FOR DEBATE....

Cushing's Syndrome, A Personal View

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The recent editorial comment (*British Medical Journal*, 1970) that the concept of an impaired "stress" response in Cushing's syndrome requires further consideration has stimulated me to set out my own interpretation of the data. The purpose of our original study of the pyrogen stress response in Cushing's syndrome was to answer a simple question: is the increased plasma cortisol concentration due to an abnormally increased response to stress? To my surprise the increase in plasma cortisol concentration after intravenous pyrogen was less than normal in patients with Cushing's syndrome, and it was therefore concluded that Cushing's syndrome was not due to an enhanced response to stress (Shuster and Flynn, 1961). This work has since been confirmed by Bethage *et al.* (1966) and James *et al.* (1968), using insulin instead of pyrogen.

This decreased response to pyrogen in Cushing's syndrome contrasts with the increased response to metyrapone which is a measure of feedback control of corticotrophin release. For this and other reasons (Shuster, 1962) I concluded that the feedback and stress-induced corticotrophin release were different in site or mechanism. Cushing's syndrome can therefore be characterized by the dissociation of hypothalamic-pituitary control mechanisms, with an impaired stress response (pyrogen and insulin) and a supranormal response of the feedback control system (metyrapone) (Shuster, 1962). One further observation which has to be included in a general hypothesis is that greater doses of exogenous corticosteroids are required to suppress corticotrophin release in patients with Cushing's syndrome than in normal subjects (Liddle, 1960). In other words feedback inhibition of corticotrophin secretion occurs at higher levels of circulating cortisol. These three facts can be reshuffled as follows: (1) stress-induced secretion of corticotrophin is decreased; and (2) feedback secretion is enhanced; the feedback response to a decreased circulating cortisol is increased and it is less easily inhibited by an increase in circulating cortisol—that is, the "setting" of the feedback centre is higher. This upward setting of feedback control would of course lead to Cushing's syndrome.

My hypothesis is that the upward resetting of feedback control, which is the immediate cause of Cushing's syndrome, is itself due to the impaired stress response. Stress-induced release of corticotrophin is rapid and must consist of already synthesized corticotrophin: impaired release in response to stress would therefore lead to accumulation of corticotrophin in the pituitary (this would explain the increased pituitary response to lysine vasopression in the face of the decreased hypothalamic response to intravenous insulin which Jacobs and Nabarro (1969) found in Cushing's syndrome). Consequently more corticotrophin would be available for release by negative feedback and the response to a change in circulating cortisol would be incrementally greater. Thus the physiological response to a decreased plasma cortisol would be greater (enhanced response to metyrapone) and, conversely, the response to an increased plasma cortisol would be reduced (pituitary suppression requiring higher doses of exogenous corticosteroid). A primary impairment of stress release of corticotrophin could therefore lead to upward resetting of the feedback control of corticotrophin release and hence Cushing's syndrome.

To complicate this simple hypothesis there is a second mechanism by which upward resetting of the feedback centre could be maintained. There is good if circumstantial evidence that tissues habituate to corticosteroids in the true physical sense (Shuster and Williams, 1961), and I believe this explains features of the corticosteroid withdrawal syndrome; the desquamation which occurs after adrenalectomy for Cushing's syndrome and the facial rash which follows withdrawal of topical corticosteroids are further examples of this habituation. Pituitary-adrenal function is not inhibited by small oral doses of corticosteroids within the physiological range (Shuster and Williams, 1961), and it is conceivable, therefore, that an extremely slow increase in plasma cortisol might lead to upward resetting of the feedback "centre" by the process of habituation. Is this the situation in patients with bronchogenic carcinoma where a long-standing increase in circulating cortisol (Shuster, 1960) may lead to Cushing's syndrome?

The merit of these ideas is that they can easily be destroyed by experiment—if, indeed, they haven't been already. It should, for example, be possible to test the setting of feedback cortisol in patients with neurological lesions leading to an impaired pyrogen or insulin stress response. Likewise with habituation, the critical experiments are self-evident, ranging from the grossly biological to enzyme induction at the cellular level.

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