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Editorial: Adrenal Replacement Therapy: Time for an Inward Look to the Medulla?

Endocrinologists have traditionally replaced patients with adrenal insufficiency with a combination of glucocorticoids (hydrocortisone or cortisol, cortisone, other synthetic steroids), mineralocorticoids (fludrocortisone), and more recently androgens (dehydroepiandrosterone), depending upon the underlying etiology (1). Based on original radioisotopic measures of cortisol secretion rates subsequently updated with more accurate stable isotopic methods, usual daily hydrocortisone replacement doses vary between 10 and 30 mg in adults and between 10 and 15 mg/m^2 in children, given as regimes of two or three times per day (2). Confounding effects of other endocrine deficiencies such as GH and thyroid hormone upon cortisol metabolism (3) might explain why patients with secondary hypoadrenalism in the context of hypopituitarism appear to require slightly less hydrocortisone than patients with primary adrenal insufficiency (Addison's disease). The consequences of overreplacement are all too apparent and may contribute to growth delay, short stature and obesity, reduced bone mineral density, and arguably premature vascular mortality in adults. Underreplacement runs the risk of recurrent adrenal crises or failure of suppression of adrenal hyperandrogenism in patients with congenital adrenal hyperplasia (CAH).

Such patients fail to mount an adrenocortical response to stress. Based on seminal studies that defined the cortisol response to illness and surgical stress (4), patients are advised to double or triple their daily cortisol replacement in the face of intercurrent illness such as a febrile illness and to receive parenteral hydrocortisone in doses of 100–200 mg/d for those undergoing major surgery (5, 6). Advice relating to other short-term insults such as psychological stresses (anxiety, examinations) and endurance exercise have been conflicting, reflecting the lack of an evidence base (7).

The paper by Merke and colleagues (8) from the National Institutes of Health (NIH) in this issue of *JCEM* suggests that a doubling of the usual morning dose of hydrocortisone replacement in an adolescent group with adrenal insufficiency secondary to CAH has no impact upon either the metabolic or performance response to an exercise challenge. The key observation, however, endorsed in this and earlier papers from the NIH group (9), is the defective metabolic response to exercise in CAH when compared with a sex- and BMI-matched control group. CAH patients demonstrated a reduced glucose response to maximal exercise, and the fact that this was still seen in patients taking normal and supraphysiological doses of hydrocortisone replacement suggests that such a defect cannot be explained on the basis of any differences in circulating cortisol. Parenthetically, this would be a nice paradigm to investigate any differences between cortisol and cortisone replacement to ask whether the autocrine generation of cortisol from orally administered cortisone, *viz.* 11β-hydroxysteroid dehydrogenase type 1, has a more beneficial effect on hepatic glucose output (10). However, this aside, other candidates including GH, insulin, and glucagon were also excluded (8, 9). They argue that such a defect might lead to hypoglycemia in such individuals exposed to more prolonged endurance exercise or profound stress. The most likely explanation put forward by the authors is that this reflects epinephrine deficiency leading to impaired gluconeogenesis and hepatic glucose output. In support of this, epinephrine levels were reduced at baseline and rose to only 20% of normal after exercise in their adrenal insufficient group; norepinephrine levels were unaltered (8, 9).

The relationship between the adrenal medulla and cortex is more than anatomical. The adrenal medulla clearly plays a role in regulating adrenocortical function, but perhaps the most striking functional interplay is the critical requirement of glucocorticoid for development and function of the adrenal medulla. Recombinant mice lacking the glucocorticoid receptor (11) or pathways involved in adrenocortical biosynthesis (12) have little if any adrenal medulla/chromaffin tissue, and patients with congenital adrenal hyperplasia have adrenomedullary dysplasia (13). Cortisol is known to regulate catecholamine biosynthetic pathways; importantly the conversion of norepinephrine to epinephrine by phenylethanolamine *N*-methyltransferase is critically dependent upon glucocorticoid (14). The adrenal vasculature together with the presence of cortical rays or islands within the normal medulla facilitates the delivery of high concentrations of cortisol to medullary chromaffin tissue. It is easy therefore to envisage how patients with adrenocortical insufficiency are also deficient in epinephrine. This is evident in patients with congenital adrenal deficiency states [21-hydroxylase deficiency (7, 8), ACTH-receptor mutations (15)] but also functionally in patients with hypopituitarism (16), suggesting that this is far more than a differentiation effect of cortisol upon the developing adrenal gland. Replacement glucocorticoid has little if any impact on circulating epinephrine levels in these patients (7); it appears that the high adrenal-derived cortisol is required to ensure adequacy of function of the adrenal medulla and normal epinephrine secretion.

Feasibilty issues aside, we are still some way off recommending epinephrine replacement or supplementation. Pioneering adrenalectomy studies performed over 70 yr ago (17) and subsequently endorsed by many groups inform us that the deleterious cardiovascular effects of adrenocortical and adrenomedullary deficiency can be completely reversed with appropriate adrenocortical replacement; catecholamines

Abbreviation: CAH, Congenital adrenal hyperplasia.

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are not required. The metabolic deficits attributable to epinephrine deficiency have come from studies that have exclusively focused on children or adolescents with adrenal insufficiency; as a group they are more prone to hypoglycemia in this context than adults. This might reflect the observation that epinephrine is not thought to play a critical role in the counterregulatory response to hypoglycemia in adults (18), and experiments similar to those performed by Merke and colleagues (8) are now required in an adult hypoadrenal group. Nevertheless, as we seek to refine endocrine replacement regimes to improve both the quantity and quality of life in our patients, Merke and colleagues establish a phenotype for adrenomedullary deficiency that requires further investigation.

Paul M. Stewart
Professor of Medicine
University of Birmingham
Queen Elizabeth Hospital
Edgbaston
Birmingham, United Kingdom B15 2TH

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Address all correspondence and requests for reprints to: Paul M. Stewart, M.D., F.Med.Sci., Professor of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham, United Kingdom B15 2TH. E-mail: p.m.stewart@bham.ac.uk.

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