Correspondence

EDITED BY KHALIDA ISMAIL

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Cortisol, stress and depression

Strickland et al (2002) are to be congratulated for their Herculean task of testing the elegant hypothesis that cortisol is the biological link between stressful life events and the onset of depression. In a large community sample they found that cortisol was not elevated in currently depressed or vulnerable subjects, but was increased after recent life events, and hence concluded that ‘the hypothalamic–pituitary–adrenal [HPA] axis is sensitive to social stress but does not mediate vulnerability to depression’ (italics added). However, it is possibly premature to bury the ‘HPA-hypothesis’ under this evidence alone.

The rationale for a community study is that it captures the effects of life events, but this exclusive approach misses the other naturalistic event in depression, namely admission to hospital. Thus, the proportion of patients in the ‘depressed’ group showing severe illness was less than 10% (9 out of 94), leaving more than 90% with mild (51%, n=48) to moderate (41%, n=37) illness. Given the well-replicated finding of elevated cortisol in major depression (Harris et al, 2000) it would be helpful to provide a subgroup analysis for the severely depressed sample. Nevertheless, it is particularly interesting that there was significantly elevated cortisol in a subgroup of women who had experienced recent life events, whether or not they were currently depressed. It is possible that exposure to life events is a watershed in the evolution of depression, some people enhancing serotonin activity and avoiding depression, and others showing reduced serotonin function and becoming depressed, as suggested by animal studies (McAllister-Williams et al, 2001).

Moreover, the investigation of state and trait abnormalities in major depression by Bhagwagar et al (2002) shows that recovery from depression is accompanied by a restoration of HPA-axis function, suggesting that cortisol is a trait marker for depression. One inference of these combined findings is that life events preceding depression lead to raised cortisol and lowered serotonin, whereas life events not leading to depression are associated with raised cortisol and normal or even enhanced serotonin function (in what might be described as the ‘depression-resistant’ subgroup). In order to disentangle these apparently disparate findings it seems that a longitudinal study including a subgroup analysis of people with major depression is inevitable, and I am sure that Strickland’s group will not disappoint us.

The study of Strickland et al (2002) underpins the considerable inconsistency in the literature that addresses the area of peripheral markers in depression. It has been argued that neuroendocrine challenge tests (such as the prolactin response to dexfenfluramine used by the authors) is not a valid probe of central neuronal function (for discussion see Weiss & Coccaro, 1997) and this may account for the negative findings of the study. More perplexing is the lack of association between depression and a reliable index of hypothalamic–pituitary–adrenal (HPA) axis activation, late-night salivary cortisol (reviewed by Kirschbaum & Hellhammer, 1994). In both humans and animals various models of acute and chronic stress (e.g. physical trauma, public speaking, caregiver stress in carers of people with Alzheimer’s disease) are reliably associated with hypercortisolaemia (Kirschbaum & Hellhammer, 1994). If depression is considered to be an extreme form of chronic stress, why is there so little consistency between studies examining cortisol in populations with depression (Haskett, 1993)?

Strickland et al may have serendipitously discovered a crucial, if seemingly trivial, psycho-biological ‘co-factor’ in depression that dramatically distinguishes between cases with or without HPA axis activation: perceived stress (as measured by the Life Events and Difficulties Schedule (LEDs), see Strickland et al; p. 170, Fig. 1c). Equally depressed patients may not be equally ‘stressed’ and this may have biological as well as clinical consequences. The increased cardiac (Carney et al, 1997) and oncological (Persky et al, 1987) morbidity and mortality associated with depression may particularly apply to the depressed–stressed–hypercortisolaemic subgroup. Clearly more research is needed to explore this possibility.


Authors' reply: In our study we found that recent severe life events were associated with increased salivary cortisol but that depression was not. This is incompatible with the widely held theory that stress predisposes to depression through its effects on the hypothalamic–pituitary–adrenal (HPA) axis. Dr Moore hopes that those with more severe depression may have shown evidence of cortisol hypersecretion. Unfortunately for the stress–HPA theory of depression there is no such evidence – not even in the 9 out of 94 cases with ICD–10 severe depression. The median 23.00 h cortisol levels are identical for the non-depressed subjects and those with depression at all levels of ICD–10 severity. For the 09.00 h cortisol levels, the ‘severe depression’ group median is 7.5 compared with 7.0 for the controls, with interquartile ranges of 5.75 and 5 respectively (i.e. almost total overlap between the groups).

Although it has become dogma that cortisol secretion is increased in depression, increased cortisol secretion is only reliably recorded in severe and often psychotic depression in hospital in-patients. We suggest that this reflects a primary disorder of the HPA in patients with bipolar and psychotic illness, which is unlikely to be connected with psychosocial stress. Our findings indicate that most depression occurs with normal or slightly reduced cortisol secretion and this finding is already present in the literature. For example, Stokes et al (1984) found that only 15–20% of subjects with depression in the community had elevated plasma cortisol concentrations. It seems inescapable that sustained hypercortisolism is not how social adversity causes depression. However, there is evidence from our study that depression is associated with sensitisation of the HPA axis to chronic stress. Chronic stress occurred in many non-depressed subjects but had no effect on cortisol, whereas in subjects with depression cortisol was increased in those who were chronically stressed. Therefore, increased cortisol in those with chronic stress is due to the depression and not vice versa; it is a marker for brain vulnerability to depression and not the proximal cause of the depressed state. As the findings of Maes et al (1994) suggest, the profound stress of admission to a psychiatric hospital may be the factor that induces hypercortisolism in hospital studies of depression, since cortisol was not increased in community patients with equal levels of depression. Similarly, as Garland importantly points out, degree of stress may be the key factor in determining physical morbidity and mortality associated with depression; the interaction of stress with being depressed may be all-important in determining the physical and psychiatric outcome of depression.

Contrary to Garland’s assertion, the dexfenfluramine results were not ‘negative’; we found enhanced responses in the ‘depressed’ group. Perhaps he regards the failure to observe blunting in depression as a negative result. But our study is arguably the largest and best-controlled ever performed. Furthermore, exaggerated 5-HT 

response in depression have been observed in studies using 5-hydroxytryptophan challenge (Meltzer et al, 1984). Serotonin abnormalities, like the cortisol response to chronic stress, may be seen as effects of depression. As Cowen points out in his commentary (Cowen, 2002), life events appear to increase fenfluramine responses only in the ‘depressed’ group. Fenfluramine responses were in fact lower (P<0.1; Strickland et al, 2002: Fig. 1c) in the small number of depressed subjects without life events. A small amount of serotonin release, induced by life events, playing onto supersensitive 5-HT 

receptors together with subsensitive autoreceptors, could account for the exaggerated serotonergic responses to life events in the ‘depressed’ group. If so, then biological vulnerability to depression could involve an underlying presynaptic impairment of serotonin function. On this interpretation, some of the symptoms of depression, such as anxiety, might still be mediated by unstable excessive stimulation of 5-HT 

receptors together with impaired 5-HT 

resilience mechanisms as suggested by Deakin & Graeff (1991). Dr Moore’s suggestion that resistance to depression in the face of life events might be mediated by normal or enhanced serotonin responsiveness is compatible with this line of reasoning. However, his suggestion that life events act on a vulnerable serotonin system through cortisol responses is not compatible with our evidence – depression in the community is not associated with hypercortisolism.

Declaration of interest

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Non-right-handedness and schizophrenia

Sommor et al (2001: p. 349) found ‘compelling evidence . . . for decreased cerebral dominance in schizophrenia’, from a review of studies of handedness and other functional and anatomical asymmetries, consistent with the theory that schizophrenia is associated with an anomaly of the mechanisms of cerebral dominance (Crow, 1997), possibly a ‘right-shift factor’. They suggested that reduced asymmetry may help identify risk for schizophrenia. Procopio (2001) welcomed the review but cautioned that the ‘right shift’ is only a hypothesis and that findings for asymmetry in twins demonstrate an important environmental component.

The Sommer et al review puts it beyond doubt, in my opinion, that asymmetries are reduced in schizophrenia but this needs careful interpretation. The right-shift theory (for review see Annett, 2002) suggests that the main agent of asymmetry is environmental, random accidents of early growth in bilaterally symmetrical creatures. Random accidents occur in monzygotic twins as individuals, just as in other individuals. What is interesting about humans is that several chance distributions
of asymmetry are shifted in typical directions when the hypothesised RS+ gene is present. The gene may be absent, or when present its expression may be reduced by factors that influence early growth. Among the variables associated with reduction in the shift of the chance distribution for handedness are male gender, twinning, low birth weight, poor phonological processing (occurs in many people with dyslexia) and early brain lesions. These reductions must be detected against a base rate of non-right-handedness in about one-third of the general population. Differences in asymmetry are not causal, but rather the results of changes in the frequency or expression of the RS+ gene. They are not likely to be useful markers for any specific clinical disorder.

In schizophrenia, I have suggested that the gene may lose its directional coding and become ‘agnostic’ for right or left. Symptoms of schizophrenia are hypothesised to occur when speech cortex is impaired on both sides of the brain, as expected in 50% of the relevant genotypes. Until the RS+ gene and its variants are found, however, the theory remains a hypothesis.


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Genetic variation in European suicide rates

The fact that Hungary and Finland had among the highest reported suicide rates in Europe has led to speculations about the possible involvement of a common genetic factor in this phenomenon (Marušić & Farmer, 2001). Both Finns and Hungarians, as some linguists believe, belong to the Finno-Ugric family of ethnic groups, with certain similarities in their ancient language. The high suicide rates in the various groups of Finno-Ugrians suggested to Kondrichin (1995) that ‘during the early stages of Finno-Ugric ethnogenesis, certain behavioural traits predisposing to suicide became fixed in the gene pool’.

We (Hrdina & Faludi, 2001) have examined the available molecular genetic data on serotonergic candidate genes and their allomorphic association with suicide (Nielsen et al, 1994; Du et al, 2000) for any similarities or differences in allelic frequencies between the various populations, particularly between Finns and Hungarians. A direct comparison between the findings of association between serotonergic gene polymorphism and suicidal behaviour is difficult, since in the reports of positive associations different phenotypes (suicide attempt, completed suicide) were investigated. However, if certain serotonergic gene variants increase the disposition for, or vulnerability to, suicide in some populations that share higher rates of suicide and that may share some similarities in their ethnological origins, then the frequency of these predisposing gene variants should be comparable in those populations.

Table 1 summarises the allelic distributions of serotonergic gene polymorphisms in some selected populations. It is clearly apparent that the allelic distributions of the two polymorphisms (5-HT transporter S/L polymorphism and tryptophan hydroxylase gene 218 A/C polymorphism) are remarkably different in Hungarian and Finnish populations. In fact, the frequencies of the S and L alleles of the 5-HT transporter in the Hungarian subjects are closer to those found in the British population.

The limited scientific evidence so far would suggest that there is no Finno-Ugric ‘suicide gene’ or a shared genetic risk factor. It is unlikely that such a complex phenomenon as suicidal behaviour is genetically determined by a single gene or even a few gene variants. A more likely scenario is that the genetic contribution to suicide will be represented by small size effects of many gene variants associated with processes involved in suicidal behaviour, and by interaction of these genetic factors with environmental ones.


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Chronic fatigue syndrome or neurasthenia?

The interesting study reported by Hickie et al. (2002) draws attention to the prevalence of ICD–10 neurasthenia (World Health Organization, 1992) in a large sample of the Australian general population. The authors’ findings are of the utmost importance for clinicians concerned with the disabling effects of fatigue but also provide food for thought in the wake of the CFS/ME Working Group (2002) report to the Chief Medical Officer. In this report, the term chronic fatigue syndrome/myalgic

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Table I Allelic distribution of serotonergic gene polymorphisms in selected populations

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<td>S allele (%)</td>
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<tr>
<td>Hungarian</td>
<td>48.8</td>
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<tr>
<td>Finnish</td>
<td>33.0</td>
<td>67.0</td>
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<td>British</td>
<td>45.6</td>
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S-HT, serotonin; TPH, tryptophan hydroxylase.
encephalomyelitis (CFS/ME) is used as an ‘umbrella term’ because of the ‘need for patients and clinicians to agree a satisfactory term as a means of communication’ but the concept of neurasthenia is not used. The report’s authors state that CFS is ‘widely used among clinicians’ and seem to consider it to be a disorder more physical than psychiatric. Equally, CFS/ME is not included in DSM-IV (American Psychiatric Association, 1994) or ICD-10. On the other hand, neurasthenia as defined in the ICD-10 is a psychiatric disorder whose main feature is ‘persistent and distressing complaints of increased fatigue after mental effort, or persistent and distressing complaints of bodily weakness and exhaustion after minimal effort’. This fatigue could be associated with muscular aches, dizziness, tension headaches, sleep disturbances, irritability, dyspepsia and inability to relax. Neurasthenia includes ‘fatigue syndrome’ but excludes ‘post viral fatigue syndrome’. Using ICD-10 criteria in the general population, Hickie et al (2002) found that 1.5% of the 10 641 people who participated in the study met the criteria for neurasthenia in the past year. For females aged between 18 and 24 years, the 12-month prevalence rises to 2.4%. If it is reasonable to compare the Australian and the British populations, we could probably expect a similar proportion of people here to be affected by this psychiatric disorder; the question here is what diagnosis is applied to them? If it is the case that CFS/ME is suggested, this would have adverse implications both for these patients essentially in need of treatment for a psychiatric disorder, and for any research on the aetiology and the treatment of CFS/ME.


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Explanatory models in psychiatry

Bhui & Bhugra (2002) rightly identify the importance of eliciting patient explanatory models in routine clinical psychiatric practice. Also, they highlight the difficulties in applying this socio-anthropological perspective in routine clinical practice and mental health research. The reductionistic nature of psychiatric classifications, the inherent diversity within diagnostic categories, the fact that choice of therapy is not category-specific but is based on clinical presentation and symptoms, and the variability of outcomes demand the individualisation of care (Jacob, 1999). Bhui & Bhugra attempt to address this complex reality related to mental illness by taking a pragmatic approach.

I agree with Bhui & Bhugra that the transition from illness experience to disorder is determined by social decision points rather than biomedically determined levels of disorder. This is conceptually sound from a socio-anthropological point of view which has approached the issues from a sociocultural perspective. Hitherto, medical anthropologists and sociologists viewed individuals’ explanatory models as alternatives to the biomedical model. This would be an oversimplified application of an anthropological perspective in psychiatric practice. Although individual explanatory models are arguably more appropriate, they are not alternatives. Given the incomplete understanding of mental illness by the scientific community, it is not clear whether explanatory models alone are able to capture the complex mental health needs of patients across cultures.

As Bhui & Bhugra mentioned, in many cases the clinical reality is that individual explanatory models and biomedical diagnostic categories are not mutually exclusive but complementary. Medical/biological perspectives and cultural/anthropological views in isolation are inadequate for the understanding of mental disorders (Jacob, 1999). Examining the interconnection between the biomedical model and the individual explanatory model will produce a comprehensive assessment schedule that will be both internationally and locally valid and can form the basis of culturally appropriate modes of treatment that take into account the effect of culture, as well as individual differences, on courses and outcomes. This attempt may furnish the clinician with an opportunity to consider how best to help the patient.


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I read Drs Bhui & Bhugra’s (2002) editorial with interest. The authors advocate a socio-anthropologically informed method for both clinical and academic psychiatry, an opinion with which I strongly agree and one that may have come to psychiatry earlier. If one returns to the pages of Jaspers’ General Psychopathology (Jaspers, 1913, current edition in English translation 1997), and his seminal paper ‘The phenomenological approach in psychopathology’ (Jaspers, 1912), there is a clear tension between his claim to practice a phenomenology of mental illness, where the transcendently ideal mental state abnormalities are elucidated and described, and his call to ‘understand’ the patient’s symptoms in the light of their world view. This latter approach owes much to his mentor Weber’s conception of ‘ideal types’ and there is a clear debt to the hermeneutics and historicism of Dilthey in his suggestion that Verstehen (variously translated as interpretive understanding or empathy) is the correct method for psychopathology, rather than the phenomenology of Husserl (Berrios, 1993). The approach of Husserl in Logical Investigations (1913, current edition in English translation 2001) could be described as the search for certain features of consciousness that are ideal, pure and a priori and structure the meaning of experience and as such are true for all men at all times. Dilthey, in contrast, would argue for the contingency of world view which could only be viewed in others by a thorough, and possibly impossible, immersion in the meaningful structure of their lived environment – Verstehen (Outhwaite, 1986). This latter method is likely to be only partially successful, even in the hands of a very skilled practitioner, as in a very real sense, one’s life can only ever be lived from ‘within-in’ and it is a question of degree as to how far an external observer could ever appreciate its subtleties. For the attempt to be made, however, would require a depth of knowledge of the various socio-anthropological models before an investigator could
even begin to frame hypotheses regarding explanatory models of distress. Thus, the insights of a sociologically and anthropologically informed psychopathology may have been with us sooner, rather than us constantly having to be on guard against seduction by the ideal forms of psychopathology handed down to us by Jaspers. After all, the psychotic disorders and their symptoms are unlikely to be wholly discrete entities and, similarly, psychosis lies along a continuum with normal reasoning and experiences.


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Sexual dysfunction and antipsychotics

The adverse side-effects of antipsychotic medication, including sexual dysfunction, are believed to be one of the main reasons for non-compliance (Smith et al, 2002). However, it is the broader issue of sexual behaviour in psychiatry that we need to focus on. Sexuality is important to most patients, as the drive to procreate is strong. Psychiatric professionals tend not to be interested in discussing sexual behaviour, for reasons such as that they feel it is not important enough, or that it is something private. Apart from embarrassment, worries also arise because of the sensitivity of this issue in the litigation-ridden atmosphere of current practice. Patients’ sexual behaviour is usually considered when it is perceived as deviant or when others are felt to be at risk (e.g. in the context of sexual abuse or harassment).

Buckley and colleagues, having emphasised the importance of sexuality to in-patients, have conducted surveys on psychiatric in-patient units. These have shown a ‘wide variety of differing management approaches’ (Buckley & Robben, 2000) to in-patient sexual behaviour. Also, most mental health facilities perceive sexual behaviour as an ‘infrequent problem’ (Buckley & Weichers, 1999).

Healthy expression of sexuality is frowned upon and pornographic material is discouraged on most general adult psychiatric wards. This is justified, as it would not be appropriate. Little consideration is given to the idea that freer expression of sexuality may be therapeutic. Psychiatric in-patients are vulnerable, yet inhibition of sexual behaviour may increase distress, which can be detrimental to mental health. In the era of holistic medicine such an important facet of patient care has to be catered for. We should offer patients ways by which they can express themselves sexually in a safe and private environment. The way forward is to design in-patient wards, and write management policies, that are more ‘person-friendly’.


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One hundred years ago

The Edinburgh scheme for a psychiatric clinic

To the Editors of THE LANCET

Sirs,—In your leading article on “The Edinburgh Scheme for a Psychiatric Clinic” in THE LANCET of Feb 1st, p. 318, you appear to bestow your unqualified blessing upon the London County Council scheme for the establishment of reception houses for the preliminary treatment of the insane. You apparently are unaware that each Poor-law district in London possesses one or more such reception houses in the shape of fully-equipped and up-to-date mental wards attached to the various infirmaries. The buildings belonging to the Lewisham Infirmary consist of a handsome separate block, accommodating 11 male and 11 female patients, and fitted with all modern appliances. The system which upon my recommendation has been carried out by the local magistrates and guardians of the poor is to detain all cases of alleged lunacy in the mental block for a variable period before deciding upon their transfer to an asylum. The most gratifying results have attended our treatment. Out of 1382 cases treated during the past seven years 742 have been discharged cured, 144 have died, 20 have been sent to imbecute establishments, and only 476 have been sent to asylums. The majority of the deaths were cases of senile dementia.

The objections to the London County Council scheme are many. The change will simply be from one authority to another, but it will involve the enormous expenditure associated with the building and staffing of at least four large institutions. I anticipate that the buildings alone would cost over £300 000. The expense of collecting the patients from the wide area feeding each reception house must be considered. There is also the hardship inflicted upon the relatives and friends of the patients by making them travel long distances for the purposes of visiting, &c.; but the strongest argument against the proposed change is the stigma of “lunacy” which will rest upon the reputation of every patient who enters a reception house. Under existing

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arrangements no such stigma is attached, the patient has simply “gone into the infirmary,” a circumstance to which no disgrace is attached. There is an adage which asserts “that because the kittens were born in the oven it did not make them loaves of bread,” but it will be found that by whatever euphemistic title the reception houses may be called they will be lunatic asylums to the public, and it is only those whose work brings them into contact with lunacy who can appreciate the fearful stain left upon a bread-winner and his family by the circumstance that he has been “sent to an asylum.” In conclusion, I have no hesitation in asserting that the “early” mental cases are treated efficiently and thoroughly in the London infirmaries and that any change would be for the worse and not for the better. If there be a demand for the utilisation of these unfortunate cases for clinical study, the medical staff of the infirmaries is thoroughly capable of giving that instruction. Your statement that “the expense and moral cruelty of sending to an asylum those early cases which only required a few days’ care . . . . . led to the suggestion of receiving houses” is incorrect, as for many years past the London county asylums have been quite full and it is rare to obtain a vacancy until the lapse of a fortnight and often a month after application.

I am, Sirs, yours faithfully,
F. S. TOOGOOD, M. D. Lond., Medical Superintendent of the Lewisham Infirmary, Lewisham, Feb. 1st, 1902.

“* It was with a full knowledge of the existence of insane wards in workhouses and also of the treatment of patients in them that we advocated the system of “reception houses.” The limited experience of those in charge of the “reception house in the shape of an up-to-date mental ward” at the Lewisham Infirmary is confirmatory of the principle laid down. But before the workhouse wards, where the people of unsound mind are detained prior to being sent to asylums, can be considered as fully equipped and suitable for a psychiatric clinic a great deal would have to be done, as anyone who is fully cognisant of the present system ought to know. Our correspondent’s views as to the manner in which the public will estimate the receiving houses (we proposed the term “hospitals”) are not in accordance with the views of those who have had larger experience, and his assertion that “any change would be for the worse” is merely the record of an opinion which ought to receive a rude shock. Dr. Toogood concludes his letter by flatly contradicting us, and on completely irrelevant grounds. If he had been familiar with the work and reports of the medical superintendents of asylums he would not have done so, that is, if he has any regard for the accuracy of what he writes. – Ed. L.

REFERENCE

Lancet, 8 February 1902, p. 403.
Researched by Henry Rollin, Emeritus Consultant Psychiatrist, Horton Hospital, Epsom, Surrey
Cortisol, stress and depression
B. Moore
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