

Principles of Clinical Endocrinology

Youthful-Optimal Standard: The goal of endocrinology is to restore youthful-optimal health and quality of life.

Clinical Endocrinology: Both diagnosis and treatment must be based upon history, signs and symptoms first, and serum free hormone levels second.

Clinical Trial: When indicated, the physician should offer the patient a trial of hormone optimization.

Bioidentical Hormone Replacement: Use only the correct molecules, whenever possible.

Route of Delivery: Understand the effects of various routes of delivery; tailor the route to patients' needs.

Endocrine Balance: Restore multiple hormones as required to achieve youthful-optimal balance.

Feedback Systems: Understand the effects of exogenous hormone on endogenous production.

Endocrine Freedom: Respect all persons' right to choose endocrine treatment that improves their quality of life; as they see it, regardless of imagined or real risks.

1 The Need for Personalized Clinical Endocrinology

We now live in the 21st century. Our knowledge of the complexity and fallibility of the endocrine system has advanced considerably. We must move beyond disease-based endocrinology. We now know that endocrine dysfunction can occur at any level, in any part of these complex systems, from the hypothalamus all the way down to the cellular receptor and effector mechanisms. We now know that the loss of hormones with aging is deleterious, not adaptive. We have accurate tests that reflect the amounts of bioavailable hormones in the serum. We have bioidentical hormone products that allow us to safely optimize hormone levels/effects. We can test for and replace most hormones easily and at relatively low cost. We also have a much higher physician-to-patient ratio than in the past, at least in Western countries. We have enough physicians to allow many of them to specialize in the diagnosis and treatment of deficiencies of hormone effect.

Due to the power of hormones and their widespread and varied effects, endocrinology is central to the practice of medicine. It is not just a small branch: it is a part of the trunk of the tree of medicine. An effective endocrinology is required for the effective practice of medicine. The consequences of severe hormone deficiencies on both mental and physical function and health are well known; but they are just the tip of the iceberg. We now know, from thousands of studies performed in recent decades, that partial hormone deficiencies due to dysfunctional endocrine systems are common and that they degrade our ability to function, our quality of life, and our long-term health. Therefore endocrinology needs a new paradigm: it must be based upon the best indicators of actual hormone effect in the tissues. For now, the best indicators are the patient's signs and symptoms. All non-specific constitutional symptoms that cannot be explained by any other theory should be considered endocrine until proven otherwise. This includes all unexplained fatigue, exertion intolerance, depression, pain, headache, muscle dysfunction, cognitive dysfunction, gastrointestinal complaints, anxiety, insomnia,

environmental sensitivities, low libido, skin conditions, etc. Literally, any dysfunction of any organ or system may have an endocrine cause.

Contrary to the attitude ingrained into most physicians during their training, the patients who consult them are not frequently frivolous or stupid. They should be taken seriously when they expend their time and money to consult a physician about the problems that they perceive with their physical and/or mental state. In this modern era, we know that solutions exist. We are not willing to suffer throughout our lives, hoping for a better afterlife. We are not content to just exist. We want to thrive—to be energetic and productive. We want to enjoy life to its fullest for as long as possible into our old age. To achieve these goals we need optimal health, and this requires optimal hormone levels and effects. We are deciding, more and more, that we do not want to be loaded down with drugs that degrade their health and quality of life. They want, whenever possible, natural solutions including nutrient and hormone optimization.

When no other cause is apparent, and the symptoms are compatible with an endocrine deficiency, the physician is ethically obligated to investigate and to treat. The hormone levels in the serum can serve as a guide, but ultimately the diagnosis must be determined by symptoms. If the symptoms could be caused by deficient hormone action, he should offer the patient a trial of hormone optimization. If the patient feels/functions better then he/she was suffering from a hormone deficiency. The physician should not simply normalize some blood test but should try to eliminate all symptoms of hormone deficiency. He should do his best to help each patient feel and function as well as possible. The resultant hormone levels may be mid-range, high-in-range or even high. Many persons will have multiple hormone deficiencies. The physician should restore one hormone or group of hormones at a time, assess the results of the intervention, adjust the doses, and the restore additional hormones as required in order to optimize the individual's quality of life and health.

To meet this increasing demand for natural endocrine therapies, hormone replacement and anti-aging clinics have sprung up all over the world. Non-endocrinologists are now doing most endocrine therapy. Endocrinology as a specialty must adapt to all the knowledge that we have gained in the last 50 years and to the needs and desires of the population; or it will remain irrelevant.

2 The Foundations of Clinical Endocrinology

A rational and effective endocrinology must be based upon these foundational concepts:

1. **Hormone Signaling/Effect:** What matters is not the level of a hormone in the blood, but the amount of hormone effect within the tissues and organs of the body.
2. **Endocrine Dysfunction:** Most hormone deficiencies are due to dysfunction of the HP system or to hormone resistance. The cases of evident glandular disease or damage are the minority.
3. **Clinical Endocrinology:** Diagnosis and treatment must always be based on signs and symptoms first and on serum hormone levels second.
4. **Endocrine Individuality:** Hormone levels and their population reference ranges do not define what is optimal for the species or for any individual. Persons vary widely in the serum levels that they require.

5. **Anti-Aging Endocrinology:** The decline in most hormones with age is deleterious, not adaptive. More youthful hormone levels/effects improve both our quality of life and long-term health.
6. **Bioidentical Therapy:** Only human hormones should be prescribed for long-term therapy.
7. **Multi-Hormone Optimization:** Most persons require the restoration of multiple hormones to restore physiological balance and to optimize their quality of life and health.
8. **Hormone Safety:** Multi-hormone optimization therapy for any individual, utilizing proper routes of delivery, physiological doses, and proper balance among hormones, must be considered safe and beneficial until proven otherwise.

While functioning within this paradigm the physician encounters a completely different medical and endocrine reality. He comes to appreciate that various degrees of deficiency of the major hormones are common in his patients; deficiencies are even universal with aging. He sees the effects of partial hormone deficiencies everywhere. He begins to realize that most of the typical problems that patients present with can be partially or wholly caused by hormone deficiencies. One might call this much more ambitious approach to endocrinology “Restorative Endocrinology”, however it is simply the realization of the full potential of clinical endocrinology. Is it not alternative, complementary, or anti-aging medicine; it is the very foundation of good medical practice:

- Optimal hormone levels/effects are essential to our health and quality of life.
- Optimal hormone levels/effects are essential to preventative medicine.
- Optimal hormone levels/effects are essential to the treatment of all diseases.

3 The Requirements of Clinical Endocrinology

The practice of clinical endocrinology is not easy. It requires thought. The body is more complex than we know. The physician must see an explanation for the patient’s symptoms and try to find a solution. He must at the same time consider all other possible medical causes. Hormone restoration is a powerful intervention that affects every aspect of a person’s health and quality of life. Restoring hormone effect is much more powerful than prescribing a drug. Hormone optimization fundamentally alters a person’s physiology. It produces changes in every system and tissue in their body. Hormone restoration can produce much more profound improvements than any drug, but it can also create serious problems if not done right. Hormone supplementation can have negative effects in some persons due either to hormone-hormone interactions or to underlying medical conditions. Hormone restoration is more complicated in persons who have certain medical conditions or who are on some medications. Hormone restoration is especially difficult and time-consuming in persons with insufficient cortisol effect (hypocortisolism) as all other hormones counteract cortisol. In addition, every person is different; there are no hard-and-fast rules in endocrinology. The physician must use his clinical judgment to decide whether to offer a trial of hormone optimization to any given patient—whether the benefits are likely to outweigh the inconveniences and risks. The physician should discuss the facts with the patient and include her in the decision-making process.

The practice of clinical endocrinology requires knowledge and skills that physicians are not taught in medical school or an endocrinology fellowship. It also requires a sincere desire and an ethical

commitment to improve every person's quality of life and ability to function, no matter how much time and effort it may take. The physician who undertakes to practice clinical endocrinology must, as much as possible:

1. Have a good grasp of general medicine in order to recognize other medical problems and so be able to differentiate endocrine from non-endocrine causes
2. Understand the many functions of each hormone in order to recognize the signs and symptoms of hormone deficiency or excess and to optimize hormone replacement
3. Understand the many interactions among the various hormones
4. Understand the nature of laboratories' reference ranges and know what the scientific literature has to say about the effects of higher vs. lower hormone levels within the ranges
5. Diagnose deficiencies and adjust replacement therapy according to signs and symptoms first, laboratory tests second
6. Prescribe only bioidentical molecules—human hormones—whenever possible
7. Understand the differences between natural hormone production and hormone replacement; including the effects of various routes of delivery, the timing of peaks and troughs after doses, and the timing of the hormone's various biological actions
8. Check hormone levels at some consistent time after the hormone dose so as to become familiar with the usual clinical effects of such levels at such a time after the dose.
9. Replace and optimize one hormone at a time, when possible, so that both the physician and patient can note its effects and avoid confusion
10. Prescribe all hormones that are needed, in the proportions needed to restore youthful/healthy endocrine levels and balance
11. Customize the vehicle and route of delivery for each hormone so that the therapy is both physiological and best suits the needs and desires of the patient
12. Understand endocrine feedback control mechanisms—how the administered hormone suppresses the patient's own HP system and primary gland, and the consequences of this suppression over time
13. Document the effects of each hormone on the patient: the benefits or problems they have had with each hormone and what levels were achieved at various doses. This information should be carried over from note-to-note as the "hormone history" of that patient.
14. Document the reasoning involved in all diagnostic and dosing decisions—what the physician thinks about the hormone's levels/effects and what changes are being made and why

4 The Practice of Clinical Endocrinology

Due to the immense and unknown complexity of human physiology, medicine is not a simple science. No laboratory test can tell the whole story; results can sometimes be "normal" when the disease/disorder is present. A medical diagnosis is actually a theory about the cause. It is an attempt to explain what is known (the signs, symptoms and test results) by what is unknown (the cause). As with theories, all diagnoses are tentative to various degrees. The ultimate confirmation of the diagnostic theory is a successful long-term outcome. In some cases the cause is obvious; in others it is not. So like a detective the physician must think. He must use his mind to gather and organize the evidence and then create the best theory he can to explain the patient's signs and symptoms. This theoretical endeavor is

informed by some simple principles which are familiar to all doctors. First, it is always better to explain all of the patient's problems as due to a single cause; with one diagnosis. It is more likely that there is one cause present instead of several. It is simply less likely that the same patient has acquired multiple diseases or disorders at the same time; but it is possible. Second, it is more likely that the cause is a disease or disorder that is common in the human population. It is less likely that it is something that is rare. Every medical student has been told, "When you hear hoof-beats, think of horses, not zebras". To produce a plausible theory of the cause, the physician must gather all the relevant information that he can. He should order tests as needed. Tests can occasionally rule certain diagnoses in or out definitively, but more often they only support or weaken the theory.

Rarely is there complete certainty in medicine. The complex cognitive effort required to find the cause is what provided much of the interest and drama in the popular television series *House*.¹ Dr. House is to medicine what Sherlock Holmes was to criminal science. House was indeed modeled on Holmes. House is a trouble person but a great physician. He is fanatical in his pursuit of the truth, which trumps all other considerations. He not only reads constantly to maintain an encyclopedic knowledge of medicine, but he thinks. He carefully weighs the relative importance of the various clues from the history, symptoms, physical examination and test results and creates a differential diagnosis—a list of possible causes. He uses the minds of his team members to help him reach the truth. He and his team debate the relative merits of each diagnostic theory. They perform tests and therapeutic trials to expose the cause and correct it. They appreciate the immense complexity of the human body and mind. They know that no test is completely reliable. Every test produces some number of false negatives and false positives. Thus they have to consider every test result within in the larger context of all other knowledge

False Positives—Symptoms, signs or test results that indicate that the disorder is present when it is not
False Negatives—Symptoms, signs or test results that indicate that the disorder is not present when it is

that they have about the patient. They often continue to argue that a disorder exists even though the test for it is negative. When one of their theories is rendered improbable by some indicator or test, they do not discard it, they simply lower its ranking compared to other theories. They will return to it if required. In the face of the immense complexity of the human body and brain, and of our ignorance, this is how the search for the cause and for the cure must be carried out. If a physician is not thinking in this way, he is not practicing medicine.

Likewise in endocrinology, the physician must weigh all the relevant facts and come up with a best theory of the cause. Along with considering non-hormonal causes, he must look for both sensitive and the specific indicators of the various possible hormonal deficiencies. He must also consider that possibility that the patient has not just one, but multiple hormone deficiencies and/or medical disorders. He must be aware of the powerful interactions among hormones. A deficiency of one hormone may be masked by the deficiency of another hormone—particularly in the case of thyroid and cortisol deficiencies. An endocrine diagnosis is the best theory that he can produce to encompass all the facts. Hormone tests with their broad population ranges certainly cannot be used to prove or disprove

¹ *House*, Heel and Toe Films, Shore Z Productions and Bad Hat Harry Productions in association with Universal Media Studios for Fox, 2004-2012.

an endocrine diagnosis. However, a high-in-range hormone level does weaken the theory that deficient hormone signaling is the cause. Likewise, a relatively low level of a hormone within the 95%-inclusive unscreened population range strengthens the theory. An apparently sufficient hormone level should cause the physician to look more carefully for other hormonal or non-hormonal causes. However, the physician must also consider the possibility that the patient is relatively resistant to the hormone.

The best available confirmation that a person's symptoms are due to a hormone deficiency is clinical: the resolution of signs and symptoms with a trial of hormone optimization. However, to perform an effective trial the physician must know how to supply the hormone in such a way that he definitely increases the hormone's effects in the patient. He must know how long it takes for various signs and symptoms to improve once hormone sufficiency is obtained. He must know when and how to measure hormone levels during supplementation. He must know what other hormonal or medical factors may interfere with the trial. If the symptoms are relieved and the patient feels and functions better, then the diagnosis of hormone deficiency is strongly supported. One may say that that it is tentatively confirmed. The longer the patient remains improved with hormone supplementation, the more certain is the diagnosis of deficiency, and the less likely it is that the cause is some other hormonal or medical disorder. If the patient is not suffering from a deficiency of hormone effect, then little benefit will be obtained by hormone supplementation. If levels/effects are already optimal, then supplementation will either produce little or no improvement, and perhaps a worsening of the symptoms. If there is no

<p>Endocrine Diagnosis: A tentative theory of the cause Therapeutic Trial: The true test of a diagnosis Clinical Response: Improvements in symptoms confirm that a hormone deficiency had been present.</p>
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improvement or if the symptoms do worsen, then there either was no deficiency of that hormone, or there was a deficiency but the higher hormone

levels/effects have exposed or worsened some other hormone deficiency or medical disorder (nutritional, toxic, metabolic, etc.). The process of finding the hormonal cause and treatment is all the more complex when the patient has multiple hormone deficiencies, e.g. a postmenopausal woman who requires not just estradiol, progesterone, testosterone but also thyroid, cortisol and DHEA. When there is a problem during treatment, blood testing may be helpful to identify over- or under-dosing, but often the physician simply has to create a theory of what is wrong, and conduct a trial by changing one hormone dose at a time to see if it alleviates or worsens the problem. With no definitive tests for the right doses, the physician must often rely upon trial-and-error.

5 Indicators of Hormone Signaling

Due to the immense and unknown complexity of human physiology and the endocrine system, endocrinology must be based upon the patient's history, signs and symptoms. The physician must gather a detailed history of the patient's symptoms: when they began, what events preceded their onset, how they have waxed and waned with various activities or medical interventions, what previous tests have shown, what diagnoses have been given, what hormones or drugs have been tried and what effect they had, etc. A careful history will often provide the diagnosis. The symptoms of cortisol

deficiency, in particular, are reliably modified by certain circumstances and drugs. The history often yields the diagnosis when tests are “normal”. The physician must also examine the patient, looking for physical signs of hormone deficiencies and other disorders.

Symptoms are generally the most sensitive indicators of a hormone deficiency. A hormone deficiency will often affect how a person feels and functions long before it will produce obvious changes in the body or “low” test results. However, symptoms must be interpreted in the context of the patient’s medical and psychosocial situation. Since hormones affect so many aspects of health and function, many

Sensitive Indicators—Symptoms, signs, or test results that are likely to be present if the disorder is present, but may be due to other causes.

Specific indicators—Symptoms, signs, or test results that are less likely to be due to another cause

of the symptoms caused by hormone deficiencies are non-specific—they could be due to other causes. Fatigue, for instance, is a non-specific indicator: it can be caused by a great number of medical problems.

However, fatigue is also a cardinal indicator of thyroid and cortisol deficiencies. If these are deficiencies are present, they will usually produce other symptoms and disorders affecting certain tissues, organs and systems in the body. Both hypothyroidism and hypocortisolism can cause depression, irritability, aches and pains, cognitive dysfunction, insomnia, gastrointestinal complaints, etc. Any one of these could also be due to other causes, but when many of them are present in one person it suggests that the cause is endocrine.

For hypothyroidism, fatigue is a sensitive but non-specific indicator—it is almost always present when a person has inadequate thyroid effect. More specific indicators of hypothyroidism, symptoms that are less likely to be due to other causes, are dry skin, cold extremities, weight gain and constipation. The more of these specific indicators and the more severe that they are, the greater the probability that hypothyroidism is present. If the patient has many sensitive and specific indicators of hypothyroidism, the probability of hypothyroidism is high. If a hormone deficiency is mild, the patient may have only one or more sensitive indicators of deficiency and no specific indicators. If the hormone deficiency is severe, he will have more of the specific indicators. The diagnosis of hypothyroidism is further supported if the patient’s free T4 and/or free T3 are low in the population ranges or below the ranges.

Based upon our current knowledge of human physiology, the indicators of deficient hormone effect (i.e. hormone deficiency) or of excess hormone effect must be considered according to their rank:

First Rank: Measures of end-organ and tissue response—the history, symptoms and signs, and when available, direct measures of hormone effect.

Second Rank: Hormone availability to the tissues, i.e., the amount of free hormone in the blood. A level that is relatively low in the population range supports the diagnosis of deficiency.

Third Rank: The serum level of the pituitary hormone that stimulates the primary gland. It helps to determine the cause of the hormone deficiency or excess that is diagnosed by the First and Second Rank indicators.

This ranking is consistent with what we know of human and animalian physiology. Current endocrine practices, unfortunately, have it backwards. Endocrinologists ignore the First Rank indicators

in favor of the Second Rank indicators—the blood tests and their population ranges. Worse, conventional thyroidology ignores both the First and Second Rank indicators in favor of a Third Rank

Indicators of Hormone Effect

First Rank—Signs, symptoms and metabolic parameters

Second Rank—Free hormone levels in the blood

Third Rank—Pituitary hormone levels, to determine cause

indicator: the TSH level in the blood. This is illogical and results in both under- and over-diagnosis and nearly universal undertreatment. (See next chapter.) The

level of TSH or any other stimulating hormone (ACTH, LH, FSH) is useful only to help determine the cause of the patient's hormone's deficiency or excess.

Blood tests can only show the level of the hormone in the blood compared to the population; we have no quantitative tests for what actually matters: the level of hormone effect in the cells of various tissues and organs of the body. A hormone's effects depend upon many factors. First, the vast majority of the hormone in the blood is bound to proteins. It is not floating freely in the water serum and so is not able to leave the blood and enter the tissues. A total serum hormone test includes all of the hormone in the blood, the majority of which is protein-bound. Whenever possible, the physician should test for much smaller amount of free hormone. Free hormone tests are much more technically demanding and therefore prone to error. This is yet another reason that a physician cannot rely upon blood test results. A healthy HP system works to maintain optimal free hormone levels.

However, having sufficient free hormone in the blood may not be enough. Persons can differ markedly in the amount of free hormone that they need in order to have sufficient effect in their tissues. This is because hormone effect is the result of a complex chain of events—and this chain can differ from tissue-to-tissue. Many hormones must be actively transported into the cell. Any abnormality

Determinants of Hormone Effect

Free hormone in the serum

Cell wall transporter proteins

Intracellular activation or deactivation

Receptors and associated proteins

DNA response-elements

of the transporter-proteins may cause diminished intracellular hormone, in all tissues or just some tissues. Once inside a cell, a hormone may be activated or inactivated by intracellular enzymes, and this too may be tissue-specific. The hormone needs to bind to receptors that are either on the surface of

the cell, in the cytoplasm, or in the nucleus. These receptors also differ from tissue-to-tissue. Receptor binding triggers a complex cascade of events within the cell involving other proteins and co-factors, resulting in either rapid effects within the cell and/or in the slower transcription of genes to produce certain proteins and thereby hormone effect. The production of proteins requires working DNA and DNA-response proteins. The transporters, receptors, proteins, cofactors or genes needed for hormone action may be dysfunctional for various reasons: genetic, toxic, metabolic, nutritional, etc. Almost all of these necessary elements for hormone effect are proteins. Any protein can be altered by single nucleotide polymorphisms (SNPs). These are genetic alterations of a single DNA base pair that change one amino acid in the protein. Thus changes, the protein's structure and function are altered. Indeed, we all have these genetic variations from the most common type, or wild-type. Sometimes SNPs reduce a protein's function, sometimes they enhance it. These genetic variations play the largest role in an individual's relative sensitivity or resistance to a hormone.

In addition, the levels/effects of other hormones also affect a person's requirement for any given hormone. For instance, cortisol counteracts thyroid hormone action—more cortisol reduces T4-to-T3 conversion and T3 effect. So a person with lower cortisol levels may have sufficient thyroid hormone effect even though her serum FT4 and FT3 levels are rather low. A person with higher cortisol levels requires higher thyroid levels to avoid hypothyroid symptoms—a form of relative thyroid resistance. DHEA counteracts cortisol also, so a person's cortisol status also depends upon his/her DHEAS levels. A person with normal cortisol levels but high DHEAS levels may have a relative deficiency of cortisol effect. We have no tests for any of these intracellular processes or interactions, which is why endocrinology must attend to First Rank indicators.

Some persons may have no symptoms of hormone deficiency even though the hormone level is low in the range, while others with the same level may suffer markedly and need hormone replacement. Endocrinologists have noted these marked differences in symptoms in persons with similar hormone levels, and have wrongly concluded that symptoms are unreliable indicators of hormonal status and should be ignored. In fact it is the blood tests and their reference ranges that are the unreliable indicators. Hormone resistance exists in many forms and is much more common than realized. The extreme cases of generalized hormone resistance due to known genetic abnormalities, and that have been reported in the literature are just the tip of an iceberg. They are usually cases where the HP system is as resistant to the hormone as all other tissues, So both the pituitary stimulating hormone and the free hormone levels are high. Today, as more people are getting DNA testing, we are finding that many have one or more SNPs affecting the genes that code for their hormone receptors, hormone-binding globulins, hormone-activating enzymes, hormone-metabolizing enzymes, etc. Thus persons vary not only in their sensitivity to any given hormone but in how rapidly they metabolize and eliminate the hormone. Rapid metabolism is well-documented in the case of cortisol—putting the person at risk for cortisol deficiency under stress and causing them to need higher cortisol replacement doses. Due to the tissue-to-tissue variations in receptors and intracellular hormone-processing enzymes, hormone sensitivity varies from tissue-to-tissue. Some tissues are relatively more sensitive to the hormone while others are relatively resistant. Again, this is why endocrinology must be a clinical discipline; it must be based upon the best indicators of hormone action in the tissues—the patient's signs and symptoms.

6 Feedback: The Suppression of Endogenous Production

If the primary hormone-producing gland or the HP system are destroyed or removed, the need for hormone replacement is undisputed—except in the case of menopause which I shall discuss later. When there is no endogenous hormone production, the only hormone in the person's body will be that which is supplied by the physician. Any dose, no matter how small, will raise that person's hormone level, and every increase in the dose will raise the levels further. Unfortunately, most physicians believe that all hormone supplementation works in this way. They think that they are raising the patient's hormone levels and effects by prescribing any amount of hormone, no matter how little. However, this is not the case when there is significant endogenous hormone production—when the person is making the

hormone, but just not making enough. This is the case in vast majority of persons with hormone deficiencies. Any hormone that the physician supplies to the blood stream will reduce the amount of hormone that the patient's system produces. Their endogenous production is reduced by a feedback mechanism. Due to the unphysiological nature of hormone supplementation, including its unnatural peak levels in the blood, the reduction in endogenous production may be greater than the amount of hormone supplied, producing a worse deficiency state.

If the primary gland is dysfunctional and the pituitary hormone is elevated, then supplying some hormone will reduce the pituitary hormone level, but not necessarily increase hormone effect. When the pituitary hormone is reduced, the gland is receiving less stimulation and therefore makes less hormone. Whether this can improve the patient's state or worsen it depends upon a number of complicated factors. Most important is the fact that the HP system will not respond to exogenous hormone exactly as it does to the primary gland's natural production. Most hormones are secreted in small, frequent pulses throughout the day and night. Getting one's entire daily hormone in one daily dose is highly unnatural. It produces superphysiological peak levels in the blood, causing the HP system to overreact and to over-reduce hormone production. This excessive suppression of HP activity can last for hours to an entire day or more. So hormone supplementation cannot be guided by the level of the relevant pituitary hormone level. I will discuss this more in later chapters, and particularly in regard to current reliance upon thyroid-stimulating hormone (TSH) levels to guide thyroid replacement therapy.

The suppression of endogenous production is particularly problematic when the cause of the deficiency is dysfunction of the HP system. In this case, the HP system "wants" to keep the hormone level lower than what the patient needs. It is not producing enough of the stimulating hormone to keep the hormone levels optimal. In such partial central hormone deficiencies, the person's own control system, the brain-HP system, is the problem. The thermostat is broken. When exogenous hormone is administered to such a person, the serum level rises above the HP system's set point. The HP system senses "too much" hormone and immediately reduces its production of the stimulating hormone (TSH, LH, ACTH, etc.). This reduces the primary gland's hormone production in an attempt to lower the hormone level back to the set point. The first dose of a hormone can raise the hormone level for hours, however, with the HP system reduces endogenous production. So with repeated dosing that may be no net increase in hormone levels or effects. In fact, due to the unnatural high peaks and other aspects of hormone administration, a subreplacement dose can make a hormone deficiency worse. It can shut off endogenous production by more than the amount of hormone supplied.

Thus hypothyroidism can thus be worsened with low doses of oral levothyroxine—as are often given to persons with a slightly high TSH. Testosterone deficiency in men can be worsened by low-doses of transdermal testosterone—as transdermally-delivered testosterone travels in the blood in a different way than endogenously-produced testosterone and can affect the HP system more than other tissues. In the case of pure primary gland disease, like primary hypothyroidism, the unphysiological peaks after doses can cause even a healthy HP system to overreact and shut down. Thus once-daily T4/T3 oral replacement that is required to restore thyroid-signaling in all tissues will usually suppress TSH

production. This feedback inhibition can cause serious problems in the treatment of partial central cortisol deficiency. High peaks caused by short-acting hydrocortisone tablets can suppress a weak HP system for longer than the cortisol levels remained raised. A few hours after a dose levels can fall lower than they ever were before starting the oral replacement therapy, producing worse cortisol deficiency symptoms than the patient had ever experienced before. Patient and doctor may consider such reactions to be sign of an allergy or other intolerance of the hormone. This cannot, however, be the case when the molecule being given to the patient is identical to the hormone that is natural to their body.

Some hypothalamic and pituitary hormones are known to have functions in the rest of the body, besides just stimulating the primary gland. There are receptors for TRH, TSH, CRH, ACTH, FSH and LH in tissues other than the pituitary and primary gland. We know very little about the peripheral functions of these HP hormones. Fortunately they do not appear to be necessary to long-term health—but we will learn more with time. As it is, we often have no choice but to suppress these hormones by providing all the hormone that the patient needs. Maybe in an ideal future, we will find a way to replace the pituitary hormones and thereby stimulate the primary gland to make sufficient hormone. Better yet, we may find a way to get the HP system to function optimally.

We do have commercially available preparations of most of the hypothalamic hormones (GNRH, CRH, TRH, etc.) and of the pituitary's gland-stimulating hormones (LH, FSH, TSH, ACTH). However, injecting these rarely works in the long term. We cannot reproduce the normal pulsatile secretion of these stimulating hormones. Injecting them initially works to stimulate more hormone production, but the pituitary or primary the gland becomes resistant to their effects. The injection of hypothalamic hormones to stimulate the pituitary is so unphysiological that it quickly starts producing the opposite effect. Sustained high levels shut off the pituitary hormone. Physicians now routinely inject GNRH agonists to shut off women's ovaries and men's testes. Even if injections of a hypothalamic or pituitary hormone would work, we are still overriding the endogenous production system, just at a higher level.

One cannot fix the dysfunctional system; one has to take over for it. So in general, to significantly raise hormone levels/effects one has to provide all the hormone needed. One has to override the dysfunctional HP system, thereby shutting it off and with it the patient's endogenous hormone production. When the HP system is shut off, it and the primary gland become atrophied through disuse.

Subreplacement Dosing—less than needed to overcome feedback reduction and raise hormone levels

Replacement Dosing—sufficient to raise hormone levels even when endogenous production ceases

The HP system and primary gland are not damaged; but are greatly weakened. The effect is similar to what happens to a muscle that is not being used. If the hormone supplementation is stopped, the HP system will sense the very low levels and will start producing the hypothalamic and pituitary hormones required to stimulate the gland to

increase its hormone production. However, it can take weeks or even many months for the system to return to pre-treatment hormone levels. In the interim the person will have much lower hormone levels than before treatment. To avoid this extreme deficiency state when stopping a hormone one must gradually taper the dose—giving the HP-primary gland system time to recover. When the level is a bit

lower than the HP set-point, the HP-glandular system becomes active and endogenous production returns. After some time, the dose can be lowered further, stimulating more endogenous production, until the exogenous hormone is stopped. However, in some persons with severe HP dysfunction, the hormone level may not return to the pre-treatment level for many months. In some, it seems that even a brief period of hormone replacement desensitizes their dysfunctional HP system permanently, leaving them with lower levels for months or even years when they stop the hormone. I have seen this in persons with partial central cortisol deficiency. After receiving a course of a high-dose oral steroid (prednisone, Medrol, etc.) for a week or two, they fall into a state of worse cortisol deficiency that lasts for many months or years. Fortunately, in most persons, the HP-glandular system is more resilient and they quickly return to their pre-treatment state after stopping hormone supplementation.

Interestingly, the primary gland does not immediately stop making hormone when the HP system is shut off by exogenous hormone. In the absence of its stimulating hormone, the gland gradually atrophies, making less and less hormone over time. So in the first weeks and months of full replacement dosing, the primary gland is still contributing to the hormone level. The blood level reflects both exogenous and endogenous hormone. With time, the primary gland contribution decreases, and so the hormone level on a given exogenous dose declines. The patient's symptoms often return and the dose must be raised to maintain optimal levels/effects. This phenomenon is most obvious with testosterone therapy in men and with T4/T3 therapy for hypothyroidism. The testes and thyroid glands continue to produce hormone long after LH/FSH and TSH are suppressed, they probably never stop producing some hormone. Levels are often rather high when first checked, but over the following month they fall. During the first year or even two years, several dose increases are required. So the clinician must periodically check levels and inquire about symptoms—every 3 months or so for the first year, then every 6 months for year, then once yearly. If the hormone level is a bit high 2 to 3 months after starting the hormone, it is best to not lower the dose as long as the patient has no symptoms of excess. The hormone level will fall. As endogenous production declines, the patient eventually becomes completely dependent upon the exogenous hormone, and their hormone level becomes stable on a given dose. This gradual suppression of endogenous production can produce dramatic results. Hormone levels on a given dose can sometimes fall lower than they were prior to treatment—due excessive HP-suppression caused by peak levels. Also, if the HP system is weak or has been suppressed for a long time, it may remain suppressed for weeks or months even when levels are lower the pre-treatment.

This suppression of endogenous production is one of the costs of obtaining higher levels/effects. One becomes dependent on hormone supplementation. It is quite natural for both the patient and the physician to want to avoid suppression of the endogenous system. They would like to get the patient's own system to make enough hormone. There is a subset of persons with hypothyroidism or hypocortisolism who can benefit from low-dose replacement without much suppression of their natural production. Low-dose T4/T3 thyroid therapy can increase thyroid effect because it raises levels of the active hormone for a while, yet not enough to suppress TSH production 24hrs/day. Likewise one or two small doses of hydrocortisone (HC) early in the day can raise cortisol levels for a few hours and produce

some improvements. The person's cortisol levels still drop low overnight and thus stimulate the normal AM ACTH-cortisol rise. Some persons can even benefit from taking HC only occasionally—when needed for higher stress or activity. Others, however, with weaker HP systems, will experience a marked reduction in their own production with taking any oral hydrocortisone dose. They must either avoid taking the cortisol altogether, or commit to full replacement dosing.

Therefore hormone replacement must not be undertaken lightly in a person who has substantial endogenous hormone production. The physician should discuss HP-glandular suppression with the patient upfront. He should present the advantages and disadvantages clearly, in a way that the patient

Costs of Hormone Supplementation

- Inconvenience
- Expense
- Dependence on exogenous hormone
- Risks of overdosing and underdosing
- Inability to replicate natural physiology

can understand. He must take the patient's particular concerns into consideration so that they come to a mutual decision. Fortunately, there is generally no downside to a trial of hormone optimization—for a month or two. During this short period most persons will not suffer any longer-term suppression of endogenous production. The trial will be

the most important factor in the patient's decision about whether to continue the hormone supplementation. If they feel better, if symptoms improve, they will usually decide to continue the hormone accept the costs. Being dependent upon exogenous hormone supplementation is a small price to pay for the restoration of one's quality of life and health. As the old maxims go: "If you want to eat an omelet, you have to break some eggs"; "You can't have your cake and eat it too". If they do not get sufficient benefit they can taper quickly taper off the hormone. The less time that the hormone is taken, the less likely that there will be long-lasting suppression. Taking the hormone for just a few weeks, for instance, is not long enough to cause significant atrophy of the HP-gland system.

The problem of suppression is most feared with cortisol replacement therapy. Physicians fear it so much that even if someone feels and functions much better on cortisol replacement, they will still tell them to stop it. Such physicians have made an unconscious judgment for the patient: that living with cortisol deficiency is better than suppressing one's cortisol production system with supplementation. For sure, the suppression of cortisol production is a greater problem than with other hormones—because cortisol is our stress-response hormone. However, patients generally will still choose cortisol replacement when it is the only way that they can feel and function well. Also, one can take simple precautions to assure that one always gets enough cortisol when one is sick or hospitalized. I will discuss this in more detail in the chapter on cortisol.

7 The Importance of Route of Delivery

Endocrine glands typically secrete hormones directly in the venous circulation, in a pulsatile fashion, throughout the day and/or night. The secreted hormones are diluted in the venous blood. They then return with the blood to the heart from which they are pumped to the rest of the body in equal proportion. All tissues receive approximately the same hormone exposure. It is impossible to replicate all aspects of this natural secretion process with hormone replacement. To do so would require a

pulsatile or continuous subcutaneous or venous infusion—as with the insulin pumps now used by diabetics. Cortisol can be delivered with these pumps also. In the future, we may be able to deliver multiple hormones with a single subcutaneously-implanted pump. For now, we have to deliver hormones the old-fashioned way—by swallowing tablets and capsules, with transdermal delivery by gels, creams or patches, by subcutaneous delivery with injections and pellets, and by mucosal with sublingual, intranasal, vaginal or rectal tablets, creams, sprays, and suppositories.

While the molecules that we provide are natural to the body, exogenous hormone supplementation is an unnatural process. It differs from natural secretion in many important ways. The various routes of administration introduce unphysiological differences in each hormone's effects in various tissues, its pharmacokinetics and its transport in the blood. Complex proteins like growth hormone and insulin are digested in the stomach and intestines, and therefore must be injected or absorbed through a mucous

Routes of Delivery

Oral: (swallowed) tablets or capsules
Subcutaneous: injections or implants
Transdermal: creams, gels, patches
Mucosal: oral, nasal, vaginal or rectal

membrane. With oral and sublingual dosing of other hormones, one must be aware of first pass effect of the swallowed hormone on the liver, and of the liver's effect upon the hormone. All swallowed hormone is absorbed in the small intestine and travels via the portal circulation directly to the

liver. The liver is thus exposed to a higher concentration of the hormone than any other tissue. The liver is the body's primary detoxification-elimination organ for hormones and other substances. It also produces many of the proteins in the blood. It can alter and even deactivate hormones that are swallowed. Testosterone is almost totally ineffective when swallowed as it is metabolized to inactive forms by the liver in this first pass. All swallowed DHEA is sulfated by the liver, and then must be desulfated to become active.

The liver's metabolism of the hormone may produce high levels of metabolites that can have unwanted effects. Oral progesterone is changed into a number of metabolites by the liver, some of

Oral and Transdermal Issues

Oral: GI effects, first pass liver effects
Transdermal: enzymatic alteration, RBC saturation, transfer to others

which are very sedating. This allows progesterone to improve sleep when swallowed at bedtime. Immunoassays for progesterone also detect these metabolites, overestimating the actual progesterone level in the blood. Swallowing

estrogens, even human estradiol, causes excessive estrogen effect in the liver. This induces the liver to make higher amounts of certain hormone-binding proteins and blood-clotting proteins. Oral estrogens thus can increase the risk of blood clots—deep venous thrombosis, strokes and heart attacks. The liver naturally gets most of its thyroid hormone effect from the T3 in the blood. So swallowing thyroid hormone, particularly T3, causes a relative thyrotoxicosis in the liver. This overstimulation leads to excessive production of sex-hormone binding globulin (SHBG) and of other substances. Looking at raised levels of these substances, physicians in the past mistakenly concluded that patients were being given too much thyroid hormone. Oral T3 has one beneficial effect in the liver; it strongly lowers total and LDL cholesterol levels, more so than oral levothyroxine (T4) therapy. Oral cortisol (hydrocortisone) tends to increase IGF-1 production by the liver.

Applying a hormone to the skin or a mucous membrane, or injecting it subcutaneously allows it to enter the venous circulation more naturally, similar to endogenous production. This avoids the first-pass effect on the liver. The hormone is diluted in a large volume of venous blood as it travels to the heart and is pumped to the rest of the body. It then reaches the liver via the hepatic artery, so the liver receives the same concentration of the hormone as does every other tissue and organ. Thus the transdermal, mucosal or subcutaneous routes are better for many hormones, particularly for the sex-steroids. Applying estradiol to the skin causes no excess effect upon the liver; it does not significantly increase the levels of binding globulins or of clotting factors.

Different routes of delivery also result in different pharmacokinetics and different effects on blood test results. With each route, the physician must know the time to peak serum levels and of the rate of decline in those levels. Transdermally-delivered steroid hormones peak in the blood at around 3 hrs, whereas orally-delivered hormones peak as early as one hour. Transdermally-delivered hormone is slowly absorbed, and so tends to raise blood hormone levels for a longer period of time. It remains in the skin and subcutaneous fat—providing a reservoir for the hormone. This evens out the daily peaks and troughs and prevents deficiency symptoms from returning for a week or two after the hormone is stopped. Transdermally-delivered steroid hormones (estradiol, testosterone, progesterone, cortisol) are also carried in the blood differently than when they are naturally-secreted. In the skin where the hormone is applied, the capillaries' walls become soaked with hormone. Red blood cells must squeeze through the capillaries, one at a time. As they do, their fatty outer membranes become soaked with the lipid-soluble steroid molecules. Thus the whole blood, including the blood cells, contains more hormone than is seen in the usual serum blood tests in which the red blood cells are removed. The red-blood-cell carried hormone is carried to all other parts of the body and is transferred to capillary walls there and eventually to tissues. Thus transdermally-applied steroid hormones have more effect than is seen in the usual serum blood tests. To account for all the steroid hormone in the blood, the physician would need to do a whole-blood hormone level. These are not available at commercial laboratories. Because of this unusual red-cell membrane saturation, transdermal hormones have an excessive effect on the saliva levels of the hormone. Saliva levels become extremely high, far out of proportion to the amount of whole-blood hormone and the actual effect of the hormone in other tissues. Therefore saliva testing cannot be used to monitor transdermal/sublingual steroid delivery. Serum tests can underestimate the full effect of a transdermally-applied hormone. This is most obvious with progesterone because it is the most lipid-soluble sex-steroid. The effects of transdermal progesterone are much greater than suggested by the serum progesterone levels. Estradiol is the least lipid-soluble of the sex hormones, and so its serum levels better represent its full effect. Testosterone is intermediate.

Transdermal delivery can also lead to unusual metabolism of the hormone. The skin, especially the genital skin, contains the enzyme 5-alpha-reductase. This converts transdermally-delivered testosterone into dihydrotestosterone (DHT). DHT is a super-potent metabolite of testosterone. DHT levels are routinely high in a person who is applying testosterone to their skin. Due to both the red-blood-cell carriage and the high DHT levels, transdermal testosterone has more androgenic effect than one sees in

the total and free serum testosterone levels. So adjusting the dose of transdermal testosterone to produce high-in-range serum total or free testosterone levels can result in relative overdosing. The subcutaneous fat also contains aromatase which converts testosterone into estradiol. This effect is more pronounced in men with higher amounts of subcutaneous fat; they will have higher estradiol levels with a given transdermal testosterone dose. Most of what I have discussed here is unknown to conventional endocrinologists. So they produce errors, both in their clinical practice and also in the design and interpretations of studies. I will discuss all these issues in more detail in the relevant chapters.

8 Endocrine Freedom

Against the authoritarian, ignorant, liability-driven and pharmaceutically-funded medical system that we have, I assert the patients' right to elect any endocrine treatment that improves his/her quality of life, in spite of theoretical or even real concerns about long-term health consequences. Patients have the right to choose. These are hormones, natural to their body. They are not drugs. They are not addictive and do not have side-effects. All adults have the right to choose a trial of hormone optimization to see if it will improve how they feel and function. They have a right to choose what risk:benefit ratio they are willing to accept. Physicians should aid patients' choices, not obstruct them. In the appendix, I will describe how a physician can set up such a cooperative hormone restoration practice within the current hostile environment.