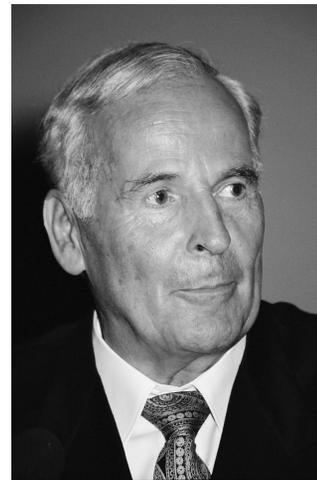


The International Menopause Society

Report on the 10th World Congress on the Menopause 10–14 June 2002, Berlin, Germany

H. P. G. Schneider, PRESIDENT OF THE CONGRESS



The aims of the Congress

The aim of this World Congress was to cover 'all aspects of health and well-being in an aging population', and thus included the integration of gender as a variable in biology, behavior, ethnicity, cultural values, environment and health-care utilization. The Congress aimed to reflect the world-wide challenge for those working in the field of mid-life medicine – not just to provide more efficient medical interventions, but to invest in a 'healthy aging' initiative with major public health implications.

The Congress was organized on a highly interdisciplinary basis and was intended to present the tremendous progress made in both basic and clinical science in climacteric medicine. The scientific program included a total of 140 different sessions, from plenary lectures and symposia to free communications, satellite meetings of national and regional societies and symposia organized by industry.

Who attended the Congress?

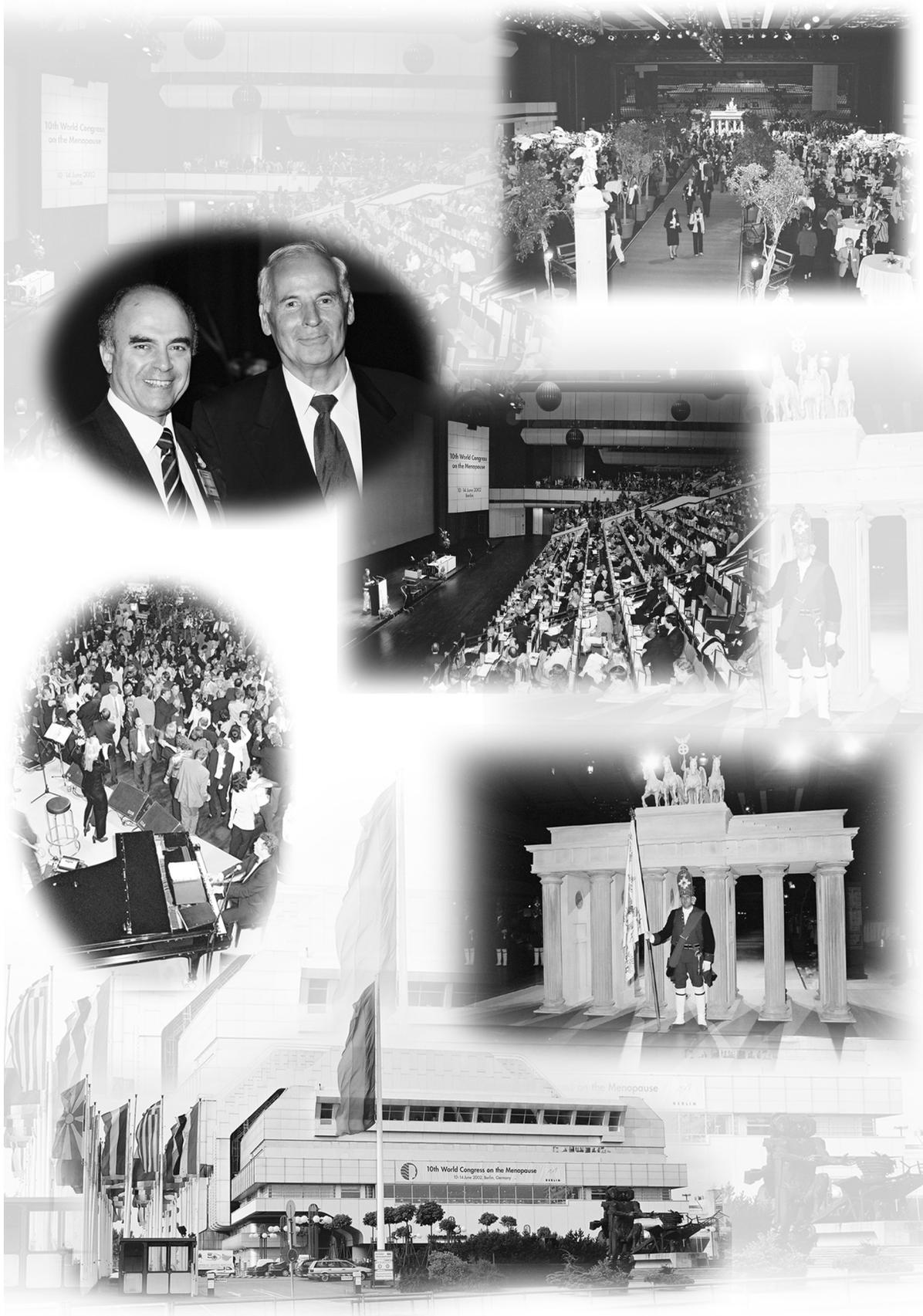
The organizers were delighted to have welcomed 4361 registered participants, 312 accompanying persons, 600 exhibiting personnel and 156 press delegates, altogether amounting to a total of 5429 attending from 87 different countries. The most widely represented areas were Germany as the host (12.1%), Italy (7.9%), Asia (6.6%), France (5.4%), the Scandinavian countries, the USA (3.4%) and Latin America.

The main topics of the Congress

The mid-life health bulletin is not all bad news. Disability rates in older age groups have declined in some areas like the USA. Throughout the world, advances in biotechnology are destined to help some who in the past would have become disabled. We are still working on answers to difficult questions about the benefits and risks of hormone therapy, particularly with respect to secondary cardiovascular prevention, long-term reproductive cancer risks and prevention of age-related mental disabilities. The progress in the field of climacteric medicine to date and what is in the pipeline of future development will certainly continue to improve the quality of life of women after the menopause.

Circulatory disease

More than 80% of deaths from circulatory disease occur in people over 65. Therefore, atherosclerosis and cardiovascular disease were head of the list of subjects discussed during the World Congress (G. Samsioe, F. Grodstein, M. E. Mendelsohn, P. Collins, G. Rosano). The development of atherosclerosis is delayed in women compared to men. Men and women of similar age supposedly have a different plaque composition. Normal ovarian hormone production counteracts the development of atherosclerosis. Estrogen deficiency is associated with the development of atherosclerosis (M. R. Adams, R. Karas). A detailed discussion of cardiovascular disease raised a variety of pertinent questions. The clinical presentation of acute



myocardial infarction in women has a greater prevalence of risk factors, slower medical intervention, a greater delay in receiving care and, in consequence, a later and less frequent therapeutic treatment such as thrombolysis.

It has been pointed out that the terms primary and secondary prevention of CHD are potentially misleading. Half of those postmenopausal women who die suddenly from myocardial infarction may never have experienced symptoms such as angina pectoris before the event. Atheroma begins very early in life and the majority of plaques that result in events are small. Instead, the term of risk-dependent intervention has been suggested (G. Assmann). Stratification of individual risk should be based on classical risk factors and algorithms (www.chd-taskforce.de).

Studies in women with proven coronary artery disease on the effects of hormone replacement have limited clinical significance. Atherosclerosis in women appears to be related to ovarian hormone deficiency. Certainly, estrogen deficiency is causally related to elevated LDL-cholesterol as well as lipoprotein(a) concentrations. In consequence, statin treatment may be required, particularly in high-risk women, to lower LDL-cholesterol levels to < 100 mg/dl. It is stabilization of plaque that is all important; this is almost certainly what statins do. Hormone replacement should remain a focus of CHD trials, particularly as timely substitution of properly dosed estrogen may be efficient. As women with acute coronary syndrome are treated less aggressively than men, this may be influencing the outcome. Gender-specific strategies should be developed for the treatment of acute coronary symptoms before we think of intervention with hormones.

Breast cancer

The topic about which women are most concerned has been widely debated. As far as the kinetics of cell activity are concerned, the average human produces 40 million cells/s, spontaneous mutations occur in every million mitoses and three to seven sequential mutations are required for the oncogenic change (B. Wren). This oncogenic change, however, necessitates modifying or eliminating genes coding for protein inhibitors or for apoptosis. It was stressed that only undifferentiated 'stem cells' undergo mitosis (J. Russo). Mature differentiated cells do not divide. As to the pathophysiology of cancer, it is apparent that an increase in mitoses increases the risk of spontaneous sporadic mutations (95% of all breast cancers). Basal

'stem' cell chromosomes may be affected by viral, chemical, irradiation or inherited factors (5%).

As the endogenous local tissue-derived production of estradiol is 20-fold that of circulating estrogen, and as a high local estrogen concentration stimulates the excretion of angiogenic growth factor, a key question was whether local production of estrogen is essential for cancer growth (E. R. Simpson, J. M. Foidart).

Aromatase in breast adipose tissue is the major source of estrogen driving growth of breast tumors in postmenopausal women. The circulating estrogen levels may have little impact on the levels present in a tumor. This may be one reason why HRT use carries minimal increased risk of breast cancer. The importance of local aromatase expression together with different promoters to regulate tissue-specific expression of aromatase leads to the concept of selective aromatase modulators (SAMs). Inhibitors of the primarily active promotor II would specifically inhibit estrogen biosynthesis in breast tissue of postmenopausal women. Thus, SAMs could find utility as the next generation of breast cancer therapeutic agents (E. R. Simpson).

Progesterone and its related progestins may initially increase the production of cyclins and cyclin-dependent kinases and thereby increase the mitosis of epithelial cells at the breast tissue level. The slow increase in protein inhibitors, e.g. P₁₆, P₁₈, P₂₁ and BCL₂, results in cellular quiescence, indicating a biphasic response. Therefore, progesterone increases proliferation and then maturation of lobular breast cells. After 100 years of continuing debate, there is still no clear evidence to implicate hormones as oncogenic (B. Wren). Cohort and case-control epidemiological studies suggest that unopposed estrogen and combined progestins increase the rate of developing breast cancer. However, *in vitro* studies as well as some clinical studies have suggested that anti-estrogens and continuous progestins may reduce the rate of developing breast cancer.

There are also strong epidemiological data indicating that HRT after breast cancer has no adverse impact on recurrence or death. Why then do hormones influence the diagnosis of breast cancer? Progestins increase maturation and thereby produce dense tissue with its negative mammographic implications. Cancer remains undiagnosed if there are fewer than 2 million cells. It takes 5–15 years from oncogenetic mutation to arrive at a palpable mass. Estradiol induces faster growth with a resultant earlier diagnosis and better prognosis.

Adding medroxyprogesterone acetate (MPA) to estrone increases the proliferation of human breast epithelial cells *in vivo*. A significant increase in breast cancer incidence in users vs. non-users of conjugated equine estrogens (CEE) plus MPA has been observed¹. Adding progesterone to estradiol decreases the proliferation of human breast epithelial cells *in vivo*. No significant increase in breast cancer incidence has been observed in users versus non-users of estradiol (non-oral) plus progesterone^{2,3}.

What can you tell your patients? Hormones are not oncogenic but estrogens combined with certain progestins increase the rate of cell mitosis. Most postmenopausal breast cancers are accidental mutations involving loss of cellular control. Anti-estrogens reduce the rate of mitosis. Continuous progestins induce maturation of alveolar cells and may also inhibit mitosis.

Brain

Another important topic was the relation of sex steroids to brain function (D. Murphy, A. R. Genazzani, R. Diaz Brinton). A neurodegenerative process of the brain causes a slow progressive loss of mental function. The prevalence of Alzheimer's disease in 1997 was estimated to be 4 million in the USA. Approximately 50% of those over the age of 85 years have Alzheimer's disease, and the size of the older population is increasing. The rate of Alzheimer's disease may be 1.5- to 3-fold higher in women, even after accounting for the longer lifespan of women. Delaying admissions for Alzheimer's disease by 1 month could save \$1.2 million annually in the USA.

Only one out of ten brain cells is a neuron. Most of the rest are glia and are responsible for maintaining the microenvironment around neurons and guiding neuronal projections of processes to other neurons; thus, messages can be passed in the form of closed connections called synapses (F. Naftolin). All of these actions are regulated by estrogen. With aging and the effects of long-term exposure to neurotransmitters and their by-products plus decreasing blood flow to carry away harmful waste products, the brain can begin to lose its abilities to perform normally and to maintain the health of its cells. Although little evidence exists of direct brain cell-maintaining effects of estrogen in humans, there is considerable indirect evidence of protective effects of estrogen on the aging brain. Evidence is accumulating that the maintenance of premenopausal amounts of estrogen via HRT may forestall the diminution of brain function with aging and even the occurrence of diseases caused by nerve cell

loss, such as Alzheimer's disease and Parkinson's disease. Other effects of estrogen, such as antagonizing tissue oxidation (anti-oxidant) and regulating of the brain's immune system, are all properties of estrogen that maintain normal brain function. In the absence of estrogen, these functions are diminished and this can lead to clinical brain disorders. Of course, other factors also contribute to the health or disease of brain cells.

In summary, the implications for brain aging (in Alzheimer's disease, Parkinson's disease, multiple sclerosis, etc.) are as follows. Aging is accompanied by a deterioration of all cellular systems, in part owing to free-radical damage and apoptosis. The immune system plays a role in these and other processes. Since estrogen regulates the immune system, it is likely that the response to aging includes estrogen-mediated protective effects via immune cells. Evidence does not support marked effectiveness of currently available estrogens in replacing lost neurons or reversing established damage in neurons. However, estrogen may improve the function of neurons, supporting and even replacing some of the functions lost by cell death or disease. Estrogen may thus have positive effects on brain cell functions such as improved vegetative function (diminished hot flashes, improved sleep) and cognition (mental processing and specific skills). In the aging brain, estrogen appears to forestall diseases, including Alzheimer's disease. The possibility that other diseases such as Parkinson's disease may be forestalled or prevented is presently under study.

Osteoporosis

HRT is usually seen as the standard method of preventing osteoporosis and osteoporotic fractures in postmenopausal women (C. Christiansen). This view is based on non-randomized data on fractures and data on surrogate markers of risk (e.g. change in bone mineral density (BMD)). There are at least 13 cohort or case-control studies on this topic, and all have shown an association between HRT use and fracture reduction. Six of these are cohort studies. Potential biases in observational data have been pointed out repeatedly. Any non-randomized data can be biased – biases in HRT data include healthy user effects and prescription bias. Meta-analysis is a very helpful technique of statistically combining small studies into one large trial. However, meta-analysis cannot address systematic bias in observational data and therefore can give spurious statistical credibility to flawed studies.

If one takes a look at all randomized data, a total of 22 randomized controlled trials have recently been published in two meta-analyses of vertebral and non-vertebral fractures. These show that fractures were significantly reduced by HRT (D. Torgerson). In consequence, the data from observational studies, the HERS and meta-analysis of randomized controlled trials all suggest an attenuation of the effect of HRT on non-vertebral fractures with increasing age of the woman. As long as evidence from randomized controlled trials does not prove the contrary, osteoporotic women over the age of 70 years should probably be offered alternatives to HRT (e.g. bisphosphonates) for fracture prevention.

Pregnancy and lactation are considered to be risk factors for postmenopausal osteoporosis, owing to the transfer of 30 g of calcium to the child. Quantitative ultrasonometry of the calcaneus of postmenopausal women (F. Fischer) has been assessed in a cross-sectional study of 2080 postmenopausal women. Neither the matched-pair analysis nor the multiple, linear regression analysis showed a significant difference of the results, considering the number of pregnancies or the duration of lactation.

Have antiresorptives reached their full potential? R. M. Lindsay has discussed possible anabolic agents such as strontium, anabolic steroids/selective androgen receptor modulators (SARMs), statins, growth hormone axis agents, sodium fluoride, prostaglandin E₂ and parathyroid hormone (PTH). PTH increases the size of human bone by increasing BMD by 40%, increasing bone mass (spine) by 20% and, since BMD equals bone mass/area, bone area must have increased. Lindsay's conclusion was that there are several agents available for prevention and treatment of osteoporosis. All are antiresorptive agents and all have been shown to reduce fracture risks (by about 40–50%). The most important of these are the bisphosphonates. PTH is an exciting new agent with a novel mode of action stimulating bone remodeling, and causing new bone tissue to be formed. Intervention with PTH produces marked increments in BMD and reduces fracture risk. Short-term (1–2 years) treatment with PTH seems likely to be a useful therapeutic tool in osteoporosis.

Exercise and chronic disease

Chronic health conditions are expected to become the main cause of death and disability in the world by 2020, with enormous health-care costs for societies and governments. Therefore, the scien-

tific program also focused on exercise and chronic disease (J. Guthrie, M. Hammar). Moderate-intensity exercise such as walking is associated with substantial reduction in risk of ischemic stroke. Physical activity lowers blood pressure, increases high-density lipoprotein (HDL)-cholesterol, reduces fibrinogen and platelet aggregation, increases insulin sensitivity and facilitates weight maintenance. Intervention studies of combining walking for an extra 16–20 km/week plus a low-fat diet after 54 months produced a reduction in weight and a smaller increase in low-density lipoprotein (LDL)-cholesterol, triglycerides and glucose. In postmenopausal women, high-load resistance training programs produce slower bone loss and add bone mass, effects that are site-specific. There is also evidence of reduced risk of breast cancer in women who had engaged in high levels of physical activity. Exercise may stimulate the immune system. Osteoarthritis, a major cause of long-term disability in women over 50, is the most common cause of joint pain in mid-life women. Strengthening exercises at hip, knee and ankle joints over a 16-week period cause significant pain relief. Aerobic exercise training has beneficial effects on mood and stress, as has been shown for bicycle ergometer exercise of 20 min/day for 2–3 weeks or treadmill walking for 30 min/day. Therefore, there is evidence for a role of exercise in reducing risk factors for chronic disease and for improving quality of life for women suffering from chronic disease.

Psychiatric disease

The relationship between estrogens and schizophrenia has been investigated by A. Riecher-Roessler. Basic research has proved the existence of estrogen receptors in the limbic system. Estrogens modulate the number and the sensitivity of dopamine receptors. They also modulate different neurotransmitter systems, e.g. dopamine, serotonin, γ -aminobutyric acid and monoamine oxidase. In rodents, estrogens have similar effects to those in neuroleptics: they enhance neuroleptic-induced catalepsia and reduce amphetamine- and apomorphine-induced stereotypias. Epidemiological studies have shown a late onset of schizophrenia in women of the fertile age group and an excess of onsets around menopause. Later menarche is associated with earlier onset and there is a later menarche in schizophrenic women than in healthy controls. Also, clinical observations point to an excess of onsets and relapses in the premenstrual/menstrual low-estrogen phase of the

cycle. The symptomatology of schizophrenia correlates inversely with the serum level of estradiol and the cycle phase. Schizophrenic women in the fertile age group need less neuroleptics and there is a better therapeutic response to neuroleptics in the high-estrogen phase of the cycle. Also, a positive effect of estrogens in neuroleptic-induced tardive dyskinesia has been observed.

The symptoms and course of schizophrenia are more severe in women than in men. Chronic psychoses improve during pregnancy. After childbirth, with a rapid drop of estrogen levels, there is a massive excess of psychoses. An inverse correlation with estradiol levels is also seen in the behavior of depressive women. An excess of suicide attempts in the premenstrual/menstrual low-estrogen phase of the cycle has been described. On the other hand, women with schizophrenia have a history of delayed menarche and pubarche, menstrual abnormalities (irregular cycle, weak bleeding, mid-cycle bleeding), signs of relative hypoestrogenism (loss of hair, hirsutism), galactorrhea and infertility. During the psychotic episode, clinicians will find menstrual irregularity, low serum estradiol and progesterone levels and anovulatory cycles. As consequences for prophylaxis and therapy, estrogen substitution before and after menopause will 'save' neuroleptics. One should consider the interaction of neuroleptics with estrogens via estrogen-dependent hepatic enzyme inhibition.

Psychology and sexuality

According to the World Health Organization (WHO) definition of 1994, there exist fundamental rights for the individual, including the right to sexual health and the capacity to enjoy and control sexual and reproductive behavior in accordance with the social and personal ethic: freedom from fear, shame, guilt, false beliefs and other factors inhibiting sexual response and impairing sexual relationships; and freedom from organic disorders, disease and deficiencies that interfere with sexual and reproductive function. Gender differences in sex drive have been defined. In men, it is peripheral and shows 'high desire'; it is more urgent, more driven by fantasy, more goal-oriented, less distractible and more focused on coitus and orgasm. On the other hand, women have a more sensual attitude with 'intimacy needs'. Women are more driven by wish for intimacy than for sexual release *per se*. Their needs are more diffuse; they are more distractible and more receptive⁴.

The best predictor for mid-life sexuality is the state of the individual's earlier experience.

With age, interest in sex usually persists; frequency of sexual activity diminishes. The emphasis shifts from quantity to quality. Although sexual function may be compromised with age, gratification need not be sacrificed. The most important question, as pointed out by A. Altman, was whether one or one's partner was troubled by this.

Quality of life

Quality of life is the 'individual's perception of their position in life in the context of the cultural and value systems in which they live in relation to their goals, standards and concerns'. This WHO definition⁵ was used by B. Alder in order to define six domains that are involved with the definition of quality of life: physical health, psychological state, level of independence, social relationships, environmental features and spiritual concerns. In the aging process, people cope by moving through stages of assimilation (maintaining fitness and using cosmetics and HRT) and accommodation (as to changed goals and aspirations and reflecting on past achievements).

Clinical trials of HRT have assumed that symptom reduction improves quality of life and therefore measured reduction in symptom score would be an appropriate approach. There is more to life than symptoms, but it is relatively easy to measure symptoms. Measuring quality of life depends on the purpose of the measure, e.g. a survey of middle-aged women, clinical trials of HRT or the perspective of health professionals or individuals. As far as assessing subjective well-being is concerned, 'the only way to really get to know a person's quality of life is to stand in their shoes and walk around in them a little' (Harper Lee). The standardized menopause-specific scales have been debated. These are the Greene Climacteric Scale, the Women's Health Questionnaire, the Menopausal Symptom List, the Menopause Rating Scale, the Utian Quality of Life Score and the Ageing Male's Symptoms (AMS) Rating Scale. They all have subscale structures with different characteristics as to the number of items, rating points, rating measure and reliability of subscales. They all show excellent scientific applicability and good reliability over time. The Menopause Rating Scale appears to be less troublesome and less time-consuming and adequate for avoiding wide-ranging batteries of questionnaires. All scales may variably serve as an adequate diagnostic instrument for measuring menopausal quality of life.

Role of estrogen deficiency in men

The symptoms of the male aging syndrome include hypogonadism, hypothyroidism, lack of growth hormone, cardiovascular diseases and malignancies. Clinically speaking, these are depression, low cognitive function, erectile dysfunction, loss of libido, sarcopenia, increased fat mass, anemia and osteoporosis.

Aging-related hormonal changes and inter-individual variability have been discussed in detail (J. M. Kaufman, E. Nieschlag). Clinical manifestations of male senescence are possibly related to hypoandrogenism. A decrease in 'general well-being' and 'energy level' as well as sexual pelocity and skin thickness have been attributed to lack of androgens, as have decreased libido, increased frequency of impotence, decreased muscle mass and strength as well as increased fat mass (and altered distribution) and osteopenia.

As far as screening measures are concerned, total testosterone will often be adequate, but this has clear limitations. Free bioavailable testosterone is more reliable and is used in borderline cases. In nearly all cases, free testosterone and bioavailable testosterone give the same information (bioavailable testosterone is a multiple of free testosterone). Luteinizing hormone, follicle stimulating hormone and prolactin are only advised in the presence of low free testosterone. Androgen replacement in elderly men should be considered when free testosterone levels are found to be below normal for the young and unequivocal signs and symptoms of hypogonadism are clinically manifest. There should be no reversible cause for androgen deficiency and no contraindications.

Socioeconomics of hormone replacement therapy

In the years 1998–2001, the HRT market has grown from around €2.5 to 3.8 billion. As far as world-wide regions in the year 2001 are concerned, the USA spent €2.5 billion, Europe €0.9 billion and Latin America plus Canada about €0.3 billion. Prevalence of HRT use in different countries is quite variable, in that 47% on average took HRT in France, about 25% in the USA and Germany as compared to 3% in Italy and 2% in Japan. The reported duration of HRT treatment in a German study was 0–2 years for 29%, 2–5 years for 37%, 5–8 years for 15% and > 8 years for 8% in 1997 (current users and ex-users). If one tries to assess the annual costs of women's decreased estrogen production, it will be in terms of millions of US dollars: for the urogenital tract

about 125, for menopause and psychovegetative disturbances about 480, for the skeleton 540 and for cardiovascular and cerebral disease around 1100. These are the combined indirect (e.g. invalidity, permanent stability and death) and direct costs (e.g. hospitalization, rehabilitation, out-patient care).

More than 200 million women world-wide have osteoporosis. Estimates indicate that hip fractures will rise from 1.7 million/year to 6.3 million/year in 2050. About 32% of women who live to the age of 80 have hip fractures. The prevalence of vertebral fractures is 22% in women of advanced age and/or who have decreased BMD. The estimated world-wide costs of hip fractures for women were \$17 billion in 1990, will go up to \$42 billion in the year 2025 and are estimated to reach \$70 billion in 2050. Upon continuing such calculations, one could look at the comparison of HRT and raloxifene: vertebral fractures will be reduced by 50% with raloxifene and 30–60% with HRT; non-vertebral fractures only with HRT by 30–50%. Thus, the annual costs of HRT will reach \$37–267 million and for raloxifene to \$358 million. K. Schmidt-Gollwitzer presented further calculations on the annual costs of osteoporosis in prevention and therapy comparing calcium to HRT, fluoride, bisphosphonates, calcitonin, 1,25-OH-vitamin D and nasally administered calcitonin. While the first three are on the low side, the others (such as bisphosphonates) drive up costs drastically.

The costs for elderly patients with urinary incontinence, mental disabilities and cardiovascular disease in particular all amount to large socioeconomic challenges for our globe. The goal of cost-effectiveness could best be met with reasonable, simple and inexpensive HRT use. The main targets would be breast cancer and venous thromboembolism.

Other non-genital aspects of estrogen deficiency

Opacification of the lens is a common age-related disease. The development of cataracts has been studied experimentally by A. S. Turner. There are initiating events, oxidative damage and glutathione as a co-factor. The hypothesis was tested as to whether the ratio of reduced : oxidized glutathione in the lens of ovariectomized sheep would be different in the lens of estradiol-supplemented sheep versus sham-operated sheep. Also, the antioxidant effect of estrogen with its beneficial consequences for cataractogenesis was studied. The results clearly support epidemiological data in the human

literature of protective effects of ERT on cataractogenesis. As far as upper-angle glaucoma is concerned, early menopause confers a greater risk and higher intraocular pressure, as seen in postmenopausal women. HRT would lower intraocular pressure. The effect of selective estrogen receptor modulators (SERMs) is yet to be established.

Voice impairment during the menopause was another subject (B. Schneider). The differential diagnosis of voice disorders during the menopause relates to organic voice disorders, presbyphonia, functional and hormonal voice disorders. The conclusion of this report was that voice changes due to estrogen deficiency present a common problem in menopausal women. Voice impairment as a part of future menopause rating scales is advocated. Interdisciplinary co-operation is necessary to optimize diagnostics and therapy. HRT can be recommended for menopausal voice impairment, which includes a speaking and singing voice range profile as well as the perceptual evaluation of voice sound.

Another important aspect was the relationship of estrogen to wound healing (N. S. Ramamurthy). Re-epithelialization of the wound was investigated in ovariectomized rats. There was a minimal delay in untreated ovariectomized rats equal to < 10% in the amount of granulation tissue. Detachment of epidermis from dermis at the epidermis-dermis junction was seen. In summary, while ovariectomy reduced skin collagen content in healing wounds at day 7, the daily treatment of these animals with estrogen increased collagen and decreased various matrix metalloproteinase expressions and activity in skin wounds. Estrogen also enhanced the laminin-5 level in the wounds. These effects were seen in addition to the estrogen effect on bone.

New developments

One symposium was entitled 'Breaking News'. During this session, the delegates were reminded of the detection of a new and major estradiol metabolite with four hydroxyl groups, referred to as estetrol (H. T. J. Coelingh-Bennink). The physiological site of synthesis of estradiol is restricted to the human fetal liver during pregnancy, owing to selective expression of 15 α - and 16 α -hydroxylase. The physiological role of estetrol during human pregnancy is unknown. There are, however, known pharmacological effects. It has 2% of the antagonistic potency of estradiol in *in vitro* proliferation of MCF-7 breast cancer cells, is 15–30 times less potent than estradiol in sheep on uterine vasodilatation, has a binding affinity to

the estrogen receptor in the human endometrium of 6.25% compared to that of estradiol (100%) and has very weak uterotrophic activity. The question was raised, as to whether estetrol was a SERM. Indeed, estetrol is rather tissue-selective; it binds to the estrogen receptor (ER) α and ER β , does not bind to the androgen, progesterone or glucocorticoid receptors or to 130 other known molecular drug targets. It produces 100% vaginal cornification, is estrogenic on the uterus, has proliferative effects on the endometrium at higher dosages, protects against ovariectomy-induced bone loss and decreased bone strength, provides complete suppression of hot flushes and 100% ovulation inhibition. Its safety is established in human pregnancy. One could envision estetrol-based HRT, probably combined with progestogen, or possibly at low dose as a single entity. Estetrol may be ineffective at the breast tissue site, as it will not build a pool of estrone sulfate.

Another presentation was related to SPRMs, defined as a new class of PR ligands, which show mixed progesterone agonistic and antagonistic activities *in vivo* (W. Elger). Their biological activities depend on the tissue in the presence or absence of progesterone. In cycling cynomolgus monkeys, the SPRM J867 suppressed both menstrual cyclicity and endometrial growth. In a double-blind, dose-escalation study to evaluate the effects of J867 on the menstrual and ovarian cycles and safety parameters in 60 premenopausal volunteers with a history of regular menstrual cycles, this SPRM reversibly suppressed menstruation at daily doses of ≥ 10 mg. J867 induces amenorrhea by primarily targeting the endometrium in the absence of estrogen deprivation. These observations suggest new applications for SPRMs in the treatment of gynecological disorders.

Pulsed estrogen therapy is a brief exposure of target tissues to acute administration of a small dose of 17 β -estradiol (P. Sismondi). As compared to oral estrogen, it may produce less breakthrough bleeding, and, when compared to the patch, may provide more satisfaction to patients (comfort, discretion, hygiene, rapidity and efficacy). It has not been found to produce endometrial hyperplasia at pulsed doses of 300 μ g/day, with an adequate gestational response. Also, significantly less mastalgia was observed as compared to the findings with oral estrogen. In the experimental model of chemically induced mammary tumors in ovariectomized rats, dimethylbenzanthracene (DMBA) has been introduced as a potent mammary carcinogen. The single oral administration of DMBA leads to the induction of mammary tumors, which

are estrogen-dependent and rapidly reduced in the vast majority of treated rodents. The pulsed administration of estradiol via the intravenous route when compared to oral administration, using doses of similar estrogen potency on uterine weight, was shown to lead to a significantly lower tumor incidence rate and a lower rate of tumor development. This is suggestive of lower stimulation of mammary glands with pulsed estrogen.

Mammographic density changes during different postmenopausal HRT regimens were another important subject. N. Colacurci had summarized the experience with estrogen alone versus sequential and continuous combinations with progestins. In that order, breast density rose from around 20 to 38 to 43%. Tibolone only reached less than 10% as compared to no therapy. The Italian group investigated mammographic responses to cessation of HRT according to type of abnormality and HRT. Postmenopausal women were treated with continuous transdermal estradiol (50 µg/day) plus norgestrel acetate (5 mg/day) from day 17 to day 28 of each 28-day cycle. This group was compared to surgically postmenopausal women treated with transdermal estradiol alone and to women not receiving any treatment as controls. The mammographic pattern was classified according to type I (less than 25% of mammary gland covered by dense tissue), type II (from 25–75%) and type III (> 75%). Mammographic density at second mammography was drastically reduced in all groups upon acute withdrawal. The authors concluded that hormone administration would induce epithelial proliferation, stromal edema, vasodilatation and fibrosis, and therefore increase mammographic density, while hormone withdrawal would induce spontaneous apoptosis, reduce stromal edema, vasodilatation and fibrosis and thereby decrease mammographic density essentially to control levels. This certainly has major implications for a proper interpretation of mammographic changes with HRT.

Another important subject was testosterone replacement in peri- and postmenopausal women. For the past 50 years, the treatment of menopausal symptoms has largely focused on estrogen-progestin replacement. Androgen levels fall during the perimenopause. Randomized controlled trials have suggested that testosterone replacement may improve libido and energy. Available products include oral preparations, injections, implants, patches and creams. The introduction of a transdermal drug delivery system (1% testosterone) was indicative of significantly increasing serum testosterone levels on day 1 of the cream treatment into

the upper limit of normal, and steady-state levels at day 14 with a mean around 4 nmol/l. It appears to be safe with few, if any, short-term side-effects. Short-term clinical trials with both gels and patches were shown to improve sexuality and well-being scores (phase-II trials; J. Shifren).

Future aspects in the 21st century

The mission of the Office of Research on Women's Health at the National Institutes of Health in the USA has been defined. They set an agenda for future directions in women's health research, to increase and fund research projects on women's health and sex/gender-related factors and to ensure that women are appropriately represented in biomedical clinical research studies. Opportunities should be developed for recruitment, retention, re-entry and advancement of girls and women in biomedical careers. Major recommendations from the Institute of Medicine Report on gender in basic biological research relate to difference in health and disease, healthy living and prevention of chronic disorders, interdisciplinary approaches to chronic multisystemic diseases with multifactorial etiology, sex/gender differences in response to therapeutic interventions and mental and addictive disorders. Specific research priorities are reproductive health, infections (including sexually transmitted diseases), care-giving and health-related quality-of-life issues, cancer, neurobiology (brain disorders, pain syndromes) and complementary and alternative medicines as well as dietary supplements.

Ultralow-dose estrogen: is this the future?

Doses of 0.3 mg CEE or 0.025 mg three times a day of estradiol will reduce hot flushes to 40% of baseline within 8 weeks. In the HOPE study, 0.3 mg CEE/day was also shown to be effective in increasing hip and spine BMD. There was a linear estrogen dose response. Combinations with MPA showed no added BMD benefit⁶. If one looks at the relationship of baseline postmenopausal levels of circulating estradiol, it will be seen that, below 30 pg/ml, there is still a 1.1% change in BMD, below 20 pg/ml a change of more than 0.9%, while less than 10 pg/ml shows losses of about 3%. Low-dose estrogen combined with MPA, calcium and vitamin D is particularly effective for BMD in elderly women beyond 65 years of age, both at the hip and the spine. The Nurses' Health Study has demonstrated optimal efficiency of estrogen on cardiovascular disease incidence with as low a dose of CEE as 0.3 mg (relative risk of myocardial

infarction (MI) 0.58 and of stroke 0.54) while higher doses (0.625 mg) had an effect on MI only and proved to increase the incidence of stroke. B. Ettinger reported on a randomized, placebo-controlled, 2-year clinical trial.

Ultralow transdermal estradiol 12.5 µg was given to 417 women, aged 60 years and older, with low BMD. It was demonstrated that low dose was far better than no dose. A minimum dose may not exist. One should consider low-dose administration after 5–10 years in those 55 years and older and always be aware that duration is at least as important as dose. Whether these doses will be effective in reducing fracture risk or CHD risk and preventing Alzheimer's disease, macula degeneration or colon cancer remains to be seen. The other aspect will be safety with respect to the reduction of breast cancer.

International collaboration of the IMS with national and regional societies

The Council of Affiliated Menopause Societies (CAMS) is one of the organs of the International Menopause Society (IMS). It was created with several specific objectives in mind. The first was to provide a democratic forum with equal membership and voting rights for all national societies affiliated with the IMS. The controlling committee of the IMS (the Board), by virtue of its limited size, could not have a member from every country on its rostrum. CAMS, on the other hand, irrespective of the number of members of a national or regional society, allows one member from each onto its Board.

The second main objective of CAMS is to develop ideas for projects that have international pertinence to the scientific basis and health-care delivery aspects of menopause. These ideas, once carefully considered and approved, must then in

turn be submitted to the parent Board of the IMS for approval. The projects are then allocated to specific teams for development and, when the program has been developed and approved by the CAMS voting membership, is sent once again to the IMS Board for final approval before being activated.

As the Chairman of CAMS, Wulf Utian pointed out that discussions between many IMS members over the years had highlighted the need for the IMS to produce a clear set of guidelines as to what would comprise the minimum level of health care that should be delivered to women world-wide. Such a document should be useful to both health-care providers in day-to-day practice as well as to controlling authorities such as local or central governments and reimbursing agencies in setting their priorities and budgets. The background to the Adult Women's Health Plan (AWHP) project has involved considerable effort by a large number of participants world-wide. The ultimate outcome was planned to design a general handbook with guidelines applicable to all member nations, and for a series of region-specific appendices that would deal with local medical, economic, cultural and other aspects. AWHP has been presented in Berlin; the handbook is to be published in the near future.

The world has altered much in this time, but the real progress that is made is because of international organizations like the IMS. We have the admirable objective of enhancing women's health and quality of life through and beyond menopause. We work together as equals and have mutual respect for each other. We share our ideas and energy freely, with no personal reward, but only the interests of others at heart.

For further details, please refer to <http://www.imsociety.org/pages/cams.html>.

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