Exposure to Postnatal Depression Predicts Elevated Cortisol in Adolescent Offspring
Sarah L. Halligan, Joe Herbert, Ian M. Goodyer, and Lynne Murray

**Background:** Animal research shows that early adverse experience results in altered glucocorticoid levels in adulthood, either raised basal levels or accentuated responses to stress. If a similar phenomenon operates in humans, this suggests a biological mechanism whereby early adversity might transmit risk for major depression, glucocorticoid elevations being associated with the development of this disorder.

**Methods:** We measured salivary cortisol at 8:00 am and 8:00 pm over 10 days in 13-year-old adolescents who had (n = 48) or had not (n = 39) been exposed to postnatal maternal depression.

**Results:** Maternal postnatal depression was associated with higher, more variable morning cortisol in offspring, a pattern previously found to predict major depression.

**Conclusions:** Early adverse experiences might alter later steroid levels in humans. Because maternal depression confers added risk for depression to children, these alterations might provide a link between early events and later psychopathology.

**Key Words:** Longitudinal, adolescents, cortisol, maternal depression, postnatal depression

Maternal depression has been associated with a variety of adverse outcomes in offspring, manifest as early as the neonatal period and through subsequent stages of development to adulthood (Goodman and Gotlib 2001; Murray and Cooper 2003). Ultimately, the offspring of depressed mothers are themselves at higher risk for major depression (Beardslee et al 1993; Nomura et al 2002; Weissman et al 1986); this observation has stimulated efforts to understand the biological mechanisms involved in the transmission of intergenerational risk.

Individual differences in the activity of the hypothalamic-pituitary-adrenal axis (HPA) have recently been shown to be associated with differences in the risk for depression. Elevations in morning cortisol levels, particularly the occurrence of one or more very high morning cortisol values, predict the development of depressive disorder in those exposed to psychosocial risk factors for depression (Goodyer et al 2000; Harris et al 2000). The question, therefore, is whether early adversity can result in long-standing alterations in the HPA axis in humans. If this were the case, it might represent at least one process mediating the acquisition of risk during early life for later mental disorder.

There is considerable experimental evidence that early experience can alter later HPA activity. In general, early adversity increases either the basal secretion of glucocorticoids in adult life or the reactivity of the HPA axis to stress. In adult rats, this includes increased corticotrophin-releasing factor and glucocorticoid receptor gene expression in the hypothalamus and hippocampus, as well as enhanced behavioral response to stress in those separated from their mothers for varying periods during the postnatal period (Champagne and Meaney 2001; Francis et al 2002; Lehmann et al 2002; Weaver et al 2001). There are no comparable results for adult primates, though early maternal stress, resulting from the imposition of unpredictable foraging demands, has been associated with lasting corticotrophin-releasing factor elevations in the offspring of macaque monkeys (Coplan et al 2001), however, other paradigms examining early rearing conditions have produced divergent findings. For example, peer- versus mother-rearing has variously been found to have no effect on basal cortisol in infant rhesus monkeys (Winslow et al 2003) or to reduce both basal adrenocorticotropic hormone and cortisol levels (Clarke et al 1998). Marmoset monkeys exposed to maternal separations on postnatal days 2–28 showed reduced basal cortisol at 18–20 weeks (Dettling et al 2002).

In humans, some evidence for the role of early experience is emerging. Three-year-old children exposed to maternal depression in the postnatal period had higher salivary cortisol levels than nonexposed infants (Hessl et al 1998), although this effect was not observed when the sample was reassessed at 7 years (Ashman et al 2002). Salivary cortisol was elevated in 4.5-year-old children whose mothers were concurrently depressed only if maternal depression had also been present in the first 12 months postpartum (Essex et al 2002). The question of whether there are longer-term associations between early exposure to maternal depression and cortisol levels in offspring has not previously been addressed. We measured salivary cortisol in adolescents who were or were not exposed to maternal postnatal depression (PND). Our aims were 1) to test the prediction that maternal PND is associated with elevated morning cortisol and more extreme morning values in adolescents; and 2) to examine whether any association between maternal PND and adolescent cortisol levels is mediated by other factors (e.g., life stresses) known to contribute to the association between maternal depression and child development.

**Methods and Materials**

Participants provided written informed consent before taking part in this Cambridgeshire Local Ethics Committee–approved study. Assessments were carried out by mental-health professionals who were both trained and experienced in conducting clinical interviews. Assessors were supported by a clinical team, and diagnostic decisions were reviewed and confirmed through consensus conference.
Participants
Participants were part of a prospective, longitudinal study of the development of children of postnatally depressed and well women (Murray 1992). The sample was originally recruited at 2 months postpartum, with further assessments when the children were 18 months, 5 years, and 8 1/2 years old, in addition to the current, 13-year follow-up. At initial recruitment, a community sample of primiparous mothers of healthy, full-term infants was screened for PND by administration of the Edinburgh Postnatal Depression Scale (EPDS; Cox et al 1987) at 6 weeks postpartum. Women scoring greater than 12 on the EPDS were interviewed; 61 women who met research diagnostic criteria (Spitzer et al 1978) for depressive disorder were identified, 58 of whom were recruited for the study. Forty-two nondepressed mothers randomly selected from the same postnatal population were also recruited.

Fifty-three PND-group families (91.4%) and 41 comparison-group families (97.6%) were retained at 13 years. Of these, five PND-group and two control-group adolescents did not complete cortisol collections, owing to refusal (n = 3), medical ineligibility (diabetes, n = 1), and scheduling problems (n = 3). The final sample consisted of 48 PND and 39 comparison families.

Maternal Measures
Mental State. The presence and timing of maternal depression were assessed with the Structured Clinical Interview for DSM-IV (Spitzer et al 1995). Because maternal clinical interviews were similarly conducted at 18-month, 5-year, and 8 1/2-year assessments, detailed longitudinal information relating to maternal mental state was available and was used to establish 1) the presence or absence of current maternal depression; and 2) the overall duration of maternal depression, calculated as the total number of months of depression over the offspring’s lifetime.

Current maternal psychological symptoms were assessed with the 28-item version of the General Health Questionnaire (GHQ) (Goldberg and Williams 1988; Goldberg et al 1997). Few mothers met diagnostic criteria for current depression at 13 years. Therefore, we used the GHQ depression subscale (GHQ-D) scores as our primary measure of current maternal depression to increase the power of our analyses. Because scores on the GHQ-D were highly skewed by a large number of zero responses, we dichotomized scores based on the presence or absence of any depressive symptom (van Hemert et al 1995).

Parental Conflict. Mothers completed 10-point rating scales on perceived and felt criticism as a measure of parental conflict (Hooley and Teasdale 1989).

Adolescent Measures
Mental State. Diagnostic interviews with adolescents were conducted with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (Kaufman et al 1997). Participants completed the Mood and Feelings Questionnaire, a validated self-report measure of current depressive symptomatology (Angold et al 1995). Only a small number of individuals met diagnostic criteria for past or current depressive disorder; therefore, we adopted Mood and Feelings Questionnaire scores as the primary index of current depression.

Life Events. Adolescents completed an interview assessment of the occurrence of undesirable events and difficulties in the preceding 12 months (Goodyer et al 2000). Few individuals reported more than one undesirable event; therefore, we coded the presence or absence of any life event.

Puberty. In addition to height and weight, Tanner stage (Tanner 1966) was obtained by adolescent self-report guided by standard line drawings (Netherton et al 2004).

Cortisol. Adolescents collected saliva samples at 8:00 AM and 8:00 PM for 10 consecutive school days, following instructions supplied for home completion. We measured cortisol with enzyme-linked immunosorbent assay on 20-μL samples of saliva without extraction (antibody, Cambio, Cambridge, United Kingdom). Intra-assay variation was 4.1%, and interassay variation was 7.6%. There is a good correlation between salivary and plasma cortisol concentrations (Goodyer et al 1996), and salivary levels represent approximately 5% of those in the blood.

Salivary cortisol is subject to significant day-to-day fluctuations. The use of 10 sampling days allowed us 1) to derive a relatively accurate index of mean cortisol for each individual; and 2) to examine intra-individual variability over the 10-day sampling period, for both morning and evening saliva collections. We used the coefficient of variation (\(\text{variance/mean}/n\)) to index variability, to control for the fact that variance increased with mean levels. Arcsine transformation of the resulting scores created an unbounded variable suitable for statistical tests. In addition, we coded individuals according to whether they were “peak positive” for 8:00 AM or 8:00 PM cortisol, that is, one or more of their cortisol concentrations fell above the 90th percentile for the sample mean (percentiles calculated separately by gender and collection time) (Goodyer et al 2000; Harris et al 2000).

Data Analysis Strategy
We used simple group comparisons to examine the effects of PND on cortisol measures. When group differences were observed, we investigated the role of potential mediators (parental conflict, adolescent depressive symptoms, and adolescent life events), using regression analyses with blocked entry procedures to examine whether these factors explained associations between adolescent salivary cortisol and maternal PND. We also examined possible mediating effects of current maternal depressive symptoms and the overall duration of maternal depression in a separate set of within-group (PND vs. no PND) analyses, both these factors being highly confounded with PND. We checked continuous dependent variables for normality before carrying out parametric tests, and for each analysis we verified that all tests assumptions were met. No transformation of cortisol variables was required. Given the modest effect sizes anticipated in association with PND (a very distal predictor of offspring cortisol), the relatively small sample size, and the presence of clear hypotheses, we adopted a \(p\) value of .05 as significant for the current study.

Results
We assessed 87 mothers and their 13-year-old adolescent offspring (44 girls, 43 boys). The sample comprised white, low-to-middle-class families, consistent with the Cambridge population from which it was drawn. The PND and control groups were comparable in terms of demographic characteristics (Table 1), including age in months, gender distribution, socioeconomic status, parental marital status, height, weight, mean Tanner Stage, body mass index, and birth weight. Adolescents in the PND group were less likely to have been breast-fed to 6 weeks than those in the control group (Cooper et al 1993). Consistent with prior reports, girls had higher mean 8:00 AM cortisol than boys (girls = 3.20 ± 1.19 ng/mL, boys = 2.70 ± 1.10 ng/mL; \(t(85) = 2.07, p = .042\)), and level of pubertal development was positively associated with mean 8:00 AM cortisol (\(r = .20, p = .035\)).
Thus, group differences in 8:00 AM mean cortisol and cortisol variability were driven by differences in the occurrence of cortisol values at the high, rather than the low, end of the range. Accordingly, a higher proportion of individuals in the PND than in the control group were peak positive (i.e., one or more cortisol concentrations greater than the 90th percentile) for morning cortisol (Table 2). There were no significant group differences in 8:00 PM cortisol measures.

### Multivariate Analyses

We considered maternal marital/partner conflict, current adolescent depressive symptoms, and adolescent life events in the 12 months before interview as potential mediators between maternal PND and morning cortisol in adolescents. Adolescent life events were not associated with maternal PND, and we did not examine them further; however, PND was associated with more maternal partner conflict and higher adolescent depressive symptoms, justifying further investigation of these measures (Table 1). We conducted linear regression analyses to examine 8:00 AM cortisol mean and variability. In each instance, we entered child gender, Tanner stage, breast-feeding status, child depressive symptoms, and maternal partner conflict into the regression equation in the first step, and examined the additional contribution of PND in a second step (Table 3). Maternal PND significantly predicted variance in 8:00 AM cortisol measures over and above other factors. Pubertal development was significantly, independently, and positively associated with mean 8:00 AM cortisol, and child depressive symptoms, gender, and breast-feeding status also showed effects at the trend level of significance (p < .10).

### Interacting Maternal Depression

Mothers with PND were significantly more likely to experience further depression in the following years than non-PND...
mothers. Eighty-three percent of the PND-group mothers experienced an episode of depression subsequent to the postnatal period, versus 33% of control-group mothers [$\chi^2(1) = 22.60, p < .0005]$. Therefore, we considered overall duration of maternal depression as a possible contributor to the association between maternal PND and 8:00 AM cortisol measures in adolescents. The extent to which overall duration of maternal depression was confounded with the occurrence of PND precluded controlling for this factor across groups. Therefore, we used correlational analyses to examine associations between duration of maternal depression and adolescent cortisol measures separately for the PND and control groups. Number of months of maternal depression showed no association with offspring 8:00 AM cortisol measures, within either the PND group (mean cortisol $r = -.10$, variability $r = .11$, peak positive $r = -.05$; all $p > .10$) or the control group (for mean cortisol $r = -.31$, all $p > .05$; variability $r = -.10$, ns; peak positive $r = -.25$, ns), although in the latter there was a trend-level correlation with mean 8:00 AM cortisol, in the opposite-to-predicted direction.

Mothers who became depressed postnatally also had more symptoms of depression than control-group mothers at the time of the current assessment (details in Table 1), which suggests that concurrent maternal symptoms could be contributing to higher morning cortisol levels in the PND-group adolescents; however, when we compared 8:00 AM cortisol levels for PND-group adolescents vs. control group, reported current depressive symptoms, precluding confounding with the occurrence of PND precluded controlling for this factor across groups. Therefore, we used correlational analyses to examine associations between duration of maternal depression and adolescent cortisol measures separately for the PND and control groups. Number of months of maternal depression showed no association with offspring 8:00 AM cortisol measures, within either the PND group (mean cortisol $r = -.10$, variability $r = .11$, peak positive $r = -.05$; all $p > .10$) or the control group (for mean cortisol $r = -.31$, all $p > .05$; variability $r = -.10$, ns; peak positive $r = -.25$, ns), although in the latter there was a trend-level correlation with mean 8:00 AM cortisol, in the opposite-to-predicted direction.

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### Discussion

We show that maternal depression occurring in the postnatal period is associated with higher and more variable morning cortisol in adolescents 13 years later. Furthermore, current depressive symptoms in the mother or the adolescent, maternal partner conflict, overall duration of maternal depression, and the experience of undesirable life events by the adolescent, did not explain the observed association between maternal PND and adolescent cortisol. To our knowledge, this is the first study to demonstrate a direct association between maternal PND and cortisol levels in adolescent offspring.

The current findings are striking in view of the differences in cortisol that have been found to predict the development of depressive disorder. Two longitudinal studies examined salivary cortisol in adolescents and adult women with psychosocial risk factors for the development of depression (Goodyer et al 2000; Harris et al 2000). For both cohorts, individuals who had higher mean morning salivary cortisol levels, or one or more very high morning cortisol values, during initial, repeated cortisol assessments, were more likely to develop depression over a 12-month follow-up period. Thus, perturbations in morning cortisol might represent an antecedent risk factor for depressive disorder.

Research on cross-fostered rat pups has provided evidence for nongenetic, intergenerational transmission of stress reactivity and HPA-axis activity via quality of maternal care (Francis et al 1999). In humans, the availability of a sensitive caregiver serves to buffer HPA responses to environmental demand in the developing infant (Gunnar 1990; Nachmias et al 1996), and impairments in maternal responsiveness have been associated with accentuated cortisol reactivity in infants (Dawson and Ashman 2000; Field 1994). Maternal PND has detrimental effects on care-giving behaviors (Murray et al 1993, 1996). Thus, a compelling interpretation of the current data is that elevated cortisol in the PND group is an enduring consequence of adversity in infancy resulting from impairments in mother–infant interactions.

Experimental studies have emphasized the primary of experiences occurring during early development in determining HPA axis parameters (Anisman et al 1998; Coplan et al 2001). In nonhuman primates there seems to be a developmental window beyond which the effects of early social adversity can no longer be reversed by a change in social environment (Harlow and Suomi 1971). This period corresponds to 24–30 weeks postpartum in humans, suggesting that early infancy might be a time during which developing neurobiological systems are uniquely sensitive to environmental influences. The current findings are in keeping with this possibility. Maternal depression occurring in the postnatal period was related to cortisol in adolescent off-

### Table 3. Regression Analyses Examining the Prediction of 8:00 AM Cortisol Concentrations in Adolescents

<table>
<thead>
<tr>
<th>Variables Entered</th>
<th>Step 2</th>
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<th>Step 2</th>
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<tr>
<td></td>
<td>$R^2$</td>
<td>SE (B)</td>
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<td>SE (B)</td>
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<td>.25</td>
<td>.18</td>
<td>.036</td>
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<td>.06</td>
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<td>Tanner stage</td>
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<td>.22</td>
<td>.039</td>
<td>.043</td>
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<td>Adolescent depressive symptoms</td>
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<td>.002</td>
<td>.003</td>
<td>.08</td>
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<tr>
<td>Maternal dyadic conflict</td>
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<td>.05</td>
<td>-.11</td>
<td>.013</td>
<td>.015</td>
<td>.09</td>
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<tr>
<td>Breast-fed to 6 weeks (yes/no)</td>
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<td>.25</td>
<td>.20+</td>
<td>.11</td>
<td>.068</td>
<td>.18</td>
</tr>
<tr>
<td>Step 2</td>
<td>Delta $R^2$</td>
<td>SE (B)</td>
<td>$\beta$</td>
<td>Delta $R^2$</td>
<td>SE (B)</td>
<td>$\beta$</td>
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<tr>
<td>Postnatal depression</td>
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<td>.25</td>
<td>.22</td>
<td>.195</td>
<td>.069</td>
<td>.32</td>
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<tr>
<td>Overall Model</td>
<td>$R^2$</td>
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<td>$R^2$</td>
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<td></td>
<td>.22</td>
<td>.75</td>
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<td>.16</td>
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B, unstandardized coefficient; $\beta$, standardized coefficient.

*p < .10.

*p < .05.

*p < .01.

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spring, but measures of maternal depression occurring subsequent to that time were not.

Although our interpretation of the current data emphasizes the primacy of the early environment, there are genetic factors regulating individual differences in levels of cortisol (Bartels et al. 2003; Meikle et al 1988). Nothing is known of potential genetic contributions to the features of cortisol secretion or their responses to environmental demand during adolescence, or of whether associations between adrenal steroids and the onset of depression are genetically mediated. At this stage, gene–environment interactions, to explain both variations in cortisol and the onset of major depression, have yet to be specified. Similarly, intrauterine environment has been shown to have implications for offspring HPA axis development (Maccari et al 2003). To the extent that postnatally depressed mothers also differ from non-depressed mothers in the prenatal period, intrauterine effects might also be confounded with those of early environment.

It could be argued that the reliance on salivary cortisol collections limits the conclusions that can be drawn from the current research. First, prior research with adults has indicated poor compliance with collection protocols (Kudielka et al 2003; Yehuda et al 2003). Our restriction of sampling to school days, the involvement of both parents and children in salivary collections, and the long-term nature of the current study might have enhanced protocol adherence. Nonetheless, deviations in collection times might have contributed to variability in morning and evening cortisol levels. Second, morning cortisol was reported without reference to the interval between awakening and collection time (Puressner et al 2003), and reported levels might not reflect the apex of early waking secretion. Third, although salivary cortisol provides a good index of plasma cortisol (Goodyer et al 1996), its relationship to the central measures of HPA-axis activity that have been studied in animal research is complex. Further research that uses biological challenge procedures or assessments of glucocorticoid receptor activity might elucidate the biological processes underlying the observed cortisol alterations.

Whatever the exact nature of the factors determining the marked differences in morning cortisol levels observed in adolescents exposed to maternal depression early in life, it remains to be seen how such differences might contribute to any subsequent psychopathology. The role of the HPA axis in the etiology of depression is still being defined (Coven 2002; Gold et al 2002), and emergent observations that elevations in morning cortisol secretion are related to the development of depression require further study (Angold 2003). There are also broader implications to be considered. Elevated glucocorticoids increase the susceptibility of the brain to adverse events (Gubba et al 2000; Sapolsky et al 2000) and can have deleterious effects on hippocampal structure and function (Newcomer et al 1999; Sapolsky 2000). It will be of considerable interest to examine whether the observed alterations in cortisol secretion have implications for emotional and cognitive development, as well as for affective disorders.

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