The use of estrogen the prevention and treatment of estrogen deficiency symptoms was introduced into the USA by Wilson in 1966. At that time, enthusiasm over hormone therapy was great as were the expectations of the women affected by it.

I would like to discuss some aspects of hormone replacement therapy and outline to you the most likely scenario of influence and effects. The relevance of this therapy for insurance medicine promises to be interesting.

INTRODUCTION

The term menopause, from the Greek meaning month and termination, appeared for the first time in literature in 1872. At that time, the meaning of menopause was "critical condition". Today, we understand menopause to mean the last uterine bleeding controlled by the ovary, or, the final menstrual cycle in the life of a woman. This phase is followed by the so-called "postmenopause," which, in turn progresses by definition into the "senium," which refers to the period of life after age 65.

Why does menopause occur? The ovary is the only endocrine gland that stops functioning before the individual dies.

A significant reason that ovarian function ceases, is the fact that the weight of the organ decreases. The organ reaches its maximum weight at age 25 to 30, then slowly decreases. An ovary in senium, atrophied by age, weights only about one third of a fully functioning ovary. The weight loss of the ovaries is induced by early sclerosis of its blood vessels followed by a decrease in perfusion, together with an increase in fibrosis of the connective tissue as well as capsule thickening. Still another reason is the fact that the number of human gametes are limited by nature and the supply of follicles with eggs and estrogen/progesterin-forming structures has been used by the time menopause begins.

The average age of menopause in Western countries is 50-52 years. To what degree genetic, sociological, cultural and economic influences affect the menopause age has not yet been completely clarified. In a number of developing countries however menopause appears very early: Among the Punjabis in India, at age 44, for different Papua tribes in New Guinea, between 43 and 47 and among Mexican Indians, even at age 40. It is certain that malnutrition plays a great role here. A study by Sherman et al. 1979 shows that adequate nutrition at the beginning of sexual maturity appears to increase the total number of menstrual cycles. A phenomenon that has generally been observed in Western countries, is, the better the living conditions, the earlier the first period (menarche) and the later the last period (menopause). This has the effect of lengthening the total "reproductive" phase in the life of a woman. At the same time, there seems to be a correlation between lower social economic status and early onset of menopause. Unmarried women also appear to go into menopause earlier than married women.

In the case of smokers, menopause begins two years earlier than for a comparable group of nonsmokers. It is to be presumed that nicotine-induced tissue constriction decreases the blood supply to the ovaries; experiments with animals have borne out the suspicion that elements contained in cigarette smoke can induce hypothalamic dysfunction and increased follicle atresia. The influence of this on estrogen production might also be a cause for an increased osteoporosis risk among smokers resulting in a greater frequency of bone fractures.

Other factors influencing menopause are to be found in different cultures; interesting studies were presented at the 6th International Congress on
Menopause in Bangkok in 1990.\(^5\)

From China where older women traditionally enjoy great respect, there are hardly any reports on menopause-related disorders. In Japan, interestingly enough, no word exists for “hot flashes.” Here we would not suspect the reason for this to be cultural influences, but rather nutrition and the fact that the Japanese exercise regularly. The soybean, which is traditionally a staple food in Japan, is rich in estrogen, and fish in the diet supplies calcium. The incidence of heart disease is lower, fewer women suffer from osteoporosis or breast cancer. Although only 2% of all Japanese women take hormones in the postmenopause, they have the highest life expectancy in the world.

In contrast to this, in the USA, youth is the object of admiration and the older woman is held in somewhat lower regard. A study of 2,500 women from Massachusetts between 44-55, conducted by the sociologist, John McKinley, and epidemiologist Sonja McKinley showed that those who feared menopause, believed that their primary value was their appearance and sexual attractiveness.

African American women pass through menopause with fewer difficulties than Caucasian women. A study to this effect showed that African American women measure their own value less by their appearance than Caucasian women do. Their feelings of personal value are less characterized by an ideal of youth. On the whole, it appears that African American women can, in most cases, better accept menopause as an integral part of life than white women.\(^5, 6\)

Looking at the life expectancy of a woman in earlier centuries, the end of ovarian function for most women coincided with the end of life.\(^7\) In view of the life expectancies today which approach 80 years in countries with a high standard of living, a woman spends nearly one third of her life or 30 years, in postmenopause. In 1900, only 6.1% of the female population in the USA was over age 51, today more than a third of all American women are over 51, and therefore in postmenopause. In addition to this, there are hundreds of thousands of younger women who have undergone ovariectomy (oophorectomy) and are therefore classified as postmenopausal.\(^4\) On the basis of current figures, women represent 51% of the total US population, 60% of the age group over 65 and 70% of the age group over 85.\(^7\) The growing significance of statistics on menopause and postmenopause becomes evident, particularly in view of the fact that we know today, that the decease of the ovarian hormone after menopause can often cause disorders so severe, that they take on characteristics of a disease. Furthermore, we know today that long-term estrogen deficiency can over time develop into diseases that pose an acute threat to health and life. For this reason, gynecological medicine has coined a new term: “old-age gynecology.” This special field covers all functional and organic diseases of the aging woman. It is multifaceted, beginning with the climacteric (climacterium), including the severely impaired quality of life imposed by bladder incontinence, the symptoms of skin and mucous membrane atrophy, increased lower back pains and specific malignant tumors. Furthermore, with the decrease of ovarian function, there is a sudden increase in the incidence of fractures, myocardial infarction and stroke. Many problems of the climacteric and postmenopause can today be eliminated or significantly alleviated with hormone replacement therapy. We will now discuss some essential aspects of old-age gynecology.

**POSTMENOPAUSE AND OSTEOPOROSIS**

The term postmenopausal osteoporosis was invented in the 50's by the Boston endocrinologist Olbright. The reason for this was that most osteoporosis patients were female and postmenopausal. The etiological correlation observed by Olbright between estrogen deficiency and osteoporosis has today been clearly proven.\(^5, 9\)

What is interesting in this context is still another observation:\(^16\) "Training-induced amenorrhea has often been observed among highly-trained women athletes, and the phenomenon of period suppression is the rule rather than the exception among these women. It has meanwhile become a recognized fact that hard training programs drive the estrogen level in women so low that the regular cycle is interrupted. This can cause a loss of bone thickness, perhaps even leading to osteoporosis.

In the year 1994, the British Journal of Rheumatologist published the case of a competitive athlete who trained so hard that her bones became brittle and fractured under the strain of daily training. The woman was a marathon runner. Amenorrhoea set in at age 23 and at age 30 she suffered a fractured symmetry. She stopped taking the estrogen prescribed and broke an arm while swimming three months later. This case demonstrates the well-known phenomenon that estrogen deficiency and loss of bone thickness are not necessarily always postmenopausal disorders, but
can manifest themselves in younger women, whether as a consequence of excessive training, as in the case at hand, or of an ovariectomy, which induces artificial postmenopause, or as a result of a hysterectomy in early years, even where the ovaries are not removed.

In postmenopause, at least every fourth woman can expect to suffer from fractures of the vertebrae, lower-arm or hip as a consequence of osteoporosis. Spinal fractures require extensive periods of convalescence leading to long lasting physical and psychological distress. Fractures of the neck and shaft of the femur have astonishingly high disability and mortality rates due to their long-term consequences. In the USA, the Journals of Clinical Orthopedics and Related Research has determined that annual costs incurred by fractures of the neck of the femur are presently estimated at $7.2 billion and expected to increase to $16 billion by the year 2040.

Cooper et al recently published a number of estimates on the occurrence of femur fractures for different regions of the world. If we consider the figures for Western Europe, 0.29% of all men and 0.68% of all women over age 65 suffer on such fracture per year. Using Germany as an example, this means that for the year 1990, there were 65,200 fracture victims. Broken down by sex, the figures amounted to 53,600 fractures in women and 11,600 fractures in men. If we use the population estimate of the Federal Office of Statistics as a basis for calculating these frequencies, a figure approaching 95,000 femur fractures can be projected for the year 2030. This represents a 45% increase over 1990. The resulting costs that will burden the health care system are dramatic.

The advantages of hormone therapy for avoiding or alleviating the disorders of climacteric and also postmenopausal osteoporosis have been substantiated by numerous studies. For an example of this, let me quote a new study that was conducted by Lafferty and Fiske (USA) in 1994. This is the second prospective controlled study, following the publications of Nachtigall et al (USA) from the year 1979 on long-term replacement of estrogen. It covers 25 years. The results confirm the known facts, i.e., that estrogen considerably slows the decrease in bone thickness and loss of height of women attributable to osteoporosis-related fractures of the spinal column and it reduces the frequency of other bone fractures as well. Acute osteoporosis has also been successfully treated by hormone replacement therapy, even in the case of 70 year old patients and in all parts of the skeleton.

Therefore preventive and therapeutic estrogen replacement is one of the most necessary and most effective measures to be taken for old age.

**POSTMENOPAUSE AND ALZHEIMER’S DISEASE**

At an advanced age, depressive moods and sleep disturbances together with the deterioration of the capacity to concentrate, of short-term memory, of learning skills and of psychomotor agility become more pronounced. As was recently proven by means of color-coded Doppler measurements, estrogen medication improved the blood supply to the internal carotid artery and the middle cerebral artery. These partly account for the astonishing success of estrogen replacement on depressive moods, on the duration and quality of sleep, as well as on memory and learning abilities.

In a comprehensive retrospective study by Paganini-Hill and Henderson (USA) from the year 1994 it was proven that women who had undergone estrogen replacement treatment over an extended period of time were shown to have reduced the relative risk of contracting Alzheimer’s disease from 1.0% to 0.69%. This signifies a risk reduction of approximately 30%.

Furthermore, there are studies by Ohkura et al (USA) which lead us to believe that treating Alzheimer patients with estrogen replacement produces a significant improvement of cognitive functions. Positive effects were observed on attention span, orientation, moods and vegetative symptoms. All improvements deteriorated to their original state as soon as the estrogen replacement treatment was discontinued.

If future studies confirm that in a delay in the onset of Alzheimer’s disease to a more advanced age is possible, may be beyond the persons life expectancy, this would be a strong argument in favor of recommending long-term estrogen replacement.

**POSTMENOPAUSE AND CARDIOVASCULAR DISEASE**

The relative incidence of cardiovascular diseases also increases significantly in women after menopause and, at an advanced age, approaches that of men. In addition to this, postmenopausal women have a greater risk of developing cardiovascular diseases than premenopausal women of the same age.

In Western industrialized countries, cardiovascular diseases are the leading causes of morbidity and mortality for postmenopausal women. Most epidemiological studies show that the risk of getting car-
diovascular diseases in postmenopause is two to three times higher than in premenopause. According to a publication of the National Institute of Health, in 1992 approximately 360,000 women died in the USA of coronary heart diseases and an additional 87,000 of strokes.  

There is no doubt today about the relationship between the drastic increase cardiovascular diseases after menopause and the decrease of ovarian hormone production. Heart attacks among women before menopause are rare. Even other risk factors for coronary heart diseases, like hypertension, diabetes, overweight or cigarette smoking, are scarcely able to penetrate the protective estrogen shield. This situation changes drastically after menopause. It is significant that there is a higher incidence of heart attacks among younger women following removal of both ovaries where no postoperative estrogen replacement therapy is undertaken. 

In postmenopause, LDL concentration increases, so that is equals and even exceeds the level of men of the same age, whereas HDL-cholesterol remains unchanged or decreases. Numerous epidemiological, experimental and clinical test results substantiate the fact that the risk of cardiovascular diseases increases when there is a hormone deficiency. Metabolic disturbances related to estrogen deficiency promote the development of arteriosclerosis. 

As early as 1979, Kannel et al (USA) substantiated a higher incidence of heart disease among postmenopausal women with a low HDL-cholesterol level. 

Many studies conducted over the past years have confirmed the fact that hormone replacement therapy in postmenopause can significantly reduce the risk of cardiovascular disease: As an example, we have here comprehensive retrospective studies of Bush (USA), Byrd (USA), Stampfer (USA), Ross (USA) and Pfeffer (USA) from the years 1977-83, which bear out the fact that postmenopausal estrogen-replaced women suffer 30-70% fewer heart attacks. 

The above mentioned study by Lafferty and Fiske (USA) demonstrates the current status of knowledge and the effects of long-term hormone replacement on the cardiovascular risk. 

Eighty-one women given HRT were compared with 76 untreated women. It was possible to keep records on 95% of the treated women for the duration of the study. The results again showed that hypertension, ECG evidence of coronary ischemia, myocardial infarctions and cerebrovascular accidents were significantly less common among estrogen-replaced women in postmenopause than in untreated women. 

LDL-cholesterol values were 21% lower, HDL-values 37% higher among hormone-replaced women. The mortality rate in the estrogen-replaced group was 19% lower. The findings agreed with those of other studies, namely that myocardial infarctions and strokes were reduced by 30-50% with HRT. It was not possible to substantiate an increase in endometrial or breast cancer risk. This study was also able to prove that type II diabetes occurs less frequently and later among estrogen-replaced women in postmenopause than among the untreated control group. 

**POSTMENOPAUSE AND CANCER**

In the gynecological field, the incidence of cancer increases with advancing age. Cancer is the second-mist frequent cause of disease and death among women in postmenopause, following cardiovascular diseases. The most frequent cancers are breast cancers, followed by carcinomas of endometrium, ovary, colon, vulva and Fallopian tube. 

Fear of cancer (carcinophobia) is one of the main reasons that women still refuse hormone treatment today. 

As early as the 1950's or '1960's, studies were conducted on whether estrogen or estrogen and progestin are carcinogenic. In 1954, Jensen et al (USA) first established a possible correlation between estrogen and the development of endometrial cancer. A large number of studies followed, which all arrived at the conclusion that estrogen replacement increases the risk of endometrial cancer. In the 1970's, the studies of Lila Nachtigall et al shed new light on the topic of endometrial and breast cancer. This study had one of the longest follow-up observation periods, namely 22 years. Two groups of 84 women each underwent a prospective 10-year double blind treatment, one being treated with estrogen-progestin-replacement, the other with a placebo. 

In the following years, the women were allowed to decide themselves if they wished to continue the replacement treatment or not. After 10 years, the incidence of breast cancer in the placebo group amounted to 4.8%, in the hormone-replaced group, on the other hand, 0.0%. After 22 years the incidence of breast cancer in the group of women who had never taken hormones was 11.5%, whereas among women who had undergone hormone replacement treatment at some point, no breast cancers were recorded. Lila Nachtigall cautiously interpreted this data as an indication that hormone replacement therapy does not necessarily increase the risk of breast cancer. Two comprehensive
studies later confirmed that sequential progestin supplements significantly reduce the breast cancer risk.49,50 Furthermore, Nachtigall (USA) determined that there was no statistical difference in the risk of contracting endometrial cancer between hormone-replaced and non-hormone-replaced women.51

Since the beginning of the '80's, numerous epidemiological and clinical studies have appeared in professional literature which deal with the question of the potential benefits and risks of hormone replacement in pre- and postmenopause.46,51,52,53,54 These studies demonstrate that the benefits far outweigh the risks and that there are not necessarily serious health problems linked with replacement treatment. Benefits, on the other hand, include the fact that symptoms, such as hot flashes and night sweats and the occurrences of depression are clearly fewer and less severe. Nor is there any doubt in this context that changes attributable to atrophy in the urogenital area and in the skin as well can, in many cases, be improved with hormone replacement treatment.54,55

The current status of knowledge can be summarized as follows:

Estrogens themselves are not carcinogenic. As hormones which influence growth, cell proliferation, blood circulation, metabolism and regeneration estrogens can, however, create an environment in which existing carcinomas might grow more quickly, but not more invasively. This is known as a facultative syncarcinogenic effect.56,57,58,59

In contrast to this, progestin inhibits endometrial proliferation, primarily through a reduction of the estrogen receptors. It has been proven that progestin reduces the risk of cancer of the endometrium. After menopause, the rate of endometrial and breast cancers increases significantly. In this phase, however, the ovaries are no longer the main source of estrogen. With advancing age, it is primarily fatty tissue that takes on the function of transforming ovarian and adrenal androgens into estrogens. The fatty tissue in the breast apparently also has this ability. It appears that cell proliferation in the breast is not retarded by progestin in the same way as it is in the endometrium.57,58,59

As far as endometrial carcinoma is concerned, estrogen monotherapy can cause endometrial hyperplasia that must be classified as a precancerous stage of endometrial carcinoma, the risk of which increases with the dosage selected and the duration of therapy. In contrast to this, a cyclical estrogen-progestin combination therapy reduces the risk of a carcinoma in comparison with the risk that untreated women are exposed to.58,59 From prospective studies, one can conclude that the relative risk of endometrial carcinoma is 0.2-0.49,60,61 with combined estrogen-progestin treatment. On the basis of current knowledge, this means that estrogen-progestin treatment reduces the risk by 60-80% when compared with untreated women.62 In contrast to this, replacement of estrogen alone increases the risk of endometrial carcinoma by a factor of 3 to 8, as American studies have indicated.

More recent studies lead us to presume that women having undergone estrogen-progestin replacement treatment have a 30% lower risk of contracting colon cancer in comparison with untreated women. This means that estrogen receptors are probably located in the colon as well.59

Estrogen-progestin replacement treatment seems to reduce the oncogenic risk of developing an ovarian carcinoma, apparently to the same degree as for the endometrial carcinoma. The relative risk lies between 0.2 and 0.4.57,60,61

As far as breast cancer is concerned, a large number of epidemiological studies have been conducted on the coincidence of hormone replacement and breast cancer.49,50,51 At this time, the evidence that progestin has protective effects with regard to the development of a breast carcinoma is inconclusive, although progestin has favorable effects on non-malignant breast diseases. On the other hand, the evidence of aggravation of breast cancer risk through estrogen-progestin replacement is also inconclusive. Even where women have undergone estrogen monotherapy, the moderate increase in the cancer risk is presumably only existent where the dosage has been rather high and the hormones taken over a period of more than 10 years.60,61

There are studies which indicate a decrease of the breast cancer risk with a progestin supplement.62 There is still a considerable degree of uncertainty about the justification of hormone replacement in postmenopausal women who have a history of breast cancer. New studies show that women who have developed breast cancer during estrogen-progestin replacement have better chances of recovery and a longer relapse-free period.33,34,35,36,37

Finally, on the question of hormone replacement therapy and the breast cancer risk, we must not forget that the risk of suffering a fatal heart attack is 10 times greater for non-treated women than the risk of dying of a fracture of the femur neck or of breast cancer.63 In this context, it has been statistically established that a woman who has had proper replacement treatment lives 3 years longer on the average than a non-treated
woman and the mortality rate can be reduced by 60% after the age of 75 with hormone replacement.16

SUMMARY AND CONCLUSIONS:

The increasing proportion of the aged in the population is posing significant new challenges to politics, society and medicine as well. Gerontology and geriatrics are playing a role in all areas of preventive and curative medicine. Since the life expectancy of women is approximately eight years longer than that of men, gynecology draws special significance from the fact that the greater part of an aging society will primarily be comprise of women.

The medical treatment and care of women in climacteric and postmenopause in the past is seriously inadequate by today’s standards. The attitude in earlier years of not making any great investment of cost or personnel in patients over 75 can, in view of the vitality of modern-day senior citizens, no longer be justified or maintained. The necessity of establishing old-age gynecology becomes more and more clear and urgent.

The decrease of ovarian function in menopause is without doubt an important turning point in the life of a woman. The first signs of aging are inescapable. Following these years a woman still has more than one third of life expectancy ahead of her which she would like to and should spend in good mental, spiritual and physical health.

The principle of postmenopausal hormone replacement has shown itself to be amazingly successful in treating climacteric disorders and their effects on the entire organism. Treatment over many years with as board a spectrum as possible of preventive hormones to combat the long-term consequences of hormone deficiency, like osteoporosis-related fractures, heart attacks, or strokes, is one of the great medical advances of our time. Furthermore, the significance of preventing a number of genital concern manifestations through hormone replacement therapy cannot be overestimated. Gynecology has taken a remarkable step toward its goal of enabling aging women to spend the third part of their lives free of unnecessary diseases and suffering.15

In 1994, after consultation with representatives of European countries during the World Congress of the International Menopause Society, a statement was published by the menopause society of German-speaking countries. In this consensus paper, a stand was taken on hormone replacement therapy in postmenopause. The purpose of this paper was to serve as an aid in formulating and interpreting the text in the package inserts that are enclosed with hormone preparations. The most important passages were to once again summarize the present status of knowledge on hormone replacement therapy and its risks and benefits:

(Estradiol is the estrogen normally produced by a woman’s ovaries that exercises all functions of the natural follicle hormone. It is used to treat all symptoms of estrogen deficiency). Estrogen eliminates, or mitigates, all typical symptoms of estrogen deficiency in menopause, including hot flashes, night sweats and other complaints frequently observed like nervousness, sleep disturbance and depression, with great reliability.

Estrogen stimulates the cell division of an aging organism, of mucous membranes, of supportive and connective tissue. It improves the blood circulation and the salt and water content. Furthermore, estrogen prevents or eliminates deterioration in the urogenital area and the disorders that result from such deterioration. Estrogen prevents or retards bone deterioration, osteoporosis and spinal, lower arm and femur fractures.

By positively influencing HDL- and LDL-cholesterol, blood vessels and circulation, long-term estrogen replacement inhibits the development of arteriosclerosis and nearly halves the frequency of heart attacks and strokes. The mortality rate of women over 50 is therefore decreased significantly and life expectancy increased. (Benefits to the blood vessels of such preventive treatment can already be seen after five years of estrogen therapy and their benefits continue for several years after treatment is stopped. In cases of acute cardiovascular diseases as well, e.g. angina pectoris or myocardial infarction, estradiol replacement can be expected to positively influence the development of the disease.)

In contrast to the birth control pill, estrogen does not increase the blood clotting tendencies nor the frequency of thrombosis or embolism, nor does it increase blood pressure.

Long-term treatment with estrogen alone, particularly if the dosage is high and there is no progestin supplement, increases the probability of a woman contracting endometrial cancer. By adding a cyclical progestin this danger is reduced.

Long-term estrogen-progestin replacement seems to decrease the frequency of ovarian cancer.

Higher dosages of estrogen taken over a period of more than ten years, can slightly increase the risk of breast cancer. Whether a progestin supplement reduces the breast cancer risk, as in the case of endometrial cancer, is not certain at the present time.

Literature and experts in the field agree at the present time that substantiated findings speak strongly in favor of the benefits and advantages of estrogen.
replacement in and after menopause. With proper professional individual treatment and adherence to prescribed guidelines and regular medical examinations, there seems to be the possibility to avoid significant side effects or disadvantages of hormone replacement therapy in the future.

In conclusion, if hormone replacement therapy brings improved morbidity and mortality rates for postmenopausal women, which we certainly hope, this constitutes a very important prospect for the future for both life insurers with their wide variety of products and for health insurers as well.

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