Synthesis

It is generally agreed that the risk of atherosclerosis, constitutionally lower in woman before menopause, increases after the menopause, gradually becoming equivalent to that of men. This translates into a rise in number of strokes and coronary events. Many observations suggest that the increase can be attributed to postmenopausal estrogen deficiency. It is important to determine if hormone replacement therapy (HRT), prescribed to counter the symptoms of menopause, can reduce the cardiovascular risk, as it is a major public health problem.

Original studies covering all the effects of HRT on the cardiovascular risk in postmenopausal women have been analyzed by scientists (biologists, epidemiologistsÉ) or clinical specialists (gynecologists, cardiologistsÉ).

The HRT effects on the differents markers of the cardiovascular risk (lipids, coagulation parameters, arterial pressure, insulin resistance...) in postmenopausal women have been analysed. Experimental data on the activities of estrogens on the arterial cell wall were considered.

HRT and cardiovascular morbidity and mortality

Bilateral ovariectomy is accompanied by a marked rise in the risk of coronary disease relative to premenopausal women. The risk is only slightly increased after natural menopause. Mortality accelerates in the postmenopausal period relative to men, and half the rise is accounted for by cardiovascular disease.

Total crude mortality due to circulatory system diseases in France - Year 1994 (Inserm SC 8 data)

Age (years)	< 50		> 50		Total	
Sex	Male	Female	Male	Female	Male	Female
Number	3 534	1 204	73 320	89 477	76 854	90 681
Rates[1]	15.9	5.6	1 146.2	726.2	358.9	224.3

1 : per 100 000 (on the basis of data from french population registration 1990)

According to a recent study, cardiovascular mortality may depend on age at the menopause: each one-year increase in age at onset appears to be accompanied by a 2 % reduction in the risk of death from cardiovascular causes.

Mortality due to circulatory system diseases in France according to age bracket - Year 1994 (Inserm SC 8 data)

Age (yrs)	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	≥ 95
Male												
Number	1 017	1 471	1 702	2 836	4 750	7 373	11 007	8 151	16 020	13 409	6 533	1 539
Rates[1]	47.4	71.9	119.8	203.1	340.0	594.1	1 035.3	1 784.7	3 305.3	5 708.3	8 846.7	12 809.0
Female												
Number	270	413	480	812	1 711	3 416	6 525	6 861	19 617	24 709	18 094	7 252
Rates[1]	12.6	20.5	34.2	56.1	111.2	230.4	461.6	996.0	2 204.4	4471.7	7 779.0	12 695.6

1 : per 100 000

Overall, epidemiologic studies (prospectives and case-control studies) favor a protective role of postmenopausal estrogen replacement on the risk of coronary disease. The decrease in the cardiovascular risk was estimated up to 30 to 45 %. However, several questions remain : most of these studies examined the effect of oral equine estrogen alone, i.e. not combined with a progestogen ; the influence of type of administration (oral, transcutaneous or transdermal), dose and duration of HRT was not determined. Combined treatment is currently recommended in Europe, with a "natural" estrogen plus a progestogen for non hysterectomized women. The precise efficacy of hormone replacement therapy on the cardiovascular risk, especially as it is prescribed in Europe, can only be determined in controlled trials, which are now starting to be organized.

The effect of HRT on the risk of stroke is not clear. Two cohort studies showed an increased risk in women on HRT. A specific study is required to determine the effects of the different forms of estrogen, the combination of estrogen and a progestogen, and the influence of the dose and duration of treatment.

Four recent observational studies indicated an increase of the thromboembolic risk in women on HRT. The risk increased relative to untreated women in all these studies, with a relative risk of thromboembolic events ranging from 2 to 4. An increase in risk at the beginning of treatment (suggested by some of these studies), and an apparent dose-effect, remain to be confirmed ; in addition, the effect of the different forms of estrogen and that of combined therapy must be determined. As these studies were all observational, a bias may have augmented the observed effect. It is also necessary to identify possible links between HRT and the different types of thromboembolic event.

HRT and the lipid profile

Epidemiological studies in various countries have consistently shown variations in lipid and/or lipoprotein variables related to the postmenopausal loss

of female hormone function. Some of these variables are recognized risk factors for cardiovascular disease (total cholesterol, LDL, apoB) while others are protective (HDL and apoA1), but most of the relevant evidence is from studies of male cohorts. The role of other variables is controversial (HDL2, HDL3, VLDL, TG and Lp(a)).

Some epidemiologic data suggesting a causal link are of high quality. Indeed, the influence of menopause on the lipid profile in American, European and Asian women has been established in several longitudinal studies with consistent results. However, given the long observation time needed to obtain such high-quality results, consistent data are available for a limited number of lipid variables. Modifications of the lipid plasma profile include an increase in total cholesterol, LDL cholesterol and triglycerides, and a reduction in HDL cholesterol. These changes point to a link between the increased cardiovascular risk after menopause and the worsening of the lipid profile. The alterations are due to menopause itself, and not only to aging ; they begin up to three years before menopause and persist long after.

Postmenopausal lipid profile changes have been also identified in high-quality cross-sectional studies whose authors were clearly aware of the many potential biases. The main value of such studies is to explore the relevance of new lipid variables that seem of interest from recent biological data. The results of all these studies are consistent with the changes observed in longitudinal studies. Cross-sectional studies have yielded biologically consistent information such as an increase in VLDL cholesterol, ApoB and ApoB-containing lipid particles (LpB, LpB : CIII and LpB : E), and a worsening of LDL size patterns. The influence of menopause on apoA-containing lipid particles is controversial. All these results tend to show a worsening of the cardiovascular risk in postmenopausal women.

The improvement in the lipid profile during hormone replacement therapy provides good evidence of a causal link. This benefit was consistent with the effects of estrogens on the lipoproteins metabolic pathways (figure 1).

Randomized placebo-controlled trials (which cannot be blinded because of the major side effects of HRT) show a fall in total cholesterol, LDL cholesterol and Lp(a), and an increase in triglycerides and in HDL cholesterol, due mainly to a major increase in the potentially protective fraction, i.e. HDL2. These data suggest an improvement in favorable lipid variables, but also a worsening of others, such as triglycerides. An assessment of the cardiovascular risk associated with each of these variables suggests an overall reduction. However, the number of women included in studies published in peer-review journals is limited (1 262 women), the follow-up periods are highly variable (3 weeks to 3 years), and the potential influence of the route of administration is not sufficiently documented.

Clinical studies have examined the effects of the different types of estrogen on the lipid profile. Equine estrogen has a stronger action than oral estradiol-

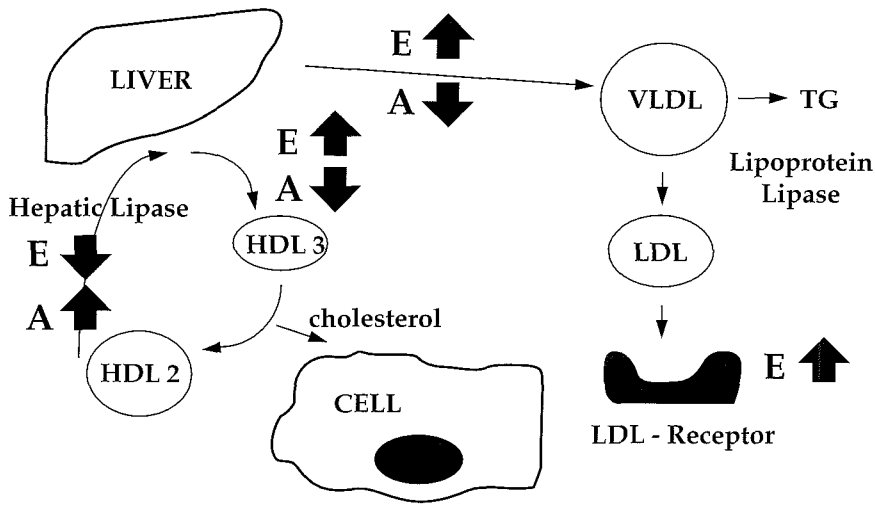

Figure 1 : Effects of estrogens (E) and androgens (A) on the lipoproteins metabolic pathways

17β and estradiol-17β valerate on lipid fractions. Nevertheless, the changes tend to go in the same direction (significant rise in HDL, especially HDL2, and triglycerides, and reductions in LDL, total cholesterol and apo B). The action of estrogen is dose-dependent, particularly reflecting the inhibition of hepatic lipase when given orally. Studies of non oral estrogen administration have demonstrated that triglyceride levels are not increased, but rather tend to fall. Most of these studies have indicated a drop in LDL cholesterol. It should be noted that lipid modifications appear more rapidly when estrogen is administered per os than by other routes.

The effects of estrogen on the lipid profile can be modulated by concomitant progestogen administration. The observed changes depend on the type of progestogen (pregnane or norsteroid) and the dose (e.g. the androgenic properties of high-dose medroxyprogesterone acetate). Norsteroid progestogens and MPA (10 mg/day) stimulate hepatic lipase, thereby countering the effect of estrogen on this parameter, with a drop in HDL and triglycerides, and a variable effect on LDL and total cholesterol. These progestogens also potentiate some effects of estrogen, through an action on regulatory mechanisms other than hepatic lipase. Pregnane progestogens other than MPA and progesterone have no apparent impact on lipid fractions.

While most studies suggest that non oral estrogen administration can reduce the level of LDL cholesterol, its action on HDL is more controversial. It seems to be less effective than oral estrogen in countering the hepatic effects of norsteroids. Thus, the combination of non oral estrogen and a norsteroid leads to a significant fall in HDL cholesterol and accentuates the fall in triglycerides.

A few clinical studies have examined the effects of oral estrogen therapy in women with hypercholesterolemia. They mainly involved women with moderate hypercholesterolemia, meaning that the amplitude of the effect according to the baseline blood cholesterol level is not known. Given the effect of non oral estrogen administration on the fall in triglycerides, it would be interesting to test such treatment in women with hypertriglyceridemia. Some studies have shown that estrogen, regardless of the type, leads to a size reduction in LDL fractions and to changes in their composition. Although these changes are supposed to be deleterious, similar modifications have been observed with statins, which have an antiatherogenic effect. Too few studies have examined the action of estrogen (alone or combined with a progestogen) on Lp(a) to show any beneficial effect. The action of estrogen on LDL oxidation *in vivo* also has to be better documented, as current results are limited by technical assay problems.

HRT and coagulation parameters

The study of factors involved in coagulation and fibrinolysis is now a key element of research into the cardiovascular risk, both arterial and venous.

Hemostasis is ensured by several mechanisms involving platelets, the coagulation cascade and the fibrinolytic system. Hemostasis is controlled by natural antithrombotic systems – antithrombin (AT), protein C (PC) and protein S (PS) – and the fibrinolytic system (figure 2).

An imbalance between the regulatory mechanisms of hemostasis can lead to thrombosis. Measurement of factors involved in coagulation and fibrinolysis are used to assess the thrombotic risk (both arterial and venous).

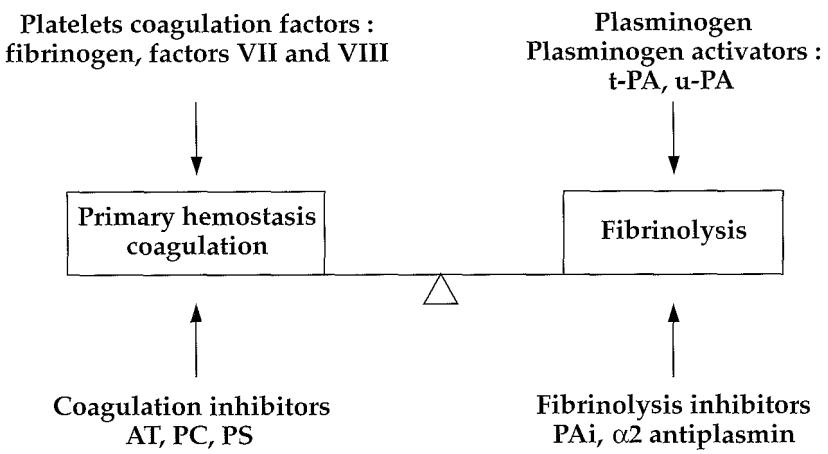

Figure 2 : Physiological equilibrium of hemostasis

Venous and arterial risk and hemostasis

Arterial risk	Venous risk	Coagulation activation markers
↗ fibrinogen	antithrombin	↗ fibrinopeptide A
↗ PAI	protein C - protein S	↗ 1+2 prothrombin fragments
↗ t-PA ag	↗ factor VIII	↗ thrombin-antithrombin
↗ factor VII		↗ D-dimers

Abbreviations used in this book are presented at the end

Venous thrombosis can be associated with a reduction in anticoagulating systems and resistance to activated protein C. This is the case of congenital deficiencies in AT, PC or PS, and of patients bearing the factor V mutation responsible for resistance to activated protein C. The hypercoagulability induced by these abnormalities translates into a rise in markers of coagulation, especially prothrombin fragments 1+2 (F 1+2).

Arterial thrombosis involves other mechanisms. The risk is practically nul in the above-mentioned congenital abnormalities. In contrast, epidemiologic studies have suggested that a rise in fibrinogen, and probably factor VII, as well as an increase in PAI-1 (the main inhibitor of the fibrinolytic system) is associated with a risk of ischemic arterial events, especially myocardial infarction.

Menopause upsets the hemostatic balance : all observational studies (mostly cross-sectional) suggest that menopause is associated with a significant rise in factor VII, fibrinogen and PAI-1 relative to non menopausal women of the same age. Only one study included a longitudinal analysis; the authors observed a significant rise in factor VII (14.9 %), fibrinogen (0.41 g/l) and antithrombin (5.1 %) after the onset of natural menopause.

Hormone replacement therapy could influence these parameters. The observational approach, which consists of analyzing links between HRT and parameters of hemostasis in epidemiologic studies, has shown a significant reduction in fibrinogen.

Only the interventional approach (controlled randomized trials) can show the effect of HRT on parameters of hemostasis. Various replacement regimens can be used, according to the nature and mode of estrogen administration (conjugated equine estrogen or estradiol, oral or transdermal route) and whether or not estrogen is combined with a progestogen (norsteroid, norpregnane, pregnane or progesterone).

Most studies have examined the effects of oral conjugated equine estrogen, and showed falls in fibrinogen and PAI that could offset the rises linked to menopause. Furthermore, a reduction in AT associated with a rise in markers of coagulation (F1+2) appears to reflect hypercoagulability. These modifica-

tions are reminiscent of the increased risk of venous thromboembolism recently reported in women on HRT.

Estradiol-17β can be administered orally or transdermally. Three intervention trials have been published. Only one compared different routes of administration of natural estrogen. The oral route was linked to activation of coagulation and to a parallel rise in fibrinolytic potential, while the transdermal route had no short-term effect on hemostasis.

Published studies indicate that oral estrogen therapy leads to a reduction in fibrinogen (an arterial risk factor) and to activation of coagulation (reflecting hypercoagulability), while transdermal HRT route has little effect on the hemostatic system. This could represent an advantage of the transdermal route as regards the venous risk, but the lack of any reduction in arterial risk factors (fibrinogen and PAI) raises doubts on the potential arterial benefit of this route.

HRT and blood pressure

Hypertension is a major cardiovascular risk factor in women, with an attributable risk of 45 to 55 %. The prevalence of hypertension increases with age (50 % in women over 60). The blood pressure changes associated with menopause remains difficult to evaluate. Longitudinal epidemiologic studies and some cross-sectional studies have shown no significant effect of menopause on age-related blood pressure changes. A few cross-sectional studies have, however, suggested a positive association, independent of age, between menopause and increase in blood pressure.

Blood pressure in postmenopausal women is characterized by an increase in systolic pressure and in stress-induced pressure response as well as by an increase in pulse pressure (systolic pressure minus diastolic pressure), which is a risk factor for left ventricular hypertrophy and coronary mortality, independent of mean arterial pressure, especially in women over 55.

In normotensive women, the results of randomized, placebo-controlled studies suggest that HRT does not change blood pressure or tends to inhibit the age-dependent pressure increase generally reported in the placebo group in long-term studies.

There are no such randomized, controlled trials involving hypertensive women, and the only available results were obtained on a small number of patients or in prospective open studies. Overall, HRT does not seem to change blood pressure significantly in hypertensive women.

However, recent data obtained in open studies (i.e. studies lacking a control group and randomization) have suggested that 30 to 50 % of hypertensive or normotensive women may show individual « susceptibility » to HRT (what-

ever the estrogen, the route of administration and whether or not a progestogen is added), characterized by a rise in blood pressure leading, in some women, to the discontinuation of HRT. These results must clearly be confirmed in appropriately designed trials, and the factors underlying this « idiosyncratic » reaction need to be identified. Studies of interactions between estrogen and the renin-angiotensin system might help to explain the individual susceptibility of some women to HRT. The potential interest of the association of HRT with antihypertensive treatment, in terms of efficacy and tolerance, remains to be determined.

HRT, insulin resistance and the waist-to-hip ratio (WHR)

Noninsulin-dependent diabetes appears to eliminate the cardiovascular protection that women enjoy before the menopause : the cardiovascular risk in diabetic women is 4 times higher than in non diabetic women and twice that in non diabetic men.

A better understanding of the influence of diabetes, and the underlying mechanisms, will be necessary to determine the possible impact of steroid hormones on these factors. The fall in carbohydrate tolerance increases the cardiovascular risk relative to normoglycemic subjects. This increased risk is probably linked more to insulin resistance and the accompanying hyperinsulinemia than to the rise in blood glucose.

Few studies have investigated links between menopause, HRT and carbohydrate metabolism. The loss of ovarian function could lead to a fall in both insulin secretion and insulin breakdown, with no significant direct effect on insulin or glucose concentrations. In contrast, after menopause the age-dependent increase in insulin resistance could gradually disturb the carbohydrate balance.

The impact of HRT on carbohydrate parameters is controversial and seems to depend on factors such as the type of estrogen and progestogen, the dose, and the route of administration. However, too few randomized trials, with inadequate populations, have been done to determine the real influence of these factors. Estradiol administered transdermally has little impact on the liver, a major site of insulin action, but seems to improve the pancreatic response to a glucose load and to reduce peripheral insulin resistance. The effects of conjugated estrogen appear to be dose-dependent, and a high dose (1.25 mg/d) may have detrimental effects on insulin resistance.

The addition of a progestogen, even one with low androgen activity such as MPA, appears to offset the beneficial effects of conjugated equine estrogen and estradiol-17β (administered transdermally) on carbohydrate metabolism and to increase insulin resistance.

HRT seems to reduce the incidence of diabetes in postmenopausal women. The use of conjugated estrogen plus an androgenic progestogen in diabetic postmenopausal women could, however, alter lipid metabolism, while transdermal estradiol and natural progesterone do not change carbohydrate metabolism, lipid metabolism or body weight.

The cardiovascular risk increases significantly with the body mass index (BMI) in women. However, it seems that obesity, based on BMI or Quetelet's index, is not an independent risk factor for cardiovascular disease in women, while abdominal obesity, based on the waist-hip ratio may be predictive of cardiovascular events, independently of other risk factors and BMI. In addition, android fat distribution is generally associated with a gradual rise in certain risk factors such as insulin resistance, arterial pressure, plasmatic triglycerides triglyceridemia and a fall in HDL-cholesterol.

Data on weight changes during menopause are controversial. Most prospective studies have shown no change in BMI at menopause, and no significant difference in BMI has emerged between postmenopausal women and premenopausal women in cross-sectional studies. In contrast, the distribution of fat changes after the menopause, with an accumulation around the abdomen instead of the normal female (gynoid) distribution on the buttocks and thighs.

Data obtained in placebo-controlled trials, which limit the selection bias, suggest that HRT does not generally alter BMI. In contrast, estrogen alone may prevent the android redistribution of fat. There are no data on the effect of combined use of estrogen and an androgenic progestogen on the prevention of abdominal obesity.

Estrogen and the arterial wall

Studies on the effects of estrogen on the cardiovascular system have shown changes in vascular reactivity and structural alterations of blood vessels that participate in vascular remodeling, whether physiological or pathophysiological (atherosclerosis, ischemia...).

Studies on animal models (mouse, rabbit, pig and monkey) suggest that the target of the antiatherogenic activity of estrogen is in the vascular wall, meaning that the impact on the circulating lipid concentration and lipoprotein profile is less important. Estrogen has a marked effect on the formation of lipid deposits. Penetration of atherogenic lipids into the intima and their subsequent oxidation induces the adhesion of circulating monocytes, their proliferation and their transformation into cholesterol-loaded macrophages which trigger the formation of atheromatous plaque. Estrogen would tend to reduce the accumulation and oxidation of atherogenic lipoproteins in the intimal space.

Other mechanisms potentially participating in the atheroprotective action of estrogen include vasorelaxation, either by a direct action on calcium-dependent potassium channels (although the molarities used experimentally are difficult to reach during replacement therapy), or indirectly through a rise in the production of vasodilatory mediators such as PGI2 (prostaglandins), EDRF (endothelium-derived relaxing factor or nitric oxide-NO). Regulation of the production of oxidative species (superoxide ions) in the vessel wall has often been forwarded, but remains to be confirmed because of technical difficulties. Estrogen could control the proliferation of endothelial and smooth muscle cells, resulting in a reduction in the intima/media ratio.

Cellular and molecular biology-based studies have confirmed the impact of estrogen on the production of vasorelaxing molecules (NO and PGI2) and cell proliferation. The mechanisms of the antiproliferative effect of estradiol on vascular smooth muscle cells are unclear. As for the proliferative effect on endothelial cells (the basis of angiogenesis), the respective importance of estrogen and angiogenic factors such as VEGF (vascular endothelium growth factor, identified in the ovaries, uterus and placenta) remains to be determined. Finally, estradiol might have a modulatory effect on the expression of integrins and adhesion molecules on endothelial cells.

The mechanism of action of estrogen involves two specific types of nuclear receptor (ERa and ERb) apparently present in cell populations of the vessel wall so far explored. The respective roles of these two receptors remain to be identified. The existence of membrane receptors has also been forwarded by several authors.

The few available clinical studies, some of which were neither randomized nor placebo-controlled, have mainly analyzed two effects of HRT : vasodilation and endothelial function.

HRT has vasodilatory effects on several arteries (aorta, uterine, brachial and carotid arteries). This effect is observed whatever the type of estrogen, the route of administration and the duration of treatment, and the use and type of combined progestogen. In contrast, only little data are available on the effect of chronic estrogen administration on the coronary circulation. The only available results concern acute effects after intravenous or intracoronary injection of estradiol : natural estrogen does not affect vascular parameters, while ethinyl estradiol has a vasodilatory effect on conductance and resistance coronary vessels.

Endothelial dysfunction is associated with aging, hypertension, atherosclerosis and hypercholesterolemia. Menopause increases the age-dependent impairment in endothelial function : in normotensive and hypertensive women, it reduces endothelium-dependent vasodilation without changing endothelium-independent vasodilation.

HRT increases endothelium-dependent vasodilation (flow-mediated or in response to acetylcholine) and does not change (or increases) endothelium-

independent vasodilation. This effect was observed in the brachial and coronary arteries, after acute administration. The persistence of the effects of HRT on endothelial function during chronic treatment is controversial. In postmenopausal women with impaired endothelial function, injection of estrogen prevents or reverses the paradoxical vasoconstriction of coronary arteries in response to acetylcholine. A NO-related mechanism may contribute to the HRT-induced improvement of arterial endothelial function.

As regards atherosclerosis, HRT could reduce the intima-media thickness of the carotid and limit plaque formation at this site. Further studies are necessary to confirm these data and to determine the underlying mechanisms in the clinical setting.

The sensitivity of the venous wall to sex hormones is well established. Ovarian steroids affect venous vasomotricity. Data are few and far between, and the respective parts played by estrogen and progesterone in these phenomena remain to be defined.

Pharmacokinetics of estrogen and progestogen

All existing data indicate that the main biological effects of oral and non oral estrogen administration are directly linked to achieved plasma estradiol-17β levels, except, of course, for ethinyl estradiol, the action of which persists (because of its resistance to enzymatic breakdown) despite lower circulating levels. Although plasma levels of estrone are very different after oral and non oral dosing, this appears to have no practical consequences. Administered *per os*, standard estrogen preparations (estradiol-17β, estrone-sulfate and conjugated equine estrogen) all lead to the entry of estrone and estrone-S into the portal circulation, a fraction of which is reconverted into estradiol-17β after transiting through the liver. Given the high degree of first-pass liver estrogen metabolism, oral doses must be sufficient to obtain adequate peripheral concentrations of estradiol-17β. The liver, however, is exposed to almost the entire oral dose (10 to 20 times the ovarian yield). This leads to a rise in hepatic synthesis of estrogen-sensitive proteins, which may have both favorable and detrimental consequences. It has been demonstrated that, at the doses recommended after the menopause, oral estrogen has no detrimental hepatic effects in healthy individuals. Because of the suspected increase in the risk of premature cardiovascular mortality, caution requires avoiding the oral route if possible in subjects at cardiovascular risk.

A linear dose-effect relationship has not been observed for all the characteristics of estrogens. For some characteristics of estrogens, maximum effects are reached at relatively low plasma levels (corresponding to those in the early follicular phase) : this is notably the case of osteoprotective effects. In contrast, certain effects on hepatic proteins show a linear relationship that

attains much higher estrogen concentrations. The dose-effect relationship of the vascular actions of estrogen (especially vasodilation) is as yet unknown in some arterial territories.

The minimal dose of oral estrogen ensuring osteoprotective effects is between 1 and 2 mg of estradiol-17β and valerate-estradiol-17β and 0.625 mg of conjugated equine estrogens. Ethinyl estradiol is not commonly used for HRT because of its marked hepatic effects.

Although several non oral routes have been studied and developed, transcutaneous estradiol-17β administration remains the most widely adopted approach. Two delivery systems are available : percutaneous gels and transdermal patches, both of which provide plasma estradiol-17β concentrations corresponding to the early follicular phase and have well-proven osteoprotective effects. Other routes such as intranasal and vaginal ones are being developed.

To overcome the poor bioavailability of oral progesterone, initial development work focused on synthetic compounds sharing the antiproliferative and secretory differentiation effects of progesterone (genomic effects) while resisting liver enzymatic metabolism in order to maintain biological activity when orally administered. The leading compound of these synthetic progestogens is medroxyprogesterone acetate (MPA), which appears to share the genomic effects of progesterone, but not to produce the effects mediated by activation of transmembrane Cl- exchanges (GABAA complex receptors). Data on the non genomic effects of pregnane and norpregnane derivatives are insufficient. Norethisterone acetate (NETA) shares some of the properties of testosterone (especially metabolic effects). Progesterone cannot be administered transdermally because of its poor cutaneous permeability and the high doses required. As a result, several teams have studied intramuscular injections and vaginal application of progesterone when a purely physiological approach is required. Clinical studies with vaginal progesterone gel have shown uterine effects clearly exceeding expectations on the basis of the (low) plasma levels achieved, suggesting that part of the dose administered is transported directly from the vagina to the uterus.

Clinical prescription of HRT

HRT, indicated for the treatment of functional disorders related to menopause and for the prevention of osteoporosis, has no detrimental effect on cardiovascular status in individual women without risk factors. Estrogen administration, whatever the type and route, has proven effective in both settings.

In the absence of cardiovascular, thromboembolic and metabolic risk factors, the mode of administration and choice of compound will depend on the indi-

vidual prescriber, the patient's wishes, and her psychological and physiological tolerance.

Progestogen prescription is recommended by a large number of authors to counter the mitogenic effects of estrogen on the uterus and breast, although it seems to reduce the possible benefit of HRT on the cardiovascular risk.