

## keynote article

# The many faces of stress

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Ecclesiastes tells us that 'there is nothing new under the sun' and it is certainly true that the notion that the mind and body may be connected has been around for a long time. But a chance discovery in the 1970's completely revolutionised our understanding of this area. At that time, Robert Ader and Nicholas Cohen were engaged in behavioural conditioning research (Ader & Cohen, 1975). They were examining whether the pairing of saccharine (their conditioned stimulus) with a substance known to produce nausea and vomiting: cyclophosphamide (the unconditioned stimulus) would result in a conditioned taste aversion response i.e., that the animals would avoid the saccharine even when presented on its own because they had been conditioned to associate it with the unpleasant side effects of cyclophosphamide. However, in their early trials they noticed an unexpected effect of their experimental manipulation. In addition to the expected taste aversion response, they found a significantly higher mortality rate in the animals exposed to the unpaired saccharine. This finding was both concerning and perplexing, until they realised that their unconditioned stimulus, cyclophosphamide, had immunosuppressant properties. This led them to speculate that, rather than simply conditioning a taste aversion response, they may have inadvertently conditioned their animals to suppress their immune systems.

This seemingly absurd proposal was tested by conducting a further conditioning experiment in which they measured antibody levels in order to

capture the effects of the conditioning paradigm on the immune system. Ader and Cohen reported that, even after a single exposure to the saccharine (their conditioned stimulus) these animals displayed evidence of significant immune suppression. Suddenly, behaviourally conditioned immune suppression was a reality, and tangible proof that the mind and body are connected was presented to the scientific world.

Ader and Cohen's findings generated, in equal measure, both enthusiasm and scepticism, but the net effect was a new area of enquiry which, today, is variously referred to as psychoneuroendocrinology, psychoneuroimmunology, etc. Whatever nomenclature is used, the area is concerned with the exquisite and dynamic interplay between the mind and body; it is inherently multidisciplinary in nature and has, in my view, psychology at its heart.

In the years that followed, replications of Ader and Cohen's work were conducted and investigators began to broaden their examination of the psychological parameters that appeared to affect our biology. This included over a decade of high quality research which demonstrated time and again that the experience of psychological stress, both acute and chronic appeared to modulate the activity of the immune system. Much of this early research was, however, conducted *in vitro*. So the clinical relevance of these observations for health was unknown. This all changed with the groundbreaking work of Sheldon Cohen and colleagues (Cohen, Tyrell & Smith, 1991). The authors assessed stress in a large group of healthy

volunteers and then exposed their participants to respiratory viruses. This was followed by a period when the participants were quarantined and monitored for the development of respiratory symptoms and clinical colds. Cohen et al. reported that stress at study entry was significantly and positively associated with both respiratory symptoms and clinical colds, such that the greater the level of stress at baseline, the greater the incidence of both respiratory symptoms and clinical colds over the follow-up period. Psychological stress, it would appear, could significantly increase our vulnerability to infectious disease.

So stress might increase disease risk in young healthy people. But does that really matter? The young and healthy can, and do, recover quickly from minor illnesses such as the common cold. What happens in populations who are more vulnerable to ill health and for whom even minor respiratory illnesses can be fatal, such as in the elderly? This issue was examined by ourselves and colleagues in the US a few years later (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey & Sheridan, 1996; Vedhara, Cox, Wilcock, et al., 1999). Both groups recruited a group of chronically stressed older adults (spousal carers of patients with dementia) and a non-caregiving control group. All participants were given an influenza vaccine and were followed up to examine the proportion of people in each group able to generate an antibody response denoting that they were protected against flu (i.e., a 4 fold increase in antibody). Both groups observed that the rate of vaccine failure was significantly higher in the chronically stressed group of caregivers, compared with the control group. In the US study, the authors observed that only 38% of their chronically stressed carers were protected against flu, compared with 68% of the control group; while our UK study demonstrated even higher rates of vaccine failure with only 16% of chronically stressed carers producing

protective levels of antibody following vaccination. Perhaps the most striking feature of these results is that they suggest that, at least in the elderly, the effects of chronic stress on the immune system appear to be so insidious that even vaccinations appear unable to protect a chronically stressed individual from the threat of disease.

The effects of stress on health are not, however, restricted to disease vulnerability. In the last two decades there has been considerable research effort devoted to exploring the effects of psychological stress on chronic disease outcomes including disease progression and disease activity. A multitude of chronic diseases have been the subject of investigation including HIV, cancers, autoimmune conditions, etc. One of the emerging areas of enquiry, concerns the effects of psychological factors on the healing of wounds. Early work in this field focused on the healing of experimental wounds in non-clinical groups; and a recent meta-analysis provided compelling evidence in support of psychological stress resulting in delayed wound healing (Walburn, Vedhara, Hankins, Rixon & Weinman, 2009). This review also noted, however, that the clinical relevance of this association is unclear as limited research had been conducted in the context of non-experimental wounds, such as chronic wounds. We recently addressed this issue in a large prospective study of patients with diabetic foot ulcers (Vedhara, Miles, Wetherell, et al., 2010). These ulcers are a common and costly complication of diabetes, accounting for approximately a third of the direct healthcare costs associated with diabetes (Driver, Fabbi, Lavery & Gibbons, 2010). The wounds are slow to heal, with 70% of ulcers remaining unhealed after 5 months. We examined the effects of psychological distress and related psychosocial processes on the healing of these ulcers over a 6 month period. Our results showed that, even after controlling for clinical and demographic

determinants of healing, patients' coping styles predicted whether or not these wounds healed over a 6 month period (patients with confrontational styles were perhaps surprisingly found to be less likely to heal); and levels of depression predicted the rate at which these wounds healed. Psychological distress and related processes would appear, therefore, to influence a range of chronic disease outcomes, including the healing of wounds.

It is clear then that persuasive associations have been documented between concurrent psychological functioning and both disease vulnerability and progression. However, the effects of the mind on the body appear to persist beyond the here and now. In particular, research has shown that the experiences of mothers during pregnancy can programme the physiology of their offspring in ways which can increase the offspring's risk of a range of chronic conditions such as hypertension, diabetes, etc. (Barker, 1995). How does this happen? It appears that adverse exposures in pregnancy and early in life may programme the biological pathways involved in our responses to stress i.e., the neuroendocrine system; and that these in turn may influence later vulnerability to disease. A range of adverse exposures have been examined in this context including maternal distress, nutrition, smoking, illness, etc. with research suggesting long-term programming of the neuroendocrine system following these exposures. For example, we have shown that maternal anxiety and depression during pregnancy can program the offspring's blood pressure and cortisol responses to stressors encountered approximately 16 years later (Vedhara, Metcalfe, Brant et al., 2012). Similarly, childhood illness in the first 5 years of life has been shown to predict cortisol levels in adulthood (Vedhara, Miles, Crown et al., 2007). Further mechanistic research in longitudinal cohorts is required to delineate how these

programming effects occur, but this area of enquiry may help us to understand enduring inequalities in health.

Observational evidence of the sort described above has done much to illuminate the relationship between the mind and the body and to hint at potential clinical relevance. But the holy-grail is, of course, to explore whether we can develop interventions which harness the mind, and in so doing, affect the body in ways which not only enhance emotional well-being, but also prolong life and/or reduce symptom burden. The results from some early intervention studies offer considerable hope and promise. For example, stress management in women positive for human papillomaviruses (viruses associated with an increased risk of cervical cancer) has been shown to significantly reduce the risk of developing cervical neoplasia (Antoni, Pereira, Marion, et al., 2008). Similarly, stress management has been shown to boost the effectiveness of influenza vaccinations in chronically stressed older individuals (Vedhara, Bennett, Clark, et al., 2003). The development of effective and cost-effective psychological interventions which can reduce our vulnerability to new diseases and moderate the progression of existing conditions is clearly the next frontier.

So in summary, it would seem that psychological stress, and associated psychological processes are highly relevant to our understanding of health and disease. In the coming decades, we will see advances in our understanding of the clinical relevance of these relationships; the mechanisms that underlie them and the development of interventions which exploit these powerful effects of the mind on the body. Enquiry into the connections between the mind and body takes many guises; but also positions health psychology as being central to our understanding of health and the management of disease. ■

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