blood cells (Chang, 2005). He has already produced a second generation of Hb-based oxygen carriers formed by linking polyhaemoglobin with the antioxidant enzymes superoxide dismutase and catalase. In animal tests, this combination prevented the ischaemia–reperfusion injuries caused by oxygen radicals that can be produced by reperfusion with an oxygen carrier alone (Chang, 2005). There are also "third generation and more complete red blood cell substitutes [in development] with longer circulation time in the form of haemoglobin lipid vesicles and… biodegradable polymeric membrane nanoartificial red blood cells with the same content as red blood cells," said Chang.

The main alternative to Hb-based solutions are PFCs, which are hydrocarbon-like substances with fluorine instead of hydrogen atoms. In the 1960s, these compounds were found to be capable of dissolving 50% or more of their own volume of O_2—about 100 times more than plasma—and large amounts of CO_2. Unlike Hb, gas molecules are not chemically bound to PFCs, but are absorbed and released by simple diffusion. An O_2-saturated PFC solution injected into the bloodstream could thus easily replace erythrocytes without the common side effects of Hb, but PFCs have other drawbacks. They are insoluble in water and must be emulsified before infusion, and they are rapidly removed from circulation and sequestered in the reticuloendothelial system, where they can cause complications. Furthermore, the oxygen-carrying capacity of PFCs depends on the oxygen partial pressure to which the solution is exposed, which also limits their use to situations with supplemental oxygen and controlled ventilation.

> Substituting blood is a complex process and even the latest products may need further refinement…

Despite these hurdles, the only oxygen carrier approved so far by the FDA is a PFC emulsion named Fluosol®, developed by Green Cross Corporation in Osaka, Japan. Until the FDA rescinded its approval in 1993, surgeons used it for enhancing oxygenation of the heart during coronary artery balloon angioplasty. Some believe that the various benefits of PFCs, such as their easy and cheap production and prolonged storage capacity, make them worth exploring further. Alliance Pharmaceutical Corporation, a biomedical company based in San Diego (CA, USA), is now developing a new PFC emulsion, Oxygent™, designed to overcome the problems that eventually caused the FDA to pull Fluosol from the market. Oxygent is intended to reduce the need for donor blood during surgery; it has already completed a phase III clinical study, the results of which showed a significant reduction in the need for transfusions compared with controls.

Whether the Hb- or PFC-based products under trial are eventually approved for clinical or battlefield use remains to be seen. Substituting blood is a complex process and even the latest products may need further refinement to overcome various side effects. "Each new generation of red blood cell substitutes is increasingly more complicated and expensive," said Chang about his research on artificial erythrocytes, but his comment applies to other approaches. Nevertheless, given the great demand for artificial blood substitutes and the increasing interest from academic researchers and biomedical companies, he and others are positive that future products will be safe enough for widespread use in surgical theatres and in the field, to rescue people after massive trauma.

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Andrea Rinaldi

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A nutraceutical a day may keep the doctor away

Consumers are turning increasingly to food supplements to improve well-being when pharmaceuticals fail

The atmosphere at the seminar on 'Treating and Preventing Chronic Illness with Natural Asian Therapies' was part medical conference, part pilgrimage to Lourdes. About 250 elderly and health-conscious adults crowded into the conference room of an upscale Manhattan hotel in May, listened eagerly, and asked urgent questions after researchers from Columbia University's Center for Holistic

Urology (New York, NY, USA) described their studies with two herbal compounds, AHCC® (active hexose correlated compound) and GCP® (genistein combined polysaccharide). AHCC is a mushroom extract that increases levels of natural killer cells, T cells, macrophages and interleukin-12, and GCP has shown anti-cancer, anti-inflammatory and anti-angiogenesis activity in early bladder cancer and possibly in prostate cancer.

> …market reports observe that the interest in nutraceuticals is growing rapidly worldwide

The seminar was just one of many that together indicate the growing interest from consumers in herbal supplements, nutritional supplements and functional foods—'nutraceuticals'. It also illustrates the industry's interest in this rapidly growing market, as the research on AHCC and GCP, the seminar and the physicians' travel expenses were all paid for by the producer of the compounds, Amino Up Chemical Co. (Sapporo, Japan). However, although many nutraceuticals clearly affect bodily functions, they are not regulated and tested as tightly as pharmaceutical drugs. As consumers in the USA, Japan and Europe rely increasingly on nutraceuticals to improve their health, regulators and lawmakers are reacting to develop appropriate regulations, given that most health claims accompanying these products are supported by little or no research.

The term 'nutraceutical' was coined in 1989 by Stephen DeFelice, a physician and founder of the Foundation for Innovation in Medicine (FIM; Cranford, NJ, USA), to describe "a food or part of a food that provides medical or health benefits, including the prevention and/or treatment of disease." Nutraceuticals now include a wide range of products, such as echinacea, St John's wort, oils from fish and flax seed, glucosamine and chondroitin, calcium-fortified juices and plant-sterol-containing butter substitutes. Iceland's largest dairy company recently introduced the world's first milk to lower high blood pressure, Finns can buy a similar product with bioactive peptides as active ingredients, and probiotic drinks to strengthen the immune system are sold all over Europe.

"The consumption of food supplements in the USA, Europe and Japan is roughly a US$170 billion industry," according to Peter Baskauskas, national sales manager of Quality of Life Labs (Purchase, NY, USA). "The US accounts for about US$75 billion of that." This figure is higher than that cited by the National Nutritional Foods Association (NNFA; Newport Beach, CA, USA), which stated that functional food and supplement sales were US$41.7 billion in 2003. Regardless of the exact figures, market reports observe that the interest in nutraceuticals is growing rapidly worldwide. In the USA alone, about 6 out of 10 consumers take some type of food supplement, and 30%–40% take herbal supplements. Whereas about a decade ago, most people took either drugs or supplements, there is now an increasing crossover between the factions, and even some physicians are recommending natural products before prescribing pharmaceuticals. Driving this boom is consumer disappointment with Western medicine and a strong interest in improving health and well-being. "The trend also reflects the growth of a new paradigm of 'self-care'," according to Fergus Clydesdale, head of the Department of Food Science at the University of Massachusetts (Amherst, MA, USA).

> Driving this boom is consumer disappointment with Western medicine and a strong interest in improving health and well-being

A 2001 poll by Harris Interactive (Rochester, NY, USA) revealed that 72% of those surveyed in the USA take supplements to feel better, 67% to prevent illness, 50% to live longer, 37% to build muscle and strength, 12% for weight management and 33% on the advice of a physician. Significantly, 53% said that nutraceuticals offer benefits not matched by conventional drugs, and 56% said they offered benefits comparable with drugs but with fewer side effects. Remarkably, 95% were satisfied with supplements (Dietary Supplement Education Alliance, 2001).

> …although many nutraceuticals clearly affect bodily functions, they are not regulated and tested as tightly as pharmaceutical drugs

Given the enormous consumer interest in nutraceuticals, it is not surprising that so many players are getting into the game: food conglomerates, health food companies, biotechnology and pharmaceutical giants, and even academic researchers. Bruce Ames, Professor of Molecular and Cell Biology at the University of California, Berkeley (USA) became a believer in nutraceuticals after showing that acetyl-L-carnitine and α-lipoic acid drastically halted and even reversed mitochondrial ageing processes in animal studies (Liu *et al*, 2002a,b). Ames and a colleague founded a company, Juvenon (Orinda, CA, USA), to produce and sell the formula as a dietary anti-ageing supplement and are now conducting clinical trials to assess its effects on cognitive performance.

However, not all products are backed up by such rigorous science as Ames's anti-ageing compounds or Amino Up's AHCC and GCP, which have undergone animal and clinical testing. Although new studies appear almost daily about the anti-cancer effects of green tea, the cholesterol-lowering properties of fish oil or the cardiovascular benefits of fibre, reliable knowledge on the effects of nutraceuticals remains limited. "I estimate that only one percent of products now on the market have been tested in clinical trials," said DeFelice. Adding to the confusion are studies that demonstrate—or debunk—the health benefits of nutraceuticals. For instance, recent studies indicated that vitamin E does not prevent, but could actually increase, the risk of coronary heart disease; echinacea does not prevent the common cold; and St John's wort may not treat depression any better than a placebo. Another recently reported trial of vitamin E supplements showed that they do not delay the onset of Alzheimer's disease in patients with mild memory changes (Petersen *et al*, 2005), while an epidemiological study by Canadian researchers indicated that vitamin E in food may be protective against Parkinson's disease (Etminan *et al*, 2005). Further problems include the fact that interactions between pharmaceutical drugs and nutraceuticals have rarely been documented, and that about half the people who take some type of nutraceutical do not tell their physician.

Moreover, because of a dearth of hard scientific evidence from animal and human studies, consumers are left mostly

to themselves to assess the deluge of health claims that adorn most nutraceuticals' packaging. Many manufacturers are unwilling to pay for research and clinical trials to test nutraceuticals, because they have a lower profit margin than drugs and can usually be marketed without the approval of the agencies that regulate therapeutic drugs. Some critics of this lenient regulatory situation are therefore demanding a more stringent approval process, whereas others want to keep the status quo or even liberalize what health claims can be made for dietary supplements.

Although regulations governing nutraceuticals vary from country to country, they are generally less stringent than the regulations applied to pharmaceutical drugs. However, with the exception of the USA, most countries treat herbal supplements as drugs and prohibit health claims that are not backed up by clinical research—Canadian law, for instance, recognizes that supplements are a form of medicine and they are judged on the basis of scientific evidence. In Japan, legislation distinguishes between only two categories: food and pharmaceutical products, according to Hajime Fujii, Chief of Research and Development at Amino Up. For non-pharmaceuticals, such as food, Japanese law prohibits the explicit statement and marketing of health benefits. "However, third-party statements from medical doctors and researchers are not only allowed, but highly respected by consumers," Fujii said.

> …consumers are left mostly to themselves to assess the deluge of health claims that adorn most nutraceuticals' packaging

In the European Union (EU), regulations are now in a state of flux. In 2002, the European Parliament and Council approved a directive to harmonize rules for food-supplement labelling, and introduced specific rules on vitamins and minerals (EC, 2002). On 26 May 2005, the EU was set to decide on the first set of laws to regulate health benefit claims for foods. "The regulatory environment is ever-changing worldwide," observed Baskauskas. "Europe has become stricter in allowing nutritional supplements, and Canada has adopted the same view […] This really has developed into quite a challenge for companies like ours in this industry."

By contrast, the 1992 US Dietary Supplement Health Education Act (DSHEA) allows manufacturers to market nutraceuticals by making claims about the ability of a compound to affect the 'structure and/or function' of the body. However, DSHEA allows only health, not medical, claims for nutraceuticals—a fine line that critics maintain is not only meaningless, but also misleading. "Because DSHEA makes a [false] distinction between health and medical claims—when there is really no difference—it forces manufacturers to lie, and not make medical claims," said DeFelice.

Some consumer advocacy groups are therefore pushing for more oversight and stringent regulations, in the hope that this will force companies to test their products rigorously. DeFelice also advocates more clinical trials to prove efficacy. Similarly, consumer watchdog groups, such as Public Citizen (PC; Washington, DC, USA), favour tougher oversight to increase safety. PC head Sidney Wolfe has been a particularly outspoken critic of the US Food and Drug Administration (FDA) for leaving too many untested products on the market, and had blasted the agency for allowing ephedra to remain on the market in spite of 140 cases of adverse effects reported by 1999, including heart attacks, arrhythmias, strokes and death (Wolfe, 2003).

The example of ephedra illustrates some of the tensions between consumer watchdog advocates and their opponents—libertarians concerned with the autonomy of consumers and nutraceutical makers. The stimulant was used widely in supplements for allergies, weight loss and sports performance until 2004, when the FDA finally banned it after numerous deaths. However, after an ephedra supplement manufacturer filed a lawsuit, a Utah district court reversed the ban in April 2005, arguing that no proof had been given to show that the herb is unsafe at all doses. As such, the ban was struck down on doses of 10 mg and less. It is no coincidence that the ruling came from Utah; the state is home to many nutraceutical manufacturers, and Utah's Republican Senator Orrin Hatch has long been a vocal supporter of nutraceuticals.

"The problems with ephedra sparked an interest [among consumer advocates] in revisiting the Dietary Supplement Health Education Act [to make it stricter]" said Tracy Taylor, Vice President of Public Affairs and Communications at the NNFA. In the meantime, reacting to industry pressure, the FDA stated in 2002 that it would consider allowing "qualified health claims" for nutraceuticals and would evaluate those by a 'weight of scientific evidence' standard, which is less stringent than the previous 'significant scientific agreement' standard. A new bill, the Dietary Supplement Access and Awareness Act, introduced a few years ago, would place nutraceuticals under stricter oversight if passed. Taylor said that her group was now less worried that it would be passed.

Substances that have hormonal action, such as DHEA and androstenedione, are further muddying the waters; although they have clear drug-like actions, they are still regulated as nutraceuticals in the USA. To draw a distinction, the US Anabolic Steroid Control Act, sponsored by Senator Hatch and supported by numerous nutraceutical trade groups, was passed in 2004. It obliges manufacturers to list steroid hormones and their precursors on product packaging—however, they are still marketed as nutraceuticals and are regulated as foods despite drug-like actions.

EXAMPLES OF HEALTH/DISEASE CLAIMS

Permissible structure/function claims
- Helps support cartilage and joint function
- Helps to maintain cholesterol levels that are already within the normal range
- Maintains healthy lung function
- Improves absentmindedness
- Relieves tension and stress

Impermissible claims
- Prevents bone fragility in post-menopausal women
- Maintains normal bone density in post-menopausal women
- Lowers cholesterol
- Inhibits platelet aggregation
- Maintains healthy lungs in smokers
- Prevents an irregular heartbeat
- Relieves alcohol intoxication
- Promotes general well-being during the cold and flu season
- Maintains a healthy blood sugar level when taking insulin

(Information taken from IFT, 2005.)

Table 1 | Nutraceuticals tested or being tested

Nutraceutical	Disease/Condition	Tested	Being tested
Soy protein (genistein)	Coronary heart disease (reduces low-density lipoproteins)	Yes	–
Stanol/sterol esters	Coronary heart disease (reduces low-density lipoproteins)	Yes	–
Omega-3 oil	Coronary heart disease	Yes	–
β-glucans	Cardiovascular disease	–	Yes
Cranberry	Urinary tract infections	Yes	–
Hoodia	Weight reduction (acts on hypothalamus)	–	Yes
Soy isoflavones	Breast, prostate and bone cancer	Yes	–
Phytoestrogens	Cognition in post-menopausal women	Yes	–
Black cohosh	Menopausal hot flashes (serotonin modulation)	–	Yes
Phytoestrogens	Bone metabolism	–	Yes
Chinese mushrooms	Prostate and bladder cancer	Yes	–
Red clover	Hormonal actions	Yes	–
Black haw (*Virburnum prunifolium*)	Premenstrual tension	–	Yes
Chasteberry (vitex)	Menstrual disorders	–	Yes
Polyphenols	Cancer	–	Yes
Isothiocyanates	Cancer	–	Yes
Lycopene	Cancer	–	Yes
Green tea	Cancer	–	Yes
Lutein	Macular degeneration	–	Yes

Perhaps it would be more informative to carry out studies on how nutrients affect molecular processes in the body and on the variable effects of dietary components on each individual, according to an expert report by the Institute of Food Technologists (IFT; Chicago, IL, USA; IFT, 2005). It cites the three disciplines of nutrigenomics, proteomics and metabolomics, and the integration of genomics and nutrition, for understanding how diet affects gene expression and health. But to make true health claims, the challenges facing nutrigenomics are similar to those encountered in drug development, according to the IFT report. Consequently, the authors make recommendations about permissible health claims (see sidebar). Funding for such studies exists, but remains relatively small. The National Institutes of Health (Bethesda, MD, USA) founded the National Center for Complementary and Alternative Medicine (NCAAM; http://nccam.nih.gov) in 1992,

But to make true health claims, the challenges facing nutrigenomics are similar to those encountered in drug development…

which is now partnered with a growing number of universities to test the biological activity of nutraceuticals.

With a budget of US$123 million in 2005—which includes studies on non-nutriceutical treatments such as acupuncture—the current priorities of NCAAM are arthritis, cardiovascular disease, digestive disorders, infectious disease, mental health and neurological disorders. NCAAM-supported research includes hormone therapy alternatives for women's health: black cohosh and red clover for menopausal hot flashes and phytoestrogens for cognition improvement (Table 1). It is also investigating dietary soy and tamoxifen interactions, and the effects of Chinese herbs on transcription and cell proliferation in oestrogen pathways.

The list of nutraceuticals being studied is changing continually and reflects ongoing research, market developments and consumer interest. For instance, NCAAM noted that in 2002, one-fifth of Americans used natural products, such as echinacea, ginseng, ginkgo biloba, St John's wort and fish oils, in descending order of prevalence. But today, consumption of fish oils is up, while ginkgo and echinacea are down. Similar to the use of pharmaceuticals, the consumption of nutraceuticals has shifted during the past few years, in response to studies that show efficacy or a lack thereof. Until nutraceuticals are more routinely put through rigorous testing, and yield hard scientific data, it will be difficult to determine whether they work any better than placebos or the water of Lourdes.

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Vicki Brower

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