Overhauling the French research system to make it fit for the future requires dedicated political leadership. Claudie Haigneré, minister for research since June 2002, is dedicated to bringing about change. A medical doctor, the nation's first female astronaut, and the only woman qualified to bring the International Space Station's *Soyuz* lifeboat back to Earth, she is both sympathetic to the plight of young researchers and aware of the faults of the system. Haigneré plans a radical reform that concentrates on investing more in younger scientists by ensuring their independence and high-quality projects and by overhauling the funding system. She would like to put an end to premature lifetime recruitment by enforcing an interim fixed-term-contract phase of 3–5 years, during which young scientists are offered attractive research conditions and must prove their worth. This initiative is intended to soften up the current rigid system and promote the mobility of young scientists who want to change laboratory after their PhD; the French ministry does not plan to do away with lifetime recruitment altogether, it only intends to delay it. Haigneré has already introduced a postdoctoral system, through which 400 fellowships were granted in 2003 and 600 are to be distributed in 2004 among the CNRS, INSERM and other organizations. However, the duration of these grants is only 12 months with the possibility of a six-month extension, which is a rather short time for ambitious postdoctoral projects.

Overhauling the French research system to make it fit for the future requires dedicated political leadership

As for funding, Haigneré agrees that a more competitive allocation of funds on the basis of peer-review, following the Anglo-Saxon model, could improve the existing system. Things cannot be changed with the stroke of a magic wand, however, and it is certainly going to take time to realize this measure. In the meantime, the French government passed a law last August to facilitate the creation of new foundations devoted to raising funds for fundamental research, and to alleviate the fiscal burden of donors and contributors by reducing the taxes on such donations by 60%.

Despite its weaknesses or imperfections, the French research system is not necessarily in a crisis and can still draw on an outstanding scientific tradition. Pierre and Marie Curie, Louis Pasteur, Jacques Monod, Francois Jacob, André Lwoff and Boris Ephrussi all conducted their research and achieved their success in France. But one cannot rely on tradition alone, particularly in a fast-changing world with increasing globalization, so a genuine, introspective rethinking of the system is clearly needed.

And while many European countries are trying to fix defects in their national research systems, it is also a crucial time for Europe as a whole to consider its goals and responsibilities in the management of science. Change may therefore not just come about from within, but also from the outside with the creation of new European research and funding institutions.

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A second chance for hormone replacement therapy?

Hormone replacement therapy for older women has been vilified after two major studies showed that it increased their susceptibility to various diseases. But scientists maintain that, used differently, it can still help to protect against neurological and cardiovascular diseases

The results of two large-scale studies on the health risks and benefits of hormone replacement therapy (HRT) for post-menopausal women dropped a bombshell of bad news this year. The Women's Health Initiative (WHI) study, sponsored by the US National Institutes of Health (NIH), and the UK's Million Women Study, sponsored by the British Medical Research Council (MRC) and Cancer Research UK, both found that HRT significantly increases the risk of invasive breast cancer. The US study also found higher risks of heart attack, stroke and blood clotting. The NIH took the unusual step of halting the WHI trial and recommended that women stop taking HRT for mild menopausal symptoms. However, many researchers maintain that these studies tell only one side of the story and that HRT, if the right drugs are used with the right regimen in the right patients, can indeed be beneficial to women's health.

The WHI reported in several publications (Anderson *et al.*, 2003; Shumaker *et al.*, 2003; Rapp *et al.*, 2003; Wassertheil-Smoller *et al.*, 2003) that for the 16,608 women in the study who took a combination of oestrogen and progesterone, the risk of breast cancer increased by 26%, heart attack by 24% and stroke by 41%. Combination therapy also doubled the risk of ovarian cancer and all types of dementia, including Alzheimer's disease. Although the study found a reduction in colon cancer risk and osteoporosis (Cauley *et al.*, 2003), the WHI concluded that the risks outweigh the benefits and stopped its study after five years. The oestrogen-only part of the study is still underway, with results expected in 2005. The British study similarly showed that women between the ages of 50 and 64 taking a combination therapy had a 22% higher risk of death from breast cancer compared with women taking a placebo (Million Women Study Collaborators, 2003). All told, these two major trials show that the risks by far outweigh the benefits of treating post-menopausal symptoms, such as hot flashes, sleep disruption and vaginal atrophy, with combination HRT. The US and UK governments immediately issued new guidelines stating that the only reason to consider HRT is for treatment of moderate-to-severe symptoms at the lowest possible dose and for

the shortest amount of time, while taking the patient's individual risk factors into consideration. For most physicians and patients, HRT is now no longer considered a 'lifestyle' drug for women, but a choice that comes with considerable risk.

For the approximately 50 million post-menopausal women in the USA and millions of others in Europe, however, the debate has first and foremost caused a great deal of confusion and fear. Bruno Muller-Oerlinghausen, chairman of the German Commission on the Safety of Medicines (Berlin) called the thousands of breast cancer deaths from HRT "a national and international tragedy" and stated in the UK *Sunday Herald* that "more women have probably died from the hormone therapy than damaged children were born in the wake of the thalidomide scandal." The UK's MRC estimates that HRT has caused 20,000 deaths from breast cancer over the past ten years in the UK alone. Sales of Wyeth's (Madison, NJ, USA) Premarin® (conjugated equine oestrogen) and PremPro™ (a combination of Premarin and synthetic progesterone) dropped precipitously over the past 18 months and the *British Medical Journal* recently reported that 40% of women in New Zealand had stopped taking HRT after results from the WHI study were published (Lawton *et al.*, 2003).

The controversy was further fuelled by women's health journalist and activist Barbara Seaman's best-selling book *The Greatest Experiment Ever Performed on Women: Exploding the Estrogen Myth* (Hyperion, New York) that blamed drug companies, such as Wyeth and Schering in Berlin, Germany, for putting profits above the well-being of women. She details the development and marketing of Premarin and diethylstilbestrol, a synthetic oestrogen once prescribed to pregnant women to prevent miscarriage and later found to cause gynaecological cancers in their daughters. Premarin in particular has been marketed as a 'lifestyle' drug, helping women to stay 'forever feminine' and avoid the emotional and physical tolls of menopause, despite early evidence that the drug could cause breast and cervical cancer. Although the Nurses' Health Study (Grodstein & Stampfer, 1996) and the 2002 Cache County Study (Zandi *et al.*, 2002) showed that HRT might help to prevent heart disease and dementia,

these observations have been interpreted as the 'healthy user effect'—the fact that women in this study were healthier and took better care of themselves—according to Nananda Col in the Department of Medicine at Brigham & Women's Hospital and Harvard Medical School (Boston, MA, USA).

For most physicians and patients, HRT is now no longer considered a 'lifestyle' drug for women, but a choice that comes with considerable risk

A similar controversy over hormone replacement therapy for men is also heating up. Approximately 5.6 million men in the USA now take testosterone to treat a range of age-related symptoms, including diminished libido, and loss of muscle mass and strength, in spite of evidence that testosterone replacement may fuel prostate cancer and atherosclerosis. On the basis of the results with HRT for women and the scientific literature on testosterone, the Institute of Medicine (Washington, DC, USA) is now considering a large, government-sponsored study in the USA to investigate whether testosterone treatment creates health risks for men.

Despite the damning trial results, the debate over HRT has not been resolved. While many scientists, including Marcia Stefanick, Associate Professor at Stanford University's School of Medicine (Stanford, CA, USA) and Chair of the WHI Steering Committee, say that the case is closed for treating women with HRT, others disagree. They believe that the studies only show that treating post-menopausal women with certain forms of oestrogen and progesterone is harmful, but maintain that there is strong scientific evidence that younger women could in fact benefit from other formulations of hormones that reduce the risk of cardiovascular and neurological diseases. This will be difficult to prove. Stefanick said that "additional studies would be a waste of taxpayers' dollars," and Wyeth is not planning any new trials with Premarin or PremPro, said company spokesperson Natalie DeVane. It is, however, starting a phase III trial with the next-generation SERM (selective oestrogen-receptor modulator) bazedoxifene

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combined with Premarin in postmenopausal women with osteoporosis and menopausal symptoms. Unlike oestrogen, SERMs do not have proliferative effects on the uterus, but they may actually produce some menopausal-like vasomotor symptoms, such as hot flashes. "In principle, there should be new large-scale trials, but in practice, I doubt they will happen," said Wulf Utian, head of the North American Menopause Society (Cleveland, OH, USA).

One small trial is being planned, however. S. Mitchell Harman, head of the Kronos Longevity Research Institute (Phoenix, AZ, USA), is designing a study that will test different forms of hormones in younger women for the prevention of cardiovascular disease, KEEPS (Kronos Early Estrogen Prevention Study). According to Harman, 450 women, aged 45–55, will be studied for five years, beginning this summer: 150 will receive transdermal oestradiol and oral placebo, 150 will get conjugated equine oestrogen and a placebo skin patch, and 150 will receive a placebo tablet and skin patch. "Ideally, we should study 24,000 women for 10 years, but we don't have that kind of funding," he said. The trial will cost US \$12 million.

Approximately 5.6 million men in the USA now take testosterone to treat a range of age-related symptoms [...] in spite of evidence that testosterone replacement may fuel prostate cancer and atherosclerosis

Harman believes that HRT has benefits for women and that the WHI's failure to show protection against cardiovascular diseases can be blamed on the age of women tested (median age 63) and on the hormones used. "The WHI was based on the premise that if oestrogen is good earlier [in life], it's good later; we don't believe that. [...] Intervening for heart disease 10 years after menopause is simply too late. It takes 5–10 years after menopause for rates of heart attacks in women to rise, and by then, the damage is done and it can't be reversed," he said. Harman also noted that cardiovascular disease in older women occurs about five times as frequently as breast cancer and that there is a pressing

need to find a way to protect them even if it raises breast cancer risk in a small number of women. By using transdermal oestrogen, he believes that the carcinogenicity of oestrogen can be reduced or eliminated, because oral oestrogen is metabolized by the liver and results in extremely high concentrations in the blood. Harman also noted that oestrogen raises levels of endogenous pro-coagulants and lowers anticoagulants, which creates a higher risk for women after the age of 55–60.

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He also cited data from experiments with female monkeys that had their ovaries removed and were given a high-fat diet to induce atherosclerosis, which showed a reduction in the number of heart attacks in animals given HRT. But Stefanick disagrees that such an animal model is relevant to humans. "Women at menopause and even 10–15 years later are more similar to each other than they are to teenage monkeys who have had their ovaries removed [and are put on hormones]," she remarked. She doubts that testing 1,500 younger women with other types of hormone will yield data any different to the WHI study, which had included younger women who did not test better than the older women.

Another reason for the discouraging results in the WHI and UK trials may be the use of artificial progesterone, some researchers believe. "The real culprit in WHI was the synthetic progesterone used," according to C. Dominique Toran-Allerand, a professor in the Department of Anatomy and Cell Biology at Columbia University (New York, NY, USA). "Provera [methoxyprogesterone acetate (MPA), the synthetic progesterone in PremPro] is a promiscuous compound, binding to many other receptors, including some in the breast which can cause cell division and cause harm if one is at risk for cancer." Synthetic progestin is not a good substitute for

natural progesterone, she continued, because it also antagonizes the effect of oestrogen, whereas under normal physiological conditions, the natural forms of these hormones work synergistically.

Moreover, there is "ample literature showing that oestrogen and progesterone given at the onset of menopause have neurological benefits if given in a cyclical manner—for memory, mood disorders and depression," Toran-Allerand said, but if the treatment is started too late, cognitive deficits can no longer be corrected. Research on oestrogen's neuroprotective abilities applies mostly to younger women, echoed Roberta Diaz Brinton of the University of Southern California (Los Angeles, CA, USA). In 2002, Brinton showed how MPA negates the potential benefits of oestrogens on cognitive function and prevention of Alzheimer's disease (Nilsen & Brinton, 2002a), which further supports her earlier research, which showed that oestradiol and progesterone—but not MPA—can protect neurons (Nilsen & Brinton, 2002b). A more recent article (Nilsen & Brinton, 2003) investigated how and why natural progesterone and MPA have such different effects. Oestrogen exerts its neuroprotective effects by acting as a free-radical scavenger and regulating calcium levels in neurons, but it can do so only if another enzyme, extracellular receptor kinase (ERK), is activated. Brinton's work showed that only oestradiol and progesterone, but not MPA, activate nuclear ERK in hippocampal neurons; in fact, MPA blocks oestradiol-induced nuclear activation.

"Oestrogen is a 'Goldilocks' molecule."

"Oestrogen is a 'Goldilocks' molecule," explained Brinton. "It has to be given at a dose that is 'just right'—too much or too little has the same effect: none." Consequently, there is a narrow window of dose response for the hormone's beneficial effects on memory function and protection of neurons. In addition, oestrogen has a 'healthy-cell bias'—it confers a survival advantage to healthy neurons challenged with a neurotoxin, but not in patients whose supply of oestrogen has been attenuated for an extended duration. "In the past, women have been treated with oestrogen a year

after their last menstrual cycle; but during perimenopause, their brains are likely to be more responsive," Brinton said. Furthermore, women with a healthy uterus cannot take an oestrogen-only formulation because of the hormone's proliferative effects on the endometrium, the blood-rich mucous membrane that lines the inside of the uterus.

What scientists, such as Brinton, Harman and others, say is that the book on HRT is not closed—it has potential health benefits for women. However, more research is needed to determine what route of administration, oral or local, and which formulations for which patient groups are most effective to benefit the heart and brain while not damaging other organ systems. This may be difficult to show. Even if scientific evidence points to beneficial aspects of hormone treatment, these can only be determined in large-scale studies. After the huge controversy and public reaction to the WHI and Million Women Study debacles, it may be difficult to lure women into clinical trials again.

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