemical markers are high sensitivity, specificity and positive predictive value; the laboratory technology should be simple and cheap, and the procedure should involve little imposition on the subject.

Some biochemical markers of bone turnover have been evaluated in terms of their predictive capability. Christiansen et al. (*259*) incorporated several biochemical markers into an algorithm that also included measurement of initial bone mass. This approach has not been widely applied, but warrants evaluation using more specific markers.

Markers of bone formation, including osteocalcin and bone-specific alkaline phosphatase, are well characterized. Measurement of bone resorption has been less satisfactory because biochemical indices, such as hydroxyproline/creatinine and calcium/creatinine ratios in urine, are neither sensitive nor specific enough (*238*). Recently developed marker assays hold more promise. Cross-linking structures found only in the mature collagen of cartilage and bone, hydroxylysyl pyridinoline (HP) and lysyl pyridinoline (LP), can be measured using high-performance liquid chromatography or immunoassay methods (*260, 261*). The excretion of pyridinoline cross-links in the urine is elevated in states characterized by excess bone resorption. Excretion is higher in postmenopausal women than in premenopausal women (*262*); levels fall after commencement of estrogen therapy, either alone or in combination with a progestogen (*263*), and also correlate with the extent of vertebral osteoporosis (*264*). The recent development of a monoclonal antibody-based enzyme immunoassay for *N*-telopeptides of type 1 collagen shows considerable promise as a sensitive, specific, convenient assay of bone resorption (*265*).

8.3.4 *Genetic markers*

The recent identification of allelic variants of the vitamin D receptor gene, which correlate with bone density, indicates the potential for future development of genetic screening tests for osteoporosis risk.

8.4 Prevention of osteoporosis and fractures

Measures to prevent osteoporosis should start in early childhood and continue into old age. Many of the factors listed in section 8.2 are important in the early years of life including adequate calcium intake, moderate exercise, and avoidance of smoking and excessive alcohol consumption. Later in life, estrogen therapy, either alone or in combination with a progestogen, can mitigate the accelerated bone loss that occurs in the early postmenopausal years, and calcium and vitamin D supplementation has been shown to reduce fracture incidence rates in some elderly populations.

8.4.1 *Calcium and vitamin D*

The existing data on children and adolescent girls suggest that current levels of calcium intake in industrialized countries are not sufficient to enable them to achieve maximum bone density at maturity. In two randomized trials, children and adolescents receiving supplementary calcium achieved greater gain in bone mass than subjects not receiving supplements (*266, 267*). Whether supplementary calcium results in an increased peak bone mass remains to be determined. The optimal calcium intake between the ages of 2 years and 30 years appears to be within the range of 1000-1600 mg/day for people eating a normal USA diet (*268*).

In postmenopausal women, calcium supplementation with or without vitamin D has been shown to reduce bone loss and fractures in randomized controlled trials (*269-272*). The benefits are greatest in women who are more than 5 or 6 years beyond the menopause. Bone loss in the early postmenopausal years appears to be primarily due to estrogen deprivation. Calcium supplementation by itself is not sufficient to slow bone loss in the first 5 years after the menopause (*269*). A current recommendation for postmenopausal women who eat a normal USA diet is a calcium intake of at least 1500 mg/day (*268*). This figure was derived from a consensus conference held in the USA in 1984 (*273*) and also from calcium balance studies in postmenopausal women (*274, 275*).

Vitamin D has many effects including facilitation of intestinal absorption of calcium and phosphorus, stimulation of osteoblast synthesis of osteocalcin, and promotion of cell differentiation (*268, 276*).

Serum levels of vitamin D decline with age, and at latitudes existing in the USA, values in young adults are generally >100 nmol/litre, but for people aged over 80 years, the values are often <30 nmol/litre (*268*). The age-

related decline is due to reduced exposure to sunlight, decreased efficiency of vitamin D synthesis in the skin and metabolism in the kidney, and low consumption of foods containing vitamin D associated with reduced intestinal absorption of the vitamin D that is consumed (*268, 277, 278*). The administration of physiological amounts of vitamin D to persons with low serum levels will reverse many of these changes (*279*).

Two clinical trials on vitamin D supplementation in elderly persons have been reported. In a study in France, bone loss ceased and hip fracture incidence was markedly reduced in elderly women (mean age 84 years) who received vitamin D and calcium supplements when compared to untreated women of the same age (*270*). In a study in Finland, vitamin D (without calcium) was supplied by injection to elderly men and women aged over 75 years, resulting in a significant reduction in fractures of the hip and other bones (*280*). In 1982 the American Society for Clinical Nutrition recommended supplementing the diet of elderly persons with 20 µg/day (800 IU) of vitamin D (*281*). Data from developed countries suggest that a significant reduction in the fracture burden could be achieved by adherence to this recommendation (*268*).

8.4.2 *Physical exercise*

The value of exercise in maintaining or increasing bone density is not fully resolved. Cross-sectional studies show higher bone mineral density in the lumbar spines of women who exercise compared to sedentary women (*282*).

However, longitudinal studies show smaller differences between those who exercise and those who do not. The studies are difficult to compare because the definition of exercise varies from study to study; the ages, characteristics, and comparability of women also vary; and loss to follow-up with the resulting potential for bias is a problem in the prospective studies (*283*). It is well established, however, that without weight-bearing exercise, loss of skeletal bone mass will occur (*284-290*). Regular, moderate, weight-bearing exercise is recommended because of its likely benefit to the skeleton, as well as to almost all other organ systems in the body (*238*). Exercise increases muscle strength, coordination and flexibility; these features are particularly important to the elderly and can help them to avoid falls.

Excessive exercise associated with menstrual disturbances should be avoided since it is detrimental to bone (*291*).

8.4.3 *Smoking and alcohol*

Cigarette smoking approximately doubles the risk of fractures (*238*). Evidence for the link between smoking and bone density and fractures comes from both cross-sectional and longitudinal studies (*292*). A recent study of bone density in female twins discordant for smoking history

showed that the women who smoked had lower bone density (*293*). The adverse effect of smoking on bone is likely to be mediated through changes in endogenous estrogen metabolism; estrogen production is decreased and metabolic clearance is increased in smokers (*294*), although this explanation has not been confirmed in all studies (*295*).

Chronic alcohol abuse is associated with reduced bone mass and an increased risk of fractures (*238*). Moderate consumption of alcohol, i.e. one or two standard drinks per day, does not appear to be deleterious (*296, 297*).

8.4.4 *Administration of estrogens and progestogens*

Administration of exogenous estrogens or an estrogen plus a progestogen is effective in maintaining bone density in postmenopausal women. Many studies have evaluated the effects of estrogen administration on bone density and the conclusions have been consistent (*298*). Estrogen administration reduces bone remodelling to premenopausal levels and thus reduces the rate of loss of skeletal tissue. The effects persist for as long as therapy is continued and cease when estrogens are discontinued (*299*). Fracture rates are also reduced by estrogen therapy (*298, 300-302*). However, recent observational studies have shown that estrogen therapy for some years after the menopause does not provide adequate protection against hip fractures in later life (*303, 304*).

The addition of progestogens does not reduce the efficacy of estrogens; 19-nortestosterone derivatives may actually enhance the skeletal response (*305*). All routes of estrogen administration (oral, transdermal, implant) are effective in maintaining or even increasing bone mineral density. The oral and transdermal routes are the most commonly employed. The important factors for the skeleton appear to be the estrogen dose and the duration of administration, rather than the route (*301*). A dose of 0.625 mg daily of conjugated equine estrogens has been regarded as adequate to preserve bone. However, more recent dose-response studies suggest that 0.625 mg may be sufficient to protect the spine, but not the hip (*306*). Micronized estradiol (0.5 mg) protects both the spine and the hip (*307*), but doses of up to 2 mg/day of estradiol valerate appear to be required (*308*). Calcium supplementation may permit the use of lower estrogen doses (*309*).

Premature loss of ovarian function, whether spontaneous or induced, leads to an early acceleration of bone loss and is an indication for prophylactic therapy.

8.4.5 *Avoidance of trauma*

Hip fractures in elderly people are almost always the result of falls. The median age of people who suffer hip fractures is 80 years (*223*). The elimination of environmental hazards, the avoidance of drugs which impair balance (*250*) and management of neuromuscular disorders all

play a role in fracture prevention (*238*). Regular exercise improves muscle strength and coordination and reduces the tendency to fall.

It is thought that most hip fractures are caused by direct trauma near the hip associated with a fall. Energy absorption at the hip appears to be an important determinant of hip fractures. In a recent controlled trial conducted in a nursing home setting, the use of external hip protectors was associated with a significant reduction in hip fracture risk (*310*). Further evaluation of such interventions is warranted.

8.5 Treatment of osteoporosis and fractures

The goal of treatment in established osteoporosis is to reduce the frequency of fracture occurrence. To meet this goal, the existing bone mass must be maintained and preferably increased. All the topics relevant to prevention (section 8.4) are also applicable to treatment. Diet (particularly intake of calcium and vitamin D), exercise, advice against smoking and excess alcohol intake, and environmental safety are areas in which the woman herself can actively participate and contribute to the therapeutic process. In most countries the first line of drug therapy remains estrogens, either alone or in combination with a progestogen, supplemented with at least 1000 mg of calcium daily. In patients at risk of vitamin D deficiency an oral supplement of 800 IU per day should be provided.

In patients unsuitable for estrogen and progestogen therapy, other specific agents can be considered.

8.5.1 *Calcitonin*

Calcitonin is a polypeptide hormone produced by the thyroid gland. Salmon calcitonin is the form most commonly used; it is administered by intramuscular or subcutaneous injections, or by intranasal spray. Calcitonin acts through receptors on osteoclasts to alter both the structure and function of the osteoclast, such that bone resorption is inhibited (*311*). Calcitonin has been shown to prevent hip fractures (*312*) and new vertebral fractures in women over the age of 50 who have already had one or more vertebral crush fractures (*313*). In established osteoporosis, bone pain is one of the major complaints. Calcitonin has a potent analgesic effect, reducing the duration of confinement to bed and decreasing the need for concomitant analgesic medications (*311*).

8.5.2 *Bisphosphonates*

Bisphosphonates are synthetic compounds that bind to hydroxyapatite crystals of bone and function by suppressing osteoclastic bone resorption (*314*). These compounds are administered orally and most often intermittently. Doses must be carefully controlled because high doses can cause defective bone mineralization (*314*). In randomized, controlled trials etidronate, an early-generation bisphosphonate, has been shown to

reduce vertebral fracture rates and to cause a moderate increase in spinal bone mass (*315, 316*). Development and testing of newer bisphosphonates are currently in progress.

8.5.3 *Vitamin D sterols*

Calcitriol (1,25-dihydroxyvitamin D_3) is a potent vitamin D metabolite which stimulates intestinal calcium absorption and may act directly on osteoblasts. Vertebral fracture rates have been found to be reduced after 2 or 3 years of use (*317*). Adverse effects, e.g. hypercalciuria and hypercalcaemia, require monitoring during clinical use. Further long-term trials are needed.

A vitamin D analogue, alfacalcidiol, has been shown to be effective in reducing vertebral fractures in a Japanese population (*318*).

8.5.4 *Fluoride*

Fluoride is cheap and is the only agent for treatment of osteoporosis and fractures that has a marked anabolic effect on bone. It has been shown to be mitogenic for osteoblasts (*319*). Clinical trials have shown that fluoride can increase spinal bone mass to a significant degree (*238*) and a study in France showed a reduction in vertebral fracture rate (*320*). However, in another study, non-vertebral fractures were actually increased in women taking fluoride (*321*). Dosage may be a factor in determining the effect on axial and appendicular bone, but safety and efficacy continue to be important issues (*322-325*). Randomized clinical trials are needed to resolve the issues of possible risk of peripheral fracture, other side-effects, pharmacological formulation, optimal dosage and duration of treatment (*238*).

8.5.5 *Other potential therapies*

Other potential therapeutic agents currently being investigated include human parathyroid hormone (1-34), human growth hormone and insulin-like growth factor 1, progestogens (without estrogens), thiazides, ipriflavone and tibolone. Anabolic steroids and combination therapy which includes testosterone may be effective on bone, but the use of these therapies is limited by their side-effects. Several anti-estrogens with partial estrogen agonist activity are being investigated for estrogen-like effects on bone.

8.6 Conclusions

1. There are large geographical variations in the prevalence of osteoporosis and the incidence of fractures. The highest hip fracture rates are reported in the USA and the lowest in the South African Bantu.
2. The risk factors for osteoporosis in women are numerous. The contribution of family history may be explained by one or more

markers of genetic susceptibility. Inadequate acquisition of vitamin D, low calcium intake, smoking, high alcohol consumption and inactivity all increase the risk of osteoporosis.

3. Reduced bone mass is a major risk factor for fracture, although the magnitude of the risk may vary between populations. Fracture risk is also affected by bone fragility, length of the femoral neck (for hip fracture), history of prior fracture (for vertebral fracture) and falls.
4. Prevention of osteoporosis is a high priority, especially because treatment of the established disease remains unsatisfactory.
5. Feasible methods for accurate measurement of bone density are available for both epidemiological surveillance and clinical diagnosis of osteoporosis. SPA is the most suitable method for epidemiological purposes, whereas DEXA may be the most appropriate in tertiary care clinical settings.
6. Some risk factors can be modified to prevent osteoporosis and/or fractures. Postmenopausal bone loss can be inhibited with estrogen or estrogen plus progestogen therapy. Bone loss in the elderly can be moderated with supplementary calcium and vitamin D. Maintenance of muscle tone and strength through exercise may reduce falls, which are a significant cause of osteoporotic fracture in the elderly.
7. First-line therapy for established osteoporosis in women in many countries is an estrogen or an estrogen plus a progestogen, calcium and vitamin D.
8. The ability to predict a woman's fracture risk at the time of menopause, or earlier in life, would allow for selection of individuals who could benefit most from preventive interventions. The existing densitometric techniques can be used for this purpose.

8.7 Recommendations

1. Studies are needed to determine the worldwide prevalence of osteoporotic fractures, to assess the associated morbidity and to estimate the relevant costs. The causes of the increasing incidence rates of fractures of the hip and other bones should be investigated.
2. Further studies are required of the application of densitometric techniques to the prediction of fractures. Long-term prospective studies of bone density in peri- and postmenopausal women are required to determine whether such techniques can be used to predict lifetime fracture risk. The possibility of more general applications for simple techniques such as ultrasound of bone should be explored.
3. There is a need for population-based studies on the variation in age-specific bone mass in pre- and postmenopausal women and in men from diverse population groups with concurrent collection of risk factor data. Studies of the incidence of hip and vertebral fractures

should be conducted in the same populations so that the association between bone mass and fracture occurrence can be quantified.

4. Development of new biochemical markers of bone turnover, and further assessment of existing markers, should be actively pursued. Markers should be evaluated for the purpose of identifying women at high risk of rapid bone loss in mid- and later life. Prospective studies should be carried out to determine the rate of bone loss at different skeletal sites, both before and after the menopause.
5. Genetic markers for the risk of osteoporosis, such as the allelic variants of the vitamin D receptor gene, should be evaluated in different populations and their relationship to bone density and fracture incidence should be quantified.
6. The causal relationship between potentially modifiable lifestyle factors and fracture risk should be more precisely established and the applicability of prevention strategies to whole populations should be assessed.
7. Research is necessary to determine the optimal time for the initiation and the optimal duration of hormonal therapy for fracture prevention, and also on the effect of cessation of therapy on risk of fracture.
8. Research on the effects of interventions other than estrogen and progestogen therapy on fracture risk should be encouraged.
9. Randomized trials of well defined exercise programmes conducted over prolonged periods of time in women (and men) of different ages are needed to answer the important questions relating exercise patterns to bone density and fractures.
10. The influence of repeated childbearing and long-term breast-feeding on the prevalence of osteoporosis requires investigation in countries where these reproductive patterns are common.

9. Cardiovascular diseases and hormone therapy

9.1 Background

Cardiovascular diseases (CVDs) are one of the most common causes of death in women and men in almost all parts of the world (*10*). They are the most common cause of death in men over the age of 35 and in women over the age of 65. Between the ages of 55 and 64, CVD mortality rates in women in many developed countries are exceeded only by those for malignant neoplasms. Mortality rates for CVDs in women are lower than those for men at all ages, but the gender gap is much greater in middle age than in old age.

Although CVD mortality rates increase exponentially with age, when plotted on a logarithmic scale, there is no increase in the slope of the rates

around the age of 50, the approximate age of menopause in much of the world (*10, 326, 327*). However, for women in industrialized countries a positive inflexion in the age-specific death rates due to circulatory diseases has been noted in the 65-74-year age group (*10*). If cessation of ovarian function and reduced levels of sex steroid hormones had an effect on CVD mortality, one would expect the rate of increase in mortality rates to accelerate after the age of 50; this would be evident by an increasing slope of the age-incidence curve. It is not clear whether the inflexion observed some 20 years after average age at natural menopause can be explained by the cessation of ovarian function.

The argument that cessation of ovarian function might increase the risk of CVD has also been explored in studies of age at natural menopause and age at bilateral oophorectomy; the latter should significantly reduce the total lifetime exposure to endogenous estrogens. The majority of studies have identified an inverse relationship between menopausal age and risk of CVD (*328*). A large cohort study in the USA (*329*) found that surgically induced menopause, but not natural menopause, was associated with a significantly increased risk of coronary heart disease (CHD), an effect that was not evident among women who had received estrogen therapy.

Numerous studies show that, compared to premenopausal women of the same age, postmenopausal women have more risk factors for CHD. They have higher levels of serum cholesterol and low-density lipoprotein (LDL) cholesterol and lower levels of high-density lipoprotein (HDL) cholesterol (*330-332*). These distinctions between age effects and menopausal effects are of some importance in that they imply different causes and different potential therapies.

9.2 Epidemiological studies of hormone therapy

Several epidemiological studies have demonstrated a reduction in risk of CHD in postmenopausal women treated with oral estrogens compared with untreated women. Three meta-analyses estimated an overall reduction in risk of almost 50% for women who had at any time received estrogen therapy (*333-335*). Psaty et al. (*336*) further summarized the studies analysed by Stampfer & Colditz (*334*) by grouping them according to study design (Table 4). The summary risk estimate from all the studies is 0.56 (95% CI 0.50-0.61). Only the hospital-based case-control studies show no reduction in risk of CHD in women using estrogens; however, these may be considered the weakest of the study designs listed.

Details of the estrogen regimen were not available in all these studies. Many compared the risk of CHD among women who had at any time used estrogens with that among women who had never used them. When more detailed information was reported about the history of estrogen use, however, current use was the most important factor for risk reduction

Table 4
Meta-analysis of the association between coronary heart disease and the use of estrogens according to study design[a]

Type of study	Number of studies	Number of cases	Relative risk[b]	95% confidence interval
Hospital-based case-control	6	668	1.33	0.93-1.91
Population-based case-control	7	1253	0.76	0.61-0.94
Cohort with internal controls	12	772	0.58	0.48-0.69
Cross-sectional angiography	3	1551	0.41	0.34-0.50
Cohort with external controls	3	62	0.36	0.28-0.47
All studies combined	31	4306	0.56	0.50-0.61

[a] Reproduced from reference *336*, with the permission of the publisher. Copyright 1993, American Medical Association.
[b] Calculated as the risk of coronary heart disease among women who had at any time received estrogen therapy compared with that among women who had never received it.

(*337, 338*). Long-term use, especially among current users, may confer additional protection against mortality from CHD (*339*). A daily dosage of 0.625 mg of conjugated estrogens produced a beneficial effect, but there was no apparent advantage from higher doses. The risk of CHD was reduced whether or not women had known risk factors for CHD (*334*). The magnitude of the protective effect was greater in women who had had a bilateral oophorectomy; no protective effect was evident in women whose age at natural menopause was 55 years or more (*338*).

The addition of progestogens to estrogen therapy is recommended for women with an intact uterus because of the potential for estrogen-induced endometrial cancer, but few data are available on combined therapy. Two longitudinal studies, one from Sweden (on myocardial infarction) and one from England (on CVD), showed similar relative risk reductions in women who had at any time used combined hormone therapy compared with those who had used estrogens alone (*340, 341*). A case-control study from the USA showed no reduction in risk of non-fatal myocardial infarction in women given combined hormones (*342*). Further studies are required to make any conclusions on the cardiovascular effects of combined hormone therapy, and this is the issue of greatest relevance to clinical practice.

The magnitude and relative consistency of the reduction in risk of CHD provided by estrogen administration is impressive in these observational epidemiological studies. However, the amount of protection may be less than the 50% reported. A review by Armitage (*343*) noted that treatments that appear to provide 50% protection in observational studies often give 20% or less protection when studied by randomized clinical trial. Posthuma et al. (*344*) recently reported that the studies of hormone

replacement therapy which showed the largest reduction in CVD also showed the largest reduction in cancer risk, suggesting the possibility of a "healthy woman" effect among those using hormone therapy.

Selection factors cannot be fully controlled in observational studies, and the effect of estrogen therapy in postmenopausal users may be confounded with socioeconomic factors; users are likely to be upper middle-class, well educated, Caucasian, health conscious and lean (i.e. have no superfluous fat) (*328, 337, 345*). It has also been shown that such women are more likely to comply with treatment than women from other socioeconomic groups (compliance bias), which may account for some of the apparent beneficial effect (*346*). Women with heart disease, hypertension, diabetes mellitus or risk factors for these conditions are less likely to be prescribed estrogen than women without these conditions. Physicians have been influenced in their prescribing of hormone therapy by the increased risk of CHD and stroke that was observed with the high-dose oral contraceptives (*327, 347*).

9.3 Coronary atherosclerosis

Four studies have examined the association between estrogen use and angiographically defined coronary artery disease in postmenopausal women (*348-351*). As shown in Table 5, the calculated odds ratios for severe coronary stenosis or ≥70% occlusion were 0.50 or lower for estrogen users as compared with non-users.

A reduction in mortality among women with diagnosed coronary atherosclerosis has been reported in relation to estrogen use. Sullivan et al. (*352*) reported that the 10-year survival rate for women whose baseline coronary angiogram showed 70% or greater occlusion was statistically significantly better for estrogen users than non-users. In women who had less coronary stenosis, the survival benefits were reduced or nonexistent.

Table 5
Studies of estrogen use and angiographically defined coronary artery disease in postmenopausal women[a]

First author (year) (*reference*)	Age (years)	Estrogen use (%)	Number of women	End-point	Odds ratio
Sullivan (1988) (*348*)	63	<5	2188	≥70% occlusion	0.44
Gruchow (1988) (*349*)	60	20	933	Severe stenosis Moderate stenosis	0.37 0.59
McFarland (1989) (*350*)	51	41	345	≥70% occlusion	0.50
Hong (1992) (*351*)	62	20	90	≥25% occlusion	0.13

[a] Reproduced, with minor editorial amendments, from reference 328, with the permission of the publisher. Copyright 1991, American Medical Association.

9.4 Mechanisms of hormonal effects

The mechanisms underlying the protective effect of estrogen therapy against CVD have been the focus of numerous studies. Part of the protective effect may be explained by changes in serum lipoproteins, particularly in LDL cholesterol and in HDL cholesterol. However, an estimated 50-75% of the protective effect is due to other mechanisms (*328*). There is some evidence that the lipoprotein system has metabolic links with the coagulation and fibrinolytic systems, the imbalance of which could result in thrombo-occlusive disorders. Other possible links exist between these systems and the vasoactive factors produced by the vascular endothelium and in platelets. Thus, the risk of CVD is probably determined by a complex interplay of several risk factor systems (*353*).

9.4.1 *Lipids*

Changes in serum lipids associated with the menopause are well established. Total serum cholesterol, LDL cholesterol and triglyceride concentrations increase, and HDL cholesterol decreases (*330, 331, 354-356*). All of these changes increase the risk of CVD. These changes begin about 2 years before natural menopause occurs (*331*). Analysis of LDL subfractions has shown that LDL particles may be smaller in postmenopausal than in premenopausal women (*356-358*). The small, dense LDL particles are particularly atherogenic.

Commonly used forms and doses of natural estrogens (0.625 mg of oral conjugated estrogen or 1.5-2.0 mg of oral estradiol) result in significant decreases in total and LDL cholesterol and in apolipoprotein B concentrations. There is a concomitant increase in HDL cholesterol, mainly of the HDL2 fraction (*359-361*). On average, estrogen replacement results in a 4% decrease in LDL cholesterol and a 10% increase in HDL cholesterol (*359*). However, the extent of the decrease depends on the initial concentration of LDL cholesterol; initially high concentrations are reduced effectively while initially low levels are less altered (*362*). Triglyceride content of both LDL and HDL particles increases during estrogen administration, resulting in an increased proportion of triglyceride in the major circulating lipoprotein species (*363*).

Data are accumulating on the effects of combined estrogen and progestogen hormone therapy on lipids and lipoproteins. The effect of progestogens on the lipoprotein pattern is largely dependent on the type and dose. The 19-nortestosterone compounds have marked androgenic properties with pronounced HDL cholesterol-lowering activity. Either levonorgestrel, 125-250 μg daily, or norethisterone, 5 mg daily, when added for 10-14 days per month to the estrogen regimen, may reduce HDL cholesterol to below baseline levels (*364, 365*). Limited data suggest that lower doses of androgenic progestogens or commonly used doses of 17-hydroxyprogesterone-derived progestogens produce a small, if any, reduction in HDL cholesterol (*366*). Androgenic progestogens of

the 19-nortestosterone type tend to lower serum triglyceride levels (*366*), while 17-hydroxyprogesterone-derived progestogens have little or no effect.

Continuous combined low-dose regimens consisting of both an estrogen and a progestogen given daily have been introduced in some countries. Preliminary data indicate that these regimens appear to attenuate the expected reduction in LDL cholesterol and the increase in HDL cholesterol (*360, 367*).

Another mode of hormone therapy recently introduced is transdermally administered estradiol given alone or in combination with norethisterone which is also administered transdermally. The few data available on transdermal administration suggest an attenuated effect on HDL cholesterol (*363*).

Preliminary evidence suggests that elevated levels of lipoprotein(a), which are thought to be predictive of CVDs, may be reduced by some estrogens and estrogen-progestogen combinations (*368, 369*).

9.4.2 *Coagulation and fibrinolysis*

Much of the concern that hormone therapy might enhance coagulation and thrombus formation is based on the literature on early oral contraceptives which contained high doses of synthetic estrogens. The thromboembolic complications reported with these early products (*166*) have not been evident with the smaller doses of natural estrogens employed in hormone therapy (*370, 371*).

The results of studies of hormonal effects on clotting factors differ depending on the dose and type of estrogen, and on whether or not a progestogen was added. In some studies, estrogens appear to lower the concentration of fibrinogen (*372*) which is thought to decrease the risk of CVD. Antithrombin III activity was lowered by conjugated equine estrogens (*373*) but was not altered by 2 mg/day of estradiol valerate (*374*). The activation of coagulation factor VII has been reported in association with estrogen-induced hypertriglyceridaemia (*375*). In contrast, an oral estrogen plus a progestogen given for one year to 60 postmenopausal women caused a decrease in the concentration of factor VII (*373*). The impaired fibrinolysis associated with estrogen-induced hypertriglyceridaemia is not fully understood. The evidence on hormonal effects on multiple clotting factors shows complex relationships which, when taken together, suggest that hormones at the doses currently used for postmenopausal therapy would not increase the risk of thromboembolism (*353, 376*).

9.4.3 *Insulin resistance*

Disturbances of glucose and insulin metabolism are important markers in the development of CHD. Impaired glucose tolerance is a predictor of CHD (*377, 378*). Elevated insulin concentrations are frequently found in both

men and women with CHD (*379, 380*), although no prospective studies have found that hyperinsulinaemia is a predictor of heart disease (*381*).

In vitro and *in vivo* studies have demonstrated that administration of estrogens increases pancreatic insulin secretion and improves insulin sensitivity. Furthermore, estradiol-17β has been shown to have this effect in postmenopausal women (*382*). However, alkylated and equine estrogens have no effect on insulin or glucose plasma levels, as demonstrated by glucose tolerance tests performed before and after 6 months of estrogen treatment (*383*). Progestogens increase pancreatic insulin secretion but, in contrast to estrogens, they increase insulin resistance. The effects of progestogens may partly depend on the androgenicity of the steroid used. In one study, treatment with either oral conjugated equine estrogens 0.625 mg daily and cyclic (±)-norgestrel 0.15 mg, or continuous transdermal estradiol-17β, 0.5 mg, and cyclic transdermal norethisterone 0.25 mg, produced no change in glucose tolerance and a reduction in insulin resistance after one year of treatment (*384*). These data suggest that non-androgenic progestogens do not oppose an estradiol-induced improvement in insulin sensitivity.

Increased central or upper body fat (android fat) is associated with an increased risk of CHD (*385*), unlike fat in the lower body segment (gynoid fat). The proportion of android fat correlates positively with insulin resistance. The menopause may be associated with a significant increase in the proportion of android fat and a significant reduction in the proportion of gynoid fat (*386*). Estrogen treatment appears to reverse these changes in body fat distribution (*380*). This beneficial redistribution of fat could be a contributory factor to the reduction in risk of CHD reported in postmenopausal women taking estrogens.

9.4.4 *Vascular tone*

The previously demonstrated association between high-dose oral contraceptives and hypertension (*387*) has given rise to concern that PHT might have similar effects. However, epidemiological studies have shown no adverse effect on blood pressure in either normotensive or hypertensive women as a result of postmenopausal hormone use (*388, 389*). In two small clinical trials oral estrogen therapy was associated with a reduction in both mean systolic and diastolic blood pressure in normotensive and hypertensive women (*390, 391*).

Studies on animals have demonstrated that short-term administration of estradiol-17β can increase blood flow in a number of vascular beds (*392*). Estradiol-17β increases peripheral blood flow in postmenopausal women after both short-term (*393*) and long-term administration (*394*). Other human studies have shown that estrogens induce favourable changes in the carotid artery pulsatility index (*395*) and increase stroke volume and the acceleration of blood flow in the aorta (*396*). The beneficial effects of estrogens on blood flow in the internal carotid and middle cerebral arteries are not modified by the addition of a cyclical progestogen to the

treatment regimen (*397*). These findings suggest that estrogens may have a beneficial effect on blood flow and vascular resistance in the vascular beds of postmenopausal women.

Estrogens can produce relaxation of coronary arteries in animal models. The sex hormone milieu of the animal may influence the relaxation response to estrogens, which may be mediated by the release of nitric oxide from the vascular endothelium (*398*). Acute estrogen therapy has recently been shown to attenuate acetylcholine-induced constriction in atherosclerotic coronary arteries in animals and humans (*398-400*).

In a randomized double-blind crossover study of the acute effects of sublingual estradiol-17β on exercise-induced myocardial ischaemia in 11 postmenopausal women with coronary artery disease, estradiol was shown to increase significantly the time to depression of the ST segment of the electrocardiogram and the total exercise time (*401*).

These recent studies provide evidence for an acute effect of estrogens on both peripheral and coronary blood flow in animals and humans. Whether estrogens exert direct or indirect actions on the vasculature over the long term is not yet known.

9.5 Implications for developing countries

It is not known whether these data on hormone therapy and CVD which were generated in industrialized countries can be generalized to developing countries. It is clear that women aged 55 years and over throughout the world have high rates of coronary heart disease, but information on risk factors, precursor lesions, clinical presentation and prognosis is not readily available. Neither the extent to which diet and the sociocultural environment affect risk, nor the prevalence of "Western risk factors", e.g. elevated cholesterol, hypertension, diabetes and smoking, is known. Differences in metabolism of relevant lipids and hormones between various ethnic groups may be expected. Without greater knowledge of the natural history of coronary heart disease in different cultural settings, and its relationship to both menopause and the ageing process, it is not possible to know either the benefits or the possible risks of PHT for women in developing countries.

9.6 Conclusions

1. Cessation of ovarian function at the menopause is associated with an increase in LDL cholesterol and a decrease in HDL cholesterol. These changes increase the risk of CHD.
2. Daily estrogen therapy increases HDL cholesterol and decreases total cholesterol and LDL cholesterol. Conjugated estrogens also increase triglyceride concentrations. These effects are most pronounced in women with low HDL and high LDL baseline cholesterol concentrations.

3. When a progestogen is added for 10-14 days per month to the estrogen regimen, the effects on serum lipids depend on the type and dose of the progestogen. Androgenic 19-nortestosterone compounds in the usual therapeutic doses decrease both HDL cholesterol and triglycerides. The 17-hydroxyprogestogens and the newer generation 19-nortestosterone derivatives which are less androgenic have little effect on lipid concentrations.

4. In epidemiological studies, therapy with estrogens alone produces a marked reduction in risk of CHD; the summary estimate of relative risk is 0.56. In randomized clinical trials the observed benefit would be expected to be less.

5. The reduction in CHD risk is most pronounced among current users of estrogens. Long-term use (10-15 years) may confer some added benefit. Doses greater than 0.625 mg of conjugated estrogens do not reduce risks further.

6. The reduction in CHD risk by estrogen therapy is evident for most subgroups of women whether or not they have known risk factors for CHD. The reduction is greater among women who have had a bilateral oophorectomy or a premature natural menopause, and less among women who have had a late natural menopause.

7. The sparse epidemiological data available on the use of estrogens plus progestogens by postmenopausal women show inconsistent results with respect to the reduction in CHD risk.

8. Sublingual and transdermal estrogen administration increases blood flow and decreases resistance in the peripheral vascular beds. Acute estrogen administration may improve arterial compliance in the coronary vasculature. The action of estrogens on the vasculature over the long term is not known.

9.7 Recommendations

1. Randomized double-blind trials of estrogens and progestogens in postmenopausal women are needed to identify and quantify any reduction in cardiovascular risk that combined hormone regimens may provide. The trials should allow for evaluation of different progestogen types, doses and schedules as well as for different routes of administration of both estrogens and progestogens. Of particular interest are the differences in potential benefits and adverse effects between oral and parenteral routes of administration, and between continuous and interrupted dosage schedules.

2. Both short-term and long-term clinical trials are needed of the effects of combined hormone regimens on lipid concentrations, clotting factors, and vascular tone and thickness, using clinically relevant hormone doses and schedules.

3. Randomized double-blind trials of estrogen therapy and of combined estrogen-progestogen regimens in postmenopausal women with diagnosed coronary artery disease are needed, using both recurrent myocardial infarction and survival as end-points.
4. Risk factor profiles for CVD and incidence surveys in developing countries should be conducted to characterize better these diseases and their precursors, and to identify their frequency by age, sex and menopausal status in women. Only with this knowledge do rational preventive strategies become tenable.
5. Estrogen therapy should be recommended for women who have had a bilateral oophorectomy or a premature natural menopause. The addition of a progestogen is largely determined by whether the uterus remains intact.

10. Hormone therapy and breast cancer

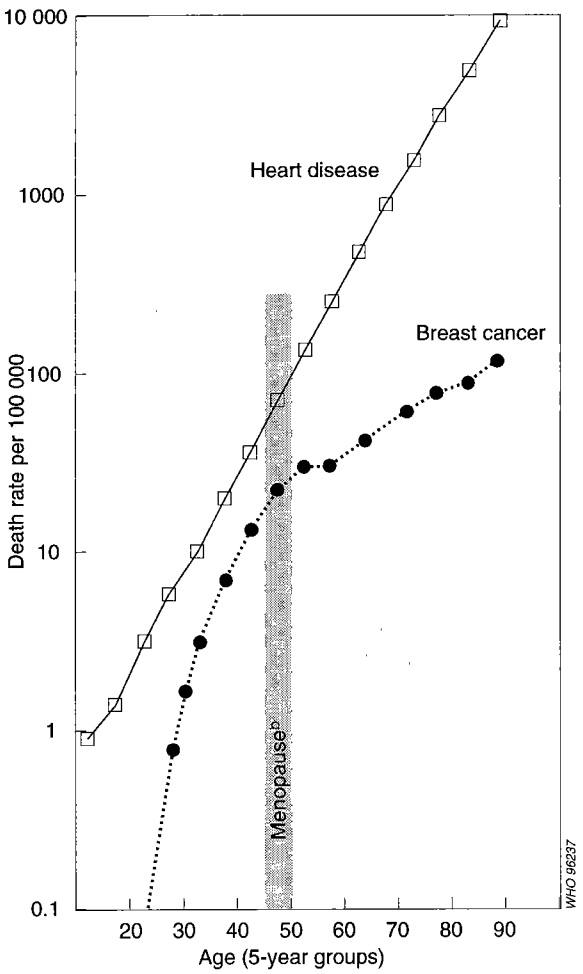
10.1 Background

One of the most controversial aspects of hormone therapy is its possible association with an increased risk of breast cancer. Breast cancer is the most common malignant disease in women in all developed countries (except for Japan), as well as in the Caribbean, Micronesia/Polynesia, northern Africa, South America and western Asia. In 1985, the worldwide incidence of breast cancer was estimated to be 720 000 new cases per year, corresponding to 19% of all cancers (*402*). The incidence rates of breast cancer are increasing all over the world, particularly in areas of low incidence such as Asia. If this trend continues, the incidence may reach one million cases annually by the year 2000 (*403*).

Concerns about the possible association between hormone therapy and the risk of breast cancer have arisen from a number of sources. The experience with cancer-inducing effects of exogenous estrogens on the endometrium (see section 11.1) raised the prospect of similar effects on the breast. Both organs contain estrogen receptors and are target tissues for steroid hormones. Data from animal models and *in vitro* systems show that sex steroid hormones are involved in the genesis and progression of breast tumours. Administration of estrogens to animal models increases the number of mammary neoplasms formed and the rapidity of their development (*404, 405*). *In vitro* systems of cell lines derived from human breast tissue can be induced to develop malignant properties through administration of estrogens alone or in combination with other hormones (*406, 407*). Thymidine-labelling studies of normal human breast tissue show maximal proliferative activity in the luteal (progestational) phase of the menstrual cycle, rather than in the follicular (estrogenic) phase (*408*).

Epidemiological data on the risk associated with endogenous hormonal indicators suggest that exogenous hormones could contribute to the risk of breast cancer. Female gender is the primary risk factor; for women, the cumulative incidence rate at the age of 74 is about 100 times that for men (*409*). The age-specific death rates from breast cancer among women increase up to the age of 50 years, then level off to resume an increase at a slower rate (see Fig. 6, *410*). It has been known since the early 1950s that surgical oophorectomy at an early age reduces the risk of breast cancer (*411*). This benefit is attributed to the removal of the primary

Figure 6
Semilogarithmic plots of age-specific death rates versus age ("Gompertz" plots) for women in the United States[a]



[a] Reprinted from reference *326*, with kind permission from Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, OX1 1GB, England.

[b] In industrialized countries, the average age at menopause is now taken as 51 years.

source of estrogen and progesterone production and the concomitant reduction in the lifetime number of menstrual cycles (*412-414*).

Early age at menarche and late age at menopause are risk factors for breast cancer (*415*). One or more full-term pregnancies decrease the risk relative to nulliparity; greater risk reduction is achieved only by five or more full-term pregnancies (*416*). A young age at first pregnancy (<20 years) reduces the risk, whereas after the age of 30 a first full-term pregnancy may increase the risk relative to the nulliparous state (*417*). The increased risk is postulated to arise from epithelial mitotic activity in response to sex steroid hormone stimulation (*418*). The reduction in risk resulting from an early full-term pregnancy is thought to be due to differentiation of stem cells in the terminal ductal lobular unit, rendering these cells more resistant to subsequent carcinogenic initiation (*419*).

Obesity in postmenopausal women increases the risk of breast cancer (*416*). This may be a function of the higher levels of serum estrone in obese postmenopausal women compared with leaner women (*67*). After cessation of ovarian function, androstenedione derived from the adrenal gland undergoes aromatization preferentially in adipose cells to form estrone. Preliminary evidence suggests that higher endogenous androgen levels are associated with an increased risk of breast cancer in postmenopausal women (*420-423*).

10.2 Exogenous hormones

These observations on endogenous hormonal events have led to the intensive study of therapeutic estrogens in menopausal women and their effect on the risk of breast cancer. Numerous studies have been reported since the mid-1970s. Those reported since 1985 are probably of most interest since the numbers of subjects are large, and the studies were able to examine a possible association with long duration of use. Several critical reviews of these studies have been published (*424-427*). Table 6 lists those studies regarded as being of an adequate quality by these reviews together with their overall relative risk estimates and the risk estimates for the longest duration of use reported in each study (*425*). Compared to the risk in women who had never used estrogens, the relative risk of breast cancer among those who had at any time used estrogens was estimated to be approximately 1.0. However, this comparison has little meaning with regard to assessment of exposure or of biological effect. Women classified into the "use at any time" category range from those who have taken the hormone for a month or two to those who have adhered to a prescribed regimen for 10–20 years or more.

In the majority of studies use of estrogens for 10–15 years was associated with an increased risk of breast cancer. The risk was often 50% or greater than that for non-users. While all the studies took some account of confounding factors, there are enough differences between the characteristics of estrogen users and non-users to raise the possibility of residual confounding (*410*).

Table 6
Relative risks of breast cancer from use of hormone therapy at any time and for longest duration of use, from recent epidemiological studies[a]

First author (year of publication)	Reference no.	Use at any time, relative risk (95% CI)	Longest duration of use	
			Duration (months)	Relative risk (95% CI)
Brinton (1986)	428	1.0 (0.9-1.2)	≥240	1.5 (0.9-2.3)
McDonald (1986)	429	0.9 (0.5-1.3)	≥72	0.7 (not given)
Nomura (1986)	430	1.0 (0.9-1.2)	≥73	1.3 (0.7-2.6)
Hunt (1987)	341	1.6 (1.2-2.1)	≥73	3.6 (0.9-15.0)
Wingo (1987)	431	1.0 (0.9-1.2)	≥240	1.8 (0.6-5.8)
Ewertz (1988)	432	1.3 (0.9-1.7)	≥144	2.3 (1.3-4.1)
Rohan (1988)	433	1.0 (0.6-1.7)	≥24	0.9 (0.4-2.2)
Bergkvist (1989)	434	1.1 (1.0-1.3)	≥109	1.7 (1.1-2.7)
Mills (1989)	435	1.7 (1.1-2.6)	≥120	1.5 (0.9-2.5)
Kaufman (1991)	436	1.2 (1.0-1.4)	≥180	0.9 (0.4-2.1)
Palmer (1991)	437	0.9 (0.6-1.2)	≥180	1.5 (0.6-3.8)
Yang (1992)	438	1.0 (0.8-1.3)	≥120	1.6 (1.1-2.5)
Colditz (1992)	439	1.1 (0.9-1.2)	≥120	1.2 (0.8-1.7)
La Vecchia (1992)	440	1.3 (1.0-1.8)	≥36	1.5 (0.9-2.6)

[a] Reproduced from reference 2, with the permission of the publisher.

The uncertainty regarding the interpretation of the observed increase in risk associated with long-term estrogen use is unfortunate since a true relative increase of 50% or more in the already high rate of breast cancer in European and North American women corresponds to a large absolute increase. From data provided by the International Agency on Cancer Research on breast cancer incidence rates in the USA it can be estimated that white American women aged 50-74 years have a cumulative risk of breast cancer of 8% (*409*). For long-term users of hormone therapy this risk increases to 10% if the true relative risk for long-term users is 1.3. If the same relative increase in risk was to occur among women in regions where the incidence of breast cancer is low, the absolute increase in risk associated with long-term estrogen use would be considerably smaller. No relevant data are available on this issue.

No subgroups of women, defined on the basis of a family history of breast cancer, prior benign breast disease, oophorectomy status, etc., have been consistently found to have an unusually high risk of breast cancer

associated with estrogen use. However, the methods used to characterize some subgroups have been far from precise. For example, it has only recently become possible to define family history in terms of specific markers of genetic susceptibility. It is possible that genetic susceptibility could enhance the risk associated with hormonal therapy (*441*).

The impact of combined estrogen–progestogen therapy on the incidence of breast cancer in postmenopausal women is uncertain (*442*). Though several of the small number of relevant studies suggest a risk of breast cancer greater than that for hormone non-users, this finding is not consistent across studies. Also, the number of women who have used combined therapy, particularly for long periods, has been relatively small until quite recently. It is likely that another decade will elapse before sufficient experience has accumulated to evaluate the effects of different progestogen dosages and schedules including the currently popular low-dose, continuous regimens.

The safety of hormone use in postmenopausal women following the diagnosis of breast cancer is controversial. Several studies are currently under way to evaluate the influence of exogenous hormones on the recurrence of breast cancer and associated mortality.

10.3 International perspective

The public health implications of a possible risk of breast cancer from long-term hormone therapy may be dependent on the underlying incidence of breast cancer in a given country. Table 7 gives estimates of the cumulative incidence rates of breast cancer for women up to 74 years of age for selected countries in various regions of the world in 1980 (*2*). In countries where incidence of and mortality from breast cancer are low, a small increase in relative risk from hormone therapy would also have a small effect in terms of the number of women affected by breast cancer.

10.4 Conclusions

1. Data from animal models and *in vitro* systems show that:
   (a) In the normal menstrual cycle epithelial cells of the breast exhibit their greatest proliferative activity during the progestational phase.
   (b) Estrogens, or estrogens plus progestogens, administered to animal models following a single dose of a carcinogenic agent cause an increase in the number and the rapidity of development of mammary neoplasms.
   (c) In *in vitro* systems, human breast epithelial cells (normal or malignant) exhibit enhanced proliferation when estrogens, or estrogens plus progestogens, are administered.

Table 7
Cumulative incidence rates of breast cancer in women up to 74 years of age in selected areas and countries, 1980[a]

Country or area	Rate per 100 (standard error)
United States, white, SEER[b]	10.26 (0.05)
Canada	8.05 (0.04)
Denmark	7.58 (0.07)
Italy, Florence	7.29 (0.18)
United States, black, SEER[b]	7.22 (0.12)
Australia, NSW	6.54 (0.07)
England, Yorkshire	6.44 (0.08)
Germany, Saarland	6.29 (0.14)
Czechoslovakia	4.98 (0.04)
Colombia, Cali	3.89 (0.16)
Cuba	3.79 (0.10)
Hong Kong	3.55 (0.06)
Costa Rica	3.05 (0.12)
Japan, Osaka	2.36 (0.03)
India, Bangalore	1.99 (0.08)
Mali, Bamako	1.18 (0.23)

[a] Reproduced from reference 2, with the permission of the publisher.
[b] Surveillance, Epidemiology and End Results Program, US National Cancer Institute.

2. Existing epidemiological evidence indicates that:

   (a)
   - The use by postmenopausal women of estrogens alone for less than 5 years appears to have no effect on risk of breast cancer.
   - Use of estrogens alone for 5-9 years may have a small effect on breast cancer risk, but results are highly variable across studies.
   - Use of estrogens alone for 10 years or more may be associated with a 30-80% increase in relative risk.

   (b) Addition of progestogens to estrogens may be associated with an increase in risk of breast cancer.

10.5 Recommendations

1. Studies of risk of breast cancer in relation to use of estrogens in postmenopausal women are needed in ethnically diverse and geographically dispersed populations. Such studies should have adequate power to examine the effects of different estrogen and progestogen types, dosages, durations of use and modes of administration.

2. Research is needed to quantify the risk of breast cancer possibly incurred by the interaction between hormone use and genetic susceptibility to breast cancer. Such studies could clarify whether there are particular subgroups of women who should be cautious about the use of hormones.
3. Hormone therapy following diagnosis and treatment of breast cancer in postmenopausal women is increasingly common, and the impact of this use on recurrence of breast cancer and subsequent survival should be evaluated.
4. In view of possible associations between endogenous and exogenous androgens and risk of breast cancer, further studies are required to clarify the risk associated with the therapeutic use of androgens in postmenopausal women.

11. Hormone therapy and gynaecological cancers

11.1 Endometrial cancer

11.1.1 *Estrogens alone*

Until recently, the large majority of women in North America receiving hormone therapy were given estrogens alone. In Europe, various combinations of sex steroid hormones were more commonly prescribed. Evidence from diverse studies supports the existence of a cancer-inducing effect of unopposed estrogens on the endometrium.

- Estrogen use is associated with a large increase in the risk of endometrial hyperplasia (*443*); atypical hyperplasia is a precursor of invasive carcinoma (*444*).
- The variation in the incidence of endometrial cancer with time and geographical area corresponds well with the variation in the prevalence of estrogen use.
- Both endogenous and exogenous estrogens stimulate the proliferation of endometrial cells, and cellular proliferation is a prerequisite for carcinogenesis (*445*).
- A number of risk factors for endometrial cancer are characterized by their association with high levels of endogenous estrogens; these include estrogen-secreting ovarian tumours, obesity and polycystic ovaries (*446*). In addition, increased plasma levels of estradiol and estrone have been found in women with endometrial cancer (*447, 448*).
- Estrogen use increases the risk of endometrial cancer; for use at any time, the relative risk is 3.0 or more (*449*). The risk rises steadily with increasing duration of use; compared to the risk in women who have never used estrogens, the relative risk associated with 10–15 years of use is close to 10. Once estrogen use is discontinued the risk declines, although many studies show a residual elevation to that of women who have never used estrogens.

Oral conjugated estrogens and oral synthetic estrogens both increase the risk of endometrial cancer. The commonly used doses (0.625 mg per day and 1.25 mg per day) of conjugated estrogens are associated with a substantial increase in the risk of endometrial cancer (*449*). Too few women have used exclusively a lower dose (0.3 mg per day) to evaluate its effects. The risk from long-term use of vaginal, transdermal and intramuscular estrogen preparations has not been adequately studied, but any mode of administration in which estrogens reach the systemic circulation in biologically significant concentrations is likely to have similar effects on the endometrium.

While long-term estrogen use can induce aggressive endometrial cancers, it is most strongly associated with early stage, low-grade lesions (*450*). Those tumours which arise during estrogen therapy have been reported to have a better prognosis than those which occur spontaneously (*451-453*).

11.1.2 *Estrogens plus progestogens*

Several lines of evidence suggest that progestogen administration should reduce the increased risk of endometrial cancer associated with estrogen use:

- Progesterone secreted by premenopausal women arrests endometrial proliferation and promotes differentiation of the endometrial glands.
- Progestogen administration to women with endometrial hyperplasia is usually successful in reversing this condition to produce a secretory or atrophic endometrium.
- Women who use oral contraceptives containing both an estrogen and a progestogen are at markedly lower risk of endometrial cancer than women who do not use them (*446*).
- Postmenopausal women who take progestogens together with estrogens have a lower incidence of atypical endometrial hyperplasia than those who take estrogens alone (*454*).

The incidence of endometrial cancer appears to be significantly lower in users of preparations containing both an estrogen and a progestogen than in users of estrogens alone (*450, 455-457*). However, the extent of the reduction is not uniform across studies; the reduction in risk ranges from 13% to 64% of the risk observed in users of estrogens alone.

Studies of endometrial hyperplasia suggest that the greater the number of days per month that combined hormones are used, the greater the likely reduction in risk of endometrial cancer (*458*). Two studies which evaluated the effect of combined therapy found that women with endometrial cancer had taken a lower monthly dose of progestogens than had controls (*450, 459*). For women who use hormones cyclically, the current clinical recommendation is to take the progestogen for at least 10 days per month. This duration of progestogen use does not appear to increase the risk of endometrial cancer beyond that of menopausal women who have not used hormones. The effects of daily low-dose

progestogens and estrogens are not known because this regimen has only recently become popular. The risk of endometrial cancer in estrogen users who switch to combined therapy has not been adequately studied.

As further modifications occur in the ways in which estrogens and progestogens are administered, additional studies will be needed to assess their influence on the occurrence of endometrial cancer.

11.2 Ovarian cancer

While there has been some inconsistency in the results of studies of estrogen therapy in relation to the risk of ovarian cancer in menopausal women, on balance there appears to be no association (*460-464*).

The studies of ovarian cancer, which were conducted in Europe and North America, included too few postmenopausal women who had used a progestogen to assess the impact of these agents on risk. The data on combined oral contraceptives show a reduction in risk of ovarian cancer (*186*).

11.3 Cervical cancer

Several lines of evidence suggest that the development of cervical cancer may be related to hormonal factors. At puberty, growth and development of normal cervical tissue are supported by sex steroid hormones. Both benign and malignant cervical cells from premenopausal and postmenopausal women express estrogen and progesterone receptors (*465, 466*). Human papillomavirus is a recognized etiological agent for cervical carcinoma and recent evidence indicates that malignant transformation of cells in culture in the presence of human papillomavirus may be mediated by progesterone (*467-469*).

Two epidemiological studies on the relationship between sex steroid hormones and cervical cancer have been reported. A cohort of 23 244 Swedish women who had received a prescription for postmenopausal estrogen were followed for an average of 80 months. Invasive cervical cancers developed in 27 women, producing a relative risk of 0.8 compared with the general population (*470*). The relative risks were not statistically different from unity for users of either conjugated estrogens or estradiol or of estrogen derivatives (mainly estriol) (*470*).

In the second study, a cohort of 4544 British women received a mean of 67 months of hormone therapy of which, on average, 57% was estrogens only and 43% was estrogens plus progestogens. Only two cases of *in situ* or invasive cervical cancer were diagnosed, suggesting a relative risk of 0.5 compared with the general population (*471*).

There are insufficient data on hormone therapy and the occurrence of cervical cancer to address a possible association between them. Studies on this topic face distinctive problems of potential confounding which have been noted in reports on oral contraceptives (*472*). In countries

where cytological screening of the cervix is common, the risk estimates from studies of either *in situ* or invasive cervical cancer may be biased. Hormone users are also more likely than non-users to have regular cervical smears as attendance at a health care facility is necessary to obtain a hormone prescription. The effect of disproportionate screening between users and non-users will be to diagnose (and treat) more pre-neoplastic and *in situ* lesions in hormone users, and therefore prevent the occurrence of invasive cervical cancer. This in turn will create an artefactual increase in the risk of *in situ* disease and a decrease in the risk of invasive cancer for hormone users. Appropriate data collection and analytical adjustment for frequency and recency of screening can help to minimize this source of confounding.

11.4 Cancer of the vulva

Vulval cancer arises in hormone-dependent tissue and so its occurrence could be influenced by exogenous hormones. Both normal and malignant vulval tissue demonstrate receptors for estrogens and progesterone, although to a lesser extent than has been seen in other hormone-dependent sites (*473-475*). Human papillomavirus has been also linked with vulval carcinoma.

The few epidemiological studies which have explored the association between use of estrogens by menopausal women and vulval cancer have provided no evidence of an association (*476-478*). The relative risk estimates have ranged from 1.0 to 1.2, irrespective of whether the cases of invasive and *in situ* vulval cancer have been considered together or separately. The only report on the addition of progestogens to estrogen regimens showed no elevation in risk for either *in situ* or invasive cancer and possibly a reduced risk for invasive cancer (*478*).

11.5 International implications

Cancers of the endometrium and ovary each account for about 4% of all female cancers. In 1985 the worldwide incidence was estimated as being 162 000 ovarian cancers and 140 000 endometrial cancers per year (*402*). The predominant symptom of endometrial cancer is bleeding which is sufficiently unusual in postmenopausal women to result in attendance at a health care facility for diagnosis and treatment. Thus, in the developed world the prognosis of early-detected endometrial cancer (stage 1) is good, with 5-year survival rates of about 90% (*452*). As previously noted, the estrogen-induced lesions are usually of low stage and grade and have an excellent prognosis.

This characterization of endometrial cancer, its diagnosis and prognosis, may be very different in parts of the world where health care facilities are not readily available and vaginal bleeding cannot be readily diagnosed and treated. In the absence of these facilities and resources, endometrial cancer is likely to be diagnosed at a late stage, resulting in serious morbidity and mortality. It should also be noted that women throughout

the world may not be equally aware of the importance of postmenopausal bleeding. Intermittent bleeding in the absence of pain or disability may not be perceived as sufficiently important to justify the effort to seek medical attention. The implications of hormone therapy and its potential risks are dependent on the availability of services for screening, diagnosis and treatment of endometrial cancer.

Cervical cancer is the second most frequent cancer in women, with an estimated 437 000 new cases worldwide in 1985, of which just over one-quarter occurred in southern Asia (*402*). Any effect that hormone therapy might have on the development of cervical cancer would be extremely important. The sparse data currently available do not suggest an adverse effect, but are insufficient for an adequate evaluation.

11.6 Conclusions

11.6.1 *Endometrial cancer*

(a) Estrogens alone

- Estrogen therapy is a cause of endometrial hyperplasia, including the atypical form, a known precursor of endometrial carcinoma.
- Estrogen therapy causes endometrial cancer in some women. These cancers are usually of low stage and grade and usually have a good prognosis.
- Increased duration of estrogen use markedly increases the risk of endometrial cancer (e.g. 10–15 years of use may produce a relative risk of 10 compared with women who have never used estrogens).
- A dose of 0.625 mg of conjugated estrogens daily or cyclically is sufficient to produce an increased risk of atypical endometrial hyperplasia and cancer.

(b) Estrogens plus progestogens

- The action of progestogens counteracts the proliferative effect of estrogens on the endometrium.
- The use of a combined regimen of estrogens plus progestogens for 10 days or more per month is associated with little or no increase in risk of endometrial cancer compared with menopausal women who have not used hormones.

11.6.2 *Ovarian cancer*

Data from Europe and North America show no association between menopausal estrogen therapy and risk of ovarian cancer. Data are not available from other countries.

11.6.3 *Cervical cancer*

Existing data on menopausal hormone therapy and the occurrence of cervical cancer are inadequate to address a possible association between them.

11.7 Recommendations

1. Studies are needed of the effect of estrogens plus progestogens in various doses and schedules, including the low-dose combined daily regimen, on the risk of endometrial cancer.
2. Studies are needed of the influence of combined estrogen plus progestogen therapy on the incidence of cancers other than of the endometrium and breast in both developed and developing countries.

12. Health promotion and the menopause

Strategies for the management of specific health problems occurring as a result of the menopause have been discussed in previous sections of this report. Little has been said about how this information might be combined to help women, health care providers and policy-makers to make health-related decisions that are appropriate for individual women living in diverse sociocultural environments. In fact the sparsity of scientific data from developing countries makes generalizations almost impossible. In addition, concerns have been raised about the validity of some of the data from developed countries. The menopause does not stand alone in the course of life events. As stated in a recent review, "the menopause is, in fact, no more than a ripple in the stream of events reflecting the process of reproductive ageing" (*479*). It is, however, a discrete, measurable event and the termination of fertility has significant biological and psychological consequences.

12.1 Setting of the menopause

The health and well-being of menopausal women are strongly influenced by the cultural and economic settings in which they live. For many women in developing countries, their health at the menopause has already been undermined by difficult environmental conditions at work and at home, by repeated childbearing and traumatic reproductive experiences, inadequate diet, exposure to infectious agents, and inadequate public health and medical care services.

The perception of menopause in the youth-oriented cultures of developed countries is frequently intertwined with fears of ageing, loss of status and loss of sexuality. In societies that have different cultural values the psychological reaction to menopause may be different. The end of fertility and menstruation marks an improvement in the lives of many women, freeing them from the risks of childbirth and from cultural restrictions on their social and religious lives. In sub-Saharan Africa, for example, the postmenopausal years are often viewed positively as a time when women gain respect in their families and communities.

12.2 Symptoms of the menopause

Symptoms encompassing almost all parts of the body have at one time or another been attributed to the menopause. These include urinary problems, depression, nervous tension, palpitations, headaches, insomnia, lack of energy, fluid retention, backache, difficulty in concentrating and dizzy spells. However, it is now recognized that most of these symptoms are not specific to the menopause. Many are related to the ageing process or occur because of stresses in the mid-life years and most are common to both women and men.

Hot flushes and night sweats are the symptoms most consistently associated with the menopause, although their prevalence varies in different cultures. In general, they are more common in European and North American women than in other populations and are estimated to occur in 45% of North American women and up to 80% of Dutch women. In contrast they are reported to affect only about 17% of Japanese women and do not occur at all in Mayan women from Central America. Hot flushes and night sweats are usually more severe in women who have had an induced menopause than in those who have had a natural menopause.

12.3 Disease prevention

Health status at the menopause is best predicted by health status in childhood and during the earlier reproductive years. This in turn is determined by conditions of family and working life, environmental stresses to which the woman has been exposed, and access to health care services. Health care at the menopause can be most effective where maintenance of good health is part of a total life plan. This is well illustrated in the context of osteoporosis and osteoporotic fractures. Since maximal bone density is achieved before the age of 30, intake of calcium and other nutrients during childhood and young adulthood will be significant determinants of bone density in later life. Similar observations may be made about the risk of cardiovascular disease. The primary prevention for cardiovascular disease starts with lifestyle behaviours initiated early in life, including good diet, regular exercise and abstention from smoking.

Where circumstances permit, selected screening (e.g. for hypertension and cancer) and education should be an integral part of health care for women in the mid-life years. Health care providers should be well informed and should encourage women to stop smoking, take regular exercise, eat a balanced diet, practise safe sex, control their weight and use appropriate methods for family planning.

PHT is one aspect of health care in women in this age group. The rationale seems clear: with the cessation of ovarian function, the number of ovarian follicles is depleted and production of estrogen and progesterone declines. Postmenopausal women have low levels of both hormones compared to premenopausal women, although there are wide variations between individuals. But other changes also occur at the level

of the ovary (fall in the peptide hormone inhibin), the pituitary (increase in FSH and LH) and the hypothalamus. What are the health consequences of these biochemical changes? How are they altered in response to PHT? Also, the factors that influence follicle numbers and the rate of their depletion should be considered. If the maintenance of premenopausal hormone levels is desirable for health, factors which might delay the natural menopause should be considered and induced menopause should be avoided. Cigarette smoking is the primary modifiable factor that lowers age at natural menopause.

12.4 Hormone therapy

In developed countries, estrogens and progestogens are widely prescribed for postmenopausal women. As reviewed in this report, there are two different categories of indications for their use: short-term use for relief of menopausal complaints, specifically vasomotor symptoms, and long-term use for preventive purposes, primarily osteoporotic fractures and cardiovascular diseases. The distinction between short-term therapeutic and long-term preventive goals for hormone use should be clearly understood by physicians and potential hormone users alike, since the risks and benefits of the two types of therapy are very different (*480*). Some long-term preventive regimens are associated with an increased risk of endometrial cancer and possibly breast cancer.

Two recent analyses have evaluated the risks and benefits (*335*) and cost-effectiveness (*481*) of hormone therapy. These analyses are mainly concerned with long-term therapy for preventive purposes. In the first analysis, which was based on data from the USA, the outcome measures were changes in lifetime probabilities of various diseases and in overall life expectancy. The second analysis, based on data from the United Kingdom, considered years of life gained or lost, and deaths caused or prevented by diagnosis, in relation to 10 years of hormone therapy use prior to the age of 70. A fairly consistent pattern of results emerges from these quantitative analyses. For women who have had a hysterectomy, and for whom estrogens alone can be prescribed, the benefits of hormone therapy exceed the risks and at reasonable cost. For women with an intact uterus the results are less certain, primarily because the data on long-term use of combined estrogens plus progestogens are sparse and less precise. In general, the gain in life expectancy is highly dependent on the amount of risk reduction that is assumed in the model for cardiovascular diseases, particularly myocardial infarction. This estimate, in turn, is imprecise. Depending on the progestogen used, the blood lipid profile may be adversely affected, thereby decreasing the reduction in cardiovascular risk. Given these uncertainties, the benefit in life expectancy from long-term PHT may lie between 0.1 and 1.0 years (*335, 481*). For a woman at high risk of myocardial infarction, the benefit from PHT will be greater. On the other hand, for a woman at high risk of breast cancer the net effect of PHT may be detrimental, causing a small reduction in life expectancy.

The results from any analytical approach depend on the adequacy of existing data and the assumptions made in the models, particularly with respect to the amount of risk reduction or enhancement expected for a particular disease. The data employed in the analyses described above were derived from observational, epidemiological studies from Europe and North America. Observational data are potentially subject to biases. Furthermore, many assumptions had to be made as a consequence of inadequate data.

If these analyses had been based on data from a developing country, the results would be different. The fact that cardiovascular diseases do not cause such a large proportion of deaths in developing countries would affect the risk-benefit and cost-effectiveness ratios as would varying rates of breast cancer incidence.

It is difficult to evaluate women's preferences in these quantitative analyses. Most women are usually more concerned about the resolution of symptoms of the menopause through the use of PHT than the possible long-term risks of such treatment. Hormones have both positive and negative effects on those attributes ascribed to quality of life. Potential benefits may include prevention of kyphosis, preservation of urinary and sexual function, and an improved sense of well-being (*482*). In contrast, the unpleasant side-effects of irregular bleeding (or regular bleeding) in older women, breast tenderness or premenstrual-type syndrome, the need for regular medication and visits to a physician, and the fear of cancer can negate the possible benefits. The decision on whether or not to take hormones needs to be made on the basis of accurate information and personal priorities.

It is evident from many studies that women do not necessarily adhere to prescribed hormonal regimens (*483-486*). Studies indicate that 20-30% of women fail to have prescriptions filled and that the continuation rate after 8-12 months is only 30-40%. These data illustrate the need to understand women's reasons for not adhering to prescribed regimens.

In addition to the conditions discussed in this report, other disorders have been attributed to estrogen deficiency, estrogen therapy or both. It is said that depression and arthritis are worsened or improved with PHT (*487-489*). The risk of gallbladder disease increases with PHT (*389*). There is little evidence that PHT increases the risk of thrombophlebitis or pulmonary embolism (*389*). Studies provide contradictory results on whether or not PHT reduces the risk of dementia (*490, 491*), although one study found that estrogens appear to have a beneficial effect on verbal memory skills in healthy postmenopausal women (*492*). Some studies suggest a lower risk of colon cancer in women treated with PHT (*493-496*), possibly reflecting the selection of healthy women for hormone treatment (*342*).

The perimenopausal and postmenopausal periods of life are part of the ageing process and do not necessarily require therapy. Hot flushes and

symptoms of urogenital atrophy, however, may require intervals of hormone treatment. Given the existing evidence for acceleration of bone loss after the menopause, and the increased risk of cardiovascular disease, pharmacological interventions may be appropriate for selected women. It should be recognized that prevention of osteoporotic fractures and cardiovascular diseases may require lifetime use of PHT. An early natural or induced menopause (before the age of 40) is an indication for long-term hormone treatment at least up to the average age of natural menopause.

Public health policy is based on a different set of priorities from those involved in care at an individual level. Governmental resources for public health need to be expended so as to maximize the benefits for the population. Cost and resource allocation must be considered. The application of preventive strategies carries special requirements and expectations. Preventive interventions applied to asymptomatic women must meet standards of safety and efficacy in excess of those required when treating life-threatening illness. Appropriate health policy recommendations for women in developing countries can be made only when more data are available from these countries on the types and magnitude of menopause-associated problems.

12.5 Conclusions

1. The menopause is only one point in a continuum of life stages and health status at this time will be largely determined by prior health status, reproductive patterns, lifestyle and environmental factors.
2. If estrogens and progestogens are prescribed at the time of the menopause, the goals of therapy must be clearly understood; i.e. either short-term relief of menopausal symptoms or long-term use to reduce the risk of cardiovascular disease and fractures, or to achieve both these goals.
3. Risk-benefit or cost-effectiveness analyses based on data from developed countries are generally consistent in showing benefits from estrogen alone when taken by women who have had a hysterectomy. The results from these analyses for estrogens plus progestogens are less consistent. This is because there are fewer data on combined hormone usage, the regimens and types of progestogens are variable and the estimates of cardiovascular benefits are less certain.
4. Findings from the risk-benefit analyses cannot be extrapolated to developing countries where the incidence of cardiovascular disease is lower and data on hormone use and the relevant disease outcomes are rare.
5. The decision about whether or not to use hormones for both short-term and long-term preventive purposes should be based on an understanding of the risks and benefits of this type of therapy as well as on the personal preferences of the woman.

6. For women who experience a premature menopause, whether induced or natural, hormone therapy is recommended at least up to the usual age of natural menopause.
7. Therapies designed to target specific risk factors for major diseases may be appropriate alternatives to the use of steroid hormones as multipurpose health-promoting agents.

12.6 Recommendations

1. Detailed studies are required on the biochemical and physiological changes associated with the menopausal transition and the early postmenopausal years. The effects of these changes on the health of women in diverse populations should be evaluated.
2. Data are needed from developing countries on the age-specific incidence of cardiovascular diseases, osteoporotic fractures and endometrial and breast cancers, since these conditions are the most likely to be influenced by long-term hormone therapy.
3. The costs of prolonged pharmacological interventions to reduce risks of disease in the distant future, and of the health care facilities and personnel required to monitor use of medication and manage side-effects, should be subjected to further quantitative economic analyses.
4. Since rates of mortality from cardiovascular disease are declining and rates of breast cancer are increasing in many developed and developing countries, the recommendation by some for universal prescription of PHT may not be well founded. As new data become available continuing research is required to assess the balance of benefit and risk in those women predisposed to cardiovascular disease, osteoporosis or breast cancer.

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