**SUPPLEMENTAL DIGITAL CONTENT**

**Dynamic model of human *in vivo* cortisol secretion, binding and elimination:**

The dynamic model consists of five compartments. These five compartments are shown in three ellipses and illustrated schematically in Figure 1 below. Total cortisol is represented by the sum of concentrations in three compartments: (i) free cortisol (F), (ii) corticosteroid-binding globulin (CBG)-bound cortisol, and (iii) albumin-bound cortisol. Total CBG is the sum of concentrations in two compartments: (i) free CBG and CBG-bound cortisol. Total albumin is similarly the sum of concentrations in two compartments: free albumin and albumin-bound cortisol. The schematic is not drawn to scale, as the concentration of free albumin is always in far excess to the concentration of albumin-bound cortisol.

Processes of free cortisol secretion (appearance) and elimination are represented by arrows to and from the free cortisol compartment. Reversible binding between free cortisol and CBG- and albumin-bound cortisol compartments is represented by bidirectional arrows. Note that both cortisol secretion and elimination are applicable only to the free cortisol compartment. In this model, only free cortisol is subject to metabolic elimination, with no direct elimination of
CBG- or albumin-bound compartments.

However, free and protein-bound cortisol compartments are in rapid equilibrium, so that exchange of cortisol between compartments can moderate rapid changes in the free cortisol concentration under non-steady state conditions. The model and solutions for rates of free cortisol appearance and elimination account for individual variation in CBG and albumin concentrations, as previously described (1,2). This is to be distinguished from alternative approaches that apply group or mean values for CBG and albumin concentrations (3,4). A more detailed description of this dynamical model involves three simultaneous, non-linear differential equations, which are previously described [1-4].

**Numerical analytic vs. algebraic solutions:** The numerical analytic approach to obtain free cortisol appearance and elimination rates for a cortisol concentration time series distinguishes the numerical analytic method [5;6] from simple algebraic solutions, such as Coolens (quadratic) [7] or cubic [7;8] equations that are used to calculate (steady-state) free cortisol
concentration at a single point in time. The numerical analytic approach is applicable to non-steady steady as well as steady state conditions, and solves for rates of free cortisol secretion (appearance) and elimination in the concentration space. Solution in the concentration space provides for good clinical utility, with the potential for point-of-care clinical application.

**Units of free cortisol appearance and elimination rates obtained by numerical method:**

Results for the rate of free cortisol secretion (appearance) and the rate constant for free cortisol elimination (\(\alpha\)) are expressed in units of mass/volume/time and time\(^{-1}\), respectively. Note that the free cortisol rate elimination constant \(\alpha\) is inversely related to the free cortisol half-life by the equation: 
\[
\alpha = \ln(2)/\text{free cortisol half-life (1-4)}.
\]

**Units of cortisol production and clearance rates obtained by stable isotope dilution method:**

The stable isotope dilution method generally considers total rather than free cortisol concentrations and solves for cortisol production and clearance rates in the organism space, with results for production and clearance expressed in units of mass/time and volume/time, respectively. The requirement for stable isotope for human use, specialized analytical procedures to distinguish endogenous and isotope-labeled cortisol, and steady-state conditions limit the use of stable isotope dilution methodology to the research setting and thus constrain clinical utility.

**CSR\(_{\text{max}}\) in relation to the sigmoidal CSR-ACTH dose-response curve:** The relationship between ACTH concentration and cortisol secretion has been described by a sigmoidal curve or logistic function (1-4). ACTH\(_{1-24}\) concentrations appear to be sufficiently high to achieve maximal rates of cortisol secretion for at least 30 min and 2 hr after ACTH\(_{1-24}\) doses of 1 and 250 \(\mu\)g, respectively (1,2). By sufficiently high we mean that there is a threshold plasma ACTH\(_{1-24}\) concentration above which the cortisol secretion rate does not continue to increase. The cortisol secretion rate associated with asymptotic part of the sigmoidal CSR-ACTH dose-response curve
is referred to as CSR$_{\text{max}}$; the term *efficacy* has also been applied to this portion of the CSR-ACTH dose-response curve (3,4).
References

1. Dorin RI, Qiao,Z, Qualls,CR et al. Estimation of maximal cortisol secretion rate in healthy humans. *J Clin Endocrinol Metab* 2012;97:1285-93.

2. Dorin RI, Qualls,CR, Torpy,DJ et al. Reversible increase in maximal cortisol secretion rate in septic shock*. *Crit Care Med* 2015;43:549-56.

3. Keenan DM, Roelfsema,F, Veldhuis,JD. Endogenous ACTH concentration-dependent drive of pulsatile cortisol secretion in the human. *Am J Physiol Endocrinol Metab* 2004;287:E652-E661.

4. Keenan DM, Roelfsema,F, Carroll,BJ et al. Sex defines the age dependence of endogenous ACTH-cortisol dose responsiveness. *Am J Physiol Regul Integr Comp Physiol* 2009;297:R515-R523.

5. *National Institute of Standards and Technology (NIST) Handbook of Mathematical Functions*. Cambridge: Cambridge University Press, 2010.

6. Trefethen LN. Numerical Analysis. In: Gowers T, Barrow-Green JLI, eds. *The Princeton Companion to Mathematics*. Princeton: Princeton University Press, 2010:604-15.

7. Coolens JL, Van Baelen H., Heyns,W. Clinical use of unbound plasma cortisol as calculated from total cortisol and corticosteroid-binding globulin. *J Steroid Biochem* 1987;26:197-202.

8. Dorin RI, Pai,HK, Ho,JT et al. Validation of a simple method of estimating plasma free cortisol: role of cortisol binding to albumin. *Clin Biochem* 2009;42:64-71.