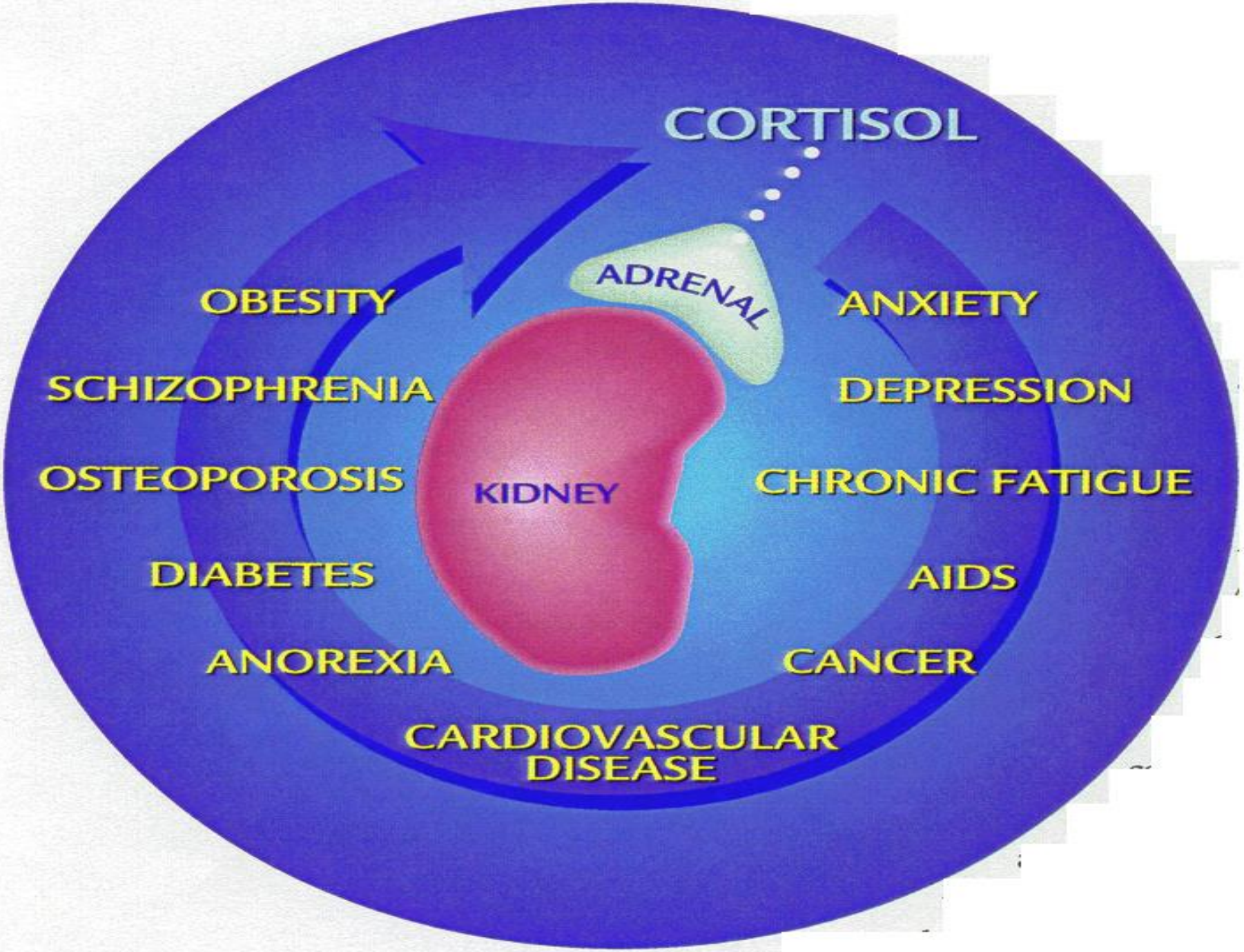
CORTISOL

Physiologic or Pharmacologic

A Tale of Two Very Different Outcomes

Cortisol (Hydrocortisone)

- Major glucocorticoid produced in humans
- Cortisone also produced in small amounts but must be converted to cortisol before affects
- Maintains blood sugar by converting fat to glucose and stimulating gluconeogenesis
- Maintains normal vascular tone in stress states
- Some electrolyte-regulating effects
- Cortisol half-life in the blood about 100 minutes. Metabolic effects less than 8 hours
- Cortef™ from Upjohn or Hydrocortone™ from Merck


CORTISOL
ADRENAL
OBESITY
ANXIETY
SCHIZOPHRENIA
DEPRESSION
OSTEOPOROSIS
KIDNEY
CHRONIC FATIGUE
DIABETES
AIDS
ANOREXIA
CANCER
CARDIOVASCULAR DISEASE

Cortisol Production

- **The cortisol production rate in normal subjects is lower than was previously believed.**
- **The normal pattern of glucocorticoid secretion includes both a diurnal rhythm and a pulsatile ultradian rhythm.**
- **Glucocorticoid access to nuclear receptors is 'gated' by the 11-beta-hydroxysteroid dehydrogenase enzymes, which interconvert active cortisol and inactive cortisone.**
- **Such complexities make the target of physiological glucocorticoid replacement therapy hard to achieve.**
- **the evidence suggests that most patients may safely be treated with a low dose of glucocorticoid (e.g. 15 mg hydrocortisone daily) in two or three divided doses**

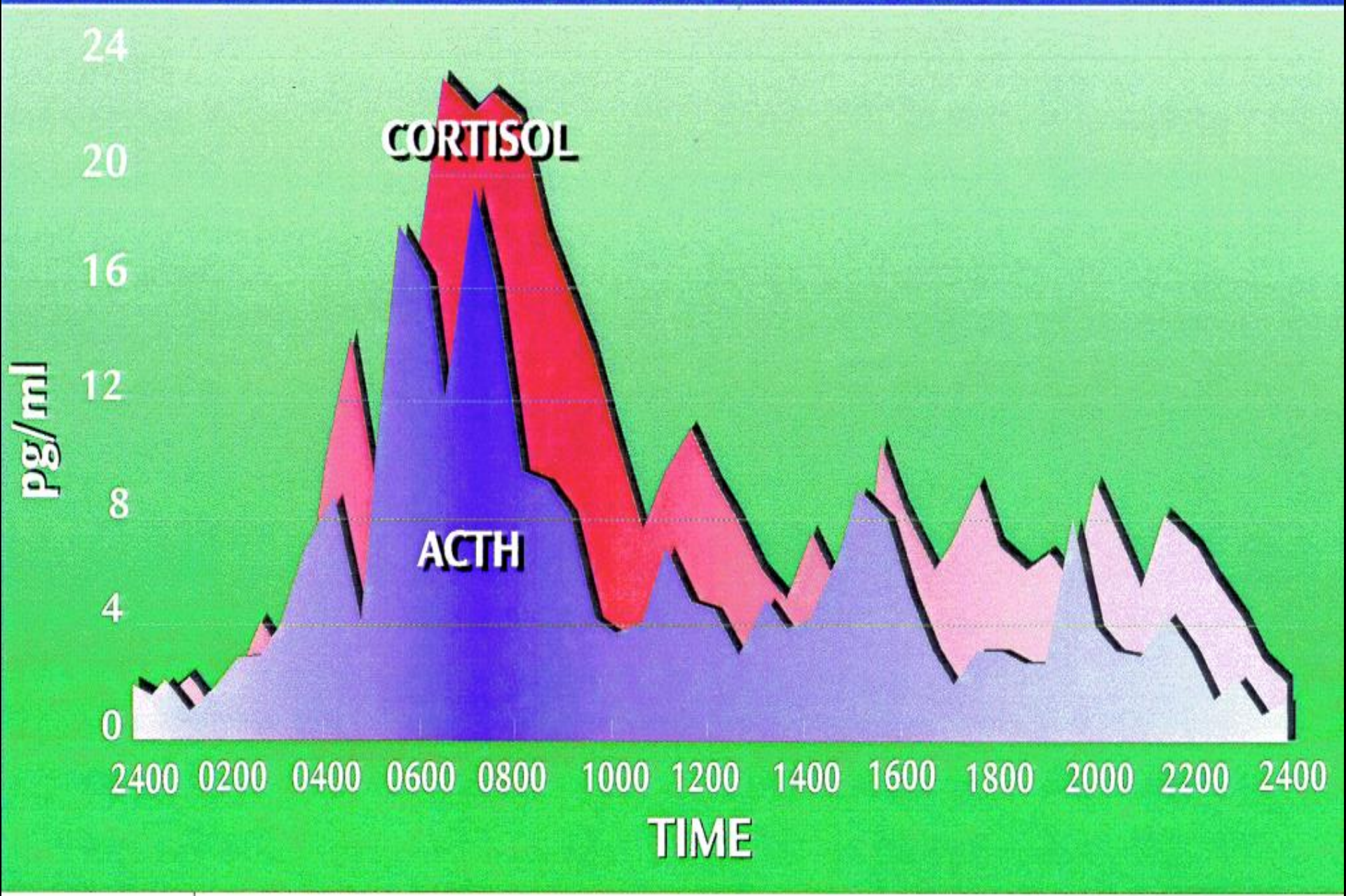
Crown, A. Lightman, S. Why is the management of glucocorticoid deficiency still controversial: a review of the literature Clin Endocrinol (Oxf) 63: 5483-92. Nov 2005.

Diurnal Variation

- In the unstressed state a person who sleeps from 11:00 PM to 7:00 AM has a maximal level of cortisol at about 8:00 AM, then it gradually decreases, reaching a low point at about 1:00 AM, following which it increases progressively during sleep to reach its maximum again by 8:00 AM the next day.
- Peak daily in normals of 20-30 mcg/100 ml
- Lowest level in normals of 5-10 mcg/100ml
- Either too little or too much glucocorticoid can impair resistance to infection, optimal levels enhance resistance

Beisel WR, Rapoport MI: interrelations between adrenocortical functions And infectious illness. N Engl J Med 280:541-546, 596-604, 1969.

Circadian rhythms of ACTH and Cortisol in humans



Cortisol Metabolism

- **The most commonly used systemic glucocorticoids are hydrocortisone, prednisolone, methylprednisolone and dexamethasone. These glucocorticoids have good oral bioavailability and are eliminated mainly by hepatic metabolism and renal excretion of the metabolites.**

Czock, D. Keller, F. Rasche, F. M. Haussler, U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids Clin Pharmacokinet; 44: 1; 61-98 2005.

11 beta hydroxysteroid dehydrogenases (11beta-HSD)

- **In peripheral tissues, corticosteroid hormone action is determined, in part, through the activity of 11beta-hydroxysteroid dehydrogenases (11beta-HSD), two isozymes of which interconvert hormonally active cortisol (F) and inactive cortisone (E). 11beta-HSD type 2 (11beta-HSD2) inactivates F to E in the kidney, whilst 11beta-HSD type 1 (11beta-HSD1) principally performs the reverse reaction activating F from E in the liver and adipose tissue.**
- **Alteration in expression of these 11beta-HSD isozymes in peripheral tissues modifies corticosteroid action: loss of 11beta-HSD2 activity in the kidney results in cortisol-induced mineralocorticoid excess, and loss of hepatic 11beta-HSD1 activity improves insulin sensitivity through a reduction in cortisol-induced gluconeogenesis and hepatic glucose output. Conversely, overexpression of 11beta-HSD1 in omental adipose tissue can stimulate glucocorticoid-induced adipocyte differentiation which may lead to central obesity.**

Stewart, P M. Toogood AA. Tomlinson, JW. Growth hormone, insulin-like growth factor-1 and the cortisol-cortisone shuttle. Horm Res; 56:Suppl 1, 1-6, 2001.

Cortisol Effects

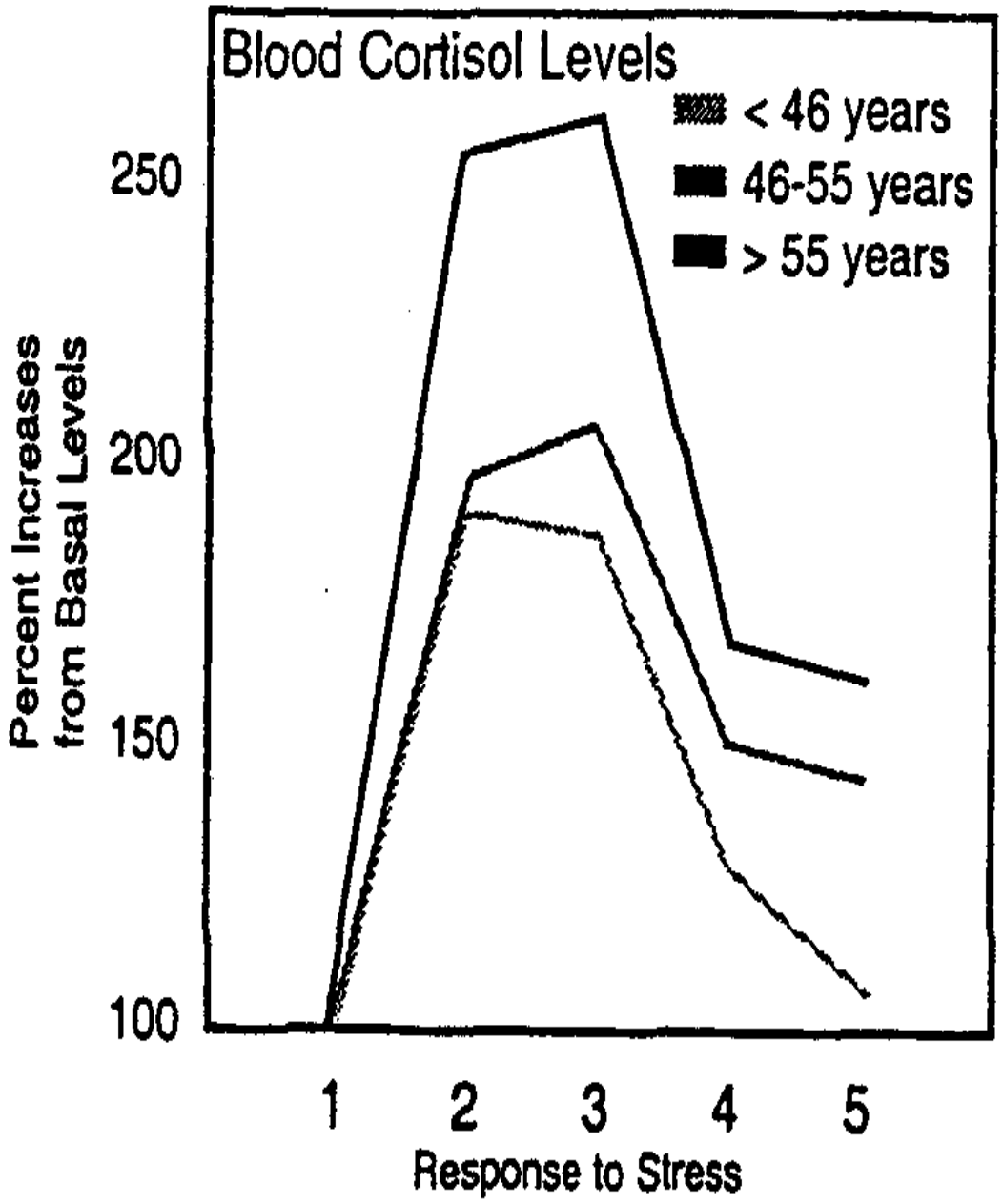
- **The effects of glucocorticoids are mediated by genomic and possibly nongenomic mechanisms.**
- **Genomic mechanisms include**
  - **activation of the cytosolic glucocorticoid receptor that leads to activation or repression of protein synthesis, including cytokines, chemokines, inflammatory enzymes and adhesion molecules.**
  - **Thus, inflammation and immune response mechanisms may be modified.**
- **Nongenomic mechanisms might play an additional role in glucocorticoid pulse therapy.**
- **Clinical efficacy depends on glucocorticoid pharmacokinetics and pharmacodynamics**.

Czock, D. Keller, F. Rasche, F. M. Haussler, U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids Clin Pharmacokinet; 44: 1; 61-98. 2005.

Exercise, Cortisol, DHEAS

- Runs of 40, 80 120 mins.
- Serum samples start, 1, 2, 3 and 4 hours after start
- Cortisol only increased in response to the 120 min run and decreased across time in all other sessions
- DHEAS increased in a dose-response manner
  - Biggest increase during 120 min run
- At low intensity, longer duration runs are necessary to stimulate increased levels of DHEAS and Cortisol and beyond 80 mins of running there is a shift to a more catabolic hormonal environment.

Tremblay, MS. Copeland, JL. Van Helder, W. Influence of exercise duration on post-exercise steroid hormone responses in trained males. Eur J Appl Physiol 94:5-6, pp. 505-513, Aug 2005.



Cortisol response to stress with age. This graph illustrates that as we grow older, the body's response to stress is greater and lasts longer.

Cortisol and Ageing

- Normal elderly subjects show severe reduction in DHEA response to a wide range of ACTH doses
  - Impairment of adrenal retricularis zone in ageing
- Elderly subjects show no cortisol and aldosterone response to a very low ACTH dose
  - Reduced sensitivity to ACTH in the fasciculata and glomerulosa zones of the adrenal gland in ageing

Giordano, R., Di Vito, L, et al, Elderly subjects show severe impairment of dehydroepiandrosterone sulphate and reduced sensitivity of cortisol and aldosterone response to the stimulatory effect of aCt(1-24). Clin Endocrinol (Oxf) 55:2 pp.259-65. Aug 2001

Cortisol and Memory

- Positive correlation between salivary cortisol levels and retrospective memory performance for neutral words
- Not correlated with prospective memory performance for negative or neutral words
- Implications for beneficial effects of low-dose cortisol treatment in post-traumatic stress disorder

Nakayama, Y. Takahashi, T. Radford, MH. Cortisol levels and prospective and retrospective memory in humans. Neuro Endocrinol Lett 26:5 pp.599-602 Oct 2005.

Cortisol and Memory

- 59 Healthy Subjects.
  - 25 mg cortisol or placebo 45 minutes before a memory test
- No global effect on verbal or non-verbal memory.
- High responders exhibited impaired verbal memory compared with low responders.

Domes, G. Rothfischer J. et al. Inverted-U function between salivary cortisol and retrieval of verbal memory after hydrocortisone treatment. Behav Neurosci 119:2 pp.512-17. Apr 2005.

HPA Dysregulation in Alzheimer's and Depression

- This study tested the hypothesis that smaller anterior cingulate cortex volumes are associated with HPA axis dysregulation in healthy older men.
- Conclusions: Smaller left anterior cingulate cortex volumes may be associated with HPA axis dysregulation in humans. These results substantiate evidence from animal studies indicating an important role for the anterior cingulate cortex in suprahypothalamic feedback regulation of the HPA axis.
- The results also have implications for disorders in which HPA axis dysregulation and abnormalities of the anterior cingulate cortex are frequently observed, such as depression and Alzheimer's disease.

Maclullich, AM. Ferguson, KJ. et al. Smaller left anterior cingulate cortex volumes are associated with impaired hypothalamic-pituitary-adrenal axis regulation inhealthy elderly men. J Clin Endocrinol Metab; Feb 7, 2006.

Cortisol and Electromagnetic Radiation

- High-level radiofrequency EMR exposure significantly increased the excretion rates of
  - cortisol ($p<0.001$),
  - adrenaline ($p=0.028$), and
  - noradrenaline ($p<0.0001$),
  - changes under low-level exposure did not reach significance
- In conclusion, the excretion of 6-sulphatoxymelatonin retained a typical diurnal pattern . . . But showed an exposure-effect relation with stress hormones.

Vangelova, KK. Israel, MS. Variations of melatonin and stress hormones under extended shifts and radiofrequency electromagnetic radiation.Rev Environ Health;20:2, pp.151-61. Apr-Jun, 2005

Noise Exposure and Cortisol

- Children under high noise exposure (L(night, 8h) = 54-70dB(A)) had in comparison to all other children significantly increased morning saliva cortisol concentrations, indicating an activation of the hypothalamus-pituitary-adrenal (HPA) axis. Analysing a subgroup of children without high noise exposure showed, that children with frequent physician contacts due to bronchitis did not have increased morning saliva cortisol. However, multiple regression analysis with stepwise exclusion of variables showed that bronchitis was correlated more closely to morning salivary cortisol than to traffic emissions.
- From these results it can be concluded that high exposure to traffic noise, especially at nighttime, activates the HPA axis and this leads in the long term to an aggravation of bronchitis in children. This seems to be more important than the effect of exhaust fumes on bronchitis symptoms.

Ising, H. Lange-Asschenfeldt, H. Moriske, H. J. Born, J. Eilts, M. Low frequency noise and stress: bronchitis and cortisol in children exposed chronically to traffic noise and exhaust fumes. Noise Health. 6: 23; 21-8 Apr-Jun, 2004 .

Cortisol and Estrogen

- **The largest difference between hypoadrenal patients and healthy individuals was observed at+30 min (9.16+/-2.8, 52.65+/-8.78 and 48.81+/- 6.9 nmol/l, in the hypoadrenal, healthy and hyperoestrogenic patients, respectively; P< 0.05).**
- **At this time-point values< 24.28 nmol/l were found in all hypoadrenal patients and cortisol levels >or= 27.6 nmol/l were found in 26 out of 28 healthy volunteers.**
- **ACTH-stimulated serum cortisol but not salivary cortisol was significantly higher in hyperoestrogenic women than in the healthy volunteers at either+30 or+60 min.**

Marcus-Perlman, Y. Tordjman, K. et al. Low dose ACTH (1 microg) salivary test: a potential alternative to the classical blood test. Clin Endocrinol (Oxf); 64:2, pp.215-8, Feb, 2006.

Cortisol and Stress in Oral Contraceptive Users

- Trier Social Stress Test induced significant increases in free cortisol in luteal phase women
- OC users showed blunted responses
- In luteal phase women a slight but insignificant decrease in glucocoticoid sensitivity of pro-inflammatory cytokines
- OC users showed a significant increase in GC sensitivity of cytokines after stress

Rohleder, N. Wolf, JM. et al. Impact of oral contraceptive use on glucocorticoid sensitivity of pro-inflammatory cytokine production after psychosocial stress. Psychoneuroendocrinology 28:3. pp. 261-73. Apr 2003.

Cortisol and Chronic Stress in Pre-menopausal Women

- Relative to non-stressed controls, stressed women had elevated evening salivary cortisol
- Stressed women had less suppression of salivary cortisol in response to low dose dexamethasone

Powell, LH. Lovallo, WR. et al. Physiologic markers of chronic stress in premenopausal, middle-aged women. Psychosom Med 64:3 pp.502-9 May-Jun 2002

Cortisol and Functional Gastrointestinal Disorders

- 30 IBS/Dyspepsia, 24 Controls
- Free salivary morning cortisol and diurnal cortisol profiles, low dose dexamethasone suppression test, CRH challenge test
- After CRH challenge, blunted adrenocorticotropic hormone and cortisol responses in IBS/Dyspepsia compared with controls

Bohmelt, AH. Nater, UM. et al. Basal and stimulated hypothalamic-pituitary-adrenal axis activity in patients with functional gastrointestinal disorders and healthy controls. Psychosom Med 67:2 pp.288-94 Mar-Apr 2005.

Chronic Stress (Burnout) and Cortisol

- **Burnout shows overlap in symptoms with chronic fatigue syndrome (CFS) and depression. Therefore, differential changes in HPA-axis functioning that resemble the hypo-functioning of the HPA-axis in CFS, or rather the hyper-functioning of the HPA-axis in depression, might have obscured the findings. However, no effect of fatigue or depressive mood on HPA-axis functioning was found in the burnout group.**
- **We concluded that HPA-axis functioning in clinically diagnosed burnout participants as tested in the present study, seems to be normal.**

Mommersteeg,PM. Heijnen, CJ. et al; Clinical burnout is not reflected in the cortisol awakening response, the day-curve or the response to a low-dose dexamethasone suppression test. Psychoneuroendocrinology, 31:2, pp. 216-25, Feb 2006.

Cortisol and Chronic Fatigue Syndrome

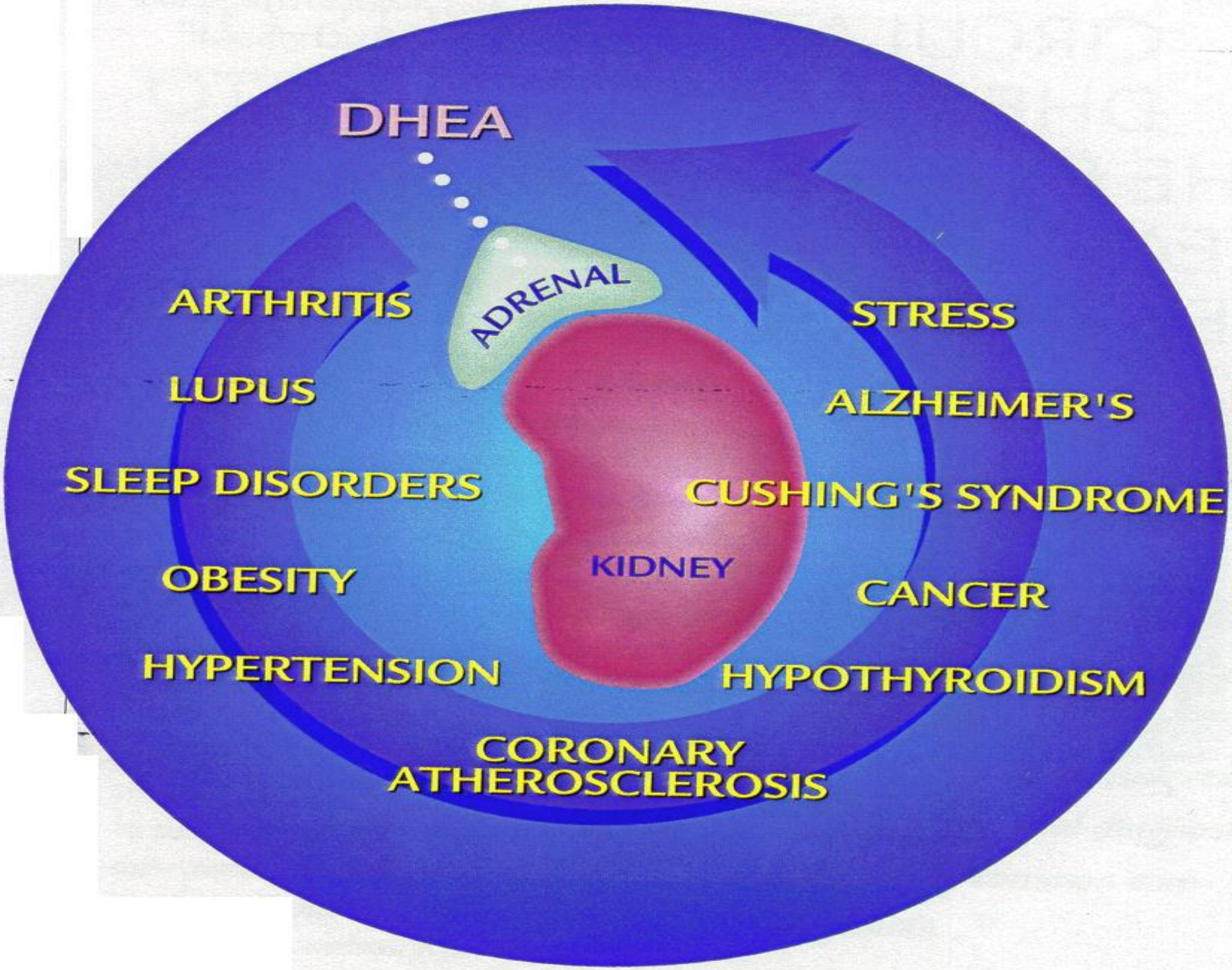
- Patients with CFS had
  - significantly lower mean cortisol levels
  - Lower peak cortisol
  - Reduced cortisol area under the curve
  - Longer time to peak cortisol
  - More pronounced in females
- Conclusions
  - Adolescents with CFS have alterations in adrenal function suggesting a reduction in central stimulation of the adrenal glands

Segal, TY. Hindmarsh, PC. Viner RM. Disturbed adrenal function in adolescents with chronic fatigue syndrome. J Pediatr Endocrinol Metab 18:3 pp. 295-301. Mar 2005.

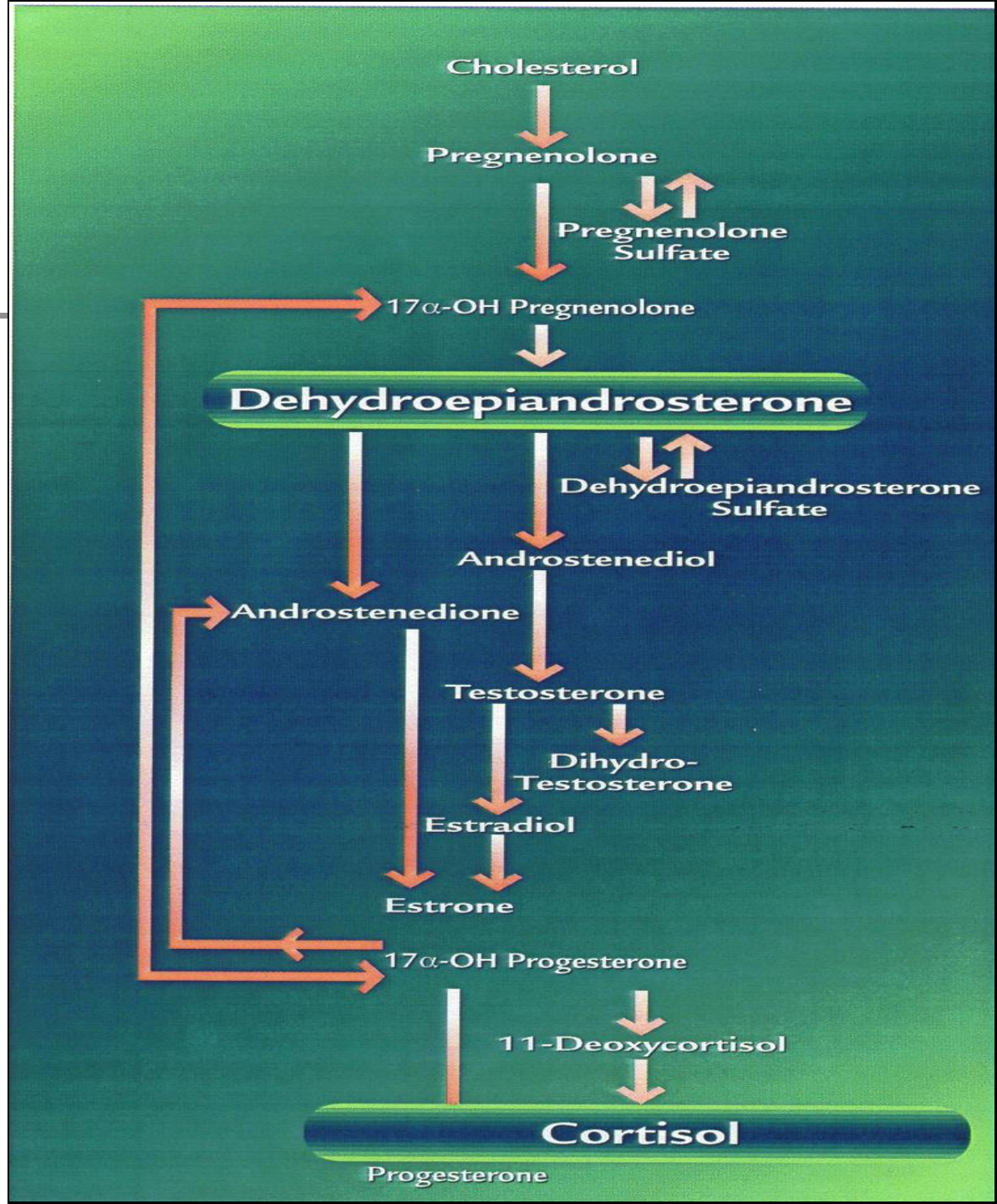
Cortisol and DHEA in Chronic Fatigue Syndrome

- 16 CFS patients without depression and 16 healthy controls
- Baseline DHEA and Cortisol, CRH test
- Baseline DHEA and Cortisol increased
  - Higher levels correlated with higher disability
- Conclusions
  - DHEA levels are raised in CFS and correlate with the degree of self-reported disability.
  - Cortisol therapy leads to a reduction of these levels toward normal, and an increased DHEA response to CRH.

Cleare, AJ. O'Keane, V. Miell, JP. Levels of DHEA and DHEAS and responses to CRH stimulation and hydrocortisone treatment in chronic fatigue syndrome. Psychoneuroendocrinology 29:6 pp. 724-32. Jul 2004.


DHEA
ADRENAL
ARTHRITIS
LUPUS
SLEEP DISORDERS
OBESITY
HYPERTENSION
STRESS
ALZHEIMER'S
CUSHING'S SYNDROME
CANCER
HYPOTHYROIDISM
KIDNEY
CORONARY ATHEROSCLEROSIS

THE RELATIONSHIP BETWEEN DHEA AND CORTISOL



Chronic Allergies

- **Adrenalectomy results in accumulation of histamine in tissues associated with a reduction of histaminase.**

Halpern BN, Benacerraf B, Briot M: Roles of cortisone, desoxycorticosterone, and adrenaline in protecting adrenalectomized animals against hommorhagic, Traumatic and histaminic shock, Br J Pharmacol 7:287-297, 1952

- **Cortisol inhibits histidine carboxylase**
  - **Converts histidine to histamine**

Slonecker CE, Lim WC: Effects of hydrocortisone on the cells in an acute inflammatory exudate. Lab Invest 27:123-128, 1972

- **Autoantibodies to β2-adrenergic receptors**

Venter JC, Fraser CM, Harrison LC: Autoantibodies to β2-adrenergic receptors: A possible cause of adrenergic hyporesponsiveness in allergic rhintis and asthma.Science 207:1361-1363, 1980.

Cortisol and Atopic Dermatitis

- Atopic Dermatitis patients showed significantly attenuated cortisol and ACTH responses to stressors
- Catecholamine levels significantly elevated in atopic dermatitis
- AD patients demonstrate a blunted HPA axis responsiveness with a concurrent overactivity of the SAM system to psychosocial stress

Buske-Kirschbaum, A. Geiben, A. et al. Altered responsiveness of the hypothalamus-pituitary-adrenal axis and the sympathetic adrenomedullary system to stress in patients with atopic dermatitis. J Clin Endocrinol Metab 87:9 pp. 4245-51. Sep 2002.

William McK. Jeffries, M.D.

- "One of the aspects of this type of therapy that has strained its credibility is the wide variety of pathologic disorders that are benefited. . . . Yet, recent findings regarding the etiologic role of autoimmunity in many diseases whose cause was unknown provide an explanation of some of these previously unexplained beneficial effects, since, for reasons that are not clear, glucocorticoids are known to benefit autoimmune disorders."

McK. Jeffries, W. Safe Uses of Cortisol, Charles C. Thomas Pulisher, Ltd., Springfield, Il, Third edition, 2004, p. xvii.

Autoimmune Polyglandular Syndrome and Cortisol

- Patients with autoimmune diseases who displayed a normal basal adrenal function
  - Showed a loss of cortisol, aldosterone and DHEA response to the very low dose ACTH stimulation
- These data indicate that a reduced sensitivity to ACTH in all adrenal zones occurs in patients with different types of autoimmune disease.

Giordano, R. Pellegrino, M. et al. Adrenal sensitivity to adrenocorticotropin 1-24 is reduced in patients with autoimmune polyglandular syndrome. J Clin Endocrinol Metab 89:2 pp.675-80 Feb 2004.

RA, SLE and Cortisol

- **Plasma ACTH levels were generally decreased significantly in comparison with Healthy Subjects (HS) in SLE with prednisolone, and in RA with/without prednisolone. Similarly, serum cortisol levels were also decreased in SLE with/without prednisolone, and in RA with prednisolone. The NPY/ACTH ratio was increased in SLE and RA, irrespective of prior prednisolone treatment. The NPY/cortisol ratio was increased in SLE with/without prednisolone, and in RA with prednisolone.**

- **CONCLUSIONS: An increased outflow of the SNS was shown and a decreased tone of the HPA axis in patients with SLE and RA. Deficiency of cortisol in relation to SNS neurotransmitters may be proinflammatory because cooperative anti-inflammatory coupling of the two endogenous response axes is missing.**

Harle, P. Straub, RH. et al. Increase of sympathetic outflow measured by neuropeptide Y and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with systemic lupus erythematosus and rheumatoid arthritis: another example of uncoupling of response systems. Ann Rheum Dis; 65:1, pp.51-6. Jan, 2006.

Chronic Material Hardship and Salivary Cortisol Levels

- **Salivary cortisol varied over the day, and by level of reported material hardship. Upon awakening, salivary cortisol levels were comparable across hardship levels. But soon after waking, women at low levels of hardship experienced both a significantly sharper morning surge and subsequently a sharper decline in salivary cortisol (16.0 and 29.5 nmol/l/h) than women with high hardship levels (5.9 and 24.3 nmol/l/h).**
- **These differences in cortisol diurnal pattern tended to be related in a dose-response way to levels of material hardship.**

- **CONCLUSIONS: Material hardship among poor women is associated with changes in the diurnal rhythms of cortisol, particularly in the waking response, which is blunted in women with high levels of hardship.**

Ranjit, N. Young, EA. Kaplan, GA. Material hardship alters the diurnal rhythm of salivary cortisol. Int J Epidemiol; 34:5; pp. 1138-43, Oct, 2005.

Abuse Survivors and Cortisol

- RESULTS: In the low-dose DST, depressed women with a history of abuse exhibited greater cortisol suppression than any comparator group and greater corticotropin suppression than healthy volunteers or nondepressed abuse survivors. There were no differences between nondepressed abuse survivors and healthy volunteers in the low-dose DST or between any subject groups in the standard DST. The PTSD analysis produced similar results.
- CONCLUSIONS: **Cortisol supersuppression is evident in psychiatrically ill trauma survivors, but not in nondepressed abuse survivors, indicating that enhanced glucocorticoid feedback is not an invariable consequence of childhood trauma but is more related to the resultant psychiatric illness in traumatized individuals.**

Newport, D. J. Heim, C. Bonsall, R. Miller, A. H. Nemeroff, C. B. Pituitary-adrenal responses to standard and low-dose dexamethasone suppression tests in adult survivors of child abuse Biol Psychiatry; 55: 1;10-20. Jan 1,2004.

Cortisol and Domestic Violence Survivors

- Domestic violence survivors with PTSD, regardless of whether or not they had comorbid depression had significantly lower baseline cortisol levels.
- Survivors with a sole diagnosis of PTSD showed significantly greater cortisol suppression to dexamethasone.
- Findings suggest that the chronic nature of domestic violence leads to a severe dysregulation of the HPA axis

Griffin, MG. Resick, PA. Yehuda R. Enhanced cortisol suppression following dexamethasone administration in domestic violence survivors. Am J Psychiatry 162:6 pp.1192-99 Jun 2005.

Cortisol and Coronary Surgery

- Adrenal insufficiency is common in patients undergoing CABG
- Adrenal function differs both in the magnitude of cortisol response to ACTH and in the time course, significantly delayed peak cortisol
- Adequate regulation of volume balance and the amount of blood loss correlates with adequacy of adrenal function

Henzen, C. Kobza, R. et al. Adrenal function during coronary artery bypass grafting. Eur J Endocrinol 148:6 pp. 663-8. Jun 2003.

Cortisol and Traumatic Brain Injury

- 50% of patients with TBI have at least transient adrenal insufficiency
- Adrenal insufficiency associated with
  - Younger age
  - Greater injury severity
  - Early ischemic results
  - Use of etomidate and metabolic suppressive agents

Cohan,P. Wang, C. et al. Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. Crit care Med 33:10 pp.2358-66 Oct 2005.

Low Dose Cortisol and Septic Shock

- Time to cessation of vasopressor support shorter
  - More profound effect in those with low adrenal reserve
- Cytokine production decreased
  - Decreased interleukin-6
  - Decreased interleukin-1 and -6 production
- Conclusions
  - Treatment with low-dose hydrocortisone accelerates shock reversal
  - Reduced production of pro-inflammatory cytokines
  - Hemodynamic improvement seemed to be related to endogenous cortisol levels
  - Immune effects independent of adrenal reserve

Oppert, M. Schindler, R. et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. Crit Care Med 33:11 pp.2457-64, Nov, 2005.

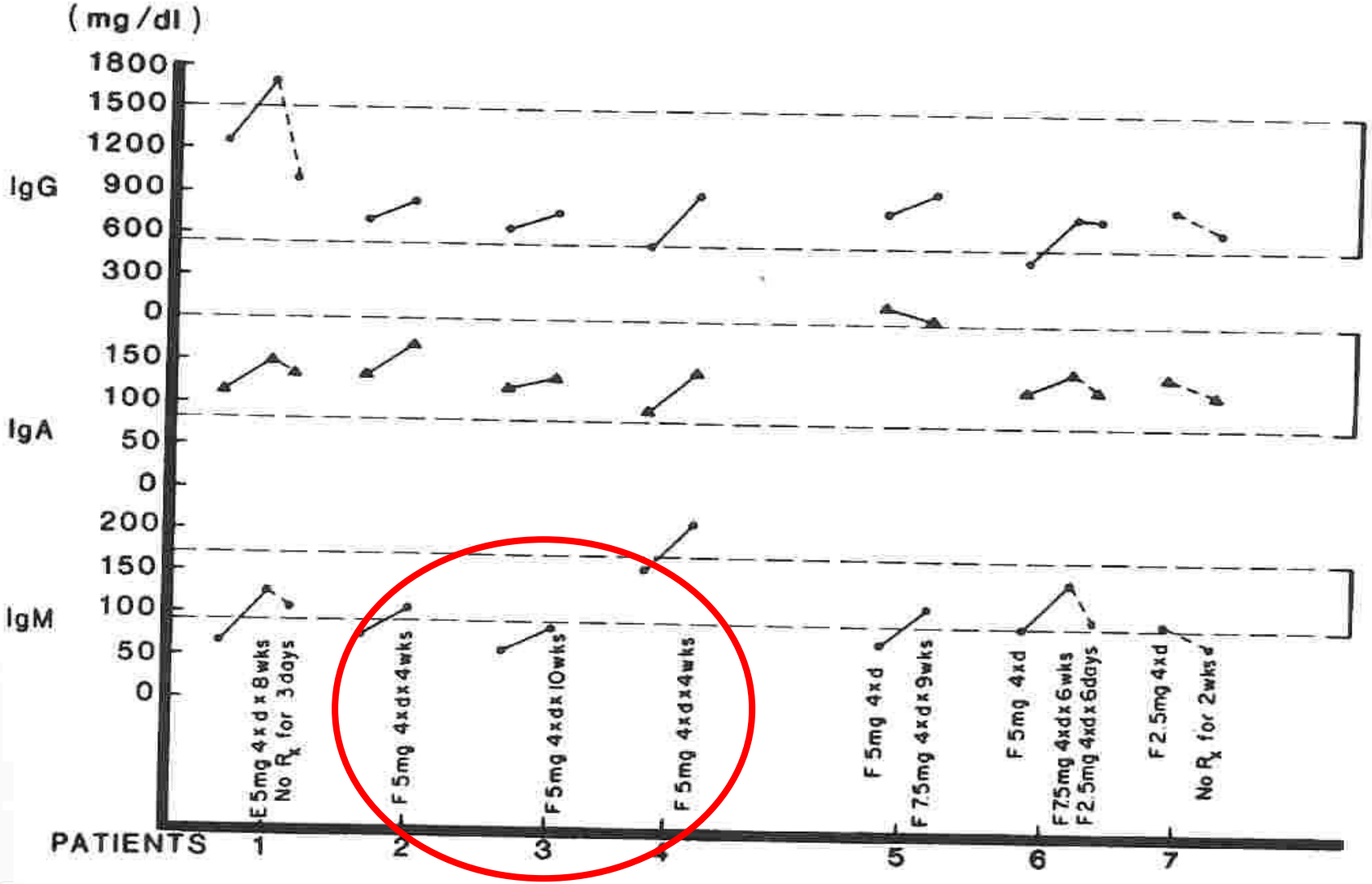


Figure 6. Effects of physiologic dosages of cortisone acetate (E) or cortisol (F) upon circulating levels of IgG, IgA, and IgM. Solid lines indicate effects of an increase in dosage, broken lines indicate effects of decrease in dosage. Horizontal interrupted lines indicate normal ranges for the technique employed.

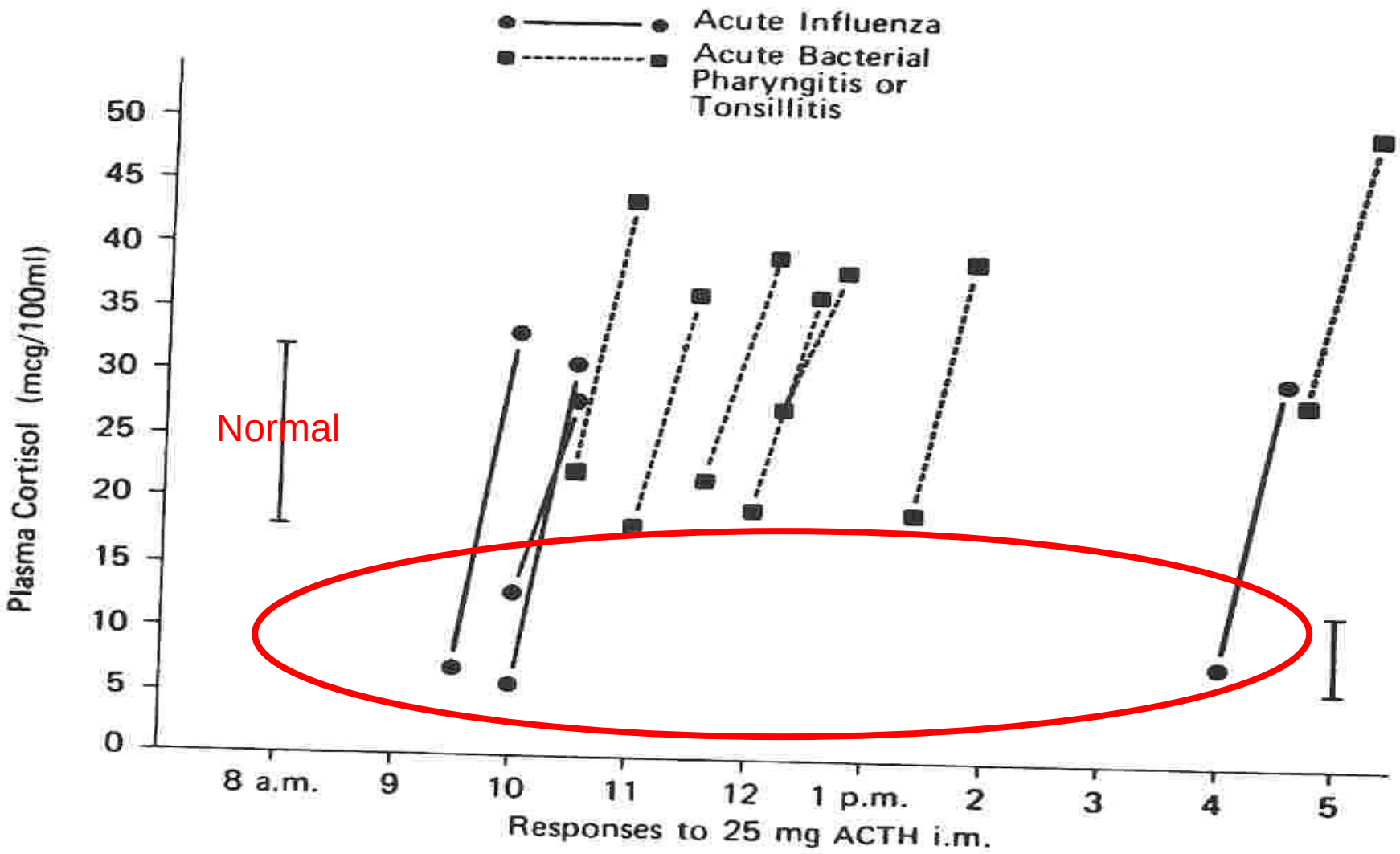


Figure 7. Plasma cortisol levels before and 30 minutes after an intramuscular injection of 25 units of cosyntropin (ACTH) in patients with acute influenza and in patients with acute bacterial pharyngitis or tonsillitis. The bars above 8 AM and 5 PM indicate the usual range of normal plasma cortisol levels for these times of day. Pre- and post-ACTH levels of patients are connected by lines to facilitate comparison.

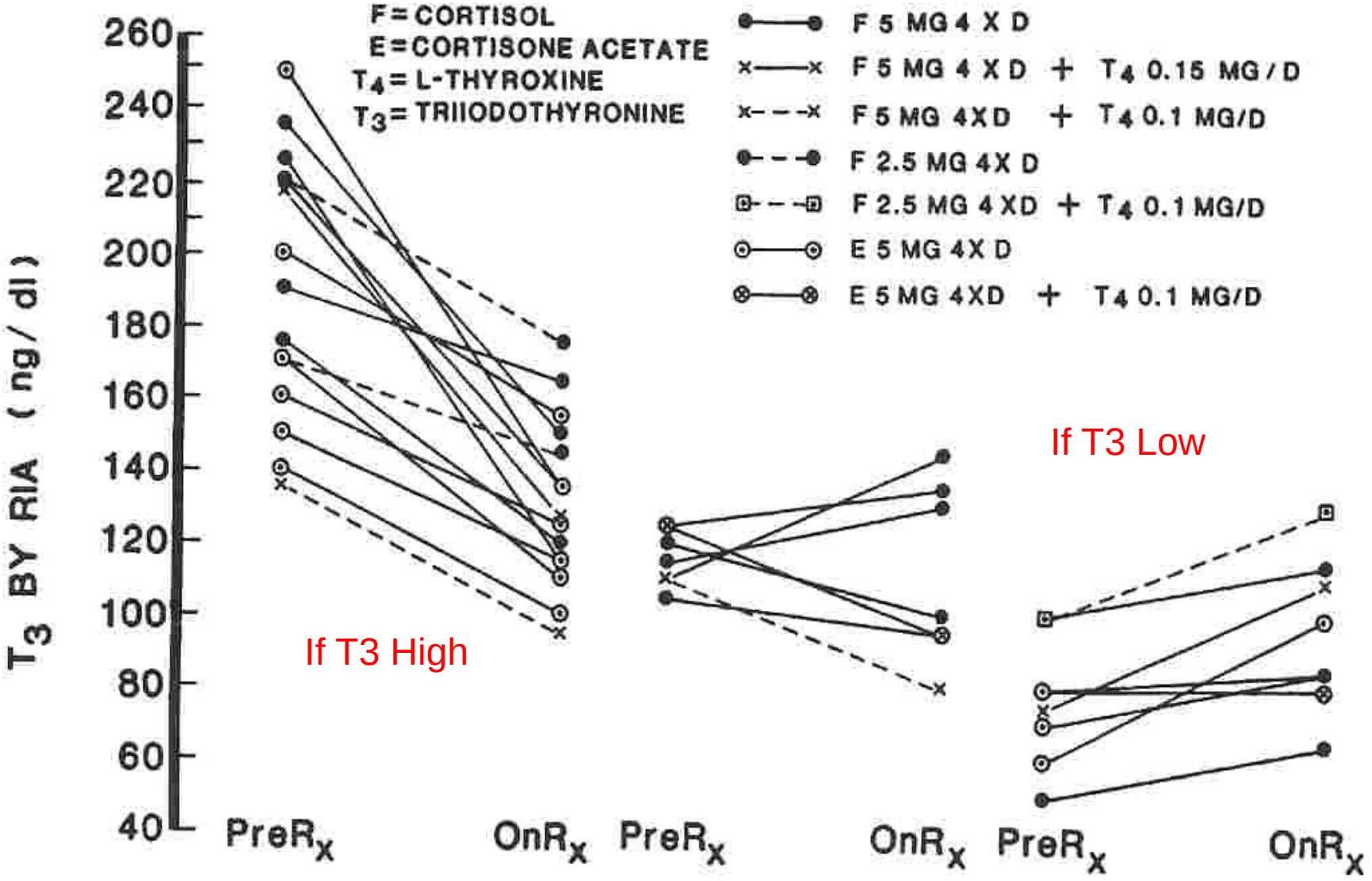


Figure 10. Effects of physiologic dosages of cortisone acetate (E) or cortisol (F) on circulating T_3. Left—subjects whose baseline T_3 was 130 ng/dl or higher; center—subjects whose baseline T_3 was 105–125; right—subjects whose baseline T_3 was 100 or less.

Diagnoses to Consider Cortisol

- **Allergy**
  - Urticaria
  - Atopic dermatits
- **Ovarian Dysfunction**
  - Dysmennorrhea, PMS, PCOS, Hirsutism
  - Chronic cystic mastitis, Acne
  - Infertility, miscarriage
- **Diabetes**
- **Regional enteritis**
- **Hypothyroid with high T3**
- **Autoimmune**
  - RA, SLE, PMR
  - Grave's, Hashimoto's
  - Ulcerative Colitis
  - MS
- **Chronic Fatigue Syndrome**
- **Fibromyalgea**
- **Jet Lag**
- **Influenza, mononucleosis, other acute viruses**

Candidates for Evaluation

- Any fatigue
  - Any Chronic disease with a fatigue component
  - Chronic Fatigue Syndromes
- Chronic Allergies
- Any autoimmune disease
- Ovarian dysfunction
  - Acne, Hirsutism
  - Infertility (better than clomithene)

Karow WG, Payne SA: Pregnancy after clomiphene citrate treatment. Fertil Steril 19:351-362, 1968.
Seegar Jones G, et al:Pathophysiology of reproductive failure after clomiphene Induced ovulation. AM J Obstet Gynecol 108:847-867, 1970.

ADRENAL SYMPTOMS & SIGNS

Symptom
Weakness, tiredness, fatigue
Gastrointestinal symptoms
Nausea
Vomiting
Constipation
Abdominal pain
Diarrhea
Anorexia
Salt craving
Postural dizziness
Muscle or joint pains

Sign
Weight loss
Hyperpigmentation
Hypotension
Loss of scalp hair
Excess facial or body hair
Vitiligo
Auricular calcification

Laboratory Testing

"Because cortisol is such a dynamic hormone, with production and utilization fluctuating from minute to minute depending upon degree of stress as well as upon diurnal variation, the assessment of adrenocortical function cannot be as exact as the measurement of function of most other glands, but the combination of measurement of plasma levels of cortisol and of adrenocorticotropic hormone (ACTH) with Cortosyn™ stimulation tests will identify most disorders."

McK. Jeffries, W. Safe Uses of Cortisol, Charles C. Thomas Pulisher, Ltd., Springfield, Il, Third edition, 2004, p. viii.

ADRENAL FUNCTION TESTS

- ORTHOSTATIC BLOOD PRESSURE
- URINARY CHLORIDE
  - BASED ON ALDOSTERONE
  - INVERSELY RELATED TO ADRENAL FUNCTION
- Heart Rate Variability
- ADRENAL STRESS INDEX
  - SALIVARY
- URINARY CATECHOLAMINES

Cortrosyn™ Stimulation Test

- No glucocorticoids for several weeks
  - At least 12 hours
- Fasting levels after a normal nights sleep of cortisol and ACTH
- Inject 25 units Cortrosyn™ (deltoid)
- 30 mins later a plasma cortisol sample drawn
- Record symptom changes for 24 hrs.
- Increase to at least double baseline values is normal
- Patients with secondary deficiency usually report mild improvement in symptoms
- Plasma cortisol by RIA usually
  - 15-30 mcg/100 ml in AM
  - 5-15 mcg/100ml in PM

Interpretation of Results

- **Low Adrenal Reserve**
  - Baseline plasma cortisol normal
  - Subnormal response to ACTH (Cortosyn™)
- **Mild Secondary Adrenal Deficiency**
  - Baseline plasma cortisol low or low normal
  - Normal response to ACTH
- **Anxiety and Depression**
  - Baseline plasma cortisol high
  - Hyperresponsive to ACTH
- **Ascorbic acid (Vitamin C) deficiency**
  - Highest concentration in adrenal cortex
  - May be involved in production of adrenocortical steroids

Cortisol Evaluation In Critical Illness

- We conclude that although random cortisol measurements and the low dose corticotropin tests reliably reflect the 24 hr. mean cortisol in critical illness, they do not take into account the pulsatile nature of cortisol secretion
- There is the potential for erroneous conclusions based on a single measurement.

Venkatesh, B. Mortimer, RH. Et al. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. Anaesth Intensive Care. 33:2; PP. 201-9. Apr, 2005.

Adrenocortical Insufficiency

- Primary
  - Inadequate production by adrenals
  - Low organ reserve
- Secondary
  - Inadequate ACTH from pituitary
  - Inadequate CRF from hypothalamus
- Defect of cellular receptors for cortisol

Spontaneous Adrenal Insufficiency

- Results from progressive destruction of adrenal tissue
- Symptoms appear when remaining tissue can not support well being
  - No adrenal reserve
  - Crashes when stressed
- Give at least 20 mg daily to patients to reduce the strain on residual adrenal tissue and recreate organ reserve
  - Provides opportunity for residual tissue to regenerate

Adrenergic Agonists

Albuterol
Amphetamine
Bitolterol
Brimonidine
Dexmedetomdine
Diethylpropion
Dipivefrin
Dobutamine
Dopamine
Ephedrine
Epinephrine
Formoterol
Guanabenz
Guanfacine
Isoetharine
Isoproternol
Levalbuterol
Levonordefrin
Mephentermine
Metaproterenol
Metaraminol
Methamphetamine
Methyldopa
Methylphenidate
Midodrine
Naphazoline
Norepinephrine
Oxymetazoline
Phenylephrine
Pirbuterol
Propylhexedrine
Pseudoephedrine
Racephedrine
Rauwolfia Alkaloids
Ritodrine
Salmetrol
Terbutaline
Tetrahydrozoline
Xylometazoline

These drugs increase Sympathetic and decrease Parasympathetic

Adrenergic Antagonists

Acebutolol
Amoxapine
Atenolol
Betaxolol
Bisoprolol
Bretylium
Carteolol
Carvedilol (Coreg)
Chlorpromazine
Clonidine
Diazoxide
Dihydroergotamine
Doxepin
Ergoloid Mesylates
Esmolol
Fluphenazine
Guanadrel
Guanethidine
Levobetaxolol
Levobunolol
Methysergide
Metoprolol
Miglitol
Molindone
Nadolol
Nefazodone
Penbutalol
Perphenazine
Phenoxybenzamine
Phentolamine
Pindolol
Prochlorperazine
Propafenone
Propranolol
Sotalol
Thioridazine
Timolol
Trifluoperazine
Yohimbine

ARB's
Doxazosin
Haloperidol
Labetalol
Prazosin
Tamsulosin
Terazosin
Thioxanthenes

ACE Inhibitors
Benazepril
Captopril
Enalapril
Fosinopril
Lisinopril
Moexepril
Perindopril
Quinapril
Ramipril
Trandolapril

Calcium Channel Blockers
Amlopidine
Bepridil
Diltiazem
Felopidine
Isradipine
Nicardipine
Nifedipine
Nimodipine
Nisoldipine
Verapamil

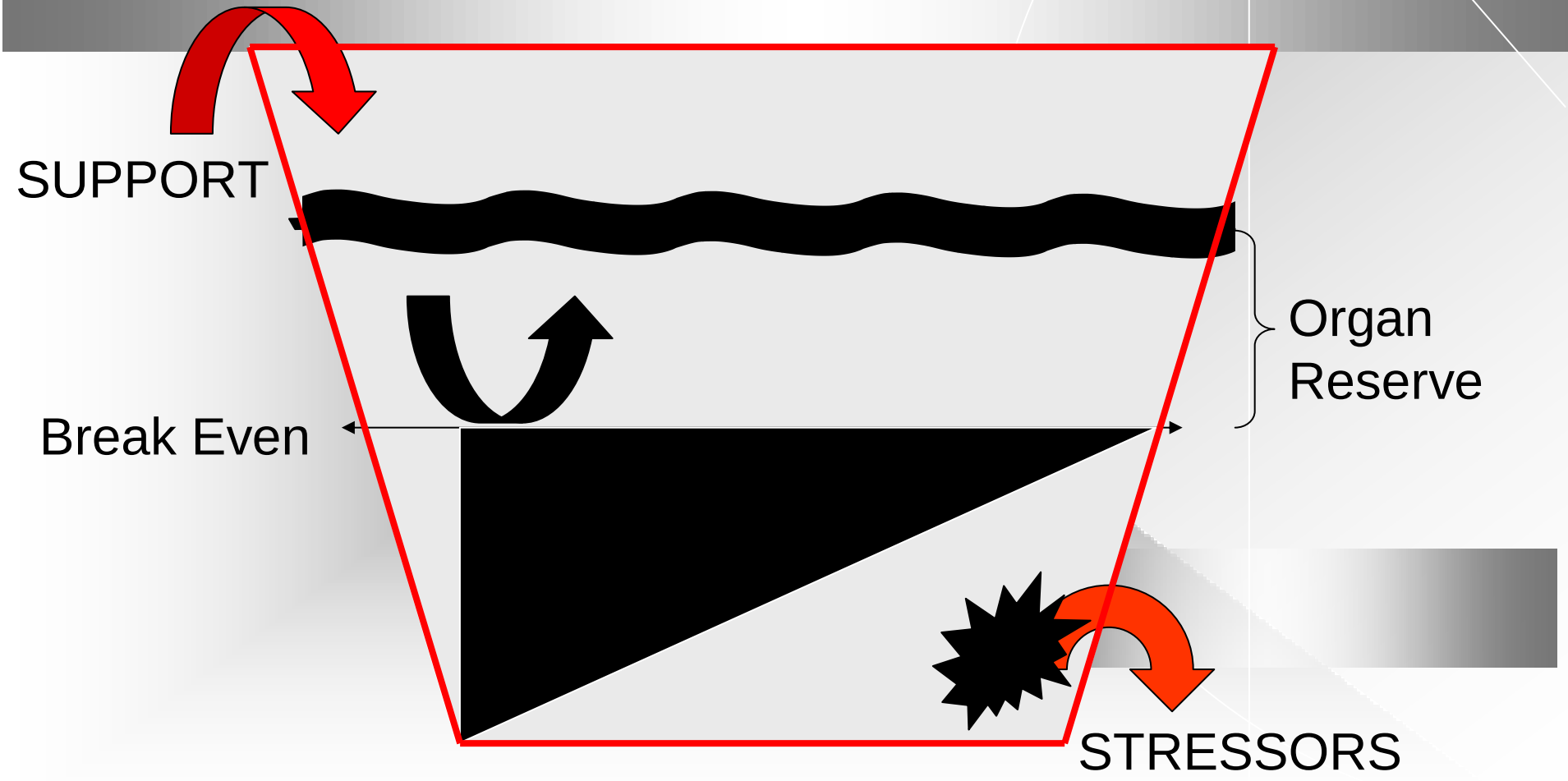
These drugs decrease Sympathetic and increase Parasympathetic

Therapeutic Trials

"It should be remembered, however, that tests within the normal range do not rule out the possibility that administration of small, physiologic dosages might be helpful, so therapeutic trials might still be indicated. This may be related to the inexactness of the recorded normal range and to the evidence that cortisol can affect uptake by cellular receptors."

McK. Jeffries, W. Safe Uses of Cortisol, Charles C. Thomas Pulisher, Ltd., Springfield, Il, Third edition, 2004, p. viii.

THE BUCKET ANALOGY CREATING & MAINTAINING ORGAN RESERVE



Treatment

"It seems preferable to administer natural hormones, especially for long term use and when treating deficiencies of these hormones. Hence, a schedule of administration that mimics the normal production pattern of cortisol as closely as is feasible seems advisable."

McK. Jeffries, W. Safe Uses of Cortisol, Charles C. Thomas Pulisher, Ltd., Springfield, Il, Third edition, 2004, p.ix.

Physiologic Dosages

It is now known that under normal, unstressed conditions the adrenals produce the equivalent of 35-45 mg of cortisone acetate taken by mouth in divided doses daily.

Jeffries, WMcK: Low dosage glucocorticoid therapy. Arch Intern Med 119:265-278, 1967.

It has been demonstrated that the same total daily dosage of cortisol taken in four divided doses before meals and bedtime is more effective than when taken in two divided dosages at twelve-hour intervals

Jeffries, WMcK: Glucocorticoids and Ovulation.
In Greenblatt RB (Ed):Ovulation. Philadelhia, Lippincott, 1966, pp.62-74.

THERAPY

- Ingestion of food tends to counteract the development of acid indigestion from the stimulation of gastric acid that may be produced by the steroid
- Taking something milky (dairy, soy or rice milk) or eating soda crackers with the bedtime dose helps
- Bedtime doses may cause nocturia
- Avoid excessive caffeine

PHYSIOLOGIC DOSING

- After initiating therapy at this dosage 10-14 days is required to achieve equilibrium in the tissues
- Dosing schedules that have shown inhibition of function or adverse effects represent individual doses three to four times higher than physiologic levels.

SUBREPLACEMENT DOSAGES

- LESS THAN NORMAL REPLACEMENT
- PARTIAL SUPPRESSION OF ENDOGENOUS ADRENAL FUNCTION
- ONLY SUPPRESSED SUFFICIENTLY TO ACHIEVE A NORMAL TOTAL GLUCOCORTICOID LEVEL
- RESIDUAL FUNCTIONING TISSUE ADEQUATE FOR NORMAL RESPONSES TO STRESS (IMPROVES RESPONSE)
- AVOIDS COMPLETE SUPPRESSION OF ENDOGENOUS ADRENAL ANDROGEN
- NEED TO TREAT BECAUSE OF NO ADRENAL RESERVE AND/OR IMPAIRED HPA RESPONSE TO STRESS

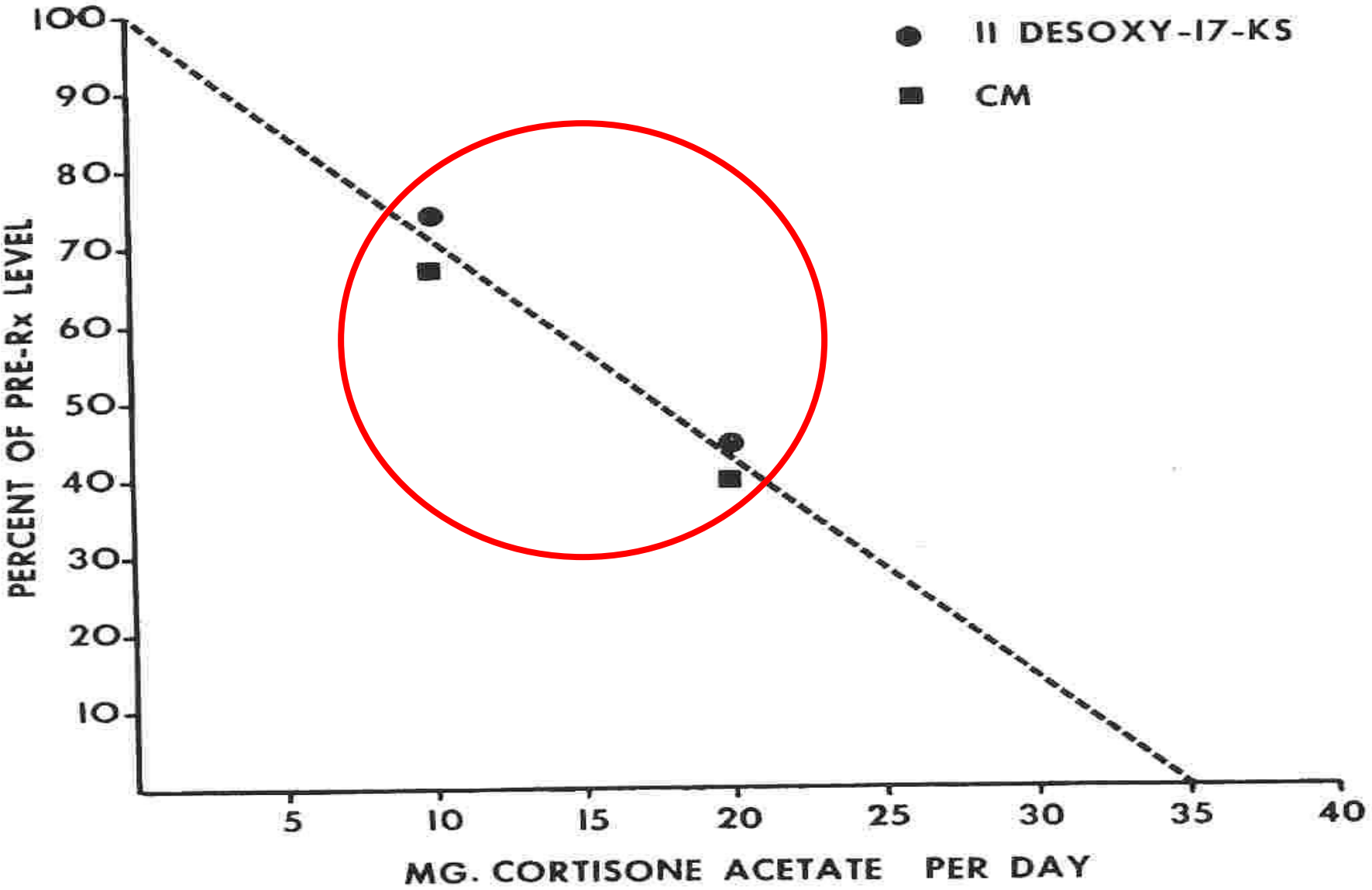


Figure 1. Effects of low dosages of cortisone acetate taken as 2.5 or 5 mg four times daily upon urinary excretion of 11-desoxy-17KS and cortisol metabolites (CM) from endogenous sources. From William McK Jefferies, Low Dosage Glucocorticoid Therapy, *Archives of Internal Medicine, 119*:265–278. Copyright 1967, the American Medical Association. Reprinted by permission.

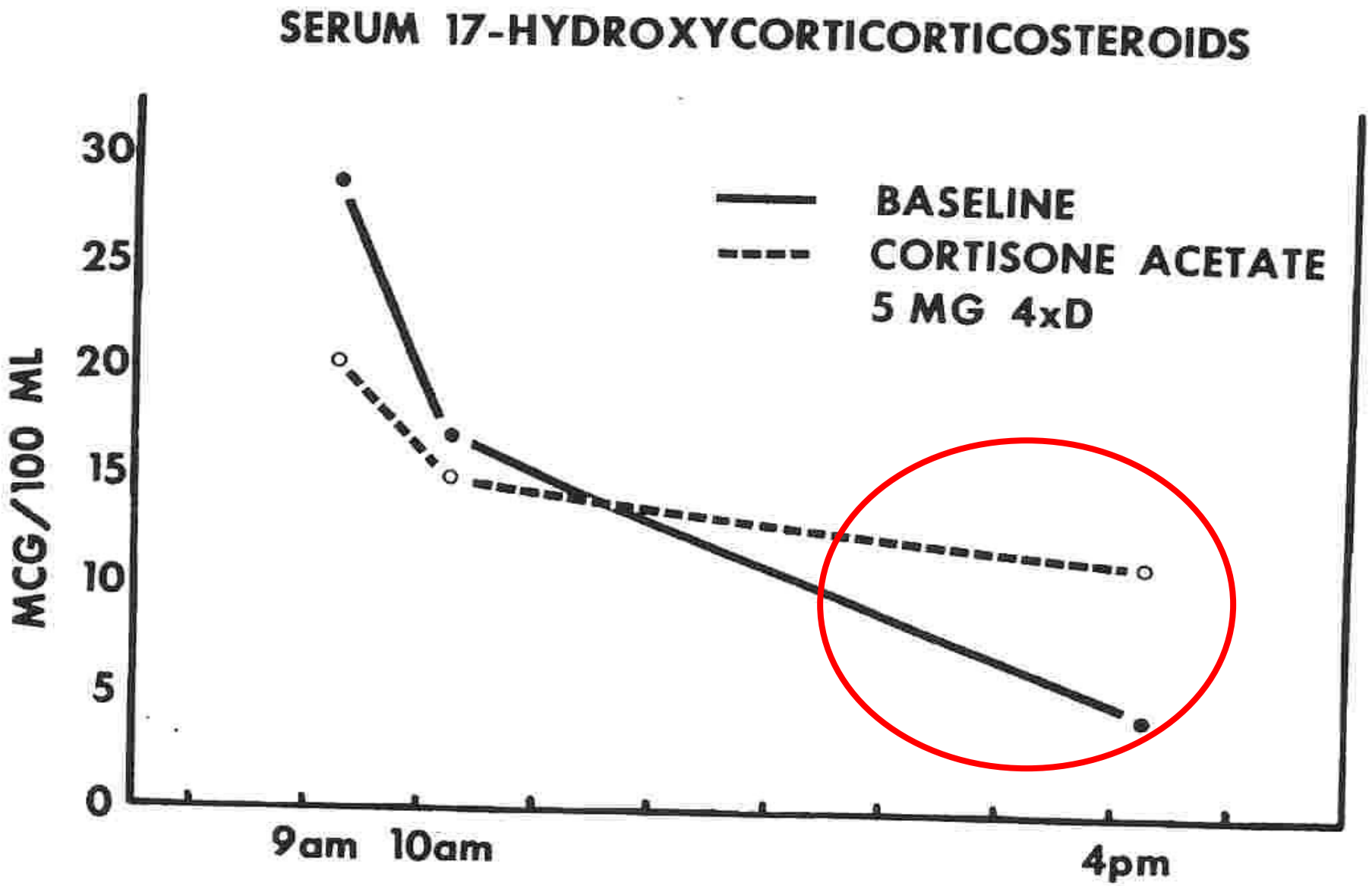


Figure 3. Effects of 5 mg cortisone acetate four times daily for 14 days upon diurnal variation of serum 17-hydroxy-corticosteroid levels in a normal male.

Figure 2. Effects of administration of a single dose of 5 mg of cortisone acetate and of 5 mg every 8 hours for 8 days upon urinary sodium, potassium, fluid, and total neutral 17-ketosteroid (17-KS) excretion. From William McK Jefferies, Low Dosage Glucocorticoid Therapy, *Archives of Internal Medicine*, *119*:265–278. Copyright 1967, the American Medical Association. Reprinted by permission.

Steroid Bursts

- If additional stress, may need additional cortisol
  - Fatigue that disappears when upping dose
  - Aches and pains that disappear with dose increase
  - Nausea, vomiting, collapse and fever if very low
- 10 mg for increased short term extra business stress
- May need 80-120 mg if uncontrolled asthma
- For most patients doubling baseline dose is adequate
- Wean to baseline dose (decrease 20 mg daily) when patient improves

SAFETY

" In over one thousand patient years of experience with the (physiologic) dosages described (<45 mg/day), none of the harmful potential of larger, pharmacologic dosages has been encountered."

McK. Jeffries, W. Safe Uses of Cortisol, Charles C. Thomas Pulisher, Ltd., Springfield, Il, Third edition, 2004, p. xviii.

Nasal Steroids and Risk

- Budesonide aqueous nasal spray in 78 children with allergic rhinitis
  - 6 weeks of therapy
- Conclusions
  - Well tolerated and safe
  - No measurable suppressive effects on HPA axis function in patients aged 2-5 with allergic rhinitis

Kim, KT. Rabinovitch, N. et al. Effect of budesonide aqueous nasal spray on hypothalamin-oituitary-adrenal axis function in children with allergic rhinitis. Ann Allergy Asthma Immunol 93:1 pp.61-7 Jul 2004.

Inhaled Steroids and Risk

- The present authors evaluated adrenal reserve in asthmatic children on long-term inhaled corticosteroids (budesonide) and whether possible adrenal suppression could be predicted by growth retardation.
- Adrenal suppression was disclosed in 15 asthmatic children (20.8%). There were no differences in height between children with and without adrenal suppression. There was no correlation between peak cortisol response and dose or duration of treatment. However, a positive relationship between height and duration of treatment was noted.

Priftis, KN. Papadimitriou, A. et al. The effect of inhaled budesonide on adrenal and growth suppression in asthmatic children. Eur Respir J; 27:2, pp.316-20, Feb, 2006.

Inhaled Steroids and Risk

- We sought to assess the efficacy and safety of ciclesonide once daily in patients with mild-to-moderate persistent asthma.
- No suppression of hypothalamic-pituitary-adrenal-axis function (as assessed by means of 24-hour urinary cortisol levels corrected for creatinine and peak serum cortisol levels after stimulation with low-dose [1 microg] cosyntropin) was observed with any dose of ciclesonide.
- CONCLUSIONS: In this integrated analysis, ciclesonide once daily administered in the morning is effective and well tolerated.

Pearlman,DS. Berger, WE. Et al. Once-daily ciclesonide improves lung function and is well tolerated with mild-to-moderate persistent asthma. J Allergy Clin Immunol; 116:6; pp.1206-12, Dec, 2005.

Cortisol and Bone Loss

- **In men, elevated peak plasma cortisol was associated with accelerated loss of mineral density in the lumbar spine (r = 0.16, P = 0.05). This relationship remained significant after adjustment for testosterone, estradiol, 25-hydroxyvitamin D, and parathyroid hormone levels (r = 0.22, P = 0.01) and after additional adjustment for age, (BM), activity, cigarette and alcohol consumption, and Kellgren/Lawrence score (r = 0.19, P = 0.03).**
- **In contrast in women, elevated peak plasma cortisol was associated with lower baseline BMD at the femoral neck (r = -0.23, P = 0.03) and greater femoral neck loss rate (r = 0.24, P = 0.02).**
- **There was no association between plasma cortisol concentrations after dexamethasone or urinary total cortisol metabolite excretion and bone density or bone loss rate at any site. These data provide evidence that circulating endogenous glucocorticoids influence the rate of involutional bone loss in healthy individuals.**

Reynolds, RM. Dennison EM, et al. Cortisol secretion rate and bone loss in a population-based cohort of elderly men and women. Calcif Tissue Int; 77:3; pp. 134-8; Sep 2005.

Different doses of steroids and effect on bone and insulin resistance

- All patients treated for 4 weeks
  - Schedule 1 Hydrocortisone 10 mg with Breakfast and 5 mg with lunch
  - Schedule 2 added 5 mg hydrocortisone at dinner
  - Schedule 3 dexamethasone 0.1 mg/15 kg body weight with breakfast
- Results
  - Serum 25-hydroxyvitamin D level not suppressed
  - Urinary FDPD (bone resorption) lower on dexamethasone
  - Increased Insulin resistance on dexamethasone

Suliman, AM. Freaney, R. et al. The impact of different glucocorticoid replacement schedules on bone turnover and insulin sensitivity in patients with adrenal insufficiency. Clin Endocrinol (Oxf). 59:3 pp. 380-7. Sep 2004.

Preventing Bone Loss When Prescribing Cortisol

- Short term uses are no problem
- To reduce bone resorption use
  - Ipriflavone 300 mg 3X/day
- Maintain adequate calcium intake
  - 1000 mg/day males, 1500 mg/day females
- Treat hypochlorhydria
  - Betaine Hcl 325-650 mg/meal
- Avoid caffeine-like substances

Clinical Trials

"The dynamic nature of adrenocortical function would make it difficult if not impossible to devise studies in which a constant dosage of cortisol for a specific period of time to a number of patients would provide a suitable test of its efficacy. . . . The effects of other hormones have never required double blind placebo studies, and the beneficial effects of small, physiologic dosages of cortisol are usually so clear that this type of confirmation has not been considered necessary."

McK. Jeffries, W. Safe Uses of Cortisol, Charles C. Thomas Pulisher, Ltd., Springfield, Il, Third edition, 2004, p. x.

Low-dose Cortisol Therapy and PTSD

- Low dose cortisol (10 mg/day) for 1 month
- Significant treatment effect
  - Cortisol related reduction of symptoms
  - PTSD Scale showed cortisol related improvements
    - Re-experiencing symptoms
    - Avoidance of symptoms
  - Conclusions
    - Low-dose cortisol treatment reduces the cardinal symptoms of PTSD

Aerni, A. Traber, R. et al. Low-dose cortisol for symptoms of posttraumatic stress disorder. Am J Psychiatry 161:8 pp.1488-90. Aug 2004.

Why give low dose cortisol?

- Intended to restore normal function and rebuild organ reserve, rather than altering normal function
- Physiological doses do not produce any excessive steroid level in the blood
- Although such doses may affect diurnal variation in plasma cortisol levels, they do not destroy normal diurnal variation
- Patient who have been taking subreplacement doses for long periods of time respond to ACTH and metyporone the same as normal subjects
- No evidence that physologic doses for over forty years have experienced any harmful effects

Why Are Physicians Unaware?

- Off patent, no financial incentive for drug companies to investigate new uses
- No discrimination between physiological and pharmacological dosing schedules implying any dose causes serious side effects
- Tendency to confuse cortisone and cortisol with more potent derivatives
  - Prednisone, Prednisolone, Methyl Prednisolone,
  - Triamcinolone, Dexamethasone
  - 5mg four times a day of derivatives is like taking 20 mg of cortisol or cortisone four times a day