

Although the UDBHR technically has no legal authority, it is not unusual for such statements to become incorporated in national legislation and court rulings

to Los Angeles has priority over the interests of society to protect itself from an ensuing epidemic that could potentially kill millions of people. That's ludicrous." He expects that policy-makers in the developed world will ignore the UDBHR, but contends that problems could emerge in the developing world.

Serra, however, does not see any major roadblocks for clinical research put forward by Article 4. "Declarations cannot exhaustively cover all possibilities," she said. And Article 27 foresees that domestic laws can overrule the Declaration's principles in the interest of public health or the protection of rights and freedoms, ten Have pointed out.

Overall, however, ten Have believes that the UDBHR is "a helpful instrument to call attention to bioethics". Advocates of bioethics in underdeveloped countries can push for change, he said, pointing out that many of their governments have already endorsed the Declaration. According to Serra, many critics are overlooking the potential good that could come from the Declaration: "The UDBHR has the stature of a UNESCO document, a fact that, by itself, gives weight, importance and respect. Despite a few shortcomings, the UDBHR will help states to establish guidelines, and help people to reflect about ethical values. This shall contribute to a better world."

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Mind–body research moves towards the mainstream

Mounting evidence for the role of the mind in disease and healing is leading to a greater acceptance of mind–body medicine

The commonsense notion that 'too much stress makes you sick' might hold more than a grain of truth. The second of two large-scale epidemiological and medical studies among civil servants in the UK, known as the Whitehall studies, found that workers in low-level jobs, in which they have high stress and little autonomy, have more than twice the risk of developing metabolic syndrome—a precursor of heart disease and diabetes—compared with employees in higher-level jobs (Chandola *et al*, 2006). The first Whitehall study showed that people from this group are also more inclined to die prematurely than colleagues who do less menial, higher-level work. In these studies, stress is defined as a high level of demand, a low level of control and little support from co-workers or supervisors. By measuring heart rate, and cortisol and adrenaline levels, researchers also found that stress affects the autonomic nervous system and neuroendocrine function (Chandola *et al*, 2006; Bjorntorp, 1991; Brunner *et al*, 2002). Other recent research showed that acute and chronic psychological stress, related to low socio-economic status, can increase the risk of heart attack by increasing circulating levels of platelet–leukocyte aggregates (Brydon *et al*, 2006). A study from the University of Utah (Salt Lake City, UT, USA), first presented at the American Psychosomatic Society meeting in March 2006, showed that hardening of the arteries is more frequent in wives when they and their husbands express hostility during marital disagreements, and more common in husbands when they or their wives act in a controlling way (Smith *et al*, 2006).

Although the understanding that emotions affect physical health dates as far back as the second-century physician Galen and the medieval physician and philosopher Moses Maimonides, modern medicine has largely continued to treat the mind and body as two separate entities. In the past 30 years, however, research into the link between health and emotions, behaviour, social and

economic status and personality has moved both research and treatment from the fringe of biomedical science into the mainstream. "According to the mind–body or biopsychosocial paradigm, which supercedes the older biomedical model, there is no real division between mind and body because of networks of communication that exist between the brain and neurological, endocrine and immune systems," said Oakley Ray, Professor Emeritus of Psychology, Psychiatry and Pharmacology at Vanderbilt University (Nashville, TN, USA).

The potential of stress reduction and social support as a therapeutic intervention became evident in the late 1980s during a study of women with breast cancer. David Spiegel, Director of the Psychosocial Research Laboratory at Stanford University (CA, USA), wanted to determine whether women with metastatic breast cancer who participated in supportive–expressive group therapy had better quality of life and symptom control than those who received only medical treatment. To his and others' surprise, not only did the women have better quality of life and less pain, but they also lived significantly longer (Spiegel *et al*, 1989).

These unexpected findings triggered a large body of research into mind–body interventions—such as group therapy, stress-reduction techniques and cognitive-behavioural therapy (CBT)—and whether they can affect survival and pain in cancer, AIDS and bone-marrow transplant patients, with findings split between positive and negative for life expectancy (Kissane *et al*, 2004; Goodwin *et al*, 2001). A main focus of research is the relationship between stress and cardiovascular disease, asthma,

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inflammatory diseases, autoimmune diseases and cancer, and whether stress reduction can extend patients' lives. One recent study, for example, found that CBT could help to reduce viral load in HIV-positive men treated with highly active antiretroviral therapy. Researchers attributed the improvement to changes in depressed mood (Antoni *et al*, 2006). Depression itself is under study for possible links to a range of inflammatory diseases; several studies show it to be an emerging risk factor for heart disease (Sundquist *et al*, 2005; Nemeroff *et al*, 1998).

An example of how far mind-body medicine has come over the past three decades is the success story of Dean Ornish, Clinical Professor of Medicine at the University of California, San Francisco (CA, USA), and founder, President, and Director of the Preventive Medicine Research Institute (Sausalito, CA, USA). When he claimed in the early 1980s that heart disease could be prevented and even reversed with 'lifestyle changes'—a combination of a very low-fat vegetarian diet, meditation or yoga, moderate exercise, stress management and social support—he was not treated seriously by mainstream medicine until studies confirmed its efficacy (Ornish *et al*, 1983; Gould *et al*, 1992; Ornish, 1998). Today, Ornish's programme has been adopted in many mainstream cardiovascular clinics throughout the USA, and he continues to research whether his programme can help prevent heart disease in patients with type 2 diabetes, as well as halt the progression of prostate cancer (Ornish *et al*, 2005).

An increasing number of US medical schools and centres now have departments devoted to mind-body research and some also to mind-body treatment, including Harvard University (Cambridge, MA), Columbia University (New York, NY), University of California, Los Angeles, and the University of Pittsburgh (PA). This now-interdisciplinary research field, which also includes behavioural medicine, is often called psychoneuroimmunology or psychoneuroendoneuroimmunology, and "incorporates ideas, belief systems, hopes, and desires as well as biochemistry, physiology, and anatomy," according to Ray (2004).

Several factors have driven this steady growth: most prominent is patients' increasing interest in self-care, wellness and alternative medicine, and their concomitant dissatisfaction with the success of allopathic medicine in preventing and treating chronic



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illnesses. The consumer demand for and use of complementary and alternative medicine has also prompted the US government to become involved. In 1992, under pressure from consumers and with the help of Ohio Congressman Tom Harkin, an alternative medicine enthusiast, Congress mandated the National Institutes of Health (NIH; Bethesda, MD, USA) to open an Office of Alternative Medicine (OAM) and gave it a US\$2 million budget (Young, 1998). "Not everyone at NIH was happy about this," commented Theodore Brown, historian of medicine at the University of Rochester (NY, USA). But consumer demand was enthusiastic: when OAM was founded, more than one-third of Americans said that they used relaxation techniques and imagery, biofeedback and hypnosis, and more than

50% used prayer as a complementary or alternative therapy (Eisenberg *et al*, 1993).

Since 1992, government funding has increased markedly. In 2005, the NIH's National Center for Complementary and Alternative Medicine (NCCAM; Bethesda, MD) funded more than 1,200 projects at about 260 institutions. Since 2000, its efforts have focused on understanding the mechanisms of action of various mind-body therapies, including the placebo effect. In its new five-year strategic plan, Director Stephen Straus designated additional funding for mind-body research into a range of diseases, including an ongoing clinical trial that is examining the use of meditation for weight loss, health and well-being enhancement in obese men and women. Overall, NCCAM's 2006 budget is US\$122.7 million, with

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about US\$16 million designated for research in mind–body medicine.

Mind–body research in the USA also receives significant money from private foundations: the Fetzer Institute (Kalamazoo, MI, USA) has spent more than US\$2 million since 2000; the MacArthur Foundation (Chicago, IL, USA), which invested US\$10 million between 1989 and 1998 in its Network on Mind–Body Interactions; and the John Templeton Foundation (West Conshohocken, PA, USA), which funds several programmes on spirituality, health and medicine. Furthermore, “a growing number of medical schools are including mind–body medicine in their curricula, and a lot of progress has been made in incorporating mind–body medicine into medical schools’ curricula, but we’ve still got a long way to go,” said James Gordon, Clinical Professor at Georgetown University (Washington, DC, USA), and founder and Director of the Center for Mind–Body Medicine.

Gordon recalled the days when the acceptance of mind–body research and medicine was less widespread. Trained as a psychiatrist, he became interested in the 1970s in what was then called psychosomatic medicine, and spent a decade at the National Institute of Mental Health (NIMH; Bethesda, MD, USA) to look for scientific evidence for mind–body medicine techniques. “While there was a feeling that mind–body interventions might be important, there was also anxiety that they might come to overshadow NIMH priorities of psychotherapy and psychopharmacology at the time,” Gordon observed. Owing to what he called institutional ‘ambivalence’, early studies were published privately rather than by the NIH.

Indeed, most scientists who became interested in this field said their efforts to investigate aspects of the mind–body connection were met with skepticism and even derision from the scientific mainstream. Esther Sternberg, a rheumatologist and now a Senior Investigator in Neuroscience at the NIH, had the same experience when she arrived at the NIH in 1980 and studied

the strange case of a man who developed severe scleroderma—an autoimmune disease—after taking an experimental epilepsy drug, which raised serotonin levels. “I wanted to and did pursue the connection between the brain and the immune system in the 1980s with many experiments, but I was told not to, that it would ruin my career,” Sternberg said. “To be taken seriously I followed the typical scientific route; I didn’t talk about emotions and beliefs, but instead tried to connect findings in immunology to neuroscience, and focused on what neuropeptides change the brain.” Discussing how emotions might have an impact on the body was taboo, she said.

In the late 1960s, Herbert Benson, now Clinical Professor of Medicine at Harvard University, coined the phrase ‘relaxation response’ to describe physiological changes that occur with meditation. A practicing cardiologist, he observed that many of his patients had high blood pressure at office visits. “On follow-up visits, I found that I had overmedicated them, and realized they were experiencing a temporary spike in blood pressure from anxiety—what we came to call ‘white coat hypertension’,” Benson explained. Intrigued by this observation, he conducted experiments to induce stress and relaxation responses in students. Strangely enough, this was in the same room at Harvard, in which, 60 years before, physiologist and neurologist Walter Cannon had uncovered a direct relationship between stress and neuroendocrine responses in animals, the ‘fight or flight’ response. “I found that the relaxation response was a physiological package, like the ‘fight or flight’ response,” Benson said. He was asked by practitioners of transcendental meditation to study their meditative states. “I had to bring them round late at night, and had to keep my practice separate from my research,” said Benson, so that his colleagues did not see his experiments, and he found the same response in the mediators as the relaxation response.

Benson noted that public acceptance of the mind–body concept came many years before science acknowledged it: “I was *persona non grata* for a long time and was reprimanded heartily when I published my popular book [on the relaxation response] in 1975.” But in 1994, the work had finally progressed far enough for Benson to found the Mind/Body Medical Institute at Harvard University. He explained that mind–body medicine provides one aspect—self-care—

of a three-legged model of medicine, which also includes pharmacology and surgery. “The average doctor does not prescribe meditation, breathing exercises or yoga, and this needs to change,” he said. NCCAM is doing its part: in February 2006, it announced a new round of fellowships to train physicians in complementary medicine techniques.

Also helping mind–body research are improved methods to visualize communication between the central nervous system, and the immune and endocrine systems, said Sternberg. “An obstacle to acceptance in the 1980s was that researchers lacked the tools, such as recombinant cytokines, to understand the connection without the possibility of contamination,” she added. Without recombinant proteins, it was difficult to show incontrovertibly that immune molecules could change the brain and vice versa. “By the mid-1990s the field had accumulated a critical mass of papers, and it started becoming acceptable to associate with psychologists... By then, enough good research had hit the radar screen, so that even skeptics began to take note,” Sternberg said. “From where I sit, there’s been a sea change in acceptance of this field over the past four years.”

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One interdisciplinary team, which has contributed much to understanding how stress affects the immune system, is immunologist Ronald Glaser and psychologist Janice Kiecolt-Glaser from Ohio State University (Columbus, OH, USA). “When we began in 1982, there was not a lot of human data on how stress changes the immune system,” said Glaser, who, while studying Epstein–Barr virus, observed that stress seemed to affect its latency. Combining forces, the team first studied how stress in medical students makes them susceptible to infection, and later, how short-term stress negatively affects wound healing by disrupting the production of pro-inflammatory cytokines (Kiecolt-Glaser *et al*, 1995). More recently, they showed that stress increases the pro-inflammatory response in caretakers of Alzheimers’ patients (Kiecolt-Glaser *et al*, 2003). “An increase of pro-inflammatory cytokines with ageing is normal, but these chronically stressed caretakers had

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a six-fold increase in these cytokines over the controls," said Glaser.

The research of Bruce McEwen, head of the neuroendocrinology lab at Rockefeller University (New York, NY, USA) has also shown that stress hormones have dual effects on the brain—protective in the short term, but damaging in the long term by impairing nerve cells in certain areas of the brain. He developed the concept of allostatic load—damaging changes that can accumulate in response to stress because the overexposure to neural, endocrine and immune stress mediators has adverse effects on various organ systems.

Chronic activation of stress responses by the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary axis leads to a permanent overproduction of glucocorticoid hormones and catecholamines (adrenaline and noradrenaline). Immune modulation by pituitary and adrenal hormones occurs through two pathways: directly by binding hormones to receptors, or indirectly by inducing the deregulation of cytokines, such as tumour necrosis factor (TNF) and interferon- γ (Glaser & Kiecolt-Glaser, 2005).

One example of a direct modulation of the immune system is the fact that various immune cells are sensitive to glucocorticoid hormones through cell surface receptors. The same receptors bind cortisol, which has a role in wound healing. Glucocorticoid hormones also interfere with NF- κ B, which regulates cytokine production. Adrenergic receptors induce transcription of genes that encode for cytokines; these changes in gene activity can lead to a deregulation of immune functions (Padgett & Glaser, 2003). Other studies have shown that depression and anxiety increase the production of the cytokines IL-6 and TNF- α , which have a pro-inflammatory effect that has been linked to cardiovascular disease, arthritis, type 2 diabetes, osteoporosis and some cancers (Raison *et al*, 2006). Despite such accumulating evidence, medicine has not moved much beyond the biomedical model, according to David Eisenberg, Director of the Osher Institute at Harvard Medical School. He attributes this to the fact that practitioners

are not exposed to the evidence supporting the biopsychosocial model.

Despite considerable evidence of efficacy in treating coronary artery disease, headaches, insomnia, incontinence, chronic lower-back pain and cancer symptoms, in their recent review of the mind-body medical literature Eisenberg and co-authors stated that, "Additional research is required to clarify the relative efficacy of different mind-body therapies, factors (such as specific patient characteristics) that might predict more or less successful outcomes, and mechanisms of action" (Astin *et al*, 2003). The Institute of Medicine (Washington, DC, USA) has now urged NCCAM to continue an evidence-based approach to verify NCCAM's claims (Institute of Medicine, 2005). And the growth in the number of dedicated institutes and centres—such as NCCAM, the Cousins Center for Psychoneuroimmunology at UCLA, Harvard's Osher Institute, and Stanford's Psychosocial Treatment Laboratory—is testament to a growing body of evidence-based research and studies. All of this might help mind-body medicine to escape its negative association with alternative medicine, Benson hopes: "We're not 'alternative' because we're empirically based."

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