Report on
5th International Symposium on
Women's Health and Menopause
New findings, new strategies, improved quality of life

Women's health care, especially in light of the aging population, has grown and changed significantly within the past few years. The field of medicine addressing the menopause is expanding rapidly and keeping pace with the new knowledge is difficult. Moreover, given the multifactorial approaches needed, the management of women's health during the menopause is posing new challenges everyday to gynecologists as well as general practitioners.
The meeting was thus focused on updating the physicians and other health care professionals on the most recent research breakthroughs and innovative clinical applications, and discussing how to transfer these new data into everyday clinical practice from the perspective of treatment, prevention, and counseling.

"The highlights of the conference included the new findings on the **biology of the estrogen receptors (ERs)**" (link 1), said Pier Giorgio Crosignani, co-chairman of the meeting and professor of Obstetrics and Gynecology at the University of Milan, Italy. Today we know that the two known ER subtypes, alpha and beta, have a widespread distribution in mammalian tissues and may play an important role in a surprisingly large number of physiological processes, including hearing and immunity. "For instance, the new data in this field," explained Crosignani, "are helping us to understand why the prevalence of some diseases, e.g. some autoimmune diseases, is higher in women than in men".

Much discussion was devoted to the **primary findings from the WHI (Women's Health Initiative) trial of conjugated estrogen only (CEE)** (link 2), published just one week prior to the symposium (JAMA,2004;291:1701-12); www.jama.ama-assn.org/cgi/content/abstract/291/14/1701, and their implications on the use of hormone replacement therapy (HRT). While HRT has been confirmed as the best therapeutic option to treat climateric symptoms, with regard to prevention, however, "the study has shown that, with no benefit to heart disease, CEE should not be used for preventing coronary heart disease (CHD) and chronic disease in postmenopausal women," said Marcia L. Stefanick, professor of Obstetrics and Gynecology at the Stanford University, Stanford, CA, USA.

Perhaps the most important moment of the meeting was the final **round table "The future of menopause"** (link 3), when a panel of experts from the major international scientific societies explained and compared the different and latest position statements on postmenopausal hormone usage, in light of the primary results of the WHI estrogen-alone trial. The result was a remarkable concordance of positions; however, several major differences were also highlighted. The lack of agreement indicates those areas in this field that need further research.

The main topics discussed during the symposium were:

1. **New insights into the biology of the ERs** (link 1)
2. **Primary findings from the WHI estrogen-alone trial and their implications for cardiovascular disease (CVD) prevention** (link 2)
3. **Hormones and cancer risk** (link 4)
4. **Metabolic syndrome, diabetes and lifestyle** (link 5)

5. **Bone and joints** (link 6)
6. **Quality of life** (link 7)
7. **Round table "The future of menopause"** (link 3)

"The new findings on the biology of the ERs show that estrogen signaling may play a central role in a huge number of physiological processes, including hearing and immunity" PierGiorgio Crosignani

"The WHI estrogen-alone trial has shown that in postmenopausal women with hysterectomy estrogen therapy (ET) is of no benefit to heart disease and should not be used for CHD prevention these women" Marcia L. Stefanick

Link 1

New insights into the biology of the ERs

The role of ERbeta in the immune and nervous systems

The most exciting breakthroughs in this research area are coming from the newly discovered roles of ERs, especially ERbeta, in the immune and nervous systems. “Since its discovery in 1995, ERbeta has caused a paradigm shift in our understanding of estrogen signaling,” said Jan-Ake Gustafsson, chairman of the Department of Bioscience at the Karolinska Institute in Huddinge, Sweden. It has become apparent that this receptor has widespread tissue distribution and consequently regulates many physiological processes. For instance, there is growing evidence that ERbeta is an important regulator of hematopoiesis and that estrogen signaling plays a central role in the regulation of the immune system, supported by the discovery that the deletion of the ERbeta gene results in a plethora of phenotypes, such as a syndrome reminiscent of chronic myeloid leukemia in mice with ERbeta deletion. These rodent models will aid in a better understanding of the mechanisms behind the well-known sexual differences in autoimmune disease, hopefully paving the way for a more effective treatment of these debilitating diseases.

Another recent and very important finding is that aging ERbeta knock-out mice show signs of grossly impaired hearing, consistent with a complete loss of the organ of Corti in the inner ear. These findings might support the notion that treatment with agonists might delay age-dependent hearing loss.

The role of ERs in the cardiovascular system: the importance of genes

Although the expression of the ERs in the cardiovascular system is established, much remains to be understood about ER-mediated events in blood vessels and heart cells. New data suggest that estrogen activates endothelial nitric oxide synthase in an ER-dependent manner, causing rapid vascular dilatation, while ERbeta plays an important role in the development and maintenance of normal vascular tone and blood pressure.

In humans, it is known that estrogen and HRT activate ERs, which in turn regulate the genes for important cardiovascular disease risk factors. However, relatively little is known about the effect of polymorphism in the ERalpha gene (ESR1) on the risk for CVD. “A recent study on the ESR1 gene variation in the offspring cohort of the Framingham Heart Study has shown that a specific genotype (c.454-397CC) is significantly associated with major CVD and subject with this genotype have a 3.2 fold greater odds of myocardial infarction compared to those with other two genotypes,” explained Michael M. Mendelsohn, of the Tufts-New England Medical Center in Boston, MA, USA. Thus, individuals with this common ERalpha variant have a substantial increase in risk of CVD and myocardial infarction. These findings further support the importance of the ERs in the cardiovascular function in both men and women. Furthermore, they may provide an explanation for recent conflicting data regarding the effects of HRT on CVD and add support to the new evidence from the early rheumatoid arthritis (ERA) and Heart and Estrogen/Progestin Replacement Study (HERS) trials suggesting that genetic variability in the ERs may account for some of the unexpected recent findings.

A new, non-classical, mechanism of action for ERs

Together with the new findings on the distribution and physiological role of the ERs, new data have been presented on the multiplicity of both classical and non-classical mechanisms of action of the ERs. “A recent study in our lab with transgenic mice has demonstrated that the ERs are transcriptionally active in reproductive and non-reproductive organs even in the absence of measurable levels of circulating estradiol,” said Adriana Maggi, of the Centre of Excellence on Neurodegenerative Diseases and Institute of Pharmacological Sciences at the University of Milan, Italy. This study has provided the first in *vivo* evidence of the relevance of mechanisms activating

the ERs in physiological states where the ligand is absent (such as in ovariectomized mice). Needless to say, the novel delineation of this ER activity will have an impact on the design of safer and more efficacious HRT.

"There's growing evidence indicating that estrogen signaling is of paramount importance for regulating the immune system" Jan-Ake Gustafsson

"Genetic variability in the ERalpha is responsible for a different susceptibility of individuals to CVD and may provide an explanation for recent conflicting data on the effect of HRT on CVD in women" Michael M. Mendelsohn

Link 2

Primary findings from the WHI estrogen-alone trial and their implications for CVD prevention

Estrogen deficiency has been assumed to be a risk factor for the development of atherosclerosis. Estrogen supplementation, therefore, has been suggested as a plausible strategy to prevent coronary atherosclerosis in postmenopausal women, an hypothesis supported by a multitude of epidemiological studies. In contrast to these observational data, recent unexpected negative results from randomized clinical trials such as the WHI have completely transformed our understanding of the effect of HRT on cardiovascular disease risk from one of presumed supposed benefit to one of possible harm.

The results from the WHI trials

The WHI estrogen plus progestin (www.nhlbi.nih.gov/whi/estro_pro.htm) trial was stopped 3.3 years early because, in healthy postmenopausal women with a uterus, estrogen plus progestin therapy (EPT) caused an increased risk of breast cancer, coronary events, stroke, and pulmonary embolism. At that point, the National Institutes of Health (NIH) decided that the risks outweighed the benefits (mainly a decreased risk of hip fractures and colon cancer). On March 1, 2004, after nearly 7 years of follow-up, the E-alone arm of the WHI (www.nhlbi.nih.gov/whi/estro_alone.htm) was stopped, almost a year before its scheduled conclusion. Women treated with E alone showed an increased risk of stroke (of similar magnitude to that reported for the estrogen + progestin (E+P) trial) without benefit with regard to the risk of heart disease, which the NIH believed was unacceptable for healthy volunteers. “The finding of no overall benefit,” explained Marcia L. Stefanick, professor of Obstetrics and Gynecology at Stanford University, “led the authors to conclude that neither therapy (estrogen plus progestin therapy and estrogen therapy) should be recommended for CVD and chronic disease prevention in postmenopausal women."

Is the case closed?

Thus, is the case closed? Given the negative results of this trial, can we assume that postmenopausal HRT is no longer an option for cardiovascular protection? Many disagree and the debate remains open and heated. “This surprising turn of events has made it clear that the effects of HRT on vascular health are far more complex than initially assumed and urgently in need of additional study,” said David M. Herrington, of the Wake Forest University School of Medicine in Winston-Salem, NC, USA. The question remains, for instance, whether the observations seen in the last randomized controlled trials should be extrapolated to HRT formulations other than those used in these trials. Another important subject of discussion is the difference between the populations studied in the previous epidemiological studies (that provided positive results) and the recent randomized clinical trials. An important potential explanation for the observed differences is the (menopausal) age and the cardiovascular condition of the study population. Future trials should therefore focus on the effect of HRT in the population that actually uses HRT, that is, young peri- and early postmenopausal women.

“Recent unexpected negative results from the WHI and other randomized clinical trials have made it clear that the effects of HRT on CVD risk are far more complex than initially assumed and urgently in need of additional study” David M. Herrington

“The authors of the WHI E-alone trial concluded that

estrogen therapy should not be recommended for chronic disease prevention in postmenopausal women with hysterectomy" Marcia L. Stefanick

Link 4

Hormones and cancer risk

Experimental, clinical, and epidemiological data support an important role for sex hormones in the etiology of some human cancers, including the three major cancer sites of importance to women: breast, endometrium, and ovary. The issue of the effect of HRT on risk for cancer is therefore a critical one. Although this has been the subject of much debate, several recent findings have suggested the need to re-think old concepts.

Breast cancer risk

As for breast cancer, there has been increasing acceptance that EPT is associated with an increased risk of breast cancer, particularly current and recent users. Recent data from large randomized controlled trials, mainly the WHI trial of estrogen plus progestin (www.nhlbi.nih.gov/whi/estro_pro.htm), have confirmed previous evidence from observational studies and raised the level of concern.

The WHI estrogen plus progestin trial was stopped early in May 2002 mainly because of an increased risk of invasive breast cancer. After an average 5.6 years of follow-up reported in 2003, the relative hazard ratio was 1.24 (95% CI 1.01-1.54), a marginally significant estimate. However, breast cancer incidence became significantly higher in E+P users after four years of exposure, earlier than anticipated from observational studies. This would suggest a growth-promoting rather than a causative effect of EPT in breast cancer.

Now that the eagerly awaited results of the WHI estrogen alone-trial are available, do things look any better? In this trial the risk of breast cancer was reduced by 23% (not statistically significant). Thus, this isolated observation suggests that 1) even the large controlled trials have intrinsic limitation; 2) "the apparent excess risk in HRT users is attributable to combined estrogen plus progestin therapy only and probably represents a harmful effect of the progestin," said Carlo La Vecchia, epidemiologist at the Istituto di Ricerche Farmacologiche "Mario Negri" in Milan, Italy.

In conclusion, the current evidence from observational epidemiological studies, as well as from randomized clinical trials, indicates that the risk of breast cancer is higher for users of the combined EPT than for users of estrogen only, increases with longer duration of use, and is limited to current and recent, but not former, users.

Endometrial and ovarian cancer

It is well established that women who use estrogens have a 10-20 increased risk of endometrial cancers compared with non-users. To counteract the adverse proliferative effects of estrogens, it has become commonplace to prescribe estrogens in combination with progestins. "However, it's still unclear whether this regimen completely eliminates the excess risk and whether newer lower dose of progestins could be effective, as well, at eliminating risk," explained Louise A. Brinton, of the National Cancer Institute in Bethesda, MD, USA.

Ovarian cancer has been less well studied than the other tumors with respect to hormone use. "Despite the reassuring findings of the first studies, the more recent investigations have found moderate risk increases associated with long-term use of ET," said Brinton. Much less is known about the effects of the combined regimen (EPT) and the effects after discontinuation, all of which deserve further research.

Colorectal cancer

During the last few decades, incidence and mortality trends from colorectal cancers have been consistently more favorable in women than in men in Europe. This may be due, in part, to a potential protective effect of the exposure to exogenous female hormones in women (HRT and perhaps oral contraceptives).

“The latest observational studies and randomized clinical trials consistently show a reduced risk of colorectal cancer among women who had ever used HRT,” said Esteve Fernandez, of the Catalan Institue of Oncology and University of Barcelona, Spain. The degree of protection varies from 20% to 40% and tends to be higher in recent users. “The WHI trial confirms definitely the protective effect of HRT for colorectal cancer, whose incidence is reduced by 37% in the treated women,” added Piero Sismondi, of the University of Torino Medical School, Italy. Nonetheless, available data are insufficient to support the use of HRT to reduce this risk at the population level and many open questions remain, including the quantification of the role of duration of HRT use and interactions with lifestyle factors.

“The WHI E-alone trial confirmed that apparent excess risk of breast cancer in HRT users is attributable to combined EPT only and probably represents a harmful effect of the progestin” Carlo La Vecchia

“The WHI trial confirms definitely the protective effect of HRT for colorectal cancer, whose incidence is reduced by 37% in the treated women” Piero Sismondi

Link 5

Metabolic syndrome, diabetes and lifestyle

Metabolic syndrome

The metabolic syndrome, characterized by a range of conditions including central obesity (especially intra-abdominal fat), insulin resistance, dyslipidemia (high triglycerides, high small dense low density lipoproteins (LDL), and low high density lipoproteins (HDL)), hypertension, and clotting abnormalities is becoming a major public concern around the world because of its increasing prevalence, particularly in western countries. The syndrome affects 20-30% of the middle-aged population and predisposes an individual to a 4-fold increased risk of cardio- and cerebrovascular disease. In particular, this condition increases in prevalence with menopause and aging in women and accounts for much of the high CVD morbidity and mortality among postmenopausal women. "It's estimated that more than half of all the cardiovascular events in postmenopausal women are related to the metabolic syndrome," said Alberto Zambon of the University of Padova, Italy.

For women with the metabolic syndrome (and diabetes) it is becoming clear that CVD risk modification should adopt a wide approach and focus not only on glycemic control and low density lipoproteins cholesterol (LDL-C) lowering, but also on triglycerides and high density lipoproteins cholesterol (HDL-C). Moreover, "therapy should aim to reduce the risk associated with multiple factors, both lipid and non-lipid, and should be associated with a correct lifestyle," said Zambon.

Diabetes in postmenopausal women: is HRT an option?

"There is urgent need of further specific HRT studies in diabetic women, with proper adjustment for confounding factors," underlined Sven O. Skouby of the Fredericksberg University Hospital of Copenhagen, Denmark. From a theoretical point of view, the effects of estrogen suggest that HRT would have the potential to reverse some of the metabolic disturbances caused by diabetes and may decrease the combined risk of the clinically most important conditions, i.e. atherothrombosis. Several observational studies support such considerations, but the results from the most recent epidemiological studies on the association between HRT and CVD development in diabetic women give conflicting evidence. Also "the results on the effect of HRT on glucose metabolism are not univocal, mainly as the consequence of the dose of estrogen and the type of progestin administered," said Angelo Cagnacci, of the Policlinico of Modena, Italy, further emphasizing the need for additional research in this specific area.

The importance of lifestyle

"The key approach in CVD prevention is lifestyle changes" said Alberto Zambon. People in developed countries tend to lead a sedentary lifestyle and are not aware of the significant relationship between sedentariness and many causes of disease and death like CVD and diabetes. We have much evidence from recent literature indicating that changes in lifestyle, diet, and physical activity may result in a significant weight loss, thus improving the correlates of the metabolic syndrome and reducing the risk of developing diabetes and CVD. "This evidence has been further confirmed in a recent trial in 173 overweight postmenopausal women in the USA showing that physical activity promotes loss of body fat, particularly the high metabolic intra-abdominal fat, and may reduce the incidence and the severity of metabolic syndrome and its related biomarkers," said Anne McTiernan of the Fred Hutchinson Cancer Research Center of Seattle, WA, USA. All data recently published on this topic give strong evidence that a change of lifestyle is mandatory for the population at all ages in order to avoid disabilities and prevent all age-related diseases.

"The key approach in CVD prevention is lifestyle changes" Alberto Zambon

"Physical exercise promotes loss of body fat and reduces metabolic syndrome prevalence" Anne McTiernan

Link 6

Bone and joints

The clinical pharmacology of osteoporosis

Robert Lindsay, professor of Clinical Medicine of the Columbia University, New York, NY, USA, reviewed in his lecture the current available options for treatment and prevention of osteoporosis in postmenopausal women: bisphosphonates, parathyroid hormone (PTH), HRT, and selective estrogen receptors modulators (SERMs).

Bisphosphonates are still the standard of care for osteoporosis, generally reducing overall fracture risk by about 50% and exerting this effect rapidly (within 1 year). The fracture preventive effect is poorly related to the gain in bone mass and seems to be produced by reduction in the rate of bone remodeling. “As there appears to be an optimum level of bone remodeling and over-suppression of this process confers a potential risk,” underlined Lindsay. “The treatment should be targeted to patients at highest risk of fractures, i.e. women with previous osteoporotic fractures or very low bone mass density.”

1-34hPTH, another bone sparing agent, is also effective in reducing the risk of vertebral and non-vertebral fractures. In contrast to bisphosphonates, however, it increases bone mass markedly. Unluckily, its effects are transient and virtually gone after 2 years of daily injections, posing the need to consider a further intervention with an antiresorptive agent.

HRT remains an option, but “given the limitations of its long-term use, SERMs are likely to play a growing role in the prevention and treatment of osteoporosis,” said Pierre D. Delmas, professor of Medicine at the University of Lyon, France

SERMs and raloxifene: what’s new?

SERMs are nonsteroidal molecules that bind to the ER and trigger either estrogen-like effects or estrogen-antagonist effects according to the target issue. Raloxifene, a second-generation SERM, is now widely available for the prevention and treatment of postmenopausal osteoporosis, and is effective in reducing bone loss and preventing fractures.

The recent Multiple Outcomes of Raloxifene Evaluation (MORE) trial has shown a marked reduction (-30% to -50%) of vertebral fractures both in women with and without prevalent vertebral fractures. “The effect is rapid (1 year), sustained (4 years), and occurs also in patients with osteopenia,” explained Delmas. No significant reduction of nonvertebral fractures was observed except in a subgroup of patients at high risk with severe osteoporosis. The only serious adverse event was an increase in venous thromboembolism (comparable to that reported with HRT). Nevertheless, “the overall safety profile for raloxifene is favorable,” said Delmas, “with a global risk/benefit score, calculated in the same way as for the WHI study, which is significantly reduced by 25%.”

In addition to clinical results, new data have been presented on raloxifene’s modulation of bone homeostasis, confirming its double action on osteoclasts and osteoblasts. Experimental evidence indicates that raloxifene inhibits osteoclastogenesis and enhances osteoblastic differentiation markers, suggesting an increase in osteoblast differentiation and function.

Several other SERMs are now under development.

A new role for estrogen and SERM: regulation of cartilage metabolism

Whereas the effects of estrogen on bone are well established, cartilage is not generally viewed as an estrogen responsive tissue. However, several studies suggest that estrogen may also be involved in the regulation of cartilage turnover and may play a role in osteoarthritis. New data have been presented on this topic. A recent study has shown that ovariectomy (OVX) is associated with an increase in cartilage erosion in rats and treatment with estrogen or levormeloxifene (a SERM) can prevent OVX-induced changes. Even more importantly, treatment with levormeloxifene decreases

by approximately 50% the urinary excretion of CTX-II, a marker of cartilage degradation, in postmenopausal women. “This study,” said Claus Christiansen, of the Center for Clinical and Basic Research in Bellerup, Denmark, “demonstrates for the first time that a SERM suppresses cartilage degradation both in rodents and humans, suggesting potential clinical benefits in the prevention of destructive joint disease such as osteoarthritis.”

“SERMs are likely to play a growing role in the prevention and treatment of postmenopausal osteoporosis” Pierre D. Delmas

“Epidemiological and animal studies suggest that estrogen may be involved also in regulation of cartilage turnover and may play a role in osteoarthritis” Claus Christiansen

Link 7

Quality of life (QOL)

Another important issue adressed by the symposium was Quality of Life (QOL).

Health-related QOL results from the E + P arm of the WHI

In 2003, health-related QOL data from the E + P arm of the WHI were published (NEJM, 2003;348:1839-54; www.nejm.org/cgi/content/abstract/348/19/1839). After one year HRT users had a statistically significant improvement in physical functioning, sleep disturbances, and bodily pain, but the effect size was too small to be considered clinically meaningful and no statistically significant benefits were found at year 3. These results are consistent with those reported from previous trials (Postmenopausal Estrogen/Progestin Interventions (PEPI) and HERS) and the authors concluded that women using HRT as preventive care are unlikely to experience significant improvement in health-related QOL.

These data, however, have to be put into perspective. There are still many questions about QOL the WHI trial cannot answer. “These results are a generalization for a large population,” said Margery Gass, of the University of Cincinnati College of Medicine, Cincinnati, OH, USA. The WHI cannot prioritize QOL for individual women; however, individual symptomatic women may achieve personal benefits. These benefits may be even more important to the woman who experiences an early menopause and the WHI does not directly address QOL for women under 50.

Using the right tools for QOL measurements

Perhaps even more important than the above issues is the adequacy of the tools used for QOL measurement. Until recently, all menopause-related QOL measures have predominantly been life-phase or disease symptom inventories or scores. Are they valid or practical? Have the studies using such tools proved whether HRT enhances QOL? “Obviously not,” said Wulf H. Utian, Executive Director of the North American Menopause Society, “because they didn’t use the right instruments to find it out.” QOL is much more than a simple presence/absence of symptoms. “QOL is a multidimensional construct involving, for instance, global sense of self satisfaction, well-being, interest in life, satisfactory interpersonal relationships, perception of physical and psychological wellness,” said Utian. Very recently, sound and validated instruments to measure QOL have been developed, like the Utian Quality of Life scale and the Greene symptom profile. At present, definitive studies using both appropriately validated QOL instruments and symptom scales in large enough randomized controlled trials are still required to prove that HRT enhances “real” QOL.

“In the WHI QOL paper HRT with estrogen plus progestin did not have a clinically meningful effect on health-related QOL, but we have to keep in mind that these results are a generalization for a large population”.
Margery Grass

“We still don’t know whether HRT enhances “real” QOL. Definitive studies using validated tools to measure QOL are still needed to answer this question” Wulf H. Utian

Link 3

Round table "The future of menopause"

The final round table "The future of menopause" was for many the most important session of the meeting because it allowed a panel of experts from the major societies involved in menopause medicine to highlight their points of view on the future of menopause, specifically on the use of hormones.

The point of view of the Office of Research on Women's Health, NIH

The round table was opened by Vivian W. Pinn, director of the Office of Research on Women's Health of the National Institutes of Health (ORWH-NIH), who focused her presentation on two keypoints:

1) the importance for women and their physicians to collaboratively engage in informed and individualized decision-making about menopausal HRT, based upon scientifically determined knowledge;
2) the absolute and urgent need to conduct more research.

Women today are better informed about their bodies and health and demand answers to questions such as: "If menopause is a natural transition, do I need HRT? If so, why, when, how?" "There is no definite answer for every woman based upon a simple formula," said Pinn, "and the decision to take hormones must be the result of a collaboration and discussion between the woman and her health care provider considering a number of personal factors, including medical and personal history for the individual woman, presence of climateric symptoms, quality of life concerns, and so on." Practitioners in their offices must be prepared to discuss with women approaching menopause many questions, including: "What are the risks and benefits of HRT? Why should I take HRT? Are there other forms or doses that might work better for me? Are there alternatives to HRT that I can use long term?" Do we have the answer to all these questions? "No, not all," said Pinn, "but we do have some. That's why it is absolutely important to design further research that can help us to get those answers we don't have today." Research is needed, for instance, to discern what the differences are between those sympoms related to aging and those that are truly related to menopause, to understand the effect of hormones on women's cognition in peri- and postmenopause, to learn more about markers, especially genetic markers, and mechanisms for adverse effect. "We have made a lot of progress, but not enough," said Pinn. Research must go on and there are currently more than 450 menopause-related studies underway or being concluded funded by the NIH.

The point of view of the North American Menopause Society (NAMS).

"There's no doubt that much of what we have done in our clinical practice is based on our clinical convictions, that we feel are right but we don't really have the evidence to prove," said Wulf H. Utian, Executive Director of NAMS. To overcome this attitude, NAMS on an annual basis puts toghether a panel of experts covering all opinions and leadership across the board and try to create a position statement to translate evidence-based knowledge into clinical reccomendations for the use of hormones. The areas with consensus are those where everybody in the board agrees, while the ones with no consensus identify the points where further research is needed "because, obviously, if we don't agree about one question, we don't really have an answer for that," said Utian. The 2003 NAMS position statement has been published (Menopause, 2003;10:113-32; Menopause, 2003;10:497-506) and is downloadable from the Web www.menopause.org/consumers/), but NAMS is already working on a new one, after the publication of the results of the E-only arm of the WHI.

During his speech Utian presented some of the key NAMS positions, but also reviewed the key points of some of the organization's position statements released after the termination of the EPT arm of the WHI in July 2002, to show the major points of similarity and variance between them. Two of the key statements in the NAMS panel are that risk tolerance varies according to the setting, so that if we are treating to alleviate acute unpleasant conditions there may be a greater tolerance for side effects, and that an individual risk depends very much on age, being lower in younger women.
One important area of no consensus is the association between HRT and early risk of CHD.
Utian noted that, despite some disagreement on certain issues such as HRT usage for osteoporosis prevention and treatment, there is remarkable conformity of position in the statements being issued by the medical community. Nonetheless, there is an ongoing debate, hampered by the lack of precise data and where emotions and fixed positions remain a powerful negative force. "There is no question that in our clinical practice we get into habits and it's difficult to change them, but we have to face the fact that we are in a situation of very rapid evolvment and we do have to keep an open mind," concluded Utian.

The point of view of European Menopause and Andropause Society (EMAS)
"In EMAS we thought it was necessary to approach the information given by the European agency and try to translate it into a clear message on how to deal with the problems or the beneficial effects associated with the use of hormones," said Sven O. Skouby of the Fredericksberg University Hospital of Copenhagen, Denmark, who represented the EMAS.
EMAS took its stand on the publication released by the European Medicines Agency (EMEA) in December last year (www.emea.eu.int/pdfs/human/press/pus/3306503en.pdf), which introduced a new paradigm, stating that, when administering HRT, the physician should lower the dose, shorten the duration of use, and only use it with women that express symptoms.
In response to EMEA, EMAS prepared a position statement that will be released in an upcoming issues of *Maturitas* www.sciencedirect.com/science/journal/03785122), but is already available on the EMAS website (http://emas.obgyn.net/healthcare.asp?page=EMASpos_short), making its position known in clear clinical terms, of course taking into account the most recent information from the estrogen only arm of the WHI.
During his presentation, Skouby gave the audience some indications on the EMAS key viewpoints in relation to HRT. For instance, about dose and regimen, in contrast with EMEA, EMAS emphasize the need to individualize them, stating that in general the appropriate dose is dependent on the menopausal age. With regard to the appropriate lenght of the treatment, EMAS states it is reasonable to consider discontinuation after 2-3 years, disagreeing with the NAMS position that extended use of HRT is acceptable, provided the individual woman is well aware of the risks and there is a strict clinical supervision. "Lastly, over and above defining the best strategy on HRT prescription," concluded Skouby, "EMAS warrants special attention to the possibility of increasing quality of life and to prevent not only CVD and osteoporotic fractures but also breast cancer by lifestyle management with particlular emphasis on exercise, a correct dietary intake, and cessation of smoking."

The point of view of the International Menopause Society (IMS)
IMS organized a special workshop in Vienna last December with thirty experts from all over the world, including representatives from the NIH who were involved in the WHI trial, to present state of the art information on all aspects of HRT, and on the WHI results in particular. After a long debate, a position statement was formulated and recently published in IMS journal *Climacteric* (www.parthpub.com/**climacteric**/home.html). The major issues addressed in this statement were highlighted by Amos Pines (Treasurer and President-Elect of IMS) in his abstract.
"Basically, IMS guidelines are in favor of using hormones, when appropriate," said Pines.
The key points of IMS position statement are the following:

1. available randomized controlled trials are not powered to test outcomes of HRT starting during the menopause transition;
2. there are no reasons to place mandatory limitations on the lenght of treatment;
3. risks of complications of HRT are an important clinical issue. However there are no general guidelines that apply, except to indicate that HRT (especially EPT) is associated with a small increase in deep vein thrombosis (DVT) and pulmonary embolism, a smaller absolute increase in breast cancer, and a reduction in risk for colorectal cancer and bone fracture.

In the opinion of IMS, HRT should be a part of an overall strategy to prevent menopause-related disorders and, in accordance with the positions of other societies, IMS members emphasize the need to individualize dose and regimen, with older women usually requiring lower doses than younger women.

The point of view of the International Society of Gynecological Endocrinology (ISGE)

Andrea Genazzani, president of ISGE , focused his presentation on what ISGE called the replacement concept, that is the need of early personalized hormone replacement to maintain estrogen action, but avoiding universal mass therapy. One of the major concepts was the possible continuation, with a tapering of the dose with age.

“The key points of the replacement concept are certainly timing and women selection,” said Genazzani.

In relation to timing, Genazzani underlined how the results of the WHI cannot be directly transferred to everyday clinical practice because the mean age of the study population was much higher (63) than that of the majority of women taking HRT. In contrast, ISGE strongly supports the concept that HRT has to be given to women at the time of the menopausal transition for two main reasons: the effects of HRT on CVD risk and on cognitive functions. “If a woman starts HRT above 50-55, the effect will be very different than that obtained if she starts earlier, when the vessels are still sensitive and estrogen can still exert an important neurotrophic effect on the brain,” explained Genazzani.

About women selection, Genazzani pointed out that the individuals who visit the practitioner’s office are biologically different not only by age, but also by incidence of diseases and once again stressed the fact that in the E-only arm of the WHI trial there was a large percentage of individuals who do not represent the healthy person and likely had some degree of atherosclerosis. Given the strong evidence that women with complicated lesions estrogen may have prothrombotic coagulatory activity, it is mandatory to treat women when they are healthy and their vessels are in good conditions. “That’s why ISGE thinks that women selection is not a bias but a requirement,” concluded Genazzani.

Where do we stand?

In his conclusory remarks, Rogerio A. Lobo, chairman of the round table and professor of Obstetrics and Gynecology at the Columbia University, New York, NY, USA, gave a picture of what has happened to prescribing habits of HRT in the US since 2002 and after the pubblictions of the WHI and HERS II results. Obviously, after July 2002 there was a dramatic decrease in prescriptions. Since then HRT use is substantially down, as shown by a number of market surveys. In the meanwhile, many menopause societies have published consensus statements to put the results coming from these studies into perspective and to give their point of view on hormone usage.

“Despite some areas of no consensus, the basic messages are essentially the same: that means that it’s appropriate to use HRT for symptomatic “healthy” women,” said Lobo.

The osteoporosis issue is still a critical one. Some surveys have shown that many women have withdrawn from HRT; however, osteoporosis medication has not replaced HRT in the withdrawal population. “Management of osteoporosis risk,” said Lobo, “remains a dilemma for women not on HRT.” Everybody agrees that prevention is a good medicine and we have good treatments for osteoporosis, but long-term effects of non-HRT preparation for prevention are not known. “Should

we wait for the development of osteoporosis before treating?" asked Lobo. This question is highly debated and at present has no definite answer.
So, what is the direction for the immediate future? "I think there are three key points to be emphasized," said Lobo. "First, communicate *accurately* the known risks and benefits of *all* HRT options; second, stress, from a public awareness perspective, the importance of lifestyle changes for the maintenance of good health: and, finally, stress research, with particular attention to studying women during that "window of opportunity" that is the perimenopause."

"Women and their physicians must be able to collaboratively engage in informed and individualized decision making about menopausal HRT, based upon scientifically determined knowledge" Vivian W. Pinn

"Risk tolerance varies according to the setting, so that a woman with acute unpleasant conditions may have a greater tolerance for side effects" Wulf H. Utian

"Dose and regimen need to be individualized and in general the appropriate dose is dependent on the menopausal age, being lower in older women" Sven O. Skouby

"Basically, IMS guidelines are in favor of using hormones when appropriate" Amos Pines

" ISGE supports the replacement concept, that is the need of an early personalized hormone replacement to maintain estrogen action, avoiding universal mass therapy" Andrea Genazzani

" Despite some areas of no consensus, the basic messages from the menopause societies are essentially the same, that is that it's appropriate to use HRT for symptomatic "healthy" women" Rogerio A. Lobo

LIST OF ACRONYMS

CEE	CONJUGATED EQUINE ESTROGEN
CHD	CORONARY HEART DISEASE
CVD	CARDIOVASCULAR DISEASE
DVT	DEEP VEIN THROMBOSIS
E + P	ESTROGEN + PROGESTIN
EMAS	EUROPEAN MENOPAUSE AND ANDROPAUSE SOCIETY
EMEA	EUROPEAN MEDICINES AGENCY
EPT	ESTROGEN PLUS PROGESTIN THERAPY
ER	ESTROGEN RECEPTOR
ERA	EARLY RHEUMATOID ARTHRITIS
ET	ESTROGEN THERAPY
HDL	HIGH DENSITY LIPOPROTEINS
HDL-C	HIGH DENSITY LIPOPROTEINS CHOLESTEROL
HERS	HEART AND ESTROGEN/PROGESTIN REPLACEMENT STUDY
HRT	HORMONE REPLACEMENT THERAPY
IMS	INTERNATIONAL MENOPAUSE SOCIETY
ISGE	INTERNATIONAL SOCIETY OF GYNECOLOGICAL ENDOCRINOLOGY
LDL	LOW DENSITY LIPOPROTEINS
LDL-C	LOW DENSITY LIPOPROTEINS CHOLESTEROL
MORE	MULTIPLE OUTCOMES OF RALOXIFENE EVALUATION
NAMS	NORTH AMERICAN MENOPAUSE SOCIETY
NIH	NATIONAL INSTITUTES OF HEALTH
ORWH	OFFICE OF RESEARCH ON WOMEN'S HEALTH
OVX	OVARIECTOMY

PEPI	POSTMENOPAUSAL ESTROGEN/PROGESTIN INTERVENTIONS
PTH	PARATHYROID HORMONE
SERMs	SELECTIVE ESTROGEN RECEPTORS MODULATORS
WHI	WOMEN'S HEALTH INITIATIVE