I. Cortisol Deficiency: DIAGNOSIS

How to detect Cortisol Deficiency

Next to lab tests, an evaluation of past health history, signs, complaints, concurrent diseases and medical imaging, if needed, will offer the best picture of the deficiency and assist in choosing the best treatment.

1. Onset of Cortisol Deficiency

When did the cortisol deficiency start (past medical history)? How can you recognize persons with untreated cortisol deficiency in childhood?

By interviewing and examining the face and body shape of many patients with cortisol deficiency, it is possible to determine whether their deficiency started in childhood or if it began in adulthood. Patients with early childhood deficiency are generally more severely afflicted. As their childhood deficiency has worsened with time, they often complain more, and their face and body often looks thinner. The thinness is the result of a poor food intake favored by a lack of appetite and nausea, and poor food absorption in the gut, a gut that is too inflamed to absorb food well.

The main differences are summarized in the following table:

Determining the Onset of (Untreated) Cortisol Deficiency		
Onset	**Childhood**	**Adult**
Severity	Greater severity	More moderate
Face	• Thinner, narrower face	• Larger face, may have become more hollow
Body	• Thinner, narrower body	• Thin body*, if the lack of appetite and/or intestinal inflammation predominates • Possibly obese, if sweet cravings predominate:
Health in childhood	• Ear, nose and throat infections, viral infections • Allergies incl. skin rashes, food-rel., asthma • Gastrointestinal troubles (liver, colitis) • Excessive emotions: anger/irritability outbursts • Anorexia, difficult to make him/her eat, except sweets; sweet cravings	• No such medical problems in childhood

Note: **but not as thin as patients with severe cortisol deficiency in childhood*

After this quick check, it is important to inquire about the timing and location of the complaints.

2. Timing and Location

When and where do cortisol physical signs and complaints occur?

When? Typically, they occur more often and with greater intensity **during stressful situations** and when **standing up**.

Where? Physical signs have a tendency to be **unequally localized to certain areas of the body** (joint inflammation or skin rashes, for example, may be more localized on one hand than the other).

3. Complaints of Cortisol Deficiency

The patient may **intensely suffer** from the deficiency in thoughts and emotions, and deep into the body, in particular in **stressful situations**.

What does the cortisol-deficient patient complain of?

The principal **mental and emotional** complaints of cortisol deficiency are summarized in the table below.

MENTAL and EMOTIONAL COMPLAINTS of Cortisol Deficiency (hypocorticism, adrenal deficiency, Addison's disease)	
Mood	• Anxiety in stressful situations[1] • Depression in stressful situations, possibly resulting in suicide attempts[1,2] • Extreme moodiness
Memory	• Memory loss in stressful situations[2]
Attention	• Confusion, absentmindedness, especially in stressful situations[2]
Stress	• Poor resistance to stress, great difficulty to function well in stressful situations or even react to them, paralyzed in stressful situations[2], experiencing stress as being too much, as an unfair event[1,2] • Excessive sensitivity to human suffering[1,3] • Excessive compassion for the pain of others
Character	• Irritability[2,3] • Negativism (experiencing reality as being more negative than it really is for others)[2,3] • Feeling of being a victim[2,3] • Paranoid-like reactions: accusatory behavior, quarrelsome[2,3]
Behavior	• Excessive emotions: outbursts of anger or anxiety, panic attacks[1] • Frequent screaming or yelling[1] • Sharp verbal retorts, use of strong, dramatized words[1]

Note: *due to* [1] *adrenaline and other catecholamine discharges*
[2] *low blood sugar (hypoglycemia)*
[3] *inflammation*

The principal **physical** complaints of cortisol deficiency are summarized in the table below.

PHYSICAL COMPLAINTS of Cortisol Deficiency			
Physical appearance	• Excessive thinness • Tends to be underweight, difficulty gaining weight • Sometimes obesity because of bulimia due to sweet and salty food cravings		• Fatigue, low energy, especially during stressful conditions[2] • Burned out syndrome, sometimes transient, but great difficulties to function after emotional discharge[3]
Hair	• Acute hair loss • Alopecia areata • (hair loss in plaques)	**Energy/ Vitality**	• In upright position: drowsiness, empty-headedness, distraction, absentmindedness, day-dreaming, vertigo[2,4]
Head	• Headaches at stress[2,3]	**Sleep**	• Longer sleep
Skin	• Inflamed skin lesions: skin rashes (nettle rash, eczema, psoriasis)[3] • Vitiligo (depigmented skin areas)[3] • Cheloids (thick scars)[3] • Iregular brown spots[6] • Suntans easily[6]	**Tempe-rature**	• Slight fever from time to time[4]
Muscles and tendons	• Myalgia (localized muscle pains)[3] • Tendonitis (recurrent tendon inflammation), especially as positive *tender points*)[3]	**Food**	• Intense hunger attacks[2] • Sweet, sugar cravings[2] • Nausea, anorexia, esp. for meat[5] • Salty food craving[4]
Joints	• Arthritis (localized pain, deformities of joints)[3]	**Digestive**	• Gastroenteritis, colitis with abdominal pain, bloating, diarrhea[3] • Nausea, vomiting[5]
Inflamma-tions	• Predisposition to all kinds of inflammatory diseases[3], e.g: • Acute allergies: ENT (Ear-Nose-Throat) allergies, conjunctivitis, otitis, rhinitis, pharyngitis, asthma, food allergies • Chronic inflammatory diseases: rheumatoid arthritis, connective tissue diseases (e.g. lupus)	**Nerves**	• Excessive sensitivity to pain[3]
		Medi-cations	• Intolerance to medications[3]
		Infec-tions	Prone to infections[3]: • Viral: mononucleosis infection, flu, etc. • Bacterial: rhinitis, otitis, sinusitis, pharyngitis, bronchitis, pneumonia, ...

***Note**: Cortisol deficiency symptoms due to: [1]adrenaline and other catecholamine discharges; [2]low blood sugar (hypoglycemia);[3]inflammation;[4]hyponatremia with hypernatriuresis;[5]mineral or nitrogen disturbances in blood (electrolyte) imbalances, azotemia ; [6]ACTH overproduction*

With this basic knowledge we can now examine the details of the body of patients suspected of having a cortisol deficiency.

4. Physical Signs of Cortisol Deficiency

What are the physical signs of cortisol deficiency?

These physical signs are summarized in the following table.

Physical Signs of Cortisol Deficiency: Table 1	
Physical appearance	• Thin body[1] • (Obese if sugar cravings)[2]
Hair	• Acute hair loss (the hair that fell out usually has elongated hair roots)[3] • Rarely: alopecia areata[3]
Face	• Yellow-brownish face[4] • Hollow cheeks[1] • Brown (hyper pigmented) spots on face[4] • Painful sinus points[3]
Eyes and **eyelids**	• Tired look[2] • Conjunctivitis (with inflamed eye globe)[3] • Dark circles under the eyes[4]
Nose	• Rhinitis[3] (colds)
Ears	• Erythematous (red) inflamed tympanic membrane[3] • Inflammation (otitis)[3]
Pharynx	• Pharyngitis (inflamed red throat)[3] • Tonsillitis (Swollen, erythematous tonsils)[3]
Neck	• Tender, swollen lymphatic nodes[3]
Abdomen	• Bloated abdomen • Pain upon abdominal palpation[3] • Colitis [3]
Armpit	• Brownish armpit fold[4] • Heavy sweating in armpits[5]
Elbow	• Brown elbow fold[4]
Hands	• Wet palms[5] • Palms: brown skin folds[4]
Feet	• Wet soles[5]
Temperature	• Episodes of above normal temperatures >98.6°F or > 36.6°C (in women not taking the pill: during the first – follicular – phase of the menstrual cycle)

Note: *Physical signs due to the following mechanisms typical to cortisol deficiency:*

[1] inadequate food absorption

[2] low blood sugar (hypoglycemia)

[3] excessive inflammation

[4] overproduction of ACTH (adrenocorticotropin); pigmentation occurs only when adrenals are weak and the pituitary is healthy enough to secrete high amounts of ACTH

[5] higher adrenaline levels

Physical Signs of Cortisol Deficiency: Table 2	
Behavior	• Nervous, irritable behavior
Language	• Accusatory or "being the victim" language[1] • Sharp verbal retorts with often melodramatic words that have negative and/or aggressive connotation ("terrible", "horrible", "impossible", etc.)[1]
Lungs	• Wheezing (if asthmatic)
Heart	• Tachycardia[5]
Blood pressure	• Hypotension • Orthostatic hypotension • Possible hypertension in stressful situation[5]
Muscles and **Tendons**	• Painful muscles with pressure[3] • Painful tendons with pressure (positive tender points)[3]
Joints	• Inflamed joints[3] • Rheumatoid arthritis • Painful joints upon mobilization
Spleen	• Painful spleen upon palpation[3]
Skin	• Plaques of skin rashes (e.g. eczema, psoriasis, nettle rash)[3] • Vitiligo (white depigmented spots) • Cheloid (excessive) scar formation[3] • Irregular brown spots, melanoderma, nevi (darker brown birth spots) and scars, darker brown skin (in Caucasians), brown spots in buccal mucosa, brown skin folds[4]

Note: *Physical signs due to the following mechanisms typical to cortisol deficiency: [3] excessive inflammation; [4] overproduction of ACTH that next to stimulate greater cortisol production by the weak adrenals stimulates melanine production by the melanocytes, resulting in increased pigmentation when the pituitary is healthy enough to secrete high amounts of ACTH ; [5] higher adrenaline levels*

After checking for complaints and for typical body signs of cortisol deficiency, it is important to look for other diseases that may develop more easily with a cortisol deficiency.

5. Susceptibility to Diseases

Cortisol deficiency increases the susceptibility to many types of diseases: Inflammatory diseases such as acute allergies (such as ENT (Ear-Nose-throat) and food allergies, asthma), infections (flu, mononucleosis, etc.), chronic inflammatory diseases (rheumatoid arthritis), connective tissue diseases (lupus, etc.)

Patients with low cortisol levels or adrenal fatigue have an increased risk of dying under life-threatening conditions such as severe infections or multiple traumatic injuries because these patients are unable to secrete adequate amounts of supplementary cortisol when needed.
There is empirical data to support a correlation between cortisol deficiency and psychiatric diseases such as paranoia and autism.

After this check it is essential to require lab tests.

6. Lab Tests for Cortisol

IMPORTANT NOTICE: Do lab tests for cortisol in sedentary conditions! Avoid stress and intense activity such as hurrying, being in a traffic jam, and vigorous exercise **24 hours before and during testing** because they abnormally increase cortisol levels that may mislead the MD.

What are the main laboratory tests for confirmation of cortisol deficiency?

Lab tests for diagnosis of cortisol deficiency

Type	Test	Time	Optimal[1]	Pr. Deficient[1]	References	Value
Blood	**Total cortisol**	8-9 AM (morning)	180	0-130	100–250 ng/mL*	Low
			550	*0-360*	*276-690 nmol/L*	
	Free cortisol[3]		20	0-13	10-30 ng/ml	Med
			55	*0-36*	*28-83 nmol/l*	
	Total cortisol[4]	4-8 PM (late afternoon)	> 45	0-45	30-100ng/ml*	Low
			> 125	*0-125*	*80-275 nmol /l**	
	Free cortisol[4]		10-12	0-7	2-20 ng/ml	Med
			30	*0-20*	*5.5-55 nmol/l*	
	Total cortisol[4,5]	15-60' after ACTH - CRF-stimulation	Increase ≥ 2 x baseline cortisol	Less than 100% increase above baseline values	Higher than baseline values	Med
	Total cortisol					Low
	ACTH		Increase			Low
	ACTH	7-9 AM	45	High >70 Low < 25	20-80 mg/l	Low
	Transcortin (CBG)	Anytime	30	> 40	20-50 mg/l	Med
Urine (24h)	Free cortisol	24h	70	0-40	10-100 µg/24h	Med
	17-OH-steroids[6] *(gas chromatography)*	24h Men	13	0-10	5.8 -15.8 mg/24h	High
			36	*0-28*	*16-44 µmol/24h*	
		24h Women	6.5-7	0-5.5	3.7-8.5 mg/24h	
			18-19	*0-15*	*10-23 µmol/24h*	
Saliva	Free Cortisol[7]	Morning	*20-30*	*0-10*	*5.1-40.2 nmol/L*	Med
		Noon	*7-11*	*0-5*	*2.1-15.7 nmol/L*	
		Evening	*6-9*	*0-4*	*1.8-12.1 nmol/L*	
		Night	*5*	*0-2.5*	*0.9-9.2 nmol/L*	

Notes: *[1] "Pr. Deficient" means "probably deficient", relates to levels where patients are generally free of complaints and signs of cortisol deficiency.*

[2] The test value is the estimated usefulness for use in practice.

[3] The free cortisol is best obtained by calculation of a formula based on total cortisol and CBG, rather than through direct measurement. This is because of the excessive fluctuations of free cortisol, while total cortisol and CBG are more stable.

[4] When it is not possible to obtain a 24-hour urine collection, two or three blood measurements of total cortisol, transcortin and free cortisol in the morning, afternoon, and evening, and/or ACTH-stimulation test can be done. However, this is less accurate than the combination of morning values of serum cortisol with 24-hour urine cortisol and total corticosteroids.

[5] Based on recent studies, the amount of ACTH to inject should be 1 microgram (µg) and not 0.5 µg, nor the high conventional 250 µg. To obtain 1 µg from the classic 1 ml solution with 250 µg of ACTH, inject 0.04 ml of the 1 ml solution with a subcutaneous syringe into a sterilized 10 ml physiologic serum solution, then extract 1 ml of this newly formed mixture to intravenously inject in the patient.

[6] The urinary 17-hydroxysteroids must be measured with the gas chromatography technique.

[7] The saliva test allow measurement of the circadian rhythm.

II. Cortisol Deficiency:TREATMENT

Cortisol and other Glucocorticoid Medications

The drugs to treat cortisol deficiency and their indications are reviewed in the table below.

Route	Product	Dose (sedentary)	Dose (stress, infection)	Dose schedule	Indication: **Cortisol deficit** with main sign:	Value
Oral	**Cortisol (Hydrocortisone)** (Cortef®, Hydrocortisone®)	**Women:** 15-40 mg/day **Men:** 20-60 mg/day	1.5 to 3 x the normal dose	2 to 4x per day (mainly morning and midday)	1st choice for: • Fatigue • Low stress resistance	High
Oral	**Cortisone** acetate	1.25 x the cortisol dose			2nd choice	Med
Oral	**Predniso(lo)ne**[2,3] (Prednicort®)	2.5-7.5 mg/day	1.5 to 3 x the normal dose	1x/day	• Inflammatory diseases (1st choice)	Med
Oral	**Methyl-prednisolone** (Medrol®)[3]	2-6 mg/day		1x/day	• Inflammatory dis. 1st choice for: • Art. hypertension • Frequent edema, • Obesity	Med
IM	**Methyl-prednisolone** (Solu-medrol®)	40 or 100 mg /day	-	1x per season	• Rheumatoid crisis, allergy prevention	Low
IV	**Methyl-prednisolone** (Solu-medrol®)	40 or 100 mg	-	1x/day	• Allergy crisis	Low
Oral	**Dexamethasone**	0.15-0.35 mg/day	-	1x/day	• Hirsutism due to adrenal androgens	Low
IV	**Dexamethasone**	5-10 mg/day	-	1x	• Surgery	Low
Aero-sol	**Buciesonide** (Pulmicort, Rhinocort®)	50-400 µg/day	-	1-2 x/day	• Asthma, • Hayfever	Low

Notes: *« IM » means intramuscular, « IV » intravenous.*

[1] *The recommended dosage for patients with a total absence of endogenous cortisol production (after surgical removal of the adrenal glands for example) is approximately for women 40 mg/day and for men 60 mg/day.*

[2] *Methylprednisolone and dexamethasone are poor salt retainers (present a low risk of swelling) prednisone and prednisolone are intermediate salt retainers, while hydrocortisone has the best salt retaining ability; on the contrary, the synthetic derivatives such as methylprednisolone and dexamethasone have better anti-inflammatory action than bioidentical hydrocortisone.*

[3] *Prednisone is the precursor that converts into prednisolone for activity.*

/IENT

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: table below.

ıdication: ol deficit with ıain sign:	Value
ıice for: gue v stress istance	High
ıoice	Med
mmatory ıses (1st choice)	Med
mmatory dis. ıice for: hypertension quer ema, esity	Med
eumatoid is, allergy vention	Low
ergy crisis	Low
sutism due to enal androgens	Low
rgery	Low
hma, yfever	Low

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Which Glucocorticoid Medication is the best?

Which glucocorticoid medication is the best for a patient to take for the rest of his life?

Hydrocortisone, the bioidentical hormone, covers most cases of cortisol deficiency and is the best for most life-long treatments. **Synthetic derivatives** work better as a temporary treatment for acute inflammatory diseases such as infections or allergies, or as a prolonged therapy for chronic inflammations such as rheumatoid arthritis or chronic colitis.

In cases where a synthetic derivative is indicated, the tactic is to start with a synthetic derivative during the first six months and once the inflammatory disease is well under control, switch over to bioidentical hydrocortisone.

The usual medications for treatment of cortisol deficiency in recommended order of use are presented in the following table.

Medication	**Indication:** Cortisol Deficiency with as main problem(s):	Strong points
Hydrocortisone	• Low energy or mood, fatigue, low resistance to stress, etc. • Low blood pressure • Most cortisol-deficient states	• Bioidentical hormone, fully adapted to the human body. • More efficient for energy, mood and blood pressure (high salt-retaining capacity)
Prednisone, Prednisolone[1]	• Acute or chronic inflammatory or infectious diseases: flu, rheumatoid arthritis, allergies, etc.)	• More efficient against inflammation (including infection) • Intermediate salt-retainer and thus has blood pressure increasing capacity
Methylprednisolone	• Fluid retention • Hypertension • Obesity	• More efficient against inflammation (including infection) • Does generally not retain salt and fluid at smaller (physiological) doses, nor cause weight gain (except if the diet is rich in sweets, grains and milk products: see dietary recommendations below)
Dexamethasone[2]	• Hirsutism (excess body hair) caused by excessive levels of androgens from adrenal gland origin	• Provides the longest (48-hour) action • Is the best drug to block the overproduction of androgens by the adrenal glands

Notes:

[1] *Prednisone must convert into prednisolone in the body to become fully active.*

[2] *When using dexamethasone, we strongly recommend to regularly check the androgen (17-ketosteroids) and glucocorticoid (17-hydroxysteroids) metabolites before and during treatment in the 24-hour urine. For further* explanation, refer to the Follow-Up section that follows.

How to begin Cortisol Therapy

In most cases, cortisol can be started at the estimated dose. The minimal efficient dose in women is usually 15-20 mg per day. In men, it is about 30 mg per day divided in at least two separate doses: one given in the morning and one at noon.

The recommended dosing for cortisol is shown in the following table:

How to start Glucocorticoid Medication?						
Patient (sex)	**Cortisol Deficiency**	**Product**	When to take the medication?			
			7-8 AM	**12 PM**	**4 PM**	**Before bed**
Men	Borderline	Hydrocortisone	15 mg	5 mg		
	Mild	**Hydrocortisone**	20 mg	10 mg	-	-
	Moderate	Hydrocortisone	25 mg	10 mg	(5 mg)	-
	Severe to total		30 mg	10 mg	(10 mg)	(5 mg)
	Borderline	Predniso(lo)ne	2.5 mg			
	Mild	**Predniso(lo)ne**	5 mg	-	-	-
	Moderate	Predniso(lo)ne	6-7.5 mg	-	-	-
	Borderline	Methylprednisolone	2 mg			
	Mild	**Methyl**prednisolone	4 mg			
	Moderate	Methylprednisolone	6-8 mg			
Women	Borderline	Hydrocortisone	10 mg	5 mg		
	Mild	**Hydrocortisone**	10 mg	10 mg	-	-
	Moderate	Hydrocortisone	15mg	10 mg	(5 mg)	-
	Severe to total		20 mg	10 mg	5 mg	5 mg
	Borderline	Predniso(lo)ne	2.5 mg			
	Mild	**Predniso(lo)ne**	5 mg	-	-	-
	Moderate	Predniso(lo)ne	7.5 mg	-	-	-
	Borderline	Methylprednisolone	2 mg			
	Mild	**Methyl**prednisolone	4 mg	-	-	-
	Moderate	Methylprednisolone	6-8 mg	-	-	-
	Hirsutism	**Dexamethasone**	0.1-0.5 mg	-	-	-

Important remarks:

Sensitivity to hydrocortisone:

Persons who tend to be sensitive to medication should start hydrocortisone at half of the estimated dose for two to three weeks. If case no signs of intolerance such as fluid retention occurs, then the dose may be slowly increased by 20 % every two to three weeks up to the optimal dose.

Obesity, swelling:

Persons with obesity generally do better on methylprednisolone (Medrol®), which at 4 mg does *not usually* cause edema and weight gain. However, if edema and weight gain occurs, it is wise to start at 2 mg per day and then increase slowly to 4 to possibly 6 mg per day.

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ıe medication?	
4 PM	Before bed
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How to prevent adverse affects of Cortisol

1) Add anabolic hormones such as DHEA

Excessive catabolism (with osteoporosis, skin thinning, etc.) is the main adverse effect to fear from cortisol treatment. Adverse effects of cortisol treatment appear at excessive doses or when the levels of anabolic hormones are low. Concurrent treatment with anabolic hormones such as DHEA prevents the tissue wasting as shown in animal studies in many tissues from the brain to the heart, liver, bone and muscles. We strongly recommend to correct any anabolic deficiency at the same time as the cortisol treatment. Our most frequent association is DHEA with cortisol, thus mimicking the healthy body's normal reaction to stress consisting of increased secretions of both hormones in relatively equal amounts.

2) Eat protein

Increased protein intake may prevent the tissue wasting of excessive glucocorticoid treatment as shown in animal studies.

Indications

The main indication for cortisol treatment is cortisol deficiency.

Other indications: Cortisol and many glucocorticoids derived from cortisol are used with success in various other indications from allergies, asthma, to rheumatoid arthritis, gastrointestinal tract inflammations, systemic infections, chronic sinusitis, and many other inflammatory diseases. For acute illnesses, glucocorticoids are used temporarily, but when the condition becomes chronic, it can require long-term glucocorticoid treatment.

Contraindications to Glucocorticoid Treatment

There are two fundamental contraindications to cortisol supplementation: when it is not necessary or when it could cause harm.
First, cortisol treatment is not needed when lab tests are normal and the person is healthy. In that case, cortisol treatment will generally not help and may, on the contrary, cause harm.
Second, cortisol treatment – even appropriate replacement doses of cortisol –may cause harm if the patient does not have sufficient levels of anabolic hormones such as DHEA and sex hormones to counter cortisol's catabolic effects. The catabolic effects of cortisol can cause excessive breakdown of the tissues of the body which result in osteoporosis (loss of bone tissue), skin atrophy (thinning), ecchymosis, petechia (bruising) and immunosuppression (decrease in immune defenses).
So the recommendation is to treat only when necessary and to do it safely with the smallest effective physiologic doses and with simultaneous correction of any deficit in anabolic hormones.

How to boost Cortisol Activity and Treatment

There are many ways to naturally boost the daytime cortisol levels and reduce the night-time cortisol levels.

First of all, improving the lifestyle, including the diet, helps to increase the cortisol levels.

The principal lifestyle changes that boost the effects of the cortisol produced by the body or supplied by treatment are summarized in the following table:

How to optimize Cortisol activity and treatment		
	What To Do	**What To Avoid**
Light	• Increase exposure to sunlight or bright artificial light, esp. in the morning[1]	• Avoid living and working in semi-darkness during the day
Diet	• Foods to choose: • Eat small frequent meals[2] • Follow a "Paleolithic" diet: fruits, vegetables, fish, eggs, poultry meat	• Avoid alcohol, vinegar, caffeinated drinks[4] • Avoid sugar, sweets, soft drinks, cookies, bread, pastas and cereals[5] • Avoid cereal fiber (whole grain bread, bran flakes) • Avoid milk products
Stress		• Avoid excessive chronic stress, including strenuous physical activities, especially in the evening or at night[6]

Notes:

[1] *Increased exposure to sunlight, especially in the morning, and maximized darkness at night, by sleeping with an eye mask for example, which helps having optimal cortisol levels during the day and minimal cortisol at night.*

[2] *At each meal blood levels of cortisol temporarily triple.*

[3] *Dietary saturated fat is necessary for the production of cortisol as saturated fat cholesterol is the first building block for cortisol synthesis*

[4] *Beverages with caffeine (coffee, tea, and cola) and alcohol should be avoided before bedtime as caffeine can increase cortisol and considerably reduce night-time secretion of melatonin, a hormone that tends to reduce any cortisol production at night.*

[5] *Dietary starch and especially sugar and sweets increase the blood sugar level, which in turn reduces cortisol production.*

[6] *Excessive prolonged stress exhausts the adrenal glands that finally become unable to produce adequate amounts of cortisol anymore (burn-out syndrome). Evening or night-time stress is a strong stimulator of cortisol secretion, but depletes the adrenal supply of cortisol, resulting in decreased cortisol levels for the next morning at a time when the serum level of cortisol should be high.*

carcinoma, mitotane can be used as a palliative drug. Further, mitotane may prolong recurrence-free survival in patients with radically resected adrenal cortical carcinoma and is presently recommended even in apparently disease-free subjects following surgery. Starting dose is 250 mg qid and with gradual increase to tolerance levels (24 g/day) should be assisted by monitoring mitotane levels to achieve, whenever possible, therapeutic levels (14 to 25 μg/mL). Severe gastrointestinal effects (nausea, vomiting, diarrhea) occur in 80% of patients. Central nervous system toxicity (somnolence, dizziness, vertigo) is common because mitotane is fat-soluble. Hypercholesterolemia, which usually requires treatment with HMG-CoA reductase inhibitors, often develops as the dose of mitotane is increased toward the effective range. Because hypoadrenalism can occur and because mitotane enhances cortisol clearance and increases CBG, serum cortisol *and* urinary free cortisol should be monitored. In advanced or recurrent disease, chemotherapy consisting of etoposide, doxorubicin, and cisplatin can be added to mitotane, achieving benefit in up to half of subjects treated.

C. Ectopic Cushing syndrome

1. **Surgery.** Removal of the ACTH-secreting tumor is the treatment of choice but is usually not feasible because of the nature of the underlying process (e.g., carcinoma of the lung). Adrenalectomy can be considered in cases of indolent yet inoperable tumors such as some medullary carcinomas of the thyroid.
2. **Adrenal enzyme inhibitors** are useful in reducing hypercortisolism in ectopic ACTH syndrome.
   a. **Metyrapone,** an 11-hydroxylase inhibitor, at an average dose of 250 to 500 mg tid, provides an effective means of normalizing cortisol levels. This agent can lead to increases in deoxycorticosterone, which has sufficient mineralocorticoid activity to cause hypertension and hypokalemia.
   b. **Aminoglutethimide,** which blocks the conversion of cholesterol to δ-5-pregnenolone, can also be used starting at 250 mg qid, up to 2 g daily. Because hypoadrenalism can result, monitoring of therapy (plasma cortisol, urinary free cortisol) is mandatory. Aminoglutethimide also enhances the metabolism of dexamethasone and can cause hypoaldosteronism.
   c. **Adrenolytic agents** such as mitotane (medical adrenalectomy) can be used when control cannot be obtained with metyrapone or aminoglutethimide. Mitotane is administered either alone or in addition to the enzyme inhibitors.
   d. **Ketoconazole,** an antifungal agent, is perhaps the **first choice** for antiadrenal therapy, because it is an effective and simple means to control hypercortisolism. This agent blocks steroidogenesis at several levels, the most important being the 20,22-desmolase catalyzing the conversion of cholesterol to pregnenolone. Doses range from 600 to 1 200 mg/day. The major toxicity is hepatocellular, so liver enzyme tests must be followed. It may cause hypogonadism. Patients have been maintained on this agent for years with good responses. Because ketoconazole blocks early (as well as late) in the steroid pathway (cholesterol side-chain cleavage enzyme), there is no accumulation of other potentially toxic steroids. Therapy can be combined with other agents (metyrapone, aminoglutethimide).

ADRENAL INSUFFICIENCY

I. GENERAL PRINCIPLES

Adrenal (or **adrenal cortical**) **insufficiency** can be caused by:

A. Primary disease at the adrenal level, involving destruction of >90% of the steroid-secreting cortex (Addison disease).

B. Destructive process at the hypothalamic-pituitary level, leading to CRH or ACTH deficiency (or both).

C. Long-term suppression of the **hypothalamic–pituitary–adrenal (HPA) axis** by exogenous or endogenous glucocorticoids followed by inappropriate withdrawal.

TABLE 12.2 Etiology of Chronic Adrenal Insufficiency

Primary
Idiopathic adrenal atrophy (autoimmune adrenalitis, with or without other components of the polyglandular autoimmune syndrome type 1 or 2)
Granulomatous diseases
Tuberculosis
Histoplasmosis
Sarcoidosis
Neoplastic infiltration
Hemochromatosis
Amyloidosis
Following bilateral adrenalectomy
Congenital and genetic hypoadrenalism
ACTH resistance syndromes
Secondary
Tumors
Pituitary tumor
Craniopharyngioma
Tumor of the third ventricle
Pituitary infarction and hemorrhage
Postpartum necrosis (Sheehan syndrome)
Hemorrhage in tumors
Granulomatous diseases
Sarcoidosis
Following hypophysectomy
Steroid withdrawal

ACTH, adrenocorticotropic hormone.

II. CHRONIC ADRENAL FAILURE (Table 12.2)

A. Primary adrenal failure

1. **Etiology.** Primary adrenal failure evolves only when there is nearly complete destruction or infiltration of the adrenal glands.
   a. **Autoimmune adrenalitis** accounts for ~70% of cases, 50% of whom present with additional forms of autoimmune endocrinopathy, i.e., polyglandular autoimmune syndrome type I or II. Polyglandular autoimmune syndrome type I, also known as **polyendocrinopathy-candidiasis-ectodermal dystrophy (APECD),** is an autosomal recessive disorder with mutations in the autoimmune regulator gene and is seen in childhood in association with 100% adrenal failure, hypoparathyroidism, and mucocutaneous candidiasis. Hypogonadism and malabsorption may also be present. In the more common type II polyglandular autoimmune syndrome, which is usually comprised of type I diabetes mellitus, autoimmune hypothyroidism, primary hypogonadism, and pernicious anemia, autoimmune adrenal insufficiency is a major component (see Table 12.2).
   b. **Infectious disease** is another cause, and disseminated **tuberculosis,** the leading cause of chronic adrenal failure in the first half of this century, now accounts for ~5% of cases. The adrenal glands are usually 100% infiltrated. Rifampin accelerates cortisol metabolism, so higher-dose steroid replacement therapy may be needed. Almost all fungal infections, an exception being candidiasis, can destroy the adrenal gland. **Histoplasmosis** is the most common cause in the United States, and **South American Blastomycosis** is the most common cause in South America. Because ketoconazole but not fluconazole or itraconazole inhibits steroid biosynthesis, it may worsen adrenal insufficiency

pigmentation. The **hyperpigmentation** can be diffuse but is usually spotty, being noted around the lips and buccal membranes and in exposed or pressure areas, e.g., the knuckles, knees, feet, elbows, and belt and brassiere lines. Multiple freckles and generalized tan may be seen along with areas of vitiligo in autoimmune adrenalitis. **Hyperkalemia** occurs in 61% of primary disease, and **hyponatremia** is even more common, because of the combined effect of loss of aldosterone secretion and absence of the physiologic inhibitory effect of cortisol on ADH secretion, leading to water retention. Secondary hypoadrenalism, on the other hand, is accompanied by hyponatremia but not by hyperkalemia.

B. Secondary adrenal insufficiency. Clinically, secondary adrenal insufficiency can be quite subtle, presenting only as weakness and fatigue. It does not cause hypoaldosteronism, because the renin–angiotensin system is intact to control aldosterone production from the zona glomerulosa. **Two clinical features** can help distinguish primary from secondary adrenal disease: **(1) hyperkalemia** is not found in secondary disease, but **hyponatremia is common; (2) hyperpigmentation** is also not present in secondary disease, because ACTH and MSH levels are low.

Additional clues of secondary adrenal insufficiency are concomitant symptoms of hypogonadism and hypothyroidism, reflecting deficiencies in luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and growth hormone (GH).

IV. ACUTE ADRENAL CRISIS

A. Etiology. Chronic adrenal insufficiency can evolve into acute adrenal crisis precipitated by severe infection, trauma, or surgery.

B. Clinical presentation includes high fever, dehydration, nausea, vomiting, and hypotension that evolves rapidly to circulatory shock. Hyperkalemia and hyponatremia are seen if mineralocorticoid deficiency is present. Elevated blood urea nitrogen (BUN) and sometimes hypercalcemia reflect extracellular fluid loss.

V. SUPPRESSION OF THE HPA AXIS

Chronic glucocorticoid therapy results in suppression of the HPA axis. Individual susceptibility to HPA suppression, with regard to steroid dosage and duration of therapy, is variable. HPA suppression can manifest in several ways, such as weakness, fatigue, depression, and hypotension occurring upon cessation of glucocorticoid therapy. Acute adrenal crisis can ensue during major stressful situations when glucocorticoids have not been appropriately increased. HPA suppression can present as undue prostration during or following relatively minor intercurrent stress or ailments such as mild upper respiratory viral infection. Subjects may present with no overt clinical manifestations and only subclinical or biochemical evidence of HPA suppression (blunted cortisol response to exogenously administered ACTH). The following situations should be considered as producing HPA suppression:

A. Any patient who has taken prednisone at a dosage of 15 to 30 mg daily for 3 to 4 weeks. Suppression of the HPA axis can last for 8 to 12 months after cessation of glucocorticoid therapy.

B. Any patient who received prednisone at a dosage of 12.5 mg daily for 4 weeks. HPA suppression can last for 1 to 4 months after cessation of therapy.

C. Any patient who has been treated with glucocorticoids and exhibits a subnormal response to the ACTH test, regardless of dose and duration of therapy.

D. Any patient with Cushing syndrome who underwent surgery for removal of an adrenal adenoma or carcinoma or transsphenoidal removal of ACTH-secreting pituitary adenoma.

VI. DIAGNOSIS OF ADRENAL INSUFFICIENCY

A. 8 A.M. Serum cortisol, plasma ACTH, and plasma renin activity (PRA). Unless the patient has low CBG (a fairly uncommon condition), serum cortisol ≤ 3 μg/dL is practically indicative of hypoadrenalism. The ACTH IRMA is a valuable ancillary tool, because ACTH concentration often rises even before significant drops in plasma cortisol occur in primary adrenal failure. When serum cortisol is low, *properly collected and transported* plasma ACTH levels should be clearly elevated in primary adrenal insufficiency. A plasma ACTH >50 to 100 pg/mL indicates primary adrenal insufficiency. Low cortisol levels associated with low ACTH concentrations are indicative of secondary hypoadrenalism, and secondary hypoadrenalism is also suggested by the combination of low cortisol levels with inappropriately "normal" plasma ACTH. ACTH level <30 pg/mL is particularly supportive of the diagnosis of secondary adrenal failure. PRA is typically increased in primary but not in secondary hypoadrenalism. *When 8 A.M. serum cortisol is higher than 3 μg/dL, additional testing will be required to confirm the presence of hypoadrenalism.*

B. Rapid ACTH stimulation test (cosyntropin [Cortrosyn] test). Cosyntropin is a potent and rapid stimulator of cortisol and aldosterone secretion. The cosyntropin test can be used on an inpatient or outpatient basis, and time of day and food intake do not alter test results. In a previously undiagnosed patient it can, and indeed should, be performed even in the emergency room, while glucocorticoid replacement with dexamethasone is initiated concomitantly.

1. Procedure

a. Draw blood for baseline serum cortisol, aldosterone, and ACTH. Aldosterone and ACTH will help differentiate primary from secondary adrenal hypofunction.

b. Inject 250 μg of cosyntropin either intravenously or intramuscularly. For intravenous injection, dilute cosyntropin in 2 to 5 mL of 0.9% sodium chloride and inject over 2 minutes.

c. Obtain repeat samples for serum cortisol (and aldosterone) 30 and 60 minutes following ACTH administration.

2. Interpretation. A normal adrenal response to ACTH consists of a rise in serum cortisol to 18 μg/dL or greater. A higher cutoff of 20 μg/dL is also used to increase the sensitivity of the test. A normal response effectively rules out primary adrenal insufficiency. Patients with secondary adrenal insufficiency usually show a blunted response to cosyntropin but occasionally have a normal response. Baseline ACTH levels in primary adrenal insufficiency are high, generally >50 to 100 pg/mL, whereas levels in secondary adrenal insufficiency are low or normal (10 pg/mL or less).

Evaluation of ACTH-induced aldosterone responses also helps to distinguish primary from secondary adrenal insufficiency. In primary adrenal insufficiency, baseline aldosterone levels are low and there is no response to cosyntropin. In secondary adrenal insufficiency, baseline aldosterone levels may be low or normal, but at 30 minutes there is an increase in plasma aldosterone of at least 4 ng/dL over baseline.

C. The low-dose (1-μg) ACTH test. This test is more sensitive and accurate than the 250-μg dose of ACTH in detecting partial adrenal gland insufficiency, especially in patients with secondary adrenal deficiency. The 250-μg dose of ACTH produces massive pharmacologic concentrations of ACTH, exceeding blood concentrations of 10,000 pg/mL, which is way above the ACTH level seen even under extreme conditions in real life. Therefore, the 250-μg dose tends to test only for maximum adrenocortical capacity and overrides any more partial loss of cortisol function. The 1-μg cosyntropin test should replace the 250-μg dose because it is more likely to detect partial or more subtle forms of adrenal insufficiency, particularly secondary adrenal insufficiency resulting from pituitary tumors or chronic glucocorticoid treatment. Two important limitations of this test should be considered, however: **(1)** standard 1-μg cosyntropin packaging is not commercially available at the present time, and care must be taken to produce the 1-μg dose accurately by serial dilutions; **(2)** the test may be unreliable in the first few weeks after acutely induced secondary hypoadrenalism (e.g., after pituitary surgery), because the evolution of impaired adrenal reserve (cortisol response to ACTH) under these conditions requires some time, yet the HPA axis may already be severely damaged as a result of ACTH deficiency.

D. Single-dose metyrapone test

1. Purpose. Metyrapone activates the HPA axis by blocking cortisol production at the 11-hydroylase step and lowering cortisol levels. This test is used to establish

or confirm the diagnosis of adrenal insufficiency and is particularly useful when secondary adrenal insufficiency is suspected. Often, patients with hypothalamic or pituitary disease have mild symptoms and a normal rapid ACTH stimulation test. Metyrapone is an inhibitor of 11β-hydroxylase, the adrenal enzyme responsible for catalyzing the conversion of 11-deoxycortisol (compound S) to cortisol—the last step in cortisol synthesis. Following metyrapone administration, cortisol synthesis is blocked, levels of cortisol fall, and ACTH release is stimulated, as is the production of adrenal steroids proximal to the enzymatic block as 11-deoxycortisol accumulates. 11-Deoxycortisol can be measured in serum or urine (as tetrahydrol 11-deoxycortisol [THS]).

2. **Procedure**
   a. **Metyrapone,** 2 to 3 g as a single dose, depending on body weight (<70 kg, 2 g; 70 to 90 kg, 2.5 g; >90 kg, 3 g), is given at midnight with a snack to minimize the nausea accompanying metyrapone.
   b. Serum cortisol and 11-deoxycortisol are collected the following morning at 8 A.M.
3. **Interpretation.** A normal response is an increase in serum 11-deoxycortisol of >7 μg/dL; patients with primary or secondary adrenal insufficiency exhibit <5 μg/dL. Cortisol levels should fall below 5 μg/dL to confirm adequate metyrapone blockade. An abnormal metyrapone test in a subject with a near-normal response to the rapid ACTH stimulation test suggests **secondary adrenal insufficiency.** The metyrapone dose needs to be increased in patients who are taking phenytoin (Dilantin), which enhances clearance of metyrapone. Adverse effects of metyrapone include gastric irritation, nausea, and vomiting. The overnight (single-dose) metyrapone test is generally safer than the standard multiple-dose metyrapone test; however, caution must be applied, especially with patients in whom primary adrenal disease is likely, because adrenal crisis can be precipitated. *Hospitalization with proper monitoring of the patient's condition is suggested for this test.* It is advisable to demonstrate some responsiveness of the adrenal cortex to ACTH before initiating a metyrapone test. If the ACTH stimulation test is already markedly blunted, then the metyrapone test may not be necessary.

E. Diagnosing hypoadrenalism in the critically ill patient. Partial impairment of the hypothalamic–pituitary–adrenal axis is frequently considered in critically ill patients, especially in association with conditions such as hypotension, hyponatremia, hyperkalemia, or a history of head trauma. Because random serum cortisol levels in the critically ill often reach levels as high as 30 to 60 μg/dL, it is clear that the diagnostic "pass" values of the aforementioned ACTH tests are entirely improper for such patients. Very high cortisol levels should not come as a surprise, as ACTH and cortisol secretion can be turned on, in the critically ill, by acute response circulating factors ("circulating CRH-like factors," e.g., tumor necrosis factor α [TNF-α]) other than ACTH. Based on the serum cortisol response to Cortrosyn, relative hypoadrenalism is reportedly fairly common in the ICU setting. On the other hand, serum free-cortisol response to ACTH test is much less frequently impaired, thus indicating that some critical illnesses modify cortisol binding in the serum because of hypoproteinemia or reduced CBG/CBG-binding capacity. Because no factually substantiated consensus on the diagnostic criteria in this setting exists at the present time, we apply the following principles to the diagnosis and management of hypoadrenalism in the critically ill.

1. Hypoadrenalism cannot be diagnosed using any of the criteria for normalcy used in the noncritically ill.
2. In the interpretation of random serum cortisol, serum protein levels should be considered.
3. When clinical suspicion is reasonably strong, and unless random cortisol level is clearly elevated (e.g., $\geq$30 to 35 μg/dL), high-dose glucocorticoid replacement therapy should be seriously considered, regardless of the outcome of dynamic testing and if no contraindication to such treatment exists, because it has been shown to benefit some patients under these circumstances.

VII. TREATMENT

A. Chronic adrenal insufficiency

1. **Primary adrenal insufficiency** requires replacement with both glucocorticoids and mineralocorticoids.
   a. **Glucocorticoid replacement** is best given with hydrocortisone. Classically, this agent was given as 20 mg in the morning and 10 mg later in the day. It is now recognized that cortisol production is <30 mg per day, so lower doses should be given, especially because the 30-mg/day dose might decrease bone density and cause other features of chronic hypercortisolism. Because cortisol levels fall markedly at night, some believe that a once-a-day dose is sufficient. Many patients receiving chronic glucocorticoid replacement therapy are candidates for attempted individual dose refinement because of such common confounders as osteoporosis, diabetes, or complaints of easy bruising, subtle puffiness, or increasing waist circumference. The use of hydrocortisone, rather than dexamethasone or prednisone, allows close dose titration based on serial serum cortisol measurements in the course of 8 to 12 hours following oral intake of hydrocortisone. Dose requirements may be higher in extremely obese or very active persons, because cortisol secretion correlates with body surface area and cortisol turnover is increased in obesity. Increased doses are also required if drugs known to enhance the metabolism of glucocorticoids are used concomitantly (e.g., barbiturates, phenytoin, rifampin). Lower doses are indicated in significant liver disease (slow metabolism of glucocorticoids), in geriatric patients, and in those with diabetes mellitus, peptic ulcer, or hypertension. Reliable indices in assessment of glucocorticoid replacement doses include appropriate weight gain and regression of pigmentation.
   b. **Mineralocorticoid replacement** is necessary in primary adrenal insufficiency, and its dose requirements can be variable. The synthetic mineralocorticoid fludrocortisone (Florinef) is given as a single daily dose of 0.1 mg after initial volume and sodium repletion have been achieved. Patients can be started on a liberal sodium intake. Persistent hypotension, orthostatic hypotension, hyperkalemia, or increased PRA indicate that increased doses are needed, whereas hypertension, hypokalemia, or edema indicate dose reduction. Dose changes are in increments of 0.05 mg/day of fludrocortisone.
   c. **Adrenal androgen replacement** may improve overall sense of well-being in both sexes and restore impaired libido in women. DHEA at doses of 25 to 50 mg/day are reportedly well tolerated but is occasionally associated with slight hyperandrogenic phenomena in women. Long-term effects and safety remain untested.
   d. **Patient education** includes instruction to adjust glucocorticoid dosage for mild illnesses and stressful events; in addition, patients should always carry a card or wear a bracelet (Medic-Alert Foundation) indicating their steroid dependency. A traveling kit that provides cortisone acetate-deoxycorticosterone acetate for intramuscular self-injection, and hydrocortisone (100-mg) or dexamethasone (4-mg/mL; Decadron) vials for emergency intravenous administration, is recommended.
   e. **Intercurrent illness** or **stress** requires an adjustment of glucocorticoid therapy but not of mineralocorticoid therapy. For minor illnesses (e.g., respiratory tract infection, dental extraction, unusual physical challenge), glucocorticoid dosage is doubled until the condition has resolved. Vomiting and diarrhea require hospitalization because they preclude oral intake of replacement therapy and result in rapid dehydration. During major stress, the maximum daily glucocorticoid requirement is equivalent to 300 mg of hydrocortisone.
   f. Although the need for any increase in the replacement dose of glucocorticoids during routine surgical procedures has been challenged in a controlled trial, the safety of maintaining the regular dose during elective major surgery has not been sufficiently tested. Traditionally, 100 mg of hydrocortisone is administered intravenously before anesthesia, followed by 100 mg every 8 hours until the patient has stabilized postoperatively. Lower doses (10 mg of

hydrocortisone per hour via continuous intravenous drip) have been also successfully applied in practice, and are perhaps suitable for lesser procedures. Medication is tapered rapidly (3 to 5 days) to the previous dosage. Acute situations do not require higher doses of mineralocorticoids because hydrocortisone at high doses has sufficient mineralocorticoid activity. Major catastrophes or emergencies (e.g., trauma, major emergency surgery, sepsis, myocardial infarction) require treatment as in acute adrenal crisis.

2. **Secondary adrenal insufficiency.** Secondary adrenal insufficiency does not require mineralocorticoid replacement. Sex hormone replacement may be needed because of the associated gonadotropin deficiency.

B. Acute adrenal (Addisonian) crisis

1. Intravenous hydrocortisone (100 mg) as a bolus.
2. Intravenous saline and glucose.
3. Hydrocortisone, 100 mg every 8 hours as a continuous infusion for the first 24 hours.
4. Hydrocortisone is then tapered during recovery by decreasing one third of the daily dose every day, until a maintenance dosage is reached, preferably within 5 to 6 days. Once the dose of hydrocortisone is <100 mg/day, fludrocortisone (0.1 mg/day) is added.

C. HPA suppression

1. **Alternate-day glucocorticoid therapy.** During treatment with pharmacologic doses of glucocorticoids, the total daily dose of steroid is best given as a single morning dose to prevent complications, using short-acting glucocorticoids (hydrocortisone, prednisone) but not long-acting agents (dexamethasone, betamethasone). Short-acting agents given once daily allow time for some HPA recovery between doses, minimizing HPA suppression. When possible, patients are switched from daily to alternate-day regimens. The total daily dose is doubled and given every other morning, such as 50 to 100 mg of prednisone every other day. One method is to shift prednisone from the day off to the day on at daily increments of 5 mg. When the day-off dosage reaches 5 mg, tapering is at 1 mg every other day.
2. **Tapering glucocorticoids.** Once prednisone is reduced to 5 mg/day, switch to 20–25 mg of hydrocortisone every morning. The short half-life of hydrocortisone allows time for recovery of the suppressed HPA system. The 8 A.M. plasma cortisol is measured monthly; a value of <10 μg/dL indicates continued HPA suppression. Once 8 A.M. plasma cortisol exceeds 10 μg /dL, hydrocortisone can be withdrawn.
3. An ACTH test (1 μg cosyntropin) that shows a normal response demonstrating peak serum cortisol >20 μg/dL indicates recovery of the HPA axis, and all replacement can be stopped. If 8 A.M. serum cortisol is >10 μg/dL but the response to ACTH is still blunted, steroid coverage for major illnesses will be necessary as long as the ACTH test yields a subnormal response.

PRIMARY HYPERALDOSTERONISM

I. General Principles

The human adrenal cortex secretes several steroids with predominantly mineralocorticoid properties, the most important being **aldosterone.** Deoxycorticosterone (DOC) is the most potent mineralocorticoid of the nonaldosterone steroids, demonstrating about one thirtieth the potency of aldosterone. Although the major adrenal glucocorticoid, cortisol, binds effectively to the mineralocorticoid receptor, it has minimum mineralocorticoid potency under normal conditions because of its rapid conversion to cortisone by 11-hydroxysteroid dehydrogenase at the receptor site. However, in excessive amounts cortisol can take on enhanced mineralocorticoid activity.

Under most physiologic conditions, the renin–angiotensin system is the main regulator of aldosterone secretion. Through generation of angiotensin II, this system

responds to alterations in sodium and volume status. **Volume depletion** induces the release of renin and the formation of angiotensin II, with subsequent angiotensin II stimulation of aldosterone secretion, leading to retention of sodium and water to restore blood volume. **Volume expansion** leads to reductions in renin, angiotensin II, and aldosterone to facilitate sodium and water excretion. Additionally, potassium and ACTH stimulate aldosterone secretion directly, independent of volume changes. Even small increments in plasma potassium lead to significant stimulation of aldosterone secretion, which, in turn, facilitates renal potassium excretion. Potassium depletion has the opposite effect, lowering aldosterone to minimize potassium excretion.

II. ETIOLOGY.

Primary hyperaldosteronism ("primary aldosteronism"; PA) implies autonomous hypersecretion of aldosterone, whereas in various forms of secondary hyperaldosteronism the stimulus is extra-adrenal. There are at least **five distinct forms**:

A. Adrenal aldosterone-producing adenoma (APA) (~60% of all cases)
B. Idiopathic hyperaldosteronism (IHA) with bilateral (micronodular) hyperplasia of the adrenals (BAH; 40%).
C. Unilateral micronodular adrenal hyperplasia (1% to 2%)
D. Glucocorticoid-remediable hyperaldosteronism, a rare familial entity characterized by bilateral adrenal hyperplasia (BAH) with reversal of clinical and biochemical abnormalities following glucocorticoid administration.
E. Aldosterone-producing adrenal carcinoma (rare)

III. Prevalence

Until the past decade, the prevalence of primary hyperaldosteronism in the hypertensive population had been estimated at 0.01% to 2.2%, but the prevailing belief now is that the rate may vary between 2% and 15%, depending on the population in question. The rate increases with severity of hypertension, such that it may be ~2% in subjects with mild to moderate hypertension, increasing to as high as 13% or even higher in severe (>180/110 mm Hg) or resistant hypertension. Although broadly supported by published data, insufficient consideration has been given in publications favoring such high prevalence of PA to either the dominant effect of aging on systolic pressure or to the fact that hypertension afflicts most of the population after the age of 60 years. None of these estimates represents a true population based study.

IV. CLINICAL FINDINGS

Most of the pathophysiologic findings in primary hyperaldosteronism can be explained by the effects of excessive aldosterone on sodium and potassium transport. Thus one observes increased renal tubular resorption of sodium and water, leading to volume expansion and hypertension, and enhanced renal excretion of potassium and hydrogen ions, leading to hypokalemia and mild metabolic alkalosis.

A. Hypertension is the most prominent and almost universal finding in the disorder and, contrary to previous beliefs, can be mild, moderate, or severe.

B. Hypokalemia is far less common than previously believed, and is present in only half of patients with APA and 17% of those with IHA. If **hypokalemia** is significant (<3.5 mEq/L), patients can have symptoms related to potassium depletion, including muscle weakness, fatigue, cramping, and, in severe cases, muscle paralysis. Potassium depletion can produce a renal concentrating defect, leading to **polyuria** and **polydipsia,** which are resistant to vasopressin. Potassium repletion, however, can completely reverse these symptoms.

Chronic hypokalemia also alters the electrical potential of myocardial cells, leading to the electrocardiographic findings of the widened QT interval and U waves in this disease.

C. Hypokalemia impairs insulin secretion from pancreatic β cells and may cause the **diminished glucose tolerance** seen in ~50% of patients with primary aldosteronism. The metabolic syndrome is commonly seen in PA, reportedly afflicting >40% of patients.

2. Make the treatment more efficient

1. First step: Above all, improve the diet, environment and lifestyle

Improve the patient's diet before any other changes are made. The patient should eat a diet that is optimal for healthy endocrine function; the Paleolithic diet based on fruits, vegetables, meat, poultry and fish, improves best the efficacy of a hormone therapy in most patients.
Dairy products such as milk, yoghurt and cheese, from the cow, goat, sheep or horse are among the worst foods to eat for the endocrine system. They disturb hormone activities by a variety of mechanisms such as digestive problems, allergies, yeast overgrowth, blood acidification, liver overload, etc.
Also unsprouted grains such as bread, cereals, pasta, baked goods, are unfit for optimal hormone activities because they often cause digestive problems with gluten, gliadin allergies, yeast overgrowth, inhibition of digestive enzymes, etc.). High glycemic index carbohydrates such as sugar, starches, sweets, chocolate, cake, corn flakes, muesli, biscuits, soft drinks, alcohol, and also the added sugar in ham, sausage, and salami, tend to ruin the benefits of various hormone treatments by promoting yeast overgrowth and slowing down the secretions of at least 6 hormones (all the hormones able to increase the blood sugar level such as cortisol, growth hormone, testosterone, DHEA, androstenedione and estradiol).

The following table presents the effects of various types of foods and drinks on hormones.

Hormone activities	High dietary intake					
	Good Protein (meat, poultry, eggs, fish)	**Bad Protein** (milk products)	**Good Carbo-hydrates** (low sugar fruits, vegetables)	**Bad Carbo-hydrates** (sugar, sweets, unsprouted cereals)	**Alcohol**	**Fats** (saturated)
	⇩	⇩	⇩	⇩	⇩	⇩
Melatonin activity	reduces	?	0?	?	severely reduces	?
Growth/IGF-1 activity	increases	reduces/ increases	0?	reduces	severely reduces	Increases/ reduces
Thyroid activity	reduces	reduces	increases	increases	reduces	reduces?
Cortisol activity	increases	reduces	0?	reduces	reduces	increases
DHEA activity	increases	reduces	0?	reduces	reduces	increases
Aldosterone		reduces?	0	reduces		
Estradiol activity	increases	reduces	0	reduces	reduces	increases
Insulin activity	improves	worsens	0?	worsens	worsens	improves/ worsen (?)
Progesterone activity	increases	reduces	0	reduces	reduces	increases
Testosterone activity	increases	reduces	0	reduces	reduces	Increases

***Notes**: The abbreviations "**reduces**" means "lowers" the activity, "**increases**" that it increases it, "0" that it has no effect and blank spaces or "?" that its effect is currently unknown.*

The principal effects as they appear in practice are summarized in the following table.

Effects of hormone therapies on the activity of other hormones

Net effect	Melatonin ⇓	GH ⇓	T3, T4 ⇓	Cortisol ⇓	DHEA ⇓	IGF-1 ⇓	Insulin ⇓	Estradiol ⇓	Progesterone ⇓	Testosterone ⇓
Melaton. activity		stim.?	Inh.	Inh.	?	?	?	stim. transd. E2[7] inh. (oral E)	stim.?	?
GH activity	stim.		stim.	stim./ 0/inh.[6]	stim.	stim.	stim./O / inh.	stim. only transd. E2[7]	stim.	stim.
Thyroid activity[1]	stim.[1]	stim.[1]		stim./ 0/inh.[5]	stim.[1]	stim.[1]	stim.[1]	inh.	stim.[1]	stim.[1]
Cortisol activity	inh.	inh.	stim./ Inh.[5]		inh./0	inh.	inh.?	inh. esp. oral E[7]	inh.[8]	stim.
DHEA activity	?	?	stim.	inh.		?	inh. ?	inh.[7] esp. oral E	?	stim.
IGF-1 activity	stim. ?	stim.	stim.	stim./ 0/inh.[6]	stim.		stim.	stim. transd. E2[7]	stim.	stim.
Insulin activity[2]	stim.	inh./ stim.	stim.	stim./0/ inh.[6]	stim.	stim.		stim.(tr.E2)[7] inh. (oral E)	?	stim.
Estradiol activity	inh.	stim.[3]	stim.	stim./ 0/inh.[6]	stim.	stim.	stim./ (inh.)		inh./ stim[7,9]	inh./ (stim)[10]
Progest. activity	inh.	stim.	stim.	stim./ 0/inh.[6]	stim./ (inh.)	stim.	stim.	stim./ inh.		stim./ (inh.)
Testost. activity	inh.?	stim.[4]	stim./ inh.	stim./ 0/inh.[6]	stim.	stim.	stim./ (inh.)	inh.	inh./ (stim)[8]	

Abbreviations: *"**inh.**" means inhibits or lowers, "**stim.**" that it stimulates/increases, "**0**" means absence of effect and "**?**" signifies yet unknown. Hormone therapies **often** have **"stim"ulating** or **"inh"ibiting** effects on other hormone activities, changes in hormone activity that can be recognized by patients.*

Notes: [1] *Several hormone therapies increase thyroid activity by accelerating the conversion of thyroid hormone T4 into the much more active T3. It is noteworthy that a minimum amount of T3 itself is necessary for the conversion.*

[2] *A stimulation of insulin activity = improvement such as an increase in insulin activity and sensitivity or a reduction in insulin resistance in insulin-resistant patients or increased insulin production in insulin-deficient persons.*

[3] *GH stimulates ovulation, boosting both estradiol and progesterone production in women.*

[4] *GH increases the amount of testosterone that diiffuses form the blood into the target cells by reducing the binding of testosterone to SHBG, the blood transporter of male hormones via a lowering of the blood levels of SHBG.. By this mechanism, GH lowers the levels of testosterone in the blood, but increases them inside of the target cells, boosting testosterone's physical effects.*

[5] *At low, physiologic doses, thyroid hormones reduce cortisol action; at high and excessive doses thyroid hormones increase the breakdown of cortisol and thus reduce cortisol activity.*

[6] *In most cases, cortisol therapy does not reduce other hormone activities when given at low doses to correct a deficiency, but prolonged intake of excessive doses may cause inhibition of hormone activity.*

[7] *Transdermal estradiol has often a completely different impact on other hormone activities than oral estrogens, as it does not much increase the blood levels of the (hormone) binding proteins. Oral estrogens reduce hormone activities by increasing the hormone (transporting) binding proteins in blood, thereby increasing the binding of the hormones, an effect that ends up in reducing the amount of bioavailable hormones that can enter the cells.*

[8] *Progesterone can reduce the salt-retaining effects of cortisol by its diuretic effect.*

[9] *Progesterone's main role is to reduce estradiol levels in men and women, but at the same time progesterone may amplify some beneficial effects of estradiol in women.*

[10] *Testosterone works in women as a progestogen and generally reduces estradiol activity, but in men and some women after menopause who do not take female hormone replacement, testosterone may convert into estradiol through the enzyme aromatase and, thus, increase the estradiol levels.*