ideologically on the doorstep of classical Western Europe, making it particularly open to investment. This has further been capitalized on by independent Slovenia, which has a booming pharmaceuticals sector, albeit in generics produced by foreign companies.

However, this is small consolation to scientists like Vito Turk, Director of the Jozef Stefan Institute in Ljubljana, who thinks that in basic and applied research, it could do much better. In total, 26% of government funding goes to the life sciences, which Turk describes as "a misunderstanding of [their] impact in the whole of research", continuing "today, you need excellent basic research if you want to make any kind of progress in applied research." As elsewhere, infrastructural funds will be diverted to establishing centres of excellence. Furthermore, nepotism and lack of objective peer review—problems common to many accession countries—need to be replaced by scientific evaluation at an international level. But while that very feature of the ERC is welcomed by Turk—admittedly with some kind of allowance for inferior infrastructures and a historical lag—he is convinced that the answer to competitiveness is to invest first nationally, rather than into a large EU pot.

For those who play the game in worn out shoes, the opening up of the labour markets and increasing mobility in Europe bring the overwhelming temptation to join a better equipped team in the West. The brain drain from Eastern Europe has long been a thorn in the flesh of scientists who want to build up the system at home, and in biology it has been frighteningly high. As Zyllicz lamented, "When I was teaching biotechnology in Gdansk, almost 100% of my students left for the USA or Germany after graduation." Although greater freedom to leave the new EU states is accompanied by greater ease of reintegration upon return, sufficient incentive to return is currently lacking in many countries. And it may be wise if the rest of the EU puts up some of this money. After all, as Turk pointed out, it is not generally to Western Europe that the brains flee, but rather out of Europe altogether, to the USA.

Brain drain is not a problem everywhere. Metspalu reported that qualified people in Estonia do not leave: of the 50 students graduating in biotechnology

each year in Tartu, most stay in Estonia, he said. Dudits also noted "a lot of our good postdocs return" despite the fact that after a PhD all students in Hungary are encouraged to go abroad. In general he thinks that brain drain from the East has been overemphasized. So too does Paces from the Czech Republic, who commented, "It is less serious than we expected. Czechs are probably rather conservative and like to stay at home."

Brain drain or not, changing the rules of participation in EC grants for new EU member states is not an option in the opinion of most scientists in those countries. A two-tier system would, as Zyllicz put it, "be a disaster." In his view, if the EC wants a more unified situation, it needs to invest more money in the infrastructure rather than changing the criteria. He continued, "In the case of Greece and Portugal [setting different criteria] was a disaster; we should not repeat this mistake. We joined Europe not to have two Europes, but to have one Europe," that is a Europe that dispenses money for basic research on the basis of merit—the antithesis of the old Soviet-style academies.

Brain drain or not, changing the rules of participation in EC grants for new EU member states is not an option in the opinion of most scientists in those countries

The ERC is, therefore, understandably supported by the new EU states—even if some see themselves not getting a '*juste retour*'—because it will put their scientists into direct competition with the best in Europe. As Zyllicz remarked, "Even if for the first few years Polish scientists don't do very well, this is the only way to adjust the average level of science in these countries." This element of 'standard-raising' competition is seen by him and others as the most important element of the ERC. But Dudits, also very pro-ERC, is anxious that its funding should come from a common EU budget and not from already creaky national funds; indeed, if the latter happens, it will not just be Hungary that ends up paying more into the EU than it gets back.

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Hormone therapy for the ageing

Despite the negative results of recent trials, hormone replacement therapy retains enticing promises for the elderly

Last year, two large trials in the USA and the UK dealt major blows to hormone replacement therapy (HRT), which was being used by millions of women to ease the effects of the menopause. The US Women's Health Initiative (WHI) and the UK Million Women Study (MWS) both showed that HRT increases the risks of breast cancer, dementia and stroke and other cardiovascular diseases (Brower, 2003). Both the US National Institutes of Health (NIH) and the British Medical Research Council halted the trials even before completion and

recommended that all women should abandon taking oestrogen and progesterone to reduce menopausal symptoms, such as hot flashes, sleep disruption and vaginal atrophy. Earlier this year, the NIH also stopped the oestrogen-only arm of the WHI trial because of a greater incidence of stroke among its participants. "Hormone replacement therapy are the three most controversial words in clinical medicine today," commented Michelle Warren and Sari Halpert from Columbia University in New York, NY, USA (Warren & Halpert, 2004).

HRT for menopausal women, therefore, seems to be dead in the water, but the underlying problem of how to ease the effects of growing old—with all its social and medical implications—still looms large over societies with increasingly ageing populations. By 2030 the global population of people older than 65 years is expected to double—from 420 million at present to 973 million—with the largest increase taking place in developing countries (Nass & Thorner, 2004). In addition, improved environmental conditions are increasing life expectancy by 2.4 and 2.2 years every decade for women and men respectively, without any signs that this trend will slow down in the near future (Westendorp, 2004). As populations are growing older, the pressure to develop treatments to allow these people to live healthier lives is also rising. But as the HRT trials have shown, such treatments harbour substantive risks. Furthermore, it is not clear whether these treatments should be paid for by the community or by the patients themselves. Payment by the community will presumably stress many health-care systems and will risk provoking protests by the younger generations about the amount of resources devoted to the elderly, while the alternative carries an inevitable injustice as only the affluent could afford to pay for treatment.

Notwithstanding these concerns, anti-ageing research has received much attention in recent years. According to Ralf Nass and Michael O. Thorner from the University of Virginia's Department of Medicine (Charlottesville, VA, USA) two major trends are discernible: understanding the biological mechanisms of ageing to find potentially life-extending treatments, and improving the quality of life in old age by preventing or reversing the functional decline of different tissues (Nass & Thorner, 2004). Work on model organisms has already unravelled some of the molecular mechanisms and genetic factors regulating longevity and ageing, and researchers are increasingly pooling their efforts. Whatever the approach, the public seems to require a new focus "on research to promote healthy ageing, rather than simply treating the diseases of old age" (Abbott, 2004), thus reducing the number of years that older people spend diseased, disabled or frail and dependent. In addition,

"there's an economic incentive, as well as a humanitarian one, for trying to break the link between old age and ill health" (Abbott, 2004), as healthier people could work longer and thus generate the money needed to pay for their own care, not to mention the implications for retirement funds.

As populations are growing older, the pressure to develop treatments to allow these people to live healthier lives is also rising

In fact, for the individual who suffers from the effects of ageing, the appeal of HRT is still strong, not just for women—the effect of hormones in men is also increasingly being recognized. Together with other biological systems, the endocrine system slowly declines as men get older, resulting in a physiological decrease in the level of hormones such as testosterone, adrenal androgen precursors, thyroid hormones, human growth hormone (hGH), insulin-like growth factor 1, renin and angiotensin (Swerdlow & Wang, 2004). Their slow disappearance is often accompanied by the development of diabetes mellitus, osteoporosis, impaired cognition and obesity, and alterations in libido and erectile function and an increase in frailty. Hormone deficiencies—particularly in testosterone—may also go beyond the limits of physiological deterioration and mark the onset of a clinical condition known as male hypogonadism, which affects both young and old men. Evidence has shown that testosterone replacement therapy benefits younger hypogonadal men, producing positive effects on libido, mood, muscle mass, muscle strength, bone mineral density and haematocrit levels (Swerdlow & Wang, 2004), and the US Food and Drug Administration (FDA) has approved testosterone for this use. What is worrying health institutions and experts, however, is the increasing use of testosterone as an 'anti-ageing tonic' among middle-aged and older men, particularly in the USA, for which the results have not been adequately assessed. In addition, many fear that the treatment could result in a higher risk of prostate cancer, benign prostatic hyperplasia and cardiovascular disease.

Some are therefore calling for a male equivalent of the WHI: a long-term, double-blind trial with a large number of participants, to clarify the risks and benefits of the prolonged use of testosterone. But a recent analysis by the US Institute of Medicine of the National Academies (Washington, DC, USA) reached different conclusions, and recommended "short-term efficacy trials to determine if there are benefits of testosterone therapy in older men. If benefits are established, then long-term trials would be appropriate" (Liverman & Blazer, 2004). Initially, the trials should enrol a few hundred men aged 65 years and older with clinically low testosterone levels, and examine whether testosterone therapy is beneficial for their body fitness and quality of life.

"there's an economic incentive, as well as a humanitarian one, for trying to break the link between old age and ill health"

A new wave of studies and clinical trials is also surging in the troubled waters of HRT for post-menopausal women. After last year's backlash, a small troop of scientists refused to admit defeat, claiming that the WHI and MWS exaggerated the risks of HRT over its benefits. They hope to restore the reputation of HRT by running smaller, disease-focused studies to demonstrate that a carefully planned hormone regimen can prevent and/or treat ageing disorders in a specific set of women. Researchers who study the effects of oestrogen on the brain are also fighting their corner. The US National Institute of Aging (NIA) in Bethesda, MD, for example, now supports clinical studies to assess the preventive and therapeutic potential of oestrogen for Alzheimer's disease. One of these trials is now recruiting 160 post-menopausal women aged 55–90, to determine the effectiveness of HRT in improving memory. "Therapeutic use of hormones for peri- and post-menopausal women is in its infancy," stressed Judith Turgeon from the University of California at Davis (CA, USA). "Clearly, one compound/one size does not fit all, and this approach is necessarily coming to an end." She highlighted that hormone therapy formulations and regimens must be tailored to the woman's health status, genetic background and the length of time she has been oestrogen-deprived at the initiation of hormone supplementation.

The NIA is also sponsoring a trial to evaluate the efficacy and safety of three alternative approaches using phyto-oestrogens to treat hot flashes and night sweats in peri- and post-menopausal women. In the meantime, a growing number of women are turning to isoflavones and lignans—oestrogen-like compounds, which are naturally occurring in plants or available as dietary supplements—believing that they might mitigate menopause symptoms with fewer adverse effects. But both efficacy and safety data for these products, for which no licence is required, are virtually absent (Tarkan, 2004). “What are the long term effects of these preparations, taken on the assumption that being natural they are safe?” asked Klim McPherson from the Churchill Hospital in Oxford (UK) in the *British Medical Journal* (McPherson, 2004), “Will adequate research be done to ensure that we avoid another half century of uncontrolled experimentation on menopausal women?”

What is worrying health institutions and experts [...] is the increasing use of testosterone as an ‘anti-ageing tonic’ among middle-aged and old men...

Investigations are already under way to substantiate or disprove observational and anecdotal knowledge surrounding phyto-oestrogens, for example that soy isoflavones attenuate cognitive decline in healthy post-menopausal women and improve memory and higher order cognitive functions in young adults. For example, a recent study by Yvonne van der Schouw and colleagues at the University Medical Center of Utrecht, in the Netherlands, found no evidence that soy supplements containing isoflavones improve cognitive function, bone mineral density or plasma lipids in healthy post-menopausal women (Kreijkamp-Kaspers *et al*, 2004). “With respect to phyto-oestrogens, there is currently no firm basis for the rapid spread of their use”, said van der Schouw. “We need clinical trials with clinically relevant outcomes, such as heart attacks instead of cholesterol levels. Furthermore, the question of the population that is to benefit from phyto-oestrogens is also relevant.”

Testosterone and phyto-oestrogens are not the only hormones being embraced as clock-reversing agents; other substances, such as hGH and dehydroepiandrosterone (DHEA)—an androgen precursor—are also becoming more popular. Indeed, their therapeutic validity—in strictly controlled HRT regimens—in alleviating specific pathologic conditions is unquestionable. hGH is used to treat children with growth retardation and adults with hypopituitarism and severe growth hormone deficiency. DHEA replacement is clinically valuable for patients with adrenal insufficiency. But the problem arises when the same therapies are used in healthy elderly people, as alleged benefits have never been demonstrated and the risks remain unpredictable. A ‘pioneer’ in this field is the Californian physician Edmund Chein, who in 1994 founded the Palm Springs Life Extension Institute “to stop or possibly even reverse the deterioration of organs and cells.” Several hormone programmes are offered, some of which include hGH—Chein’s magic bullet. On the basis of an article in the *New England Journal of Medicine* by Daniel Rudman and colleagues (Rudman *et al*, 1990), Chein developed and patented a therapy combining hGH with other hormonal injections, which he claims has remarkable rebuilding effects on muscle, skin and bone mass. The treatment is not cheap—patients pay some US\$1,500 for an initial consultation and US\$1,200–1,500 a month for maintenance—and is not covered by any health insurance. Chein’s example has been contagious, and anti-ageing clinics offering hormone treatments are now flourishing in several countries. Another, mostly online, market is growing around over-the-counter hGH-enhancing dietary supplements. Furthermore, estimates exist that one-third of prescriptions for hGH in the USA are for indications for which it is not approved by the FDA (Vance, 2003). Both the NIH and NIA have released statements warning about the potential health risks of ‘off-label’ preparations, and even Chein has stated that buying these hormone supplements at local health-food stores could be dangerous.

“Hormone use is a classic example of a new ‘treatment’ becoming available without sufficient control and evidence”

Nevertheless, as the use of hormone therapies rapidly spreads, the question of who should pay if they are made accessible to everyone remains. Bioethicist Arthur Caplan from the University of Pennsylvania (Philadelphia, PA, USA) is very clear about this: “Hormone use is a classic example of a new ‘treatment’ becoming available without sufficient control and evidence”, he said. “Without more evidence, no government programme should pay for these ‘treatments’.” The fact that the rich may use them to pursue anti-ageing means that the rich will serve as the test subjects in a very much uncontrolled experiment. There may be an irony in the fact that the most well-off in society are going to act as guinea-pigs, but so it would seem.” Rudi Westendorp, an expert on ageing at the University of Leiden in the Netherlands, is more cautious and would like to see a better definition of ageing to separate the wheat from the chaff in anti-ageing therapies (Izaks & Westendorp, 2003). “When taking the view that ageing is better described as the occurrence of disease there is in my mind no reason why insurance companies or governments should not pay for these therapies, but only when proven beneficial,” he said. Westendorp also pointed out that, contrary to popular belief, only a small proportion of the increase in health-care expenditures is explained by demographic transition.

Although the issues of social equity and financial sustainability are important factors, the very root of the problem is the credibility of many of these therapies

Although the issues of social equity and financial sustainability are important factors, the very root of the problem is the credibility of many of these therapies. “Without mandatory clinical trials this whole area will stay in the shadiest parts of medicine and there is no reason to presume that it will not take its place alongside monkey gland injections and rhinoceros horn potions as one more strategy to prevent ageing that has no basis in reality,” said Caplan. “The whole hormone treatment fad is just that—a fad.” The same thoughts are shared by Westendorp. “My more personal opinion [...] is that the

'magic' of hormone supplementation in old age is grossly overstated," he said.

Whether hormone therapies will eventually become a part of the anti-ageing medical arsenal is not possible to say at this stage. The plethora of ongoing studies will surely provide new treatments to shield our weakening bodies; an armoury aided by a deeper knowledge of the biology and mechanisms of hormones (Turgeon *et al*, 2004). Predictably, with the tremendous amount of money at stake, some will try to sell negative results as not so negative, or will strive to prove the opposite. It therefore requires increasing effort to promote public understanding of these treatments, as well as the implications of anti-ageing research and the possible consequences, which will lead to truly informed choice by patients (Juengst *et al*, 2003). What is certain, however, is that the call of hormones will remain a tantalizing siren for many years to come.

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