Clinical review

Fortnighly review

Stress, the brain, and mental illness

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Not for the first time, medicine is beginning to accept what folklore has been saying for some time—in this case, that stress causes illness. Causation is most comfortably accepted in medicine when it relates to definable physical events: bacteria cause infection, radiation can cause cancer; exposure to toxic chemicals can cause blood abnormalities, and so on, though we know that even these relations are not simple. How can stress cause anything?

Summary points

Psychological stress (such as a life event like bereavement) is known to be implicated in the onset and course of major depressive disorder

Events in the brain determine whether stress is followed by depression, and a triad of neurochemical responses (to steroids, amines, and peptides) seems to be involved

Changes in stress responsive steroid hormones are important—increased cortisol may alter mood and can damage the brain, while reduced levels of dehydroepiandrosterone (DHEA) may contribute since it is a natural cortisol antagonist

Brain serotonin, and other amines such as noradrenaline, respond to stress and may alter the brain's vulnerability to stress induced malfunction

Peptides such as corticotrophin releasing factor are potent regulators of the adaptive response to stress, and changes in peptides in parts of the brain known to be linked with emotional responses (such as the amygdala) may precipitate depressive illness

Understanding depression and finding new avenues for its treatment depend on combining social, psychological, and neurochemical information about stress and its consequences for mental health

Method

In a cross disciplinary and wide ranging paper such as this, it seems useful to give most references to books or reviews that summarise current evidence or opinion. However, the factual statements are based on the primary literature, which I accessed in the usual way: from personal collections of reprints, from databases (such as BIDS and Medline, using keywords such as "stress" or "depression" coupled with other keywords such as "adrenal steroids," "corticoids," "serotonin," etc), from reviews (some cited in this paper), from scanning key journals, and from contact with colleagues.

What is stress?

Stress is a general, not a specific, term and refers to any demand (physical or psychological) that is outside the norm and that signals a disparity between what is optimal and what actually exists. Since this is the stuff of life, some form of stress is commonplace: Selye thought that "stress ceases only at the moment of death."[1] However, there are episodic events that most people would recognise as unusually stressful. Haemorrhage is a stress; so is discovering infidelity. The two are not the same, and they require different sets of responses, though some may overlap. Coping is the process of recognising, evaluating, and adapting to persistent and adverse stress.

A particular stress will not hold the same importance for everybody—for example, an examination is likely to be viewed less severely by someone who is well prepared or to whom the result matters little.[2] Some people characteristically handle stress as a challenge to be overcome; others are overwhelmed. Some have friends that they can talk to, or who can give advice or support; others do not. As the stress continues, its importance may change as people gather resources, recruit help, or perceive the effectiveness (or otherwise) of their attempts to deal with it.[3]

The difference between a stressor (that is, the environmental event) and the response to it is critical for understanding the role of stress in mental illness. Some separate "stress" (the event) from "strain" (the response); this is a useful distinction, and it is a pity that it is little used in clinical contexts.

Stress and mental illness

Psychological stress has an important role in both the onset and course of mental illness, including

Table 1 Some examples of life events and their occurrence in a clinical sample of depressed patients and controls (adapted from Paykel, 1979; see Paykel and Cooper, 1992[5])

	Life events	
	Entrance (desirable)	**Exit (undesirable)**
	Engagement	Death of family member
	Marriage	Divorce
	Promotion	Lose job
	Birth of child	Child's marriage
% occurrence in preceding six months		
Controls	12	6
Depressed patients	14	32

schizophrenia, anxiety disorders, and depression. Life events have been most studied. These are occurrences that most people would recognise as emotionally important—for example, bereavement, loss of a job, marital separation, as well as lesser events such as moving house. The recognition that these events play a prognostic role in illness first came from the work of Rahe, although he was more concerned with physical illness.[4] A summary score was used to reflect the total impact of events occurring during a specific period.

For psychiatric disorders, the evidence linking life events to illness is clearest for depression. A considerable proportion of patients with recent onset of depression are found to have experienced a "life event"—particularly one involving some sort of loss—during the previous six months or so (table 1).[5] This suggests that it is not only stress itself, but some quality of the stress, that is important.

The kind of loss events likely to provoke a depressive disorder in women are those that are severely threatening with long term consequences.[6 7] However, depression does not inevitably follow such as experience, and there are two sets of predisposing factors. The first set concerns the women's environment: for example, the lack of a confiding relationship or a difficult marital situation (table 2). The second is found within the women themselves and includes low self esteem (which may also be a feature of lowered mood) and the tendency to ascribe what happens in their lives as being out of their control. The presence of both sets of factors means that a life event (a provoking factor, especially one that involves feelings of humiliation or of being trapped) is particularly likely to be followed by clinical depression (table 2).

Other stresses can also result in recognisable mental illness. For example, severe "danger" events are likely to precede the onset of an anxiety disorder,[8] and a threatening event clearly not part of the patient's lifestyle (such as an earthquake, a fire, or even a car crash) can result in a different set of symptoms more characteristic of post-traumatic stress disorder. However, the distinction between the two is not always absolute: life events can result in post-traumatic stress disorder, and many of those with a diagnosis of post-traumatic stress disorder are also found to be depressed.[9] "Positive" events, such as emotional support from someone close or moving to a more desirable house, can either reduce the onset of these conditions or increase chances of early recovery.

Table 2 Relation between life events and depression in a community sample, and the role of a preceding psychological factor (self esteem) in determining whether depression follows a life event. Values are the percentage of subjects in each category becoming depressed during one year follow up (data from Brown 1993[7])

Category	**% of cases**
Identifiable severe life event preceding depression	91
Onset of depression after event	22
High self esteem + no life event	0.7
Low self esteem + no life event	6
High self esteem + life event	15
Low self esteem + life event	34

Steroid hormones and stress

It is obvious that the brain is concerned with recognising, evaluating, and responding to stress, and that mental illness represents a disorder of brain function. How much do we know of what goes on in the brain?

Cortisol

The first clue comes from the endocrine response to stress. It is well known that cortisol concentrations are increased by many stresses; Selye thought that this was a generalised and central reaction to all stresses and could explain all stress associated illnesses,[1] a view that has been considerably modified over the years.[10] However, there are still persuasive arguments for the importance of cortisol in the physiological and psychological responses to stress.[11]

The glucocorticoid receptors in the brain are fully saturated (that is, activated) only by the high concentrations of cortisol induced by stress. High levels of glucocorticoids, whether therapeutic or pathological, are known to induce severe mood changes. Half or more of patients with Cushing's disease become depressed, and up to 75% of patients taking exogenous corticosteroids for prolonged periods may develop mood disturbances.[12-14] About half of patients with depression have alterations in cortisol, either raised levels or increased resistance to the negative feedback effects of administered glucocorticoid (such as dexamethasone), though neither are specific for this condition.

While it is clear that raised cortisol (or the administration of glucocorticoids) can result in a range of mental disturbances, it is not yet known whether there are stress induced changes in cortisol (or in other steroids such as dehydroepiandrosterone) that may, in some people at least, precipitate or accentuate subsequent depressive illness.

Recent experimental (and some clinical) evidence shows that elevated cortisol concentrations damage the brain.[15] In particular, the hippocampus—part of the "old" cortex implicated in certain forms of memory—seems peculiarly sensitive to cortisol. Cortisol concentrations raised for quite a short time damage hippocampal neurones and may impair memory (fig 1).

Do these findings help our understanding of the pathogenesis of mental illness? There is little direct evidence for a role for the hippocampus in mood, though it is always possible that cortisol is also damaging some other part of the brain—receptors for glucocorticoids are widespread. Hippocampal damage, however, may be involved in other aspect of stress induced mental

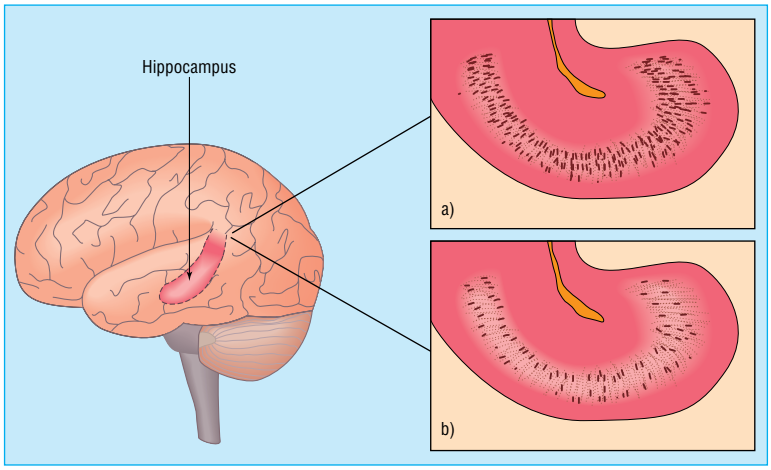

Fig 1 Left: side view of human brain showing position of the hippocampus in the medial part of the temporal lobe. Right: cross section through hippocampus from (a) dominant monkeys and (b) subordinate ones, showing degeneration of the large hippocampal neurones after persistent social stress (adapted from Sapolsky 1992[11])

dysfunction, such as cognitive deficits (for example, in working memory). Cognitive dysfunction is now recognised to be an important part of the process of becoming (and staying) depressed.[16 17] In humans hypercorticoidism is associated with cognitive impairment in a variety of conditions, including normal aging, Alzheimer's disease, Cushing's disease, and depression.[18] Administered hydrocortisone also has cognitive effects.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA), a steroid present in large amounts in the blood of young adults, is a new player in the endocrine game of stress. Its concentration is lowered in many cases of depression, at least in adolescents (the evidence in adults is still preliminary),[19] and levels may also be decreased by stress. The importance of these changes may lie in experimental evidence that DHEA can antagonise cortisol,[20] so low levels of DHEA (or high levels of cortisol, or both) might all have the same damaging results for brain function. Increased ratios of cortisol to DHEA have been associated with anorexia nervosa as well as depression.[21] However, DHEA can also act directly on a receptor for the inhibitory neurotransmitter γ-aminobutyric acid (GABA, which is widespread in the brain),[22] so this is also a possible mechanism for its role in mental illness.

DHEA has another extraordinary property that marks it out from other steroids; concentrations decrease progressively and rapidly with age,[23] and this decline—itself individually variable and subject to genetic control—has been correlated with increased heart disease, diabetes of adult onset, and reduced immune capacity.[24] The brains of older people are thus exposed to relatively increased amounts of cortisol. Whether this plays an important role in the cognitive impairments of elderly people or the timing of those neurodegenerative disease that occur during middle or later life (such as Huntington's chorea or Alzheimer's disease) or the increased vulnerability of the aging brain to toxic, ischaemic, or stress induced damage are clearly important questions. Studies on administration of DHEA in humans are scanty and short term but have shown positive effects on immune function and the sense of "well being."[25 26] No doubt many more will follow in the next few years.

Adequate trials of using DHEA to treat depression have not yet been reported, but it is possible that either this steroid or drugs related to it may find a place in treatment. So, too, may drugs that reduce cortisol concentrations in the blood or block its receptors in the brain; there is already evidence that drugs reducing blood cortisol might be effective in treating depression.[27] One obstacle to further progress is that DHEA is not patentable, so drug companies are not very interested in it.

Serotonin and other monoamines and stress

Within the brain, the serotoninergic system (5HT) is activated by stress. The role of serotonin in adapting to or coping with stress is still not understood. There are plausible suggestions that serotonin may represent part of the neural basis of resilience (or vulnerability) to the psychopathic results of stress.[28] The widespread and effective use of drugs acting on serotonin reuptake (such as selective serotonin reuptake inhibitors) in treating depression continues to provide tantalising clues, though no firm conclusions, on the part played by serotonin in its pathogenesis.

Genetic differences in the serotonin transporter—the molecule that is responsible for the reuptake of serotonin into its nerve terminals and the site of action of selective serotonin reuptake inhibitors—have been associated with affective disorder or trait anxiety, although this is controversial.[29-31] Perhaps the strongest support linking serotonin and depression comes from findings that lowering brain serotonin concentration by ingesting low tryptophan drinks can induce depressive mood in the short term, particularly in people who have recovered from depression.[32 33] Glucocorticoids are known to act on serotonin—for example, by regulating enzymes that synthesise it or the density of receptors in the brain that respond to it.[34 35] Neuroendocrine challenge tests have shown that serotonin function seems to be reduced in the presence of raised cortisol concentrations.[36 37] Perhaps this is another link between stress related hormones and neural dysfunction.[38]

However, it is equally true that other monoaminergic systems, including those containing noradrenaline and dopamine, also respond to stress so the story may be more complex and variable than is sometimes suggested. For example, dopamine has been implicated in major depression,[39] and differences in dopamine receptors have also been correlated with personality traits.[40] All the monoaminergic systems share the property of a widespread, though anatomically distinct, network of fibres spreading throughout much of the brain from a localised source (in the brain stem), so changes in their activity are likely to have equally widespread and pervasive results on brain function during stress. These include changes in cognition as well as mood.

Until the role of serotonin (or other aminergic systems) in the development or course of depression is better understood, it will be difficult to understand the way that drugs acting on these systems hasten recovery.

This is despite the current enthusiasm for drugs that interfere with the reuptake of serotonin from its nerve terminals (a potent means of increasing the activity of serotonin in the brain). However, drugs that have analogous actions on the central dopamine or noradrenaline systems are also effective in depression, and there are antidepressant drugs that increase the uptake of serotonin. The therapeutic role of these drugs is not, as some claim, good evidence for disordered amines being the root cause of depression, though monoamines clearly play an important role.

Stress and gene expression in the brain

The brain also responds to stress by altering gene expression. A class of genes called (rather inelegantly) immediate-early genes increase their expression (that is, levels of both mRNA and protein) in neurones in response to stress (and other stimuli).[41] This can be used to map patterns of neural activation in the brain (fig 2). Experimental stress results in characteristic patterns of increased expression of immediate-early genes in the brain. These include a number of neural structures known to be concerned in stress or the response to it (such as parts of the hypothalamus, amygdala, brain stem monoaminergic and autonomic nuclei, etc). If the stress is repeated, this pattern changes; some areas now show much less immediate-early gene expression, but others stay activated.[42] This, surely, is a footprint of adaptation to stress at the neural level.

The problem is that we have little idea of what these genes do, though they seem to function as transcriptional regulators; that is, the protein they make enters the nucleus, binds to DNA, and regulates the expression of other, "later" genes. It is the identity and function of these late genes that is the puzzle. Some of them may be implicated in stress induced mental disorder. Alterations in gene expression is an important part of the way the brain responds to stress, and this may represent both adaptive and maladaptive processes—such as the development of mental illness. One set of genes that may be particularly important are those regulating the amount of peptides in the brain, or the receptors that enable neurones to respond to peptides.

Peptides and stress

The limbic area of the brain, thought to be particularly important in mood, emotion, and motivation, is rich in peptides. These are released after activation of the limbic system by stress. These molecules, because they are made of strings of amino acids, can carry much more information (that is, variation in their structure can be used to code different signalling properties) than the more conventional neurotransmitters such as serotonin or glutamate. Other parts of the body, such as the

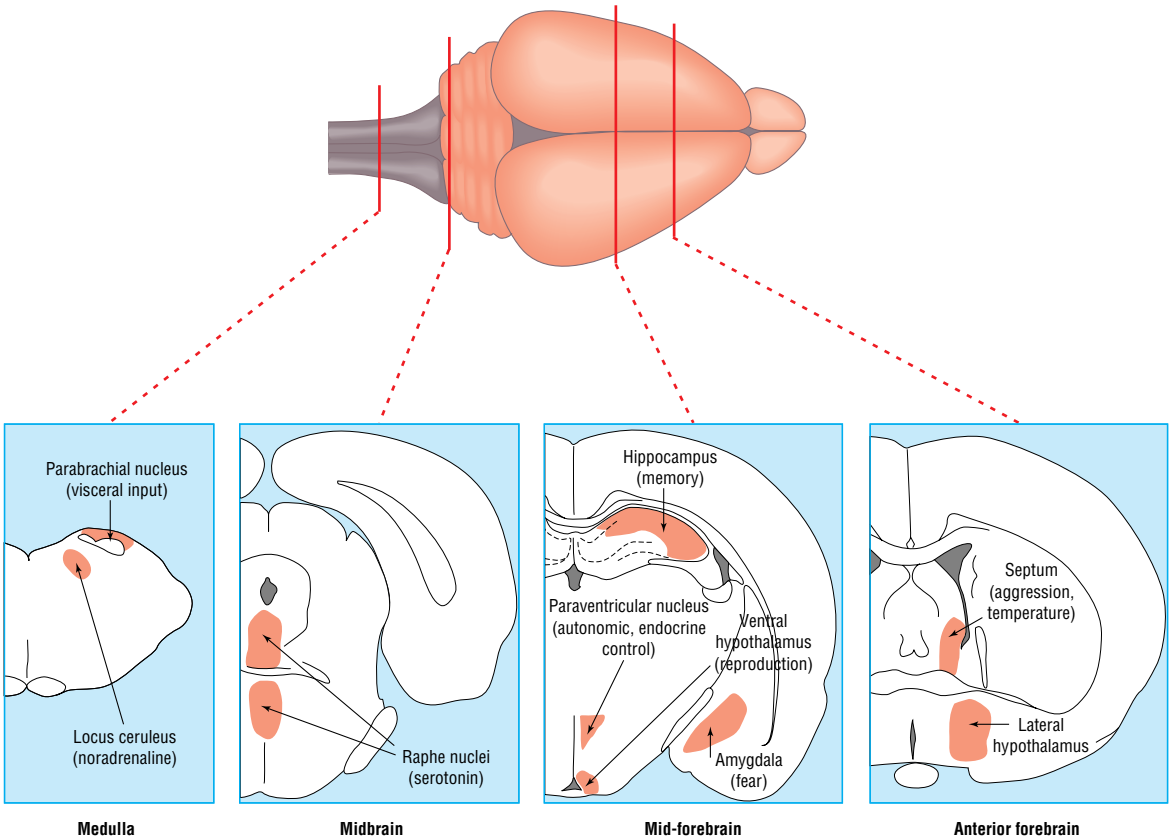

Fig 2 Distribution of increased expression of an immediate-early gene (c-fos) in the brain of an acutely stressed rat (adapted from Chen and Herbert 1995[42] and others). Repeated stress will change this map: in some areas c-fos is no longer expressed, while in others it continues. A stress related function is indicated for each area (where known), but many functions are distributed within the brain—for example, aggression involves the amygdala and hypothalamus as well as the septum, memory is not limited to the hippocampus, and many autonomic functions depend on brain stem structures as well as those in the forebrain

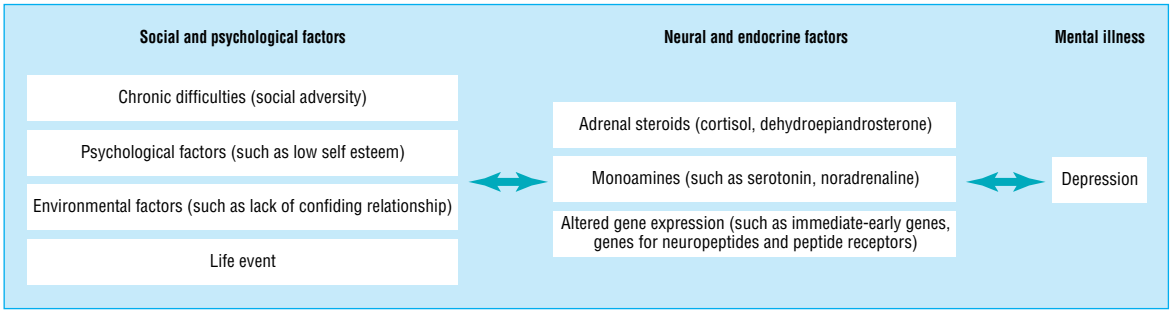

Fig 3 Social, psychological, and neural factors implicated in depression. There is continual interaction between all three sets of factors

immune system, also use peptides when a large number of distinct signals need to be sent and decoded. Neuropeptides seem to be closely concerned with adaptation to stress. Physical stresses, such as haemorrhage, are dealt with by combined actions of the autonomic system (increased heart rate, vasoconstriction), changes in hormone secretion (vasopressin, etc) and appropriate behavioural responses (thirst, drinking). Peptides (central angiotensin II in the case of haemorrhage) have the ability to evoke this coordinated and stress-specific pattern.[43]

Corticotrophin releasing factor is a peptide closely concerned with stress. First identified as a releaser of adrenocorticotrophic hormone from the pituitary, it is now clear that this peptide—in common with many others—has a wider role. Infusions of corticotrophin releasing factor into the brain induce anxiety-like behaviour and activate the cardiovascular system.[44] They also induce a pattern of immediate-early gene expression which resembles that following psychological stress. The amount of corticotrophin releasing factor in the brain (and the expression of the gene that makes it) is increased by stress. Blocking its action reduces the fear or anxiety that otherwise follows experimental stress procedures. There are reports (not unanimous) that levels of corticotrophin releasing factor are raised in the cerebrospinal fluid of depressed patients.[45] We await impatiently the arrival of clinically effective antagonists of corticotrophin releasing factor (see below). However, there are suggestions that corticotrophin releasing factor may be more concerned with reacting to acute than repeated or chronic stressors.

Vasopressin is a familiar peptide hormone in the blood, but the brain also uses it as a neurotransmitter, particularly in the limbic system. It has the interesting property of synergising with corticotrophin releasing factor to release adrenocorticotrophic hormone from the pituitary, and there is evidence that it may also be involved in the brain's response to persistent stress, which increases vasopressin expression in the brain.[46] Vasopressin potentiates the anxiogenic actions of corticotrophin releasing factor, so drugs that act on vasopressin or its receptors may also prove clinically important.

Many other peptides are involved in stress, reflecting the multiple categories of stressors, and the need to tailor coordinated responses to them. Peptides that are particularly interesting include pro-opiomelanocortin, which may be responsible for the inhibiting effect that some stressors have on the reproductive system—it is often forgotten that in men testosterone levels and sexual behaviour are highly susceptible to stress.[47] Another set includes a range of peptides that regulate appetite—including central cholecystokinin, an anorectic agent, and neuropeptide-Y, a potent appetite stimulant. Altered food intake has long been associated with stress as well as with changes in mood.

The variety of peptides in the brain, together with their potent (and, in many cases, quite specific) effects on behaviour, has naturally suggested the development of drugs that might promote or interfere with their actions. The problem has been that, until recently, nearly all such compounds were themselves peptides, which are not effective drugs in humans—they are not absorbed by mouth and do not cross the blood-brain barrier (though there are exceptions to this general rule, such as insulin, prolactin, and the newly discovered leptin, a powerful regulator of food intake). Nevertheless, the existence of morphine, a non-peptide compound acting on opioid receptors and thus mimicking peptides such as β-endorphin, and naloxone, a related antagonist, offered hope that one day non-peptide compounds might become available that could be used to regulate cerebral peptides. At last, this seems to be happening. An increasing number of such compounds (mostly antagonists) are now being developed. Some have obvious potential in mental illness—such as those blocking the action of corticotrophin releasing factor (or vasopressin) or interfering with peptides that have potent actions on appetite (for example, leptin, neuropeptide-Y, cholecysytokinin). For years, people have been predicting the arrival of a new neuropharmacology, based on agents that act on peptides. It looks as if this day is about to dawn.

Clinical implications

The experimental studies described above show that an animal's response to stress involves several interlocked but neurochemically distinct elements. Stress induced changes in steroid hormones may impair the function of the brain by acting directly upon neuronal function. They may also regulate monoamines such as serotonin. This compound is clearly an essential element in the response of the brain to stress. Both monoamines and steroids may alter the expression of peptides in the limbic system, and peptides may determine specific patterns of response to different stressors. It seems probable that

these neurochemical systems are also implicated in the genesis of psychiatric reactions to social stress, such as depression, although the exact roles of each are still obscure. The explosion of activity in the neurosciences, together with the equally impressive advances in cell and molecular biology, are bringing new hope that we will begin to understand, in a clinically meaningful way, some of the effects that stress has on the brain, why this provokes mental illness in some people, and how we can develop effective treatments to preempt illness in those specially vulnerable to it or treat those whose inability to cope with stress has made them ill.

Equally important as these technical advances has been the steady and welcome erosion of the artificial boundaries between behavioural studies and neurosciences, and between experimental and clinical research. People formally inhabiting different worlds now talk to each other and work together, recognising that they may be asking the same questions and that the breadth and rigour of cross-disciplinary research is needed to answer them (see fig 3). This is likely to result in a much greater range of effective interventions in stress induced mental disorders (particularly depression) than is currently possible. For example, recognising the critical aspects of social adversity may allow development of psychotherapy designed to increase psychological resilience; there may be genetic differences in vulnerability to stress induced depression that can be used to identify people susceptible to subsequent illness; and advances in our understanding of neurochemical and endocrine components of depression may offer better and more varied drug treatments. In short, it seems likely that the future handling of stress induced mental illness is likely to be as cross disciplinary as the research into its causes. Sadly, for the biomedical scientists of this country, with a track record unsurpassed, all this excitement comes at a time when resources for multidisciplinary research work are almost impossible to obtain.

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