Psychological Medicine, 1983, **13**, 465–468
Printed in Great Britain

EDITORIAL

Models of depression in primates[1]

Once the object of considerable scepticism and even ridicule (for example, Kubie, 1953), animal models of human psychopathology have been gaining increasing respectability among research and clinical workers alike during the past two decades. Among the most respectable animal models at present are those of depression in primates. Much of the credit for the current scientific interest in primate models clearly belongs to Harry F. Harlow, for over 40 years Professor of Psychology at the University of Wisconsin in Madison. Professor Harlow, a dominant figure in the history of psychology and a pioneer in behavioural primatology, died in December 1981, at the age of 76.

Twenty years ago Harlow and his students published the seminal study of mother–infant separation in non-human primate subjects (Seay *et al.* 1962). They reported that rhesus infant monkeys who had established a strong social bond with their mothers exhibited dramatic reactions when separated from them for a 3-week period. Some of these infant monkeys displayed a sequence of symptoms that resembled to a remarkable degree the classic reports by Spitz (1946) and Bowlby (1960, 1973) of depressive reactions shown by human infants and young children separated from their parents – both exhibited extreme agitation (protest) immediately after separation, followed within days by a contrasting period of withdrawal, lethargy, and depressed affect. Because many clinicians had interpreted these symptoms in human infants and children as representing depressive disorders (Spitz coined the term 'anaclitic depression' for the syndrome in his infant sample), Harlow claimed that the parallel behaviour patterns in his separated infant monkeys also represented depression.

Harlow's report of depressive reactions to maternal separation in young macaques was soon replicated by Hinde and his colleagues at Cambridge (Hinde *et al.* 1966) and by Kaufman & Rosenblum (1967) in New York. More recently, other research workers have found striking parallels between physiological concomitants of separation-induced depressive behaviour in young monkeys and certain physiological changes associated with the onset of depressive episodes in adult humans, including measures of pituitary–adrenal activity (Levine, 1983; Suomi 1983*a*), catecholamine and serotonin metabolism (Kraemer & McKinney, 1979; Suomi *et al.* 1981), EEG patterns during sleep, and circadian rhythm shifts (Reite *et al.* 1981). Moreover, somatic treatments known to be therapeutically effective for at least some depressed human patients likewise appear to minimize or even reverse depressive separation reactions in macaque subjects (Lewis & McKinney, 1976; Suomi *et al.* 1978). These findings provide strong arguments for the validity of separation-based primate models of depression.

However, Professor Harlow's contribution to the development of animal modelling of human psychopathology went well beyond the 'mere' demonstration of what has proved to be a viable, if not valuable, primate model of depression. Perhaps more important was his general strategy for creating useful animal models. Most previous attempts to develop animal models of human psychopathology had been essentially *symptom-based*, i.e. the investigator(s) had discovered (often serendipitously) that certain behavioural reactions to experimental stimuli in their animal subjects seemed to resemble common symptoms of known human disorders. Thus, Pavlov (1927) had noticed that some dogs developed severe anxiety when exposed to difficult learning problems, and from these observations he developed an animal model of 'experimental neurosis', while Seligman (1975) and his colleagues similarly developed the 'learned helplessness' model of reactive depression from serendipitous observations of seemingly maladaptive behaviour by dogs previously subjected to inescapable shock (Overmeir & Seligman, 1967; Seligman, 1975).

Harlow, in contrast, took a different approach. His strategy for developing an animal model of

[1] Address for correspondence: Dr S. J. Suomi, Department of Psychology and Primate Laboratory, University of Wisconsin, Madison, WI 53706, USA.

a human problem centred on recreating, as faithfully as possible, known *aetiological* factors for the human disorder in his rhesus monkeys, then determining how closely the reactions of his subjects resembled known human symptoms. In other words, he first sought to establish to what degree the human phenomenon generalized to rhesus monkeys *before* studying the phenomenon in his monkeys with sufficient experimental rigor as to provide information and insights that could be profitably utilized by research workers and clinicians working on the human psychopathology in question (cf. Harlow *et al.* 1972). This strategy provided the basis for his original separation studies, and it characterized all of his subsequent efforts towards creating primate models of depression and other forms of psychopathology. Today, this approach characterizes most successful current animal models, and it has helped to improve and define the standards by which these models are evaluated.

Twenty years ago Professor Harlow also published the first of another series of research studies that has proved to be of considerable value for primate models of depression and other disorders (Harlow, 1962). These studies focused on the *normal* development of social and other behavioural capabilities in rhesus monkeys. Data from these studies allowed Harlow not only to document the myriad of behavioural changes and shifts in preferred social partners that characterized rhesus monkey development from birth to maturity, but also to establish a range of behaviour for a given age of monkey, reared in a given environment, that would be considered 'normal' (for example, Harlow & Harlow, 1969). As before, these 'normative developmental trends' were soon replicated and extended by other primate research workers (for example, Hinde & Spencer-Booth, 1967).

The power of these normative studies for animal modelling research lay in the evaluative capabilities their data provided to anyone trying to reproduce a human syndrome in non-human primate subjects. Not only could they provide a basis for the objective diagnosis of any purported psychopathological display, but they could also be used to reconstruct aetiologies, as well as providing a standard against which subsequent therapeutic studies involving the primate model could be judged for relative efficacy (cf. Suomi, 1982). It seems remarkable to me that, even today, a normative data set of comparable behavioural detail and longitudinal completeness does not yet exist for any human culture or socioeconomic subgroup, the efforts of human ethologists notwithstanding. I suspect that were the 'normative' ranges of behavioural development in humans raised in different social settings as well established as they are for rhesus monkeys (and a few other non-human primate species) our current ability to diagnose, treat, and even prevent various forms of human psychopathology would be considerably enhanced.

Primate models of depression have come a long way since Harlow's initial efforts twenty years ago. We now know that not every maternal (or peer) separation results in depressive reactions for rhesus monkeys (or other non-human primate species). Instead, we have found that *some* rhesus monkeys become depressed virtually *every time* they are subjected to a separation of more than a few hours duration, while other monkeys of similar background *never* become depressed, no matter how often or in what circumstances they are subjected to separation. Somewhat surprisingly, those monkeys at high risk for depressive separation reactions are behaviourally indistinguishable from low-risk monkeys when both are living in stable, relatively stress-free social environments (Suomi, 1983*b*). It is only when confronted with separation or certain other social challenges that the high-risk monkeys can be differentiated from 'normal' monkeys on the basis of their respective behaviour. However, this tendency appears early in life (perhaps within the first month), and it is exceedingly stable developmentally. Indeed, we can now predict which 3- and 4-year-old monkeys will exhibit depressive reactions to separation and which ones will not, based on a knowledge of their previous reactions to separation in their first few months of life, assuming that they have lived in comparable social settings in the interim (Suomi, 1983*b*).

Monkeys at high risk for depressive separation reactions also differ from 'normal' monkeys in terms of physiological reactivity to separation and other social and non-social challenges. These differences are expressed in terms of measures of infantile heart-rate, cortisol output following standardized stressors (including separation), the degree of cortisol suppression following dexamethasone challenge, and the levels of CSF catecholamines during separation periods (this list is not necessarily exhaustive; cf. Suomi, 1983*a*). As was true for behavioural differences between monkeys

at high risk for depressive reactions and those not at risk, physiological differences between these two subgroups become evident only under conditions of behavioural and/or physiological challenge – the same measures do not differentiate between subgroups under normative baseline conditions. However, the physiological differences apparent under challenge conditions persist throughout development, and they are evident within the first month of life, as was true for the behavioural differences between these two subgroups of rhesus monkeys. Furthermore, there exists at least indirect evidence of a major genetic contribution to depressive risk status in these monkeys (Suomi *et al.* 1981; Suomi, 1983*a*).

The ability to identify individual monkeys who are at high risk for displaying depressive phenomena permits a detailed *prospective* study of the onset of depression and possible mechanisms underlying physiological differences between these monkeys and those not at risk. It also facilitates evaluation of both somatic and behavioural treatments with respect to their therapeutic efficacy, and it makes possible the development and testing of various preventive strategies. Studies along each of these lines are currently in progress. Of course, it is unlikely that findings from these studies of non-human primate depressive phenomena will generalize perfectly to all cases of human depression, and it is possible that they may generalize completely to no human cases. However, even incomplete generalizations can be of enormous practical and heuristic value in dealing with human psychopathology, and current primate models of depression appear to generalize to at least some forms of human affective disorder more completely than virtually any other existing animal model of human psychopathology (cf. Suomi, 1982).

Clearly, our ideas about depression in primates have advanced considerably since the pioneering studies of Harlow and his students. But it is doubtful that our current knowledge and modelling capabilities would be anywhere near the present state of the art had it not been for Harry Harlow's genius, imagination, and foresight. He not only demonstrated that primate models of depression can be compelling in their physical resemblance to human depressive symptomology, but he also created a new strategy for developing valid and effective animal models, and he demonstrated beyond question the great value of objective, longitudinal normative controls. Harry Harlow may no longer be with us but his contributions to our knowledge of human depression will continue to be felt for some time, despite the fact that the depression which he studied was not of human origin.

STEPHEN J. SUOMI

REFERENCES

Bowlby, J. (1960). Grief and mourning in infancy and early childhood. *Psychoanalytic Study of the Child* **15**, 9–52.

Bowlby, J. (1973). *Separation: Anxiety and Anger*. Basic Books: New York.

Harlow, H. F. (1962). The heterosexual affectional system in monkeys. *American Psychologist* **17**, 1–9.

Harlow, H. F. & Harlow, M. K. (1969). Effects of various mother–infant relationships or rhesus monkey behaviors. In *Determinants of Infant Behaviour*, Vol. 4 (ed. B. M. Foss), pp. 15–36. Methuen: London.

Harlow, H. F., Gluck, J. P. & Suomi, S. J. (1972). Generalization of behavioural data between human and nonhuman animals. *American Psychologist* **27**, 709–716.

Hinde, R. A. & Spencer-Booth, Y. (1967). The behaviour of socially living rhesus monkeys in their first two and a half years. *Animal Behaviour* **15**, 169–196.

Hinde, R. A., Spencer-Booth, Y. & Bruce, M. (1966). Effects of 6-day maternal deprivation on rhesus monkey infants. *Nature* **210**, 1021–1033.

Kaufman, I. C. & Rosenblum, L. A. (1967). Depression in infant monkeys separated from their mothers. *Science* **155**, 1030–1031.

Kraemer, G. W. & McKinney, W. T. (1979). Interactions of pharmacological agents which alter biogenic amine metabolism and depression. *Journal of Affective Disorders* **1**, 33–54.

Kubie, L. S. (1953). The concept of normality and neurosis. In *Psychoanalysis and Social Work* (ed. M. Heiman), pp. 3–13. International Universities Press: New York.

Levine, S. (1983). Hormonal correlates of mother–infant separations: The ontogeny of coping. In *Psychosocial Factors in Stress* (ed. G. P. Moberg). In the press.

Lewis, J. K. & McKinney, W. T. (1976). The effect of electrically induced convulsions on the behavior of normal and abnormal rhesus monkeys. *Diseases of the Nervous System* **37**, 687–693.

Overmeir, J. B. & Seligman, M. E. P. (1967). Effects of inescapable shock upon subsequent escape and avoidance learning. *Journal of Comparative and Physiological Psychology* **63**, 28–33.

Pavlov, I. (1927). *Conditioned Reflexes*. Oxford University Press: London.

Reite, M., Short, R., Seiler, C. & Pauley, J. D. (1981). Attachment, loss, and depression. *Journal of Child Psychology and Psychiatry* **22**, 141–169.

Seay, B., Hansen, E. W. & Harlow, H. F. (1962). Mother–infant separation in monkeys. *Journal of Child Psychology and Psychiatry* **3**, 123–132.

Seligman, M. E. P. (1975). *Helplessness: On Depression, Development, and Death*. Freeman: San Francisco.

Spitz, R. A. (1946). Anaclitic depression. *Psychoanalytic Study of the Child* **2**, 313–347.

Suomi, S. J. (1982). Animal models of human psychopathology: Relevance for clinical psychology. In *Handbook of Research Methods in Clinical Psychology* (ed. P. C. Kendall and J. N. Butcher), pp. 249–271. Wiley: New York.

Suomi, S. J. (1983*a*). Individual differences in stress reactivity in rhesus monkey infants. In *Psychosocial Factors in Stress* (ed. G. P. Moberg). In the press.

Suomi, S. J. (1983*b*). Social development in rhesus monkeys:

Consideration of individual differences. In *The Behaviour of Human Infants* (ed. A. Oliverio and M. Zappella). Plenum Press: New York. In the press.

Suomi, S. J., Seaman, S. F., Lewis, J. K., DeLizio, R. D. & McKinney, W. T. (1978). Anti-depressant effects of imipramine treatment on separation-induced social disorders in rhesus monkeys. *Archives of General Psychiatry* **35**, 321–325.

Suomi, S. J., Kraemer, G. W., Baysinger, C. M. & DeLizio, R. D. (1981). Inherited and experiential factors associated with individual differences in anxious behaviour displayed by rhesus monkeys. In *Anxiety: New Research and Changing Concepts* (ed. D. F. Klein and J. Rabkin), pp. 179–200. Raven Press: New York.