Psychological Medicine, 2003, **33**, 573–581. © 2003 Cambridge University Press
DOI: 10.1017/S003329170300775X Printed in the United Kingdom

EDITORIAL

Adolescent depression, cortisol and DHEA[1]

Since the mid-1980s Ian Goodyer and his colleagues have been engaged in trying to understand the dynamics of the relationship between acute and chronic life stresses and depression in adolescents (Goodyer *et al*. 1985, 1986). One of the great strengths of their work has been their attention to an array of potential risk factors ranging from the apparently exogenous (such as life events, e.g. Goodyer *et al*. 1988; Goodyer & Altham, 1991; Goodyer, 1999), through those of uncertain origin (e.g. peer and family relationships and problems, Goodyer *et al*. 1990), to those that can be regarded as being endogenous to the child (e.g. measures of temperament or endocrine function, Goodyer *et al*. 1993, 1996, 1998; Herbert *et al*. 1996). They have then typically attempted to determine how subsets of these factors interact in the generation of disorder (see Goodyer, 2002 for a speculative presentation of his current thinking about the relationships between social adversity and depression). A second characteristic of their research lies in its frequent attention to outcomes over time, as opposed to cross-sectional relationships (e.g. Goodyer *et al*. 1997*a*, *b*). Thirdly, in line with growing evidence that the relationships between environmental stress (and perhaps neuroanatomical correlates) and depression change as repeated episodes occur (Lewinsohn *et al*. 1999; Daley *et al*. 2000), they have distinguished among first, recurrent, remitting and chronic depressive episodes. The group's latest work, presented in this issue (Goodyer *et al*. 2003), nicely illustrates these characteristics, and their extension to consideration of potential dynamic relations among endocrine parameters in relation to psychopathology.

EARLIER STUDIES BY IAN GOODYER AND HIS COLLEAGUES OF EFFECTS OF CORTISOL AND DHEA

To begin with, let us recapitulate this group's work on cortisol, dehydroepiandrosterone (DHEA) and depression in order to see how they arrived at the study just presented. An early case–control study and a small depressed-well follow-up study found evening or night-time hypersecretion of cortisol in depressed children and adolescents (Foreman & Goodyer, 1988; Goodyer *et al*. 1991). The follow-up study also noted that some individuals were not hypercortisolaemic when depressed, but that hypercortisolaemia was associated with more severe symptomatology. Generalized hypercortisolaemia has not been observed in studies of depressed children and adolescents, rather cortisol is more likely to be elevated around sleep onset, at a time when the hypothalamo–pituitary–adrenal (HPA) axis is usually quiescent. Even this pattern is more characteristic of adolescents than of children (Kaufman & Charney, 2001). Many other studies have found that factors such as poverty, stress and family history of depression (e.g. Lupien *et al*. 2000; Bremner & Vermetten, 2001; Cicchetti & Rogosch, 2001) are also associated with hypercortisolaemia in some children and adolescents. If we accept that in some types of depression there is hypercortisolaemia at certain times, but in others there is not, then the issue becomes one of understanding this heterogeneity, and the degree to which cortisol abnormalities (when present) are correlates of depression itself as opposed to being primarily associated with other risk factors for depression or to co-morbid psychopathology. In other words, we are in a similar position to adult depression research (Pariante & Miller, 2001; Cowen, 2002; Gold *et al*. 2002; Strickland *et al*. 2002), where it has become clear that there is no single link between the hypothalamo–pituitary–adrenal (HPA) axis and depression, but rather a heterogeneous complex of relationships that we are still far from comprehending. Even so,

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it is particularly worth studying children and adolescents because they offer a window into the developmental plasticity (and potential mutability) of the HPA axis as it relates to psychopathology (Gunnar & Vazquez, 2001; Meyer *et al*. 2001).

One sensible way to begin to understand that heterogeneity of relationships, is to limit attention to a single phase of the natural history of depression. Hence the utility of Goodyer *et al*.'s concentrating on early episodes of illness (i.e. depression in children and adolescents), and as we shall see, beginning to distinguish among first episodes, remitting episodes and chronic episodes.

Next, in a case–control comparison of clinically-referred children and adolescents with major depressive disorder (MDD) Goodyer's group (1996) found that those with MDD had higher evening (8 p.m.) cortisol and lower morning (8 a.m.) DHEA levels. Given the DHEA results it is perhaps surprising that there was no corresponding effect of depression on DHEA's sulphated metabolite (DHEAS). These findings were reported to be neither age nor sex dependent, but no analyses of the interactions of these factors with DHEA or cortisol levels were reported – rather, the main effects of the hormones were apparently not attributable to age or gender (p. 253), which is not quite the same thing. The problem here was that power to detect interactions was low, and the authors rightly noted that 'further investigation for possible sex differences in the endocrine status of depressed children appears warranted' (p. 254. I shall give a more detailed description of the issues here later).

High evening cortisol was also associated with the presence of co-morbid dysthymia, while the absence of co-morbid panic or phobic disorders was associated with low morning DHEA (Herbert *et al*. 1996). A follow-up of a subset of this sample 36 weeks later indicated that those with persistent depression were more likely to have had cortisol/DHEA ratios above the 60th percentile at 8 p.m. and midnight (but not at 8 a.m., 12 p.m. or 4 p.m.) at presentation than were those who were later free of psychiatric disorder, or manifested only non-depressive disorders. High evening ratios also predicted the occurrence of disappointing life events during the follow-up period. However, both cortisol/DHEA ratio and disappointing events had independent effects in predicting depression; 86% of those with both a high cortisol/DHEA ratio and a disappointment remained depressed, compared with only 19% of those with neither factor. Higher midnight cortisol/DHEA ratios were also associated with the presence of co-morbid obsessive–compulsive disorder at presentation and the presence of obsessive–compulsive disorder was associated with persistence of depression (Goodyer *et al*. 1997*a*). The effect of high evening cortisol was maintained out to a 72 week follow-up (Goodyer *et al*. 2001*a*), but there was no continuing significant effect of DHEA or cortisol/DHEA ratio. Persistence was also associated with being older at study entry, and individuals older than $13\frac{1}{2}$ were more likely to be evening cortisol hypersecretors – a finding in line with other studies (Birmaher *et al*. 1996; Kaufman & Charney, 2001, see below for further consideration of the importance of age effects).

The present study used a community-based risk-stratified (but psychiatric disorder-free) sample of 12–16 year-olds. A study entry, neither cortisol nor DHEA were associated with depression questionnaire scores, cognitive style, or life events. However, high depression questionnaire scores and DHEA hypersecretion predicted the onset of major depression over the following year (Goodyer *et al*. 2000).

Girls were substantially over-represented in the high risk group (Goodyer *et al*. 2000), and, within the high risk group, girls were more likely to have had recent adverse life events. Girls also had higher depression scales scores, lower self-esteem, higher cortisol and higher DHEA than boys (others have also since found that adolescent girls have higher cortisol than boys from midday to late afternoon, Klimes-Dougan *et al*. 2001). In other words sex was confounded with the psychosocial and biological risk factors for depression. Although the proportion of boys and girls who became depressed over the next year was not 'significantly' different, computation of the odds ratio for this comparison reveals it to have been 2·0. It is now clear from general population surveys that the familiar 2 : 1 female preponderance in the prevalence of depression (Weissman & Klerman, 1977; Weissman *et al*. 1996) emerges between the ages of 13 and 15 (Velez *et al*. 1989; McGee *et al*. 1992; Angold *et al*. 1998; Cairney, 1998; Hankin *et al*. 1998), so we would expect to see a higher

incidence of depression in girls during the follow-up period of this study (by the end of which the participants were aged 13 to 17). Indeed, we might particularly expect to see increased depression in girls in the sort of high risk group selected here, because the evidence points to the emergence of increased genetic risk in girls during this period, and that genetic risk is also associated with an increased apparently genetic risk for recent life events (Thapar & McGuffin, 1994; Thapar *et al.* 1998; Silberg *et al.* 1999, 2001). So it is not surprising that in the studies under consideration here, sex, familial risk and recent life events were all correlated. But it is a big problem for interpreting the results, when confounding at the level of psychosocial risk is further compounded by the association between sex and the steroid hormones reported in the paper.

Furthermore, there is another potential developmental confound here. DHEA rises substantially from adrenarche (in mid-childhood) through adolescence (and through the twenties in men). Mean cortisol levels show no such degree of developmental change. So any age-dependent process could appear to be associated with increased DHEA levels, such as was seen in the 8 a.m. samples. In the conclusions section of the paper we are told that 'this finding held even after controlling for age', but it would be interesting to know whether the inclusion of age had any substantial effect on the strength of the association with DHEA. We need, however, to go a step beyond the question of whether main effects of adrenal steroids can be explained statistically by age or vice versa, to ask whether there are different associations with depression at different ages (or more properly, developmental stages). I have already mentioned that there may be different sex-specific genetic components acting in adolescent as opposed to childhood depressions, and that there is a good deal of evidence for differences in other social and biological correlates of childhood and adolescent depressions, including sleep and HPA axis associations (Birmaher *et al.* 1996; Kaufman & Charney, 2001). Once again, my expectation is that there will be interactions between risk factors of the sort measured here and age (stage) in this age-period.

The paper presented in this issue (Goodyer *et al.* 2003) describes a follow-up to 24 months of the 30 individuals who were depressed at 12 months, plus an age and sex matched sample of 30 never-depressed controls from the original sample. Once again, cortisol level at entry was not associated with persistent depression (not very surprising, given the results at 12 months), but the persistent depression group had lower DHEA levels at 8 a.m. and higher cortisol/DHEAS ratios. Remember that the apparent risk for onset was higher morning DHEA. The significant differences were between the persisters and remitters with the never-depressed lying puzzlingly between them. The persistent group were also found to have had significantly higher depression questionnaire scores and a more ruminative cognitive style at study entry. However, in contrast to the earlier finding in the clinical sample, obsessionality did not predict persistence. However, in the final logistic regression model predicting remittance *versus* persistence only cortisol/DHEAS ratio remained significant. Age does not appear to have been included as a possible covariate in developing the final model.

Does the whole story then boil down to just the cortisol/DHEA ratio? The obvious problem here is that the many necessary comparisons of the remitters with the persisters had to be conducted on groups of 19 and 10 respectively. This is an imperfect basis for stepwise regressions involving multiple potential predictors. The power problem is clearly illustrated in the bivariate comparisons for depression and rumination questionnaire levels at study entry. We are told that these '… comparisons confirmed that depression ($P<0{\cdot}05$) and rumination ($P<0{\cdot}05$) scores at entry were higher in Persist compared with NoMDD, but there was no difference between Persist and Remit'. Inspection of Table 2 (see p. 606) reveals that, in both cases, those in remission had mean scores between those for the non-depressed and the persistent group. Though it is not specifically stated, we may infer that the remitted group was also not significantly different from the NoMDD group. However, the depression score of the intermediate Remit group was about a third of a standard deviation lower than that of the Persist group, but about two-thirds of a standard deviation higher than that of the NoMDD group. Its rumination score was more than three-quarters of a standard deviation lower than that of the persisters, but less than a quarter of a standard deviation higher than that of the NoMDD group. Ignoring the 'significance' levels, therefore, the remitted group

looked more similar to the persistent group in terms of depression score at study entry, but like the NoMDD group as far as ruminations were concerned. With groups of 19 and 11, there is only a one in four chance of detecting (finding significant at the 0·05 level) a true difference of half a standard deviation (which most would regard as being a pretty substantial difference). Even for comparisons between the NoMDD group and the remitters, the probability of detecting such a difference is still only 38%. We must be careful, then, in interpreting any non-differences among these. On the other hand, the finding of a significant difference in morning DHEA/cortisol ratios in the direction predicted from the clinical study is all the more impressive, given the low power of the study.

PREDICTION OR CONCURRENCE?

The analyses presented here all take the form of measures at study inception being used to predict status 2 years later, and they beg the question 'do continuities or discontinuities between predictor status at the start of the study and at follow-up explain the apparent effects of the predictors over time'? For instance, there was no difference in the rates of recent undesirable life events in the month preceding depression onset between the remitters and persisters, but there was a big difference in the occurrence of negative events between these two groups and the never-depressed. Perhaps persistent depression and higher cortisol/DHEA ratios were associated with one another because both were linked with higher ongoing rates of life events (remember the pattern of confounding with female sex, and compare Silberg *et al*. 1999; Klimes-Dougan *et al*. 2001). Similar arguments can be applied to all the dimensions discussed in the study. The differences in patterns of adrenal hormone abnormalities seen in the group's clinical studies and this study may result from differences in stage of illness, but it would be nice to see this tested by the inclusion of follow-up hormonal measures.

WHAT SYSTEM IS BEING AFFECTED?

Ian Goodyer and his colleagues interpret their results in the light of findings that cortisol (or corticosterone in rats) can be bad for the brain (particularly the hippocampus), while DHEA has been found to protect against negative effects of cortisol (e.g. Kimonides *et al*. 1998; Gubba *et al*. 2000; Kaminska *et al*. 2000; Karishma & Herbert, 2002). Low DHEA is supposed to result in functional hypercortisolaemia in the brain, and that, in turn, promotes depression. The first problem here is that, at 1 year high DHEA was associated with the onset of depression, and that those who remitted had (albeit non-significantly) higher DHEA and lower cortisol/DHEA ratios than the non-depressed controls (see Table 3, this issue page 606). Even setting that apart, where does the 'functional hypercortisolaemia' hypothesis take us in our understanding of depression? First, we have little idea of the degree to which salivary cortisol or DHEA reflect relevant brain levels, or even which parts of the brain might be the relevant sites of action. Indeed, the correlation between Goodyer's salivary cortisol assay and serum cortisol is only 0·6, though that between salivary DHEA and serum DHEA is a more satisfactory 0·9. But, on the other hand, DHEA and DHEAS are 'neurosteroids' (see Baulieu, 1998 for useful reviews), synthesized *de novo* in the peripheral nervous systems, and capable of acting as allostearic modulators of various neurotransmitter receptors (including GABA receptors), as opposed to the more traditionally well-known intranuclear steroid modulation of gene expression. On the other hand, outside the nervous system in the peripheral intracrine tissues, they are major metabolic precursors of androgens, particularly in women (Labrie *et al*. 1997; Hunt *et al*. 2000), so, once again, there is an enormous range of possible mechanisms by which these compounds could affect depression. The authors admit 'the exact association between affective-cognitive processes and cortisol hypersecretion remains unclear', and their more detailed discussion of cortisol and DHEA in human development and psychopathology (Goodyer *et al*. 2001*b*) appropriately raises even more questions along these lines. I would suggest, then, that 'unclear' in the quotation above, could appropriately be replaced with 'entirely opaque'. On the other hand, we have to start somewhere.

WHY CHOOSE TO STUDY JUST CORTISOL AND DHEAS?

It is not really clear why Goodyer's group have picked just cortisol and DHEA to study. During the developmental period that they have concentrated on, other steroids with cognitive, neurotropic and neuroprotective effects, that are known to influence systems implicated in the pathogenesis of depression (particularly serotonin pathways), also show dramatically sex-differentiated developmental changes. Once again, let us remember that this is also the developmental period in which depression becomes sex-differentiated. Oestradiol is a leading candidate for further study in these respects (Paikoff *et al.* 1991; Goodman *et al.* 1996; Seeman, 1997; Wickelgren, 1997; Angold *et al.* 1999; Toran-Allerand *et al.* 1999). But one might also consider testosterone and the adrenal androgen androstenedione (Nottelmann *et al.* 1987*a*, *b*; Susman *et al.* 1987*a*, *b*; Brooks-Gunn & Warren, 1989; Angold *et al.* 1999). All have been associated with negative affect and/or depression in this age range (see Angold *et al.* 2003 for a review). It is also well-known that there are feedback loops between the HPA and hypothalamo–pituitary–gonadal (HPG) axes (Viau, 2002). Goodyer and his colleagues are well aware of these possibilities; they have themselves said that 'there appear to be complex and developmentally sensitive interactions between cortisol, DHEA and gonadal steroids that require further elucidation before we can determine the exact nature of the endocrine risk for psychopathology in each gender' (Goodyer *et al.* 2001*b*). It would be impossible to work through these complexities in samples as small as those of Goodyer and his colleagues, but having established an *a priori* case for the continued measurement of the cortisol/DHEA ratio, this is a direction in which we need to go. Our own studies have, so far, found no effects of DHEAS on depression, once the effects of testosterone and oestradiol were accounted for (Angold *et al.* 1999). (We measured DHEAS rather than DHEA because we took only one-off samples and DHEAS levels fluctuate less than those of DHEA.) However, when measures of the gonadal steroids were not included, then higher DHEAS appeared to be significantly associated with an increased probability of depression in girls aged 9–15. When the gonadal steroids were added to these statistical models, the DHEAS effect became non-significant, while larger effects of the gonadal steroids emerged. We interpret this as indicating that the apparent effect of DHEAS was due to its being correlated with adrenal androgen levels (both are rising) during this developmental period.† However, this is hardly the last word on the subject. Rather it points to the need for more detailed work that takes account of the possibility that there will be gender-differentiated processes that vary with level of development. Our work indicates that increases in circulating levels of testosterone and oestradiol, rather than gonadotropins, adrenal androgens, the emergence of secondary sex characteristics, or changes in life stress levels, are key factors in the increase in depression in adolescent girls (Angold *et al.* 1999, 2003). That implies that we need larger studies with in-depth measurement of both the evolution of depressive disorders, and the development of both the HPA and HPG axes.

CORTISOL/DHEA RATIO AS A SCREENING TEST?

The suggestion is made that 'measuring the cortisol/DHEA morning ratio may be able to detect adolescents in the community at high risk for persisting affective disorders with sufficient sensitivity and specificity to warrant consideration as a screening procedure' (Goodyer *et al.* 2003). However, the data do not really lend much support to this idea. Persistent depressives were best characterized by ratios that were above the 80th percentile of the original high risk sample. One hundred and eighty-one individuals were assessed at study entry, one had a spoilt cortisol, so 36 of them must have been at or above the 80th percentile. Of these, seven ended up in the persistent group, one was a remitter, but three-quarters of them (24) were never depressed over the ensuing year. According to my calculations that yields the following parameters for this potential test. Its sensitivity in this high risk group of individuals was 70% (not bad), but its specificity was only 83% (poor, unless the costs of having false positives are very low). As a result, of the screen positives, only 19% became

† Details of these unpublished studies may be obtained from the author.

persistently depressed, while 81% were false positives. Now it may be objected that onset over the following year is too conservative a criterion, and that others probably became depressed later on. Even so, given what we know about the lack of specificity of cortisol abnormalities for depression in adults, it seems unlikely that the cortisol/DHEA ratio will prove to have adequate specificity no matter how we prolong the follow-up period. The sort of long-term follow-up procedure that would have to result from such screening is also not likely to be feasible. Were proven long-term depression prevention programmes available, then identifying individuals with high probabilities of onsets in even the distant future would make sense. But no such programmes exist. We also have to bear in mind that the parameters of any test vary with the type of population in which it is used. So we cannot expect population utility on the basis of results from a highly selected sample.

IS IT TIME FOR A TRIAL OF DHEA TREATMENT FOR DEPRESSION IN CHILDREN AND ADOLESCENTS?

Given the problems with adverse effects of the currently available antiglucocorticoids, the use of a 'natural' antiglucocorticoid therapy with few known side effects might seem attractive at first (Wolkowitz & Reus, 1999; Reus & Wolkowitz, 2001), but I would hesitate to use an anabolic, androgenic steroid to treat a disorder that characteristically occurs more often in girls in mid-adolescence. In considering whether there is sufficient evidence to begin a trial of DHEA therapy with juveniles, it behoves us to consider the developmental progression of DHEA and DHEAS levels a bit further. First, in females blood levels of these hormones reach their lifetime peak at the end of the teens – just when rates of depression are two to three times higher than they were in childhood (Kroboth *et al*. 1999; Young *et al*. 1999; Salek *et al*. 2002). Why does the enormous increase in DHEA and DHEAS from adrenarche to adulthood not protect against depression? In males, levels continue to rise to a peak at the end of their twenties. Following these peaks, blood levels fall in both males and females, so that by the sixties, they are only a third or less of their peak levels (Labrie *et al*. 1997; Young *et al*. 1999). Why then do depression levels not rise dramatically from the twenties in women and the thirties in men? In later life, there has been a focus on DHEA 'replacement' to reverse these natural age effects and their correlates in numerous body and brain systems in the hope of incurring wide-ranging health benefits (Katz & Morales, 1998; Larkin, 1998; Morales *et al*. 1998; Hinson & Raven, 1999; Pepping, 2000; Martina *et al*. 2001), but it remains to be seen whether there really will be therapeutic benefits.

The relationship between DHEA and depression in adulthood is also unclear. On the positive side, as far as the justification for a clinical trial of DHEA is concerned, Osran *et al*. (1993) reported loss of DHEA diurnal variation in depressed adults. Morales and colleagues (1994) found notably positive effects on feelings of well-being in both men and women (aged 40–70) given replacement doses of DHEA, and a randomized double-blind trial of DHEA replacement in patients with Addison's disease reported significant improvements in self-esteem, mood and fatigue (Hunt *et al*. 2000). Albert and colleagues (2000) found that DHEA was lower in depressed than control adults both in the morning and evening, while values for a partly or completely remitted group were intermediate. Morning DHEA levels were also correlated with severity of depression. Evening cortisol was higher in the depressed group as was their cortisol/DHEA ratio. Young and colleagues' (2002) found that a group of mostly non-melancholic unipolar depressives did not show hypercortisolaemia, but did have elevated cortisol/DHEA ratios both in the morning and evening.

Some other studies have reported inexplicably mixed results: Van Niekerk *et al*. (2001) found that higher endogenous evening DHEA was associated with lower anxiety and negative mood in the morning, while higher endogenous morning cortisols and cortisol/DHEA ratios were associated with various manifestations of negative mood, and reduced cognitive performance. However, DHEA replacement therapy had no effect on any of the mood or performance factors measured. In regularly menstruating women aged 35 to 47, Morrison and her colleagues (2001) found a positive association between endogenous DHEAS and depression scale scores in the younger subset of the cohort, but a negative association in the older women. Harris and her colleagues (2000) reported

that morning cortisol, but not DHEA levels at study entry predicted onsets of depressive episodes in adult women, but did not look at cortisol/DHEA ratios.

Still other studies have reported apparently negative effects of DHEAS: for instance, hypercortisolaemia in depressed adults has been linked to simultaneous hypersecretion of DHEA (Heuser *et al*. 1998), and remission of depression has been associated with falling levels of DHEA and DHEAS in older adults (Fabian *et al*. 2001), as, indeed, was the case in Goodyer and colleagues' clinical follow-up study (Goodyer *et al*. 2001*a*).

At this point it would seem to be a better idea to make sure that DHEA supplementation is effective in adult depression, when levels of DHEA are lower than they are in late adolescence. A small double-blind trial suggests that it may be (Wolkowitz *et al*. 1999), but that work needs to be replicated. On the other hand, there has also been a case report of the induction of mania in a predisposed individual by the use of DHEA (Dean, 2000), so it is worth repeating the point made by Goodyer and colleagues that the apparent safety of oral DHEA may just be the product of ignorance.

CONCLUSIONS

A case for further study of hypercortisolaemia and raised cortisol/DHEAS in children and adolescents with careful attention to the phase of disorder, and the possible effects of psychiatric comorbidity, has certainly been established by Ian Goodyer and his colleagues. I conclude, however, that we need to know more about exactly which sex and developmental groups any depression-related 'functional hypercortisolaemia' really applies to before we undertake treatment trails of DHEAS in children and adolescents. It will important to the developmental analysis of these effects to incorporate direct measures of the HPG axis (particularly oestradiol and testosterone), but also to remember that adolescence and puberty are complex multifaceted processes, with psychological and social components relevant to the study of depression. But here I am preaching to the converted, because, over the years, Ian Goodyer and his colleagues have paid more attention than most of us to trying to integrate analysis at multiple levels of explanation.

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REFERENCES

Albert, J. M., Alozon, J., Paykel, E. S. & Herbertt, J. (2000). Altered salivary dehydroepiandrosterone levels in major depression in adults. *Biological Psychiatry* **48**, 989–995.

Angold, A., Costello, E. J. & Worthman, C. M. (1998). Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychological Medicine* **28**, 51–61.

Angold, A., Costello, E. J. & Worthman, C. M. (1999). Pubertal changes in hormone levels and depression in girls. *Psychological Medicine* **29**, 1043–1053.

Angold, A., Worthman, C. M., & Costello, E. J. (2003). Puberty and depression. In *Gender Differences at Puberty* (ed. C. Hayward), pp. 137–164. Cambridge University Press: New York.

Baulieu, E. E. (1998). Neurosteroids: a novel function of the brain. *Psychoneuroendocrinology* **23**, 963–987.

Birmaher, B., Neal, R., Williamson, D. E., Brent, D. A., Kaufman, J., Dahl, R. E., Perel, J. & Nelson, B. (1996). Childhood and adolescent depression: a review of the past 10 years. Part I. *Journal of the American Academy Child and Adolescent Psychiatry* **35**, 1427–1439.

Bremner, J. D. & Vermetten, E. (2001). Stress and development: behavioral and biological consequences. *Development and Psychopathology* **13**, 473–489.

Brooks-Gunn, J. & Warren, M. P. (1989). Biological and social contributions to negative affect in young adolescent girls. *Child Development* **60**, 40–55.

Cairney, J. (1998). Gender differences in the prevalence of depression among Canadian adolescents. *Canadian Journal of Public Health* **89**, 181–182.

Cicchetti, D. & Rogosch, F. A. (2001). Diverse patterns in neuroendocrine activity in maltreated children. *Development and Psychopathology* **13**, 677–693.

Cowen, P. (2002). Cortisol, serotonin and depression: all stressed out? *British Journal of Psychiatry* **180**, 99–100.

Daley, S. E., Hammen, C. & Uma, R. (2000). Predictors of first onset and recurrence of major depression in young women during the 5 years following high school graduation. *Journal of Abnormal Psychology* **109**, 525–533.

Dean, C. F. (2000). Prasterone (DHEA) and mania. *Annals of Pharmacotherapy* **34**, 1419–1422.

Fabian, T. J., Dew, M. A., Pollock, B. G., Reynolds, C. F., 3rd, Mulsant, B. H., Butters, M. A., Smuda, M. D., Linares, A. M., Trottini, M. & Kroboth, P. D. (2001). Endogenous concentrations of DHEA and DHEA-S decrease with remission of depression in older adults. *Biological Psychiatry* **50**, 767–764.

Foreman, D. & Goodyer, I. (1988). Salivary cortisol hypersecretion in juvenile depression. *Journal of Child Psychology and Psychiatry and Allied Disciplines* **29**, 311–320.

Gold, P. W., Drevets, W. C., Charney, D. S. & Drevets, W. C. (2002). New insights into the role of cortisol and the glucocorticoid receptor in severe depression. *Biological Psychiatry* **52**, 381–385.

Goodman, Y., Annadora, J. B., Cheng, B. & Mattson, M. (1996). Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid b-peptide toxicity in hippocampal neurons. *Journal of Neurochemistry* **66**, 1836–1844.

Goodyer, I. M. (1999). The influence of recent life events on the onset and outcome of major depression in young people. In *Depressive Disorders in Children and Adolescents: Epidemiology, Risk Factors,*

and Treatment (ed. C. Essau and F. Petermann), pp. 237–260. Aronson: Northvale, NJ.

Goodyer, I. M. (2002). Social adversity and mental functions in adolescents at high risk of psychopathology: position paper and suggested framework for future research (review). *British Journal of Psychiatry* **181**, 383–386.

Goodyer, I. M. & Altham, P. M. E. (1991). Lifetime exit events and recent social and family adversities in anxious and depressed school-age children and adolescents – II. *Journal of Affective Disorders* **21**, 229–238.

Goodyer, I. M., Kolvin, I. & Gatzanis, S. (1985). Recent undesirable life events and psychiatric disorder in childhood and adolescence. *British Journal of Psychiatry* **147**, 517–523.

Goodyer, I. M., Kolvin, I. & Gatzanis, S. (1986). Do age and sex influence the association between recent life events and psychiatric disorders in children and adolescents? – A controlled enquiry. *Journal of Child Psychology and Psychiatry and Allied Disciplines* **27**, 681–687.

Goodyer, I. M., Wright, C. & Altham, P. M. E. (1988). Maternal adversity and recent stressful life events in anxious and depressed children. *Journal of Child Psychology and Psychiatry and Allied Disciplines* **29**, 651–667.

Goodyer, I. M., Wright, C. & Altham, P. M. E. (1990). The friendships and recent life events of anxious and depressed school-age children. *British Journal of Psychiatry* **156**, 689–698.

Goodyer, I. M., Herbert, J., Moor, S. & Altham, P. M. E. (1991). Cortisol hypersecretion in depressed school-aged children and adolescents. *Psychiatry Research* **37**, 237–244.

Goodyer, I. M., Ashby, L., Altham, P., Vize, C. & Cooper, P. (1993). Temperament and major depression in 11 to 16 year olds. *Journal of Child Psychology and Psychiatry and Allies Disciplines* **34**, 1409–1423.

Goodyer, I. M., Herbert, J., Altham, P. M. E., Pearson, J., Secher, S. & Shiers, H. (1996). Adrenal secretion during major depression in 8- to 16-year-olds: I. Altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation. *Psychological Medicine* **26**, 245–256.

Goodyer, I. M., Herbert, J., Secher, S. & Pearson, J. (1997*a*). Short-term outcome of major depression: I. Comorbidity and severity at presentation as predictors of persistent disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* **36**, 179–187.

Goodyer, I. M., Herbert, J., Tamplin, A., Secher, S. & Pearson, J. (1997*b*). Short-term outcome of major depression: II. Life events, family dysfunction, and friendship difficulties as predictors or persistent disorder. *Journal of American Academy of Child and Adolescent Psychiatry* **36**, 474–480.

Goodyer, I. M., Herbert, J. & Altham, P. M. E. (1998). Adrenal steroid secretion and major depression in 8- to 16-year-olds: III. Influence of cortisol/DHEA ratio at presentation on subsequent rates of disappointing life events and persistent major depression. *Psychological Medicine* **28**, 265–273.

Goodyer, I. M., Herbert, J., Tamplin, A. & Altham, P. M. E. (2000). First-episode major depression in adolescents: affective, cognitive and endocrine characteristics of risk status and predictors of onset. *British Journal of Psychiatry* **176**, 142–149.

Goodyer, I. M., Park, R. J. & Herbert, J. (2001*a*). Psychosocial and endocrine features of chronic first-episode major depression in 8–16 year olds. *Society of Biological Psychiatry* **50**, 351–357.

Goodyer, I. M., Park, R. J., Netherton, C. & Herbert, J. (2001*b*). Possible role of cortisol and dehydroepiandrosterone in human development and psychopathology. *British Journal of Psychiatry* **179**, 243–249.

Goodyer, I. M., Herbert, J. & Tamplin, A. (2003). Psychoendocrine antecedents of persistent first-episode major depression in adolescents: a community-based longitudinal enquiry. *Psychological Medicine* **33**, 601–610.

Gubba, E. M., Netherton, C. M. & Herbert, J. (2000). Endangerment of the brain by glucocorticoids: experimental and clinical evidence. *Journal of Neurocytology* **29**, 439–449.

Gunnar, M. R. & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm: potential indices of risk in human development. *Development and Psychopathology* **13**, 515–538.

Hankin, B. L., Abramson, L. Y., Moffitt, T. E., Silva, P. A., McGee, R. & Angell, K. E. (1998). Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology* **107**, 128–140.

Harris, T. O., Borsanyi, S., Messari, S., Standord, K., Cleary, S. E., Shiers, H. M., Brown, G. W. & Herbert, J. (2000). Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *British Journal of Psychiatry* **177**, 505–510.

Herbert, J., Goodyer, I., Altham, P., Pearson, J., Secher, S. & Shiers, H. (1996). Adrenal secretion and major depression in 8- to 16-year-olds: II. Influence of comorbidity at presentation. *Psychological Medicine* **26**, 257–263.

Heuser, I., Deuschle, M., Luppa, P., Schweiger, U., Standhardt, H., & Weber, B. (1998). Increased diurnal plasma concentrations of dehydroepiandrosterone in depressed patients. *Journal of Clinical Endocrinology and Metabolism* **83**, 3130–3133.

Hinson, J. P. & Raven, P. W. (1999). DHEA deficiency syndrome: a new term for old age? *Journal of Endocrinology* **163**, 1–5.

Hunt, P. J., Gurnell, E. M., Huppert, F. A., Richards, C., Prevost, A. T., Wass, J. A. H., Herbert, J. & Chatterjeee, K. K. (2000). Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *Journal of Clinical Endocrinology and Metabolism* **85**, 4650–4656.

Kaminska, M., Harris, J., Gijsbers, K. & Dubrovsky, B. (2000). Dehydroepiandrosterone sulfate (DHEAS) counteracts decremental effects of corticorterone on dentate gyrus LTP. Implication for depression. *Brain Research Bulleting* **52**, 229–234.

Karishma, K. K. & Herbert, J. (2002). Dehydroepiandrosterone (DHEA) stimulates neurogenesis in the hippocampus of the rat, promotes survival of newly formed neurons and prevents corticosterone-induced suppression. *European Journal of Neuroscience* **16**, 445–453.

Katz, S. & Morales, A. J. (1998). Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DS) as therapeutic options in menopause. *Seminars in Reproductive Endocrinology* **16**, 161–170.

Kaufman, J. & Charney, D. (2001). Effects of early stress on brain structure and function: implications for understanding the relationship between child maltreatment and depression. *Development and Psychopathology* **13**, 451–471.

Kimonides, V. G., Khatibi, N. H., Svendsen, C. N., Sofroniew, M. V. & Herbert, J. (1998). Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) protect hippocampal neurons against excitatory amino acid-induced neurotoxicity. *Proceedings of the National Academy of Sciences of the United States of America* **95**, 1852–1857.

Klimes-Dougan, B., Hasting, P. D., Granger, D. A. & Zahn-Waxler, C. (2001). Adrenocortical activity in at-risk and normally developing adolescents: individual differences in salivary cortisol basal levels, diurnal variation, and responses to social challenges. *Development and Psychopathology* **13**, 695–719.

Kroboth, P. D., Salek, F. S., Pittenger, A. L., Fabian, T. J. & Frye, R. F. (1999). DHEA and DHEA-S: a review. *Journal of Clinical Pharmacology* **39**, 327–348.

Labrie, F., Belanger, A., Cusan, L., Gomez, J. L. & Candas, B. (1997). Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *Journal of Clinical Endocrinology and Metabolism* **82**, 2396–2402.

Larkin, M. (1998). DHEA: will science confirm the headlines? *Lancet* **352**, 208.

Lewinsohn, P. M., Allen, N. B., Seeley, J. R. & Gotlib, I. H. (1999). First onset versus recurrence of depression: differential processes of psychosocial risk. *Journal of Abnormal Psychology* **108**, 483–489.

Lupien, S. J., King, S., Meaney, M. J. & McEwen, B. S. (2000). Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biological Psychiatry* **48**, 976–980.

McGee, R., Feehan, M., Williams, S. & Anderson, J. (1992). DSM-III disorders from age 11 to age 15 years. *Journal of the American Academy of Child and Adolescent Psychiatry* **31**, 51–59.

Martina, V., Origlia, C., Bruno, G. A., Messina, M., Ferri, M. & Perscarmona, G. P. (2001). Serum DHEAS levels correlate with platelet cGMP in normal women. *Journal of Endocrinological Investigation* **24**, RC28–RC30.

Meyer, S. E., Chrousos, G. P. & Gold, P. W. (2001). Major depression and the stress system: a life span perspective. *Development and Psychopathology* **13**, 565–580.

Morales, A. J., Nolan, J. J., Nelson, J. C. & Yen, S. S. (1994). Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *Journal of Clinical Endocrinology and Metabolism* **78**, 1360–1367.

Morales, A. J., Haurich, R. H., Hwang, J. Y., Asajura, H. & Yen, S. C. (1998). The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clinical Endocrinology* **49**, 421–432.

Morrison, M. F., Ten, H. T., Freeman, E. W., Sammel, M. D. & Grisso, J. A. (2001). DHEA-S levels and depressive symptoms in a cohort of African American and Caucasian women in the late reproductive years. *Biological Psychiatry* **50**, 705–711.

Nottelmann, E. D., Susman, E. F., Dorn, L. D., Inoff-Germain, G., Loriaux, D. L., Cutler, G. B. & Chrousos, G. P. (1987*a*). Developmental processes in early adolescence: relations among chronological age, pubertal stage, height, weight, and serum levels of gonadotropins, sex steroids, and adrenal androgens. *Journal of Adolescent Health Care* **8**, 246–260.

Nottelmann, E. D., Susman, E. J., Inoff-Germain, G., Cutler, G. B., Loriaux, D. L. & Chrousos, G. P. (1987*b*). Developmental processes in early adolescence: relationships between adolescent adjustment problems and chronological age, pubertal stage, and puberty-related serum hormone levels. *Journal of Pediatrics* **110**, 473–480.

Osran, H., Reist, C., Chen, C. C., Lifrak, E. T., Chicz-DeMet, A. & Parker, L. N. (1993). Adrenal androgens and cortisol in major depression. *American Journal of Psychiatry* **150**, 806–809.

Paikoff, R. L., Brooks-Gunn, J. & Warren, M. P. (1991). Effects of girls' hormonal status on depressive and aggressive symptoms over the course of one year. *Journal of Youth and Adolescence* **20**, 191–215.

Pariante, C. M. & Miller, A. H. (2001). Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biological Psychiatry* **49**, 391–404.

Reus, V. I. & Wolkowitz, O. M. (2001). Antiglucocorticoid drugs in the treatment of depression. *Expert Opinion on Investigational Drugs* **10**, 1789–1796.

Salek, F. S., Bigos, K. L. & Kroboth, P. D. (2002). The influence of hormones and pharmaceutical agents on DHEA and DHEA-S concentrations: a review of clinical studies. *Journal of Clinical Psychopharmacology* **42**, 247–266.

Seeman, M. V. (1997). Psychopathology in women and men: focus on female hormones. *American Journal of Psychiatry* **154**, 1641–1647.

Silberg, J., Pickles, A., Rutter, M., John, H., Simonoff, E., Maes, H., Carbonneau, R., Murrelle, L., Foley, D. & Eaves, L. (1999). The influence of genetic factors and life stress on depression among adolescent girls. *Archives of General Psychiatry* **56**, 225–232.

Silberg, J., Rutter, M. & Eaves, L. (2001). Heterotypic continuity in symptoms of anxiety and depression in pre-pubertal and pubertal girls. *Biological Psychiatry* **49**, 1040–1049.

Strickland, P. L., Deakin, J. F. W., Percival, C., Dixon, J., Gater, R. A. & Goldberg, D. P. (2002). Bio-social origins of depression in the community: interactions between social adversity, cortisol and serotonin neurotransmission. *British Journal of Psychiatry* **180**, 168–173.

Susman, E. J., Inoff-Germain, G., Nottelmann, E. D., Loriaux, D. L., Cutler, G. B. & Chrousos, G. P. (1987*a*). Hormones, emotional dispositions, and aggressive attributes in young adolescents. *Child Development* **58**, 1114–1134.

Susman, E. J., Nottelmann, E. D., Inoff-Germain, G., Dorn, L. D. & Chrousos, G. P. (1987*b*). Hormonal influences on aspects of psychological development during adolescence. *Journal of Adolescent Health Care* **8**, 492–504.

Thapar, A. & McGuffin, P. (1994). A twin study of depressive symptoms in childhood. *British Journal of Psychiatry* **165**, 259–265.

Thapar, A., Harold, G. & McGuffin, P. (1998). Life events and depressive symptoms in childhood – shared genes or shared adversity? A research note. *Journal of Child Psychology and Psychiatry* **39**, 1153–1158.

Toran-Allerand, C., Singh, M. & Setalo, G. (1999). Novel mechanisms of estrogen action in the brain: new player in an old story. *Frontiers in Neuroendocrinology* **20**, 91–121.

Van Niekerk, J. K., Huppert, F. A. & Herbert, J. (2001). Salivary cortisol and DHEA: association with measures of cognition and well-being in normal older men, and effects of three months of DHEA supplementation. *Psychoneuroendocrinology* **26**, 591–612.

Velez, C. N., Johnson, J. & Cohen, P. (1989). A longitudinal analysis of selected risk factors of childhood psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry* **28**, 861–864.

Viau, V. (2002). Functional cross-talk between the hypothalamic–pituitary–gonadal and adrenal axes. *Journal of Neuroendocrinology* **14**, 506–513.

Weissman, M. M., Bland, R. C., Canino, G. J., Faravelli, C., Greenwald, S., Hwu, H. G., Joyce, P. R., Karam, E. G., Lee, C. K., Lellouch, J., Lepine, J. P., Newman, S. C., Rubio-Stipec, M., Wells, J. E., Wickramaratne, P. J., Wittchen, H. & Yeh, E. K. (1996). Cross-national epidemiology of major depression and bipolar disorder. *Journal of the American Medical Association* **276**, 293–299.

Weissman, M. M. & Klerman, G. L. (1977). Sex differences and the epidemiology of depression. *Archives of General Psychiatry* **34**, 98–111.

Wickelgren, I. (1997). Estrogen stakes claim to cognition. *Science* **276**, 675–678.

Wolkowitz, O. M. & Reus, V. I. (1999). Treatment of depression with antiglucocorticoid drugs. *Psychosomatic Medicine* **61**, 698–720.

Wolkowitz, O. M., Reus, V. I., Keebler, A., Nelson, N., Friedland, M., Brizendine, L. & Roberts, E. (1999). Double-blind treatment of major depression with dehydroepiandrosterone. *American Journal of Psychiatry* **156**, 646–649.

Young, A. H., Gallagher, P. B. & Porter, R. J. (2002). Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. *American Journal of Psychiatry* **159**, 1237–1239.

Young, D. G., Skibinski, G., Mason, J. I. & James, K. (1999). The influence of age and gender on serum dehydropeiandrosterone suphate (DHEA-S), IL-6, IL-6 soluble receptor (IL-6SR) and transforming growth factor beta 1 (TGF-[beta]1) levels in normal healthy blood donors. *Clinical and Experimental Immunology* **117**, 476–481.