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Depression and interferon-alpha therapy

In their case report, McAllister-Williams *et al* (2000) hypothesise that recurrence of major depression following treatment with interferon-alpha (IFNα) is related to its capacity to impair serotonin synthesis by inducing enzymes that degrade tryptophan and they cite *in vitro* evidence in support of this. We suggest that there are other *in vivo* biological effects of this treatment, which may explain the association of IFNα with depression.

First, it is possible that the pathogenesis of depressive symptoms following treatment with IFNα is related to disturbance of the hypothalamic–pituitary–adrenal (HPA) axis. Overactivity of the HPA axis occurs commonly in people with major depressive disorder (Dinan, 1994), the rates of overactivity increasing with growing severity of depression. There is evidence to suggest that the effects of antidepressants on mood may be brought about by re-equilibration of the HPA axis (Barden *et al*, 1995). Exogenous IFNα therapy has been found to increase plasma adrenocorticotrophic hormone (ACTH) and serum cortisol in humans (Shimizu *et al*, 1995). The mechanism, however, does not appear to be a direct one as exogenous IFNα is a polypeptide that does not cross the blood–brain barrier and direct application of IFNα to cultured pituitary cells does not release ACTH. Indirect effects of exogenous IFNα on the HPA axis may occur through activation of endogenous cytokines, specifically interleukin-6 (IL-6) which is known to stimulate release of corticotrophin-releasing factor from rat hypothalamus *in vitro*. Furthermore, increase in serum IL-6 following *in vivo* IFNα is positively correlated with the IFNα-induced changes in serum cortisol (Shimizu *et al*, 1995).

Second, the possible effects of IFNα on tryptophan availability to which the authors refer may be a secondary effect of immune system activation. Major depression is associated with an activation of the immune-inflammatory response system, with cell-mediated increases in serum levels of pro-inflammatory cytokines including IL-6. Reduced availability of tryptophan in depression may be a result of this inflammatory response activation (Song *et al*, 1997). Exogenous IFNα also activates pro-inflammatory cytokines.

Paradigms about the aetiology of major depressive disorder are expanding beyond a narrow monoamine-centred concept. Clearly, stress, either medical or psychological, is important in the aetiology of depression. The major stress axis, the HPA, which is overactive in major depression, is potently activated by both exogenous and endogenous cytokines.

We suggest, therefore, that these biological pathways are important in the pathophysiology of depression during treatment with IFNα.

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Sluggish economics affect health of Japanese 'business warriors'

Health among the Japanese people has been faltering since the 'bubble' economy burst in the early 1990s. The consequences of the recession are now visible. A middle-aged man committed hara-kiri, a ritual form of suicide often committed in the name of honour. In the past, samurai were willing to kill themselves to maintain the *oie* (the family which governed the territory inherited from the ancestor). The man appealed, at the expense of his life, to the company for which he had worked for decades, one of the most successful companies in Japan.

To survive the competitive business world, many Japanese companies have now embarked upon restructuring. It is those middle-age men, who contributed to the economic success of Japan since the Second World War, who are now, ironically, the target for restructuring. They have devoted almost all of their lives and often sacrificed their own family life for their companies. People have had the *aisha-seisin* (a deep spiritual attachment to their own company) exactly akin to that held by the samurai for the *oie*. The man who commited hara-kiri had trusted the company and believed that the company would not abandon the business warriors. He killed himself when he felt betrayed by the company.

There is evidence that the poor economic performance of Japanese business has affected the health of the nation. The number of deaths from suicide reached 31 734 (25.2 per 100 000 people) in 1998 (Statistical Information, Department of Health, Japan; further information available from the first author upon request); Japan's highest rate since statistics were first recorded in 1899. The rate of suicide has also risen after the end of the economic 'bubble', notably for middle-aged men, approaching 50 per 100 000 people (Taniguchi *et al*, 1998). An increase in the suicide rate, especially among middle-aged men, affected the estimate of life expectancy downward; as a consequence, the gap in expected longevity between men and women in Japan has become wider (6.85 years: Department of Health, Japan, August 6, 1999 (further information available from the first author upon request)).

Karoshi (early death due to overwork) (Lawlis, 1995) is also a result of *aisha-seisin*. These deaths can be avoided. People should realise that a strong worker–company bond and becoming a 'business warrior' is hazardous to health.

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https://doi.org/10.1192/bjp.176.5.494 Published online by Cambridge University Press

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Assessment and discharge following deliberate self-harm

The paper by Hurry & Storey (2000) raises some important points pertaining to the psychosocial assessment of young people presenting with deliberate self-harm (DSH) to accident and emergency (A&E) departments. It is disconcerting that only 54% of children in the 12–15 age group received a specialist assessment prior to discharge from A&E. Department of Health and Social Security guidelines (1984) state that admission to hospital is desirable in most cases in this age group. It is interesting that the rate of specialist assessment was not dependent upon the existence of on-site psychiatric facilities, which in many cases will be based in the community child and adolescent mental health services (CAMHS). The finding that although senior clinicians believe that admission and subsequent specialist assessment is the rule, in practice nearly half the young people in the 12–15 age group are discharged, highlights the need for good liaison between CAMHS and A&E. As minors, most 12- to 15-year-olds will be accompanied by carers, and will be discharged to their care. It is difficult to envisage a situation where a casualty officer would consider discharging a minor following DSH without the involvement of a responsible carer. In the absence of on-site specialist assessment, and with a favourable short-term risk assessment, a casualty officer may be justified in discharging a young person if he or she can be confident that rapid specialist follow-up has been arranged, and that the carer has given an undertaking to ensure that the young person attends. It is, therefore, important that casualty officers receive training in the assessment of short-term risk following DSH, and in communicating with the families of young people.

Such training, regularly undertaken, is the responsibility of senior clinicians in A&E and their psychiatric colleagues. It should ensure awareness of DSH guidelines and the route to fail-safe follow-up, and address the situation reported by Hurry & Storey (2000) of junior doctors who are believed to be ". . . ill-equipped to make such assessments adequately . . .", owing to ". . . lack of experience or lack of concern with the psychological aspects of treatment".

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Hurry & Storey (2000) highlight the relatively low rates of specialist assessment for patients who present at hospital following deliberate self-harm (DSH). One contributing factor not commented upon by the authors may be those patients who leave the accident and emergency (A&E) department prematurely.

We surveyed psychiatric presentations to an inner-London A&E department over a four-month period and found that premature discharge was taken by 32% of adult patients following an overdose and 7% of those following other forms of DSH. The majority left before assessment by a casualty officer. A survey of premature discharges from Glasgow Royal Infirmary raised a similar problem (Pennycook *et al*, 1992).

Identifying the reasons for premature discharge will form the basis of a future audit. Possible factors include ambivalence about seeking help, long waiting times and adverse interactions between staff and patients.

Premature discharge may have repercussions for patients, as well as medico-legal implications for A&E. Local guidelines for A&E staff are being drawn up, to minimise the rate of premature discharge by these patients. For those who do leave, there should be careful documentation of the attendance and an attempt to organise follow-up. This should at least include telephone contact with the general practitioner.

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Ambient iodine and lithium-associated clinical hypothyroidism

Johnston & Eagles (1999) report a prevalence of hypothyroidism, in terms of the indication for thyroxine treatment, under long-term lithium therapy which by far exceeds the estimated prevalence of clinical hypothyroidism in the local population (Aberdeen area). Like Kirov (1998), who also retrospectively found a similar prevalence in a lithium-treated cohort from London, they compare their findings with results reported from North America and Sardinia. Whereas the Italian researchers (Bocchetta *et al*, 1996) did not find an excess of hypothyroidism under long-term lithium therapy, results of studies from the USA and, above all, from Canada are close to those from the UK, suggesting a considerable excess of clinical hypothyroidism under lithium treatment.

The well-known discrepancies in results among studies of lithium's anti-thyroid effects that have emerged frequently in different parts of the world over 30 years may not only be due to different study designs. In Canada, there is an overabundance of nutritional iodine (Dussault, 1993); Italy is an iodine-deficient country. As in the general population (Laurberg *et al*, 1998), in patients treated with lithium, ambient iodine seems to play a major role in the manifestation of thyroid failure. Conversely, iodine deficiency may act as a protective factor under lithium therapy. In iodine-deficient Germany, Italy and Spain, an excess of clinical hypothyroidism in patients taking lithium has never been reported, whereas in Canada, six papers from different clinics consistently reporting high prevalence of hypothyroidism under lithium therapy have been published (Leutgeb, 1999). Sorting the studies published on this topic geographically provides a confirmation of the early (case-report-based) assumption by Shopsin *et al* (1973) of a synergism between iodine and lithium in the manifestation of thyroid failure.

Consequently, in those countries where the World Health Organization's iodisation programme is gaining ground (Dunn,

https://doi.org/10.1192/bjp.176.5.494 Published online by Cambridge University Press