

## Four 2003 Studies of Thyroid Hormone Replacement Therapies: Logical Analysis and Ethical Implications

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**ABSTRACT.** “Replacement” is the most widely used approach to thyroid hormone therapy. Clinical practice guidelines define replacement therapy as: adjustment of a patient’s thyroid hormone dosage so that his or her TSH and thyroid hormone levels remain within current laboratory reference ranges. Overall, the endocrinology specialty endorses T<sub>4</sub>-replacement as the preferable approach to thyroid hormone therapy.

Four studies published in late 2003 compared the effectiveness of two types of replacement therapy, T<sub>4</sub> alone and combined T<sub>4</sub> and T<sub>3</sub> (T<sub>4</sub>/T<sub>3</sub>). In three of the studies,<sup>[1][2][3]</sup> patients who took part had been suffering from hypothyroid symptoms despite their T<sub>4</sub>-replacement therapy. The studies showed that neither form of replacement therapy improved the patients’ symptoms. In the fourth study,<sup>[4]</sup> researchers gave psychometric tests to hypothyroid infants after they had been on either T<sub>4</sub>- or T<sub>4</sub>/T<sub>3</sub>-replacement therapy for six and then twelve months. Compared to healthy infants, hypothyroid infants on both types of replacement therapy had impaired psychomotor function.

In reporting this specific result of the studies—that neither type of *replacement therapy* effectively relieved patients’ symptoms or abnormal neuropsychological test results—three groups of people have misrepresented, perhaps inadvertently, the outcome: the endocrinology researchers who conducted the studies, the endocrinologists who commented on them, and the journalists who reported them. Rather than reporting the specific study result, these groups reported a false general conclusion: that *no* approach to T<sub>4</sub>/T<sub>3</sub> therapy (replacement is the only one they tested) was more effective than T<sub>4</sub> alone. This false general conclusion violates a rule of quality scientific reporting—that we precisely formulate our statements to accurately convey conclusions that we can validly deduce from the studies we report.

Oddly, based on the negative outcome of these studies, some endocrinologists advise that T<sub>4</sub>-replacement should remain the treatment of choice for hypothyroid patients. Their advice, however, disregards two humanitarian imperatives:

(1) The endocrinology specialty must officially and publicly concede that many patients continue to suffer from hypothyroid symptoms despite their use of replacement therapies. This is especially important in view of other studies. The other studies suggest that for many patients, T<sub>4</sub>-replacement therapy increases the incidence of potentially fatal diseases and boosts chronic drug use to control the patients’ hypothyroid symptoms and those of the other diseases.

(2) These patients must have access to alternate thyroid hormone therapies, especially TSH-suppressive therapies, that are safe and effective for them.

These imperatives require that the endocrinology specialty now impartially consider approaches to thyroid hormone therapy other than replacement.

Alternate thyroid hormone therapies are already in demand and in widespread use by hypothyroid patients for whom T<sub>4</sub>-replacement is ineffective. These patients, many clinicians, and some researchers report that the alternate therapies are far more effective for the patients than replacement therapies. The endocrinology specialty’s objections to these other therapies have been either speculative or based on invalid conclusions from studies.

This imposes an urgent scientific obligation on the endocrinology specialty: that it now open-mindedly re-evaluate its objections to alternate thyroid hormone therapies. This is essential on both humanitarian and ethical grounds. In light of this obligation, endocrinology researchers must now cooperate in comparing the safety and effectiveness of replacement therapies to the alternate therapies. They must do this by reassessing without prejudice the already available historical, scientific, and clinical evidence; and by then conducting new, well-designed comparative studies.

The endocrinology specialty faces a dilemma in considering a reassessment of its objections to alternate thyroid hormone therapies. It will find that it can best serve the welfare of hypothyroid patients for whom T<sub>4</sub>-replacement is ineffective by providing them with alternate thyroid hormone therapies. But, by providing other therapies for

these patients, the specialty will risk losing financial support from the corporations that profit from its endorsement of T<sub>4</sub>-replacement. The result for the endocrinology specialty is that it will be compelled to show a steadfast commitment to scientific truth and patient welfare, or risk being deemed corrupt.

In this critique, I explain my statements in this abstract. I also provide supporting evidence for my conclusions.

**Keywords:** Combined T<sub>4</sub> and T<sub>3</sub> • Endocrinology specialty • T<sub>4</sub>/T<sub>3</sub> • T<sub>4</sub>-replacement • TSH-suppression • Desiccated thyroid •

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## FALSE REPORTS OF 2003 STUDY RESULTS AND POTENTIAL PROBLEMS FROM THEM

In 2003, four studies were published that compared the effectiveness of two types of replacement therapy, T<sub>4</sub> alone and combined T<sub>4</sub>/T<sub>3</sub>, in the treatment of hypothyroid patients. In one study, symptoms of patients taking either T<sub>4</sub>-replacement or T<sub>4</sub>/T<sub>3</sub>-replacement improved.<sup>[3]</sup> Because both groups improved, for logical reasons we must attribute the improvement to either a placebo effect<sup>[20]</sup> or a natural variation in the patients' symptoms. Essentially, then, in this study as in the other three, neither type of replacement therapy improved the patients' symptoms or test abnormalities.<sup>[1][2][3][4]</sup> Therefore, the conclusion compelled by the outcome of the four studies is clear: *Replacement therapies are ineffective for many hypothyroid patients, leaving them symptomatic and with some abnormal neuropsychological test results.*

Based on the four studies, endocrinologists have advised that T<sub>4</sub>-replacement should remain the treatment of choice for hypothyroid patients. Their reason is that T<sub>4</sub>/T<sub>3</sub>-replacement worked no better than T<sub>4</sub>-replacement. This advice is foreboding for patients who remain symptomatic on T<sub>4</sub>-replacement, for the four studies are a concession of endocrinology researchers that the therapy leaves many patients suffering. For these patients' welfare, endocrinologists are obligated to reassess their advice in view of its predictable pernicious consequences for the patients. I explain this in the section below titled "Dilemma for the Endocrinology Specialty."

First, however, I'll point out an invalid conclusion endocrinologists stated in their reports of the study results. Patients, physicians, reporters, and the endocrinologists themselves must understand the invalidity of the conclusion; otherwise, they are likely to promulgate a false belief about the results of the studies.

## VALID AND INVALID CONCLUSIONS OF THE ENDOCRINOLOGY RESEARCHERS, COMMENTATORS, AND JOURNALISTS

The researchers accomplished what they intended in each of the four studies. They tested the relative effectiveness of *two types of replacement therapy*; they found that neither type improved patients' hypothyroid symptoms. Endocrinologists' reports of the results contain the valid conclusion that neither type improved patients' symptoms. Unfortunately, the reports also contain an invalid conclusion, one that we clearly cannot deduce from the study results: The invalid conclusion is that *no approach to T<sub>4</sub>/T<sub>3</sub> therapy—among all possible approaches—is any more effective than T<sub>4</sub> alone.*

This invalid conclusion is a linguistic reformulation of the valid one. I'll explain this in the lexicon of the logician. The endocrinologists deduced from the studies a valid existential (specific) proposition: *Neither T<sub>4</sub>-replacement nor T<sub>4</sub>/T<sub>3</sub>-replacement improved patients' hypothyroid symptoms.* Then, they reformulated that proposition into an invalid universal (all-inclusive) proposition: *No approach to T<sub>4</sub>/T<sub>3</sub> therapy is more effective than T<sub>4</sub> alone in relieving patients' hypothyroid symptoms.*

These differently formulated conclusions have entirely different meanings. The difference is the same as researchers first saying, "Our study showed that as race horses, *short* stallions are no more effective than *short* mares," and then concluding, ". . . as race horses, stallions are no more effective than mares." The first statement refers to a specific class of stallions and mares—short ones; the second refers to *all* stallions and *all* mares, despite their height. In that the researchers studied only short stallions and mares—not all stallions and mares—they cannot validly deduce their second proposition from the first. To do so is a flagrant *non sequitur*.

The endocrinologists who performed these studies committed exactly the same logical error and reported an equally flagrant *non sequitur*. They cannot validly deduce from the results of the four studies that *no* T<sub>4</sub>/T<sub>3</sub> therapy works any better than T<sub>4</sub> alone; yet this is precisely the meaning of their universal conclusion (and the implication of the titles of all four study reports).<sup>[1][2][3][4]</sup>

The endocrinologists may have reformulated their valid conclusion into an invalid one inadvertently. But that doesn't change the fact that their doing so violates a rule of quality scientific reporting—that we precisely formulate our statements to accurately convey only the valid conclusions deducible from study results.

In Addendum 1, I've excerpted statements from the endocrinologists' published reports of the studies. The excerpts show that each of the published reports contains both valid and invalid conclusions.

In response to my distinction between the valid and invalid conclusions, I predict a particular protest: I'm quibbling; what I'm referring to as an invalid conclusion is only a version of the conclusion abridged to be wieldy and understandable—an abridgment demanded by journal and newspaper editors. But to abridge is to shorten while maintaining the basic meaning—not to convert a valid specific statement into an invalid universal one.

It is understandable that reporters and editors of newspapers and newsletters sometimes fail to accurately report conclusions from studies. Most aren't practicing researchers, and we can excuse them for occasionally lacking the precision expected of researchers. To understand their imprecision, however, is not to condone it; we should implore them to accurately report the results of scientific studies. In this case, however, reporters and editors are only parroting an invalid conclusion from the researchers themselves.

Endocrinologists have perpetuated other invalid and false conclusions (see section below titled "Potential Harm from TSH-Suppressive Dosages of Thyroid Hormone") that reporters have parroted. It would be inexcusable, however, to have to add to the list the invalid conclusion now at issue.

Few physicians, patients, or reporters will read the full-text reports of the four studies. Instead, they'll read only the brief invalid conclusion of the researchers in various publications. Some will read only the abstracts of the four reports in *PubMed*. As a result, it's likely that they'll falsely believe the researchers found that no approach to T<sub>4</sub>/T<sub>3</sub> therapy is more effective than T<sub>4</sub> alone.

Already in *JAMA*, we see the title of an article,

"Combined T<sub>4</sub> and T<sub>3</sub> Therapy—Back to the Drawing Board."<sup>[20]</sup> In that this title is not properly qualified, many doctors, fast-moving by necessity, will read only the headline, and their belief system will inaccurately echo it. No more Armour or Thyrolar for their patients! After all, the doctors have an ethical obligation to go where science points. Armour and Thyrolar contain T<sub>4</sub> and T<sub>3</sub>. The studies show that these are no more effective than T<sub>4</sub> alone, so the doctors must prescribe T<sub>4</sub> alone, as the researchers advise.

Few reporters who read the researchers' full reports or abstracts of them are likely to announce to their readers what the researchers actually found. Instead, they'll quote or rephrase what they read in the reports or abstracts—the invalid conclusion. To illustrate, the invalid conclusion of the endocrinology researchers and commentators was the headline of a news article at a popular website, docguide.com: "Combination Levothyroxine/Liothyronine [T<sub>4</sub>/T<sub>3</sub>] Shows No Obvious Benefit Over Levothyroxine [T<sub>4</sub>] Alone in Patients With Primary Hypothyroidism." The first sentence of the article echoed the title: "Patients who are treated with a combination of levothyroxine plus liothyronine for primary hypothyroidism gained no apparent benefit compared with patients treated with levothyroxine monotherapy, say researchers."<sup>[21]</sup> The headline alone is certain to mislead readers who stop there. The intention of the reporter, Joene Hendry, most likely was not to mislead. But in abbreviating the studies' conclusion, that is exactly, though inadvertently, what she did.

Hence, a false belief about T<sub>4</sub>/T<sub>3</sub> therapies has already been engendered by endocrinologists' violation of this rule of quality science reporting. Researchers, physicians, patients, and reporters should exhort the endocrinologists to practice the same precision that we implore reporters to practice. Whether the endocrinologists heed the exhortation is a matter of scientific integrity.

#### **ENDOCRINOLOGISTS' ODD TREATMENT ADVICE FOR PATIENTS WHO REMAIN SYMPTOMATIC ON T<sub>4</sub>-REPLACEMENT THERAPY**

The four studies showed that replacement therapies weren't effective for many hypothyroid patients.<sup>[1][2][3][4]</sup> Patients who took part in three of the studies had hypothyroid symptoms and/or abnormal neuropsychological test scores. T<sub>4</sub>-replacement therapy clearly didn't improve the symptoms or the scores. Regardless, the researchers and other endocrinologists have since implicitly or explicitly given baffling advice based on the

studies: that T<sub>4</sub>-replacement should remain the treatment of choice for hypothyroid patients.<sup>[1][2][3][19]</sup> (For quotes from endocrinologists to this effect, see Addendum 2.)

This is the equivalent of researchers taking people who suffer from thirst when restricted to one glass of water per day; letting them try as an alternative one glass of mixed water and tea; seeing that the one-glass mixture relieves thirst no better than one glass of water; and then, based on this outcome, advising that these people continue to drink one glass of water per day. The one glass of water left the people thirsty before the study, and failure of the one-glass mixture to relieve their thirst doesn't mean one glass of water alone will now do any better than before. Similarly, many hypothyroid patients have continuing symptoms on T<sub>4</sub>-replacement, and the failure of T<sub>4</sub>/T<sub>3</sub>-replacement to relieve their symptoms doesn't mean that now T<sub>4</sub>-replacement will.

As the endocrinologists imply, T<sub>4</sub>-replacement (and T<sub>4</sub>/T<sub>3</sub>-replacement, which they discourage) will indeed work well for *some* hypothyroid patients. For others, however, replacement therapies are clearly ineffective. The studies are in fact “a randomized double-blind” admission by the endocrinology researchers that T<sub>4</sub>-replacement is not effective for many patients. (See Addendum 3 for evidence of persisting symptoms of hypothyroid patients in the studies despite their use of T<sub>4</sub>-replacement.)

Despite this, none of the endocrinologists have noted an ethical and humanitarian responsibility made clear by these studies: to provide patients for whom replacement therapies aren't effective with alternate thyroid hormone therapies that are safe and effective for them. This responsibility is made even clearer by several other studies. These studies indicate that patients on T<sub>4</sub>-replacement have an increased incidence of potentially fatal diseases, and increased chronic use of medications for these diseases (see section below titled “Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T<sub>3</sub>, and the Safety and Effectiveness of T<sub>4</sub>-replacement”). The endocrinologists' failure to note this responsibility suggests a cavalier disregard for the needs of patients who remain symptomatic and susceptible to pathology on T<sub>4</sub>-replacement therapy. The only humane option for the endocrinology specialty is to now open-mindedly reconsider thyroid hormone therapies other than replacement, replacement, including TSH-suppressive therapies.

## ALTERNATE APPROACHES TO THYROID HORMONE THERAPY

Thyroid hormone treatments other than replacement therapies are in widespread use among hypothyroid patients—mainly those who previously failed to benefit, or benefit enough, from T<sub>4</sub>-replacement. The therapies are in widespread use for one reason: they work for hypothyroid patients after replacement therapies failed them.

The most effective of these therapies involves adjusting patients' dosages of combined T<sub>4</sub>/T<sub>3</sub> or T<sub>3</sub> alone according to several indices other than TSH and thyroid hormone levels. Those indices are signs, symptoms, and various objective measures of tissue response to particular dosages. When patients' dosages are titrated according to these indices, dosages that prove safe and effective are typically TSH-suppressive.<sup>[44]</sup> Evidence is available that this therapeutic approach relieves patients' signs, symptoms, and measurable tissue abnormalities such as low resting metabolic rates (RMR) according to indirect calorimetry.

In the studies at issue, endocrinologists used thyroid function test results as the exclusive criteria by which to titrate patients' thyroid hormone dosages. Despite denials,<sup>[26]</sup> this is precisely the method used by endocrinologists at large to titrate patients' dosages. This method (which I termed “extremist medical technocracy” in *The Metabolic of Treatment Fibromyalgia*<sup>[44]</sup>) varies from that of the clinician using the protocol I describe here. This clinician uses thyroid function test results as an aid to clinical judgment—an aid that is integrated with other aids, such as objective measures of tissue response to thyroid hormone. Thyroid function test results help this clinician form an opinion as to the patient's pre-treatment thyroid status. After he establishes the patient's thyroid status, however, he seldom uses thyroid function test results to reach treatment decisions. His reason for not using them to titrate dosage is that most of his patients have previously failed to benefit from T<sub>4</sub>- or T<sub>4</sub>/T<sub>3</sub>-replacement therapies, in which, of course, physicians adjusted dosages according to the patients' TSH and/or thyroid hormone levels. Only by this clinician *not* using the replacement method for titrating dosage are most of these patients able to recover from their symptoms, signs, and objective measures of tissue hypometabolism.

The fact that so many patients have recovered from their symptoms, signs, and tissue abnormalities with this alternative to replacement therapies compels a proposition: T<sub>4</sub>-replacement therapy previously impeded these

patients from recovering their health. It becomes imperative, then, for the health and welfare of such patients that practitioners (1) not restrict them to replacement therapies, but instead, (2) permit them to undergo trials of alternate thyroid hormone therapies, and (3) determine on an individual basis, using clinical indicators and objective measures of tissue responses, whether the alternate therapies are safe and effective for each individual patient.

Despite this clear-cut imperative, Kaplan et al., in their editorial comments on the four studies, stipulated that in future studies, “TSH should be monitored dynamically and study medications adjusted according to the results, to maintain normal serum TSH concentrations.”<sup>[19,p.4541]</sup> To make this recommendation, Kaplan et al. had to ignore the major finding of the four studies: that replacement therapies—in which clinicians adjust patients’ dosages to maintain reference range TSH levels—are ineffective for many hypothyroid patients (and specifically for most patients in the four studies), leaving them to suffer from hypothyroid symptoms.

In their editorial, Kaplan et al. also appear to ignore a telling observation of their own: in one study, 15 thyroid cancer patients used TSH-suppressive dosages of thyroid hormone; their mood and cognitive function improved more than those of patients with autoimmune thyroiditis who used replacement dosages.<sup>[19,p.4540]</sup> This observation suggests that dosages higher than those dictated by the replacement concept more effectively relieve patients’ hypothyroid symptoms. Other research has shown that patients report feeling better with TSH-suppressive dosages of thyroid hormone.<sup>[23][24][25]</sup> Moreover, psychiatrists report that dosages of T<sub>3</sub> higher than replacement dosages augment the depression-relieving effects of antidepressants.<sup>[9][28][29][30][31][34]</sup> In addition, in a study of patients made hypothyroid by therapeutic destruction of the thyroid gland, some used TSH-suppressive dosages of thyroid hormone and others used T<sub>4</sub>-replacement. Those on TSH-suppressive dosages did not gain excess weight; those on T<sub>4</sub>-replacement did. The researchers concluded that T<sub>4</sub>-replacement was the cause of the excess weight gain.<sup>[55]</sup> These published reports are consistent with thousands of cases in which hypothyroid patients recovered from their symptoms and other health problems with TSH-suppressive dosages of thyroid hormone *after* T<sub>4</sub>-replacement failed to help them.

Kaplan’s observation also suggests another point: that T<sub>4</sub>-replacement keeps many hypothyroid patients’ dosages too low to relieve their symptoms is an indictment of the concept of replacement. As the cause of (1)

the continued suffering and debility of patients, (2) an increased incidence of potentially life-threatening diseases, and (3) the need for the chronic use of medications, T<sub>4</sub>-replacement constitutes a public health menace—one responsible for colossal human suffering and huge financial burden to society.

In view of this circumstance, the advice of Kaplan et al. appears to be indefensible. It also appears, based on the outcome of the four studies, that the endocrinology specialty now has an ethical and humanitarian obligation to challenge the veracity of its own presumptions about the safety and effectiveness of replacement therapies. (See section below titled “Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T<sub>3</sub>, and the Safety and Effectiveness of T<sub>4</sub>-replacement.”)

As I wrote above, alternate thyroid hormone therapies are already in widespread use, and physicians and patients who use them contend that treatment results are superior to those of T<sub>4</sub>-replacement. These reports, in light of the outcome of the four studies, should impel anyone even mildly charitable toward patients who suffer while on T<sub>4</sub>-replacement, to advocate studies comparing T<sub>4</sub>-replacement with alternate thyroid hormone therapies.

## PATIENT SAFETY

I anticipate an objection of the endocrinology specialty to my behest that it consider without prejudice the need of many patients for TSH-suppressive thyroid hormone therapies. The specialty’s reason for objecting to such therapies has long been the issue of patient safety. The specialty as a whole tenaciously argues that TSH-suppressive dosages of thyroid hormone imperil patients, risking bone demineralization, acute adrenal crisis, and atrial fibrillation.

In Addendum 4, I provide a brief summary of each of these putative adverse effects. Each is either speculative, never shown to be clinically significant, or based on invalid deductions from studies.

The specialty has argued that T<sub>4</sub>-replacement therapy is superior to other approaches to thyroid hormone therapy because it enables patients’ TSH and thyroid hormone levels to remain stably within their reference ranges. The idea that stability within the reference ranges is vital to the safety of all patients, however, is a presumption. Studies show that keeping these hormones within their reference ranges harms many patients in three ways: it perpetuates their hypothyroid symptoms, increases the incidence of potentially fatal diseases, and

increases patients' regular use of drugs to control their hypothyroid symptoms and the other diseases.

### POTENTIAL HARM FROM TSH-SUPPRESSIVE DOSAGES OF THYROID HORMONE

In arguing that physicians should permit some hypothyroid patients to use TSH-suppressive dosages of thyroid hormone, it is incumbent upon me to justify the argument. To do so, I must explain two contradictory propositions. The first, espoused by the endocrinology specialty, is that: only thyroid hormone replacement is safe for hypothyroid patients. And the second, my proposition, says that: for a subset of hypothyroid patients, TSH-suppressive dosages of thyroid hormone are safe and necessary for health.

The available evidence shows the first proposition to be false and the second true. I'll show this first by: (1) referring readers to the section below titled "Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T<sub>3</sub>, and the Safety and Effectiveness of T<sub>4</sub>-replacement," (2) presenting evidence that a subset of patients uses TSH-suppressive dosages with impunity, and (3) providing a plausible theoretical explanation for their safe and effective use of suppressive dosages.

A fitting introduction to the evidence for my viewpoint on TSH-suppressive thyroid hormone therapies is a 38-year-old statement by endocrinologist James H. Hutton. (For comments on Dr. Hutton, see Addendum 5.) His statement is on alleged harm from the use of thyroid hormone.

Thyroid is a much maligned agent. Certainly it should be administered only under the supervision of a physician, but the danger likely to result from taking it has been portrayed in such lurid fashion that many medical men seem hesitant about giving it. As a matter of fact, overdosage seldom occurs. Signs of such an event are so easily recognized before any damage is done that any medical man should use it wherever he believes it is indicated.

The tachycardia, tremor, palpitation and increased nervousness [from overdosage] are easily recognized so that one may accurately administer it without resorting to frequent determination of the BMR, etc. *The tolerance for it varies over an extremely wide range with different patients.* [Italics mine.] Patients much in need of it may tolerate less than one grain [of desiccated thyroid]

per day, others who seem to need it no worse, tolerate up to 60 grains per day without any discernible ill effects. This, of course, could have been due to a difference in absorption of the drug from the gut.<sup>[18,p.16]</sup>

Hutton wrote that 120-to-180 mg (approximately 2-to-3 grains) daily was optimal for almost all myxedematous patients.<sup>[18,p.76]</sup> I cite the 60 grains not as a recommendation for any patient, but as a segue to consideration of a concept currently lacking in decision-making about thyroid hormone dosages within conventional medicine practice. The concept is that of a normal error or variance (bell curve) distribution of tissue responsiveness to thyroid hormone among patients.

The scores of everything we can measure, when we measure enough instances, fall into a bell curve distribution. This is true of measurable phenomena classified in virtually any way, such as social (ethnic and racial prejudice), psychological (scores on an aptitude test), anatomical (heights of adult males and females), molecular (molecular weight of a chemical), environmental (yearly temperature variations), economic (stock market variations), and physical (mechanical force needed to bend apparently identical steel rods). And we can, on principle, expect that within the population of hypothyroid patients, tissue responsiveness to a particular dosage of thyroid hormone falls into a bell curve distribution. We can expect this even while allowing for variable responsiveness of different tissues within individual patients.

### CENTRAL LIMIT THEOREM AND THE INEFFECTIVENESS AND DANGERS OF REPLACEMENT THERAPY FOR MANY PATIENTS

In laboratory medicine, current practice for the most part ignores the need of some patients for dosages of thyroid hormone that exceed other patients' needs. The standard of practice implies that the optimal dosage for *all* patients is the amount that keeps the TSH within its current reference range. But this implication conflicts with what we can reasonably predict from the central limit theorem of mathematics. The theorem says that for samples that are sufficiently large, the distribution of means is almost always more or less normal. The theorem, I believe, provides an explanation for the ineffectiveness and harm of thyroid hormone replacement for many patients, and for them, the effectiveness and safety of TSH-suppressive dosages.

I don't mean to imply that laboratory medicine spe-

cialists calculate reference ranges without considering the normal variance distributions; indeed, they base the ranges on the 95% confidence intervals of the distributions.<sup>[41]</sup> I explicitly contend, however, that clinicians, as standard practice, don't consider the normal distribution of variances in interpreting laboratory thyroid function test results or in making dosage decisions.

The central limit theorem predicts that repeated measurements (reported as the means of multiple samples) of any phenomenon produce readings that vary around a mean, so that they form a normal distribution. Applied to the concept of variable tissue responsiveness, the theorem predicts the following proposition: On the left slope and flange of the bell curve of tissue responsiveness, a progressively decreasing percentage of hypothyroid patients require progressively larger dosages of thyroid hormone to prevent symptoms of hypothyroidism, and ward off pathologies secondary to hypothyroidism. The theorem also predicts that the tissues of this progressively decreasing percentage of patients are progressively more resistant to overstimulation by progressively larger dosages of thyroid hormone.

Thus, the theorem predicts that what to some patients (on the right slope and flange) is an overstimulating dosage of thyroid hormone is to others (on the left slope and flange) innocuous. Our clinical experience and studies of potential adverse effects of TSH suppression bear this out. So do studies in which only a small percentage of patients had adverse effects to TSH-suppressive dosages of thyroid hormone, while most patients had no such effects. Those who had adverse effects represent the right outer slope and flange of the bell curve, where patients' tissues are more responsive to a particular dosage of thyroid hormone than are most other patients' tissues.

Unfortunately, many researchers mistakenly conclude that since a *subset* of patients has adverse effects from TSH-suppressive dosages of thyroid hormone, physicians should protect *all* patients by denying them such dosages. What these researchers apparently fail to comprehend is a point of crucial importance to the health and safety of the subset of patients on the left end of the curve: for these patients, TSH-suppressive dosages are both harmless and necessary to their health and well-being. Of course, in the vein of patient safety, we must be ever vigilant in clinical practice for potential adverse effects, even in this left-end subset of patients. But it is equally important in the vein of safety that we be cognizant that their health and well-being are assured *only* when they use the TSH-suppressive dosages that

are harmful to patients on the right end of the curve.

The endocrinology specialty overall ignores the predictable phenomenon of a normal distribution of tissue responsiveness among the population of hypothyroid patients. Consistent with ignoring the phenomenon, the specialty implies or explicitly states that unless a patient has thyroid cancer, he/she shouldn't use a TSH-suppressive dosage of thyroid hormone. The reason the specialty gives is that the dosage is highly likely to harm the patient. For thyroid cancer patients, the specialty argues, the benefits of TSH-suppressive dosages are worth the risks, although they are still not preferable.

Consider, however, a report by nuclear medicine specialists of a man with well-differentiated thyroid cancer.<sup>[15]</sup> For ten years, he had taken a high dosage of T<sub>4</sub> to suppress his TSH level. During that time, his dosage ranged between 0.9-to-3.3 mg (900-to-3300 mcg T<sub>4</sub>; roughly equivalent to 44.6 grains of desiccated thyroid, which is close to the 60 grains that some patients tolerate well, according to Hutton). The authors wrote, "*He was essentially asymptomatic and suffered no apparent ill effects from this prolonged and markedly excessive dosage of L-thyroxine. The literature lists a wide range of ill effects from both chronic and acute thyroid hormone overdosage but also records many examples of tolerance to excessive levels of exogenous thyroid hormone.*" (Italics mine.)

Treatment of thyroid cancer patients with TSH-suppressive dosages of thyroid hormone has provided a population of patients that enables us to examine the likelihood of harm from such dosages. The general belief within the endocrinology specialty is that for thyroid cancer patients, suppressing the TSH to an undetectable level is acceptable, as long as patients avoid "clinical thyrotoxicosis."<sup>[16,p.1150]</sup> Researchers have now conducted many studies of these patients to learn whether the TSH-suppressive dosages adversely affect their bones and hearts.

The research literature contains many studies of potential adverse effects of TSH-suppressive dosages on bone. What we've learned from these studies provides us with what could evolve into principles for the safe use of such dosages by a subset of hypothyroid patients—those for whom replacement dosages aren't effective, and therefore not safe (see section below titled "Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T<sub>3</sub>, and the Safety and Effectiveness of T<sub>4</sub>-replacement").

That a patient uses a TSH-suppressive dosage of thyroid hormone *doesn't* mean that the patient will definitely have reduced bone mineral density. Whether he

or she does or doesn't depends largely on another variable: the number of other risk factors for reduced bone density that impinge on the patient. Susceptibility in an individual patient, then, is the algebraic summation of the presence or absence of multiple risk factors. I've listed the most common ones<sup>[39][40]</sup> in Table 1. It's worth noting here that the variance within any normal distribution is caused by the influences of many small random effects on the measured variable. Risk factors for reduced bone density are such random effects.

**Table 1. Risk factors for decreased bone mineral density\***

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Low calcium
Low vitamin D intake or low exposure to sunlight
Estrogen deficiency
Small body stature
Low body weight
Advanced age
Tobacco smoking
High alcohol consumption
Use of pharmacologic dosage of corticosteroids
Too little back-stretching
Too little high-impact and/or weight-bearing exercise

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\*No authors listed: Osteoporosis-prevention, diagnosis and treatment: a systematic literature review: SBU conclusions and summary. *Lakartidningen*, 100(45):3590-3595, 2003.<sup>[39]</sup>

Yoshimura, N.: Exercise and physical activities for the prevention of osteoporotic fractures: a review of the evidence. *Nippon Eiseigaku Zasshi*, 58(3):328-337, 2003.<sup>[40]</sup>

To put the role of risk factors into proper perspective, consider a bell curve of bone responsiveness to TSH-suppressive dosages of thyroid hormone. On the right end of the curve, an increasing number of risk factors for reduced density renders a decreasing percentage of patients progressively more susceptible to reduced bone mineral density from TSH-suppressive dosages of thyroid hormone. On the left end of the curve, a decreasing number or absence of risk factors for reduced bone density renders a progressively decreasing percentage of patients progressively more resistant to reduced bone mineral density from TSH-suppressive dosages.

Before treating a patient with a thyroid hormone dosage greater than a replacement dosage, we don't know where his or her tissues fall within the bell curve of tissue responsiveness to the hormone. As the four studies at issue here show, presuming that all hypothyroid patients' tissues fall close to the mean of tissue responsiveness to thyroid hormone causes some patients to continue to suffer from hypothyroid symptoms. For some—the diminishing percentage who fall on the right

flange of the curve—a particular TSH-suppressive dosage will cause thyrotoxicosis; for others—the diminishing percentage on the left flange—that same dosage is necessary for normal metabolism and freedom from hypothyroid symptoms. The further out these patients' tissue responsiveness falls in the left-side flange of the bell curve, the more resistant to thyrotoxicity they are, and the less effective thyroid hormone replacement is for them.

The 95% confidence interval that lab pathologists use to establish reference ranges is a mathematical calculation that leaves 2.5% of patients on each end of the distribution. Standard practice in medicine is to conclude that lab values within the 95% interval are “normal,” and that those in the 2.5% on each end of the distribution are “abnormal.” This conclusion is an *arbitrary social convention*—one that ignores the progressive variance that occurs as lab values proceed outward bilaterally through two standard deviations from the mean. (In general, physicians arbitrarily consider lab values that fall within two standard deviations of the mean “normal.”) Patients whose tissue responsiveness falls progressively further out on the left side of the distribution are progressively more susceptible to developing symptoms of hypothyroidism. This is true despite their tissue responsiveness being within two standard deviations of the mean. Much to the patients' misfortune, however, most physicians will conclude that their symptoms can't be caused by hypothyroidism because their TSH and thyroid hormone levels are within the “normal” reference ranges—that is, their respective 95% confidence intervals.

Appreciation of the bell curve distribution of tissue responsiveness to thyroid hormone compels us to acknowledge the existence of a diminishing percentage of patients on the left side of the curve whose tissues are progressively less responsive to a dosage of thyroid hormone that keeps most hypothyroid patients symptom-free. These patients require higher dosages of thyroid hormone—for many, TSH-suppressive dosages—to maintain normal metabolism and health. Correspondingly, these patients' tissues will predictably be progressively more resistant to dosages of thyroid hormone that for most other patients are thyrotoxic.

In my view, the recent four replacement therapy studies addressed patients on the left-side flange of the bell curve. The studies showed that replacement dosages are insufficient for relieving their hypothyroid symptoms. The studies are *ipso facto* evidence for a humanitarian imperative: that researchers and physicians now accommodate these patients' need for dosages of

thyroid hormone larger than those dictated by the concept of replacement therapies.

**PRESUMPTIONS OF THE ENDOCRINOLOGY SPECIALTY: INSTABILITY OF DESICCATED THYROID, DANGERS OF T<sub>3</sub>, AND THE SAFETY AND EFFECTIVENESS OF T<sub>4</sub>-REPLACEMENT**

The endocrinology specialty bases some of its most influential pronouncements on presumption—a basis that hardly justifies the certitude with which it expresses the pronouncements. Three presumptions appear to sustain the practice of T<sub>4</sub>-replacement. The presumptions are that desiccated thyroid is unstable, that T<sub>3</sub> is troublesome and dangerous, and that T<sub>4</sub>-replacement is invariably safe and effective.

**Instability of Desiccated Thyroid.** Since the 1960s, the endocrinology specialty has advocated and even enforced only the use of T<sub>4</sub>-replacement in lieu of desiccated thyroid as a treatment for hypothyroidism. According to endocrinologists, the reason for this advocacy and enforcement is that the potency of desiccated thyroid is difficult to standardize. That is, the endocrinologists claim that too often, desiccated thyroid tablets don't contain the amount of thyroid hormone reported on the label. They argue that the potency of synthetic T<sub>4</sub> is more stable.<sup>[42]</sup> That synthetic T<sub>4</sub> products are more stable, however, is a mere presumption. I can find no studies in which the stability of desiccated thyroid and synthetic T<sub>4</sub> were compared. When I searched for studies in *PubMed*, using the keywords “desiccated thyroid,” “Armour,” “stability,” and “potency,” I found no studies. But when I searched for “Synthroid” and either “stability” or “potency,” I found two abstracts.<sup>[67][68]</sup> In one, the authors state, “Levothyroxine tablets, 50 microg, have been marketed for many decades but have had numerous recalls due to degradation and failure to meet potency.”<sup>[67]</sup>

The specialty has tenaciously endorsed a T<sub>4</sub> product called Synthroid, perpetuating the belief that it is the pinnacle of potency-stable medications. Shomon<sup>[46]</sup> and I<sup>[47]</sup> have reported, however, that the FDA has repeatedly recalled batches of Synthroid because tablets from the batches were “subpotent.” This term means that tablets didn't contain the amount of T<sub>4</sub> claimed on the label. Despite this public record of serious problems with potency, representatives of the endocrinology specialty have doggedly continued their endorsement of Synthroid—and only Synthroid.

The fact is that all thyroid hormone products, both animal-derived and synthetic, are unstable compared to

many other drugs. Thyroid hormones consist of iodine atoms bound to the amino acid tyrosine. The iodine atoms fairly easily separate from the tyrosine. Because of this, it's prudent for both doctors and patients to be vigilant for subpotent tablets or capsules. The reassurance of the endocrinology specialty that Synthroid is more stable than other products is groundless. Because it misleads doctors and patients, often to the patients' detriment, the specialty should cease to make this pronouncement.

**Dangers of T<sub>3</sub>.** The endocrinology specialty has long opposed the use of products that contain T<sub>3</sub>. The basis of its opposition, so it claims, is the resulting brief peak blood level of T<sub>3</sub>. Members of the specialty glibly state that the peak level is in the “thyrotoxic range”<sup>[84,p.1225]</sup> and that this peak level causes heart palpitations that trouble patients. They further state that the peak level may adversely affect the heart. But, these members resound, by using Synthroid patients can avoid these problems.

The specialty's claim that T<sub>3</sub> causes these problems is a mere presumption; it is contradicted by the reports of researchers with extensive clinical experience with T<sub>3</sub>. Psychiatric researchers whose patients use T<sub>3</sub> point out that it is generally well-tolerated.<sup>[35]</sup> The experience of my research group agrees with this observation. For some fifteen years, our treatment team has worked directly with hundreds of patients using combined T<sub>4</sub>/T<sub>3</sub> products or T<sub>3</sub> alone. Our observations during that time dispute the warning that palpitations are a problem for patients who use T<sub>3</sub>-containing products. Palpitations in these patients are *exceedingly* rare. When a patient has experienced palpitations, they have been minor and of little or no concern to the patient. The palpitations have also been of no clinical significance. It's noteworthy that the researchers of the four studies, as well as those of three other studies comparing the effectiveness of T<sub>4</sub> and T<sub>4</sub>/T<sub>3</sub>-replacement, didn't report that their study patients were troubled by palpitations.<sup>[1][2][3][4][5][6][7]</sup>

I can find no study that members of the specialty have conducted confirming its prediction of adverse effects from T<sub>3</sub>. Only last year, endocrinologists Kaplan, Sarne, and Schneider wrote: “. . . the possible long-term risks of elevated or fluctuating T<sub>3</sub> levels have not been evaluated.”<sup>[19,p.4541]</sup>

Systematic studies have not conclusively ruled out long-term adverse effects. But many patients have used T<sub>3</sub> for many years without apparent adverse effects. We have, then, a positive anecdotal record and no long-term safety studies showing that T<sub>3</sub> is harmful. Regardless, the specialty has warned of potential harm in a manner

that has generated irrational fear of T<sub>3</sub> among physicians. It's common, for example, for patients who've asked their doctors to prescribe T<sub>3</sub> to hear the reply, "If you take T<sub>3</sub>, you're going to have a heart attack and die!"<sup>[48,p.10]</sup>

It goes without saying, of course, that caution is necessary with patients who have fragile cardiac conditions. This is especially true when such a patient is using a product containing T<sub>3</sub>, since T<sub>3</sub> directly affects the myocardium.<sup>[66]</sup> But *potential* harm from T<sub>3</sub> is not *actual* harm, and the endocrinology specialty has so blurred the distinction that most other physicians—and perhaps they themselves—don't know the difference.

**Safety and Effectiveness of T<sub>4</sub>-replacement Therapy.** Just as the endocrinology specialty's objections to the use of desiccated thyroid and T<sub>3</sub> are based on presumption, so is its long-standing dictum that T<sub>4</sub>-replacement is always safe and effective. Some members of the specialty have been steadfastly convinced of the fail-safe effectiveness of T<sub>4</sub>-replacement. When patients complain of continuing hypothyroid symptoms despite using "adequate T<sub>4</sub>-replacement," these members argue that something other than a thyroid hormone deficiency must be causing their symptoms.

Witness, for example, statements by thyroid surgeon Richard Guttler: "We have the most accurate thyroid testing, and if you test normal, and have symptoms, most likely your symptoms aren't due to abnormal thyroid balance." And further, "[I] rely on accurate thyroid blood testing. The thyroid tests are abnormal way before [patients] have 'thyroid related symptoms'. *Other similar symptoms, such as fatigue, and weight gain are not thyroid related if the testing is stable and normal.*"<sup>[49]</sup> (Italics mine, and incorrect punctuation is Guttler's.)

Similarly, consider a comment of influential endocrinologist M.I. Surks in a chapter on treating hypothyroidism in the widely used thyroidology textbook, *Werner's The Thyroid*: "Notwithstanding the physician's assurance that the T<sub>4</sub> dose is optimal, and the demonstration that serum TSH has decreased into the normal range, these patients may ask for a larger dose or take a larger dose on their own initiative. In this setting, *the patient should be reassured that the T<sub>4</sub> dose prescribed is appropriate, and other causes of the patient's complaints must be investigated.*"<sup>[43]</sup> (Italics mine.)

Surks' advice to reassure the patient that his or her dosage "is appropriate" *presumes* that the patient's T<sub>4</sub> dose is adequate for his or her individual needs. His advice that "other causes of the patient's complaints" be investigated suggests a preconceived notion that replacement dosages of T<sub>4</sub> are infallibly effective. In ad-

dition, his advice, like that of Guttler, implies that if a patient has hypothyroid-like symptoms despite using T<sub>4</sub>-replacement, the symptoms are probably caused by some other disorder.

Endocrinologists can maintain this belief only by ignoring published evidence showing it to be false.<sup>[8][68]</sup> Consider, for example, a finding of Fraser et al.<sup>[68]</sup> The study result reveals the harm many hypothyroid patients suffer when their physicians make dose decisions based on TSH levels.

**The Fraser Study.** Three physicians experienced in diagnosing and treating hypothyroidism assessed 148 hypothyroid patients on T<sub>4</sub>-replacement. The physicians used the Wayne clinical diagnostic index,<sup>[69]</sup> an objective tool for deciding whether a patient's thyroid hormone therapy is adequate, excessive, or insufficient. Statistical tests showed that the three physicians' judgment didn't differ in classifying patients.

Among the 148 patients, 108 were clinically normal. This means they were taking enough T<sub>4</sub> to be free from symptoms of hypothyroidism. Despite this, 53 of them (49%) had TSH levels below the lower limit of the reference range. Conventional physicians, of course, would interpret their TSH test levels as evidence that the patients were "hyperthyroid" or "thyrotoxic." This mistake is understandable when prominent endocrinologists—Dr. Anthony Toft, for example—have incorrectly termed a low TSH as a "thyrotoxic" level.<sup>[70,p.91]</sup> And probably most physicians would have required these patients to lower their dosages of T<sub>4</sub> to raise their TSH levels—even though the patients were clinically normal. As a result of lowering their dosages, however, some of them, and perhaps all, would have begun suffering from hypothyroid symptoms and risked developing diseases from too little thyroid hormone regulation.<sup>[37]</sup>

Among the 148 patients, 18 were clinically hypothyroid. This means they were taking too little T<sub>4</sub> to keep them from suffering from symptoms and signs of thyroid hormone deficiency. Despite being clinically hypothyroid, 3 of the 18 patients (17%) had TSH levels below the lower limit of the reference range. Most physicians would have required these patients to lower their T<sub>4</sub> doses to raise their TSH levels. Doing so would surely worsen their symptoms and signs of hypothyroidism,<sup>[68,p.809]</sup> and would make them more susceptible to potentially fatal diseases associated with hypothyroidism.<sup>[37]</sup>

The suffering of these patients and their potential for pathology would result from the obstinate demand by the endocrinology specialty that physicians titrate hypothyroid patients' T<sub>4</sub> doses by their TSH levels—

and *only* by those levels. Of course, some endocrinologists also advise other physicians to use the free  $T_4$  in making dosage decisions. The Fraser study showed that among the 18 clinically hypothyroid patients, the free  $T_4$ , like the TSH, led to a false interpretation of the patients' status. In 4 of the 18 patients (22%), the free  $T_4$  was above the upper limit of the reference range. This gave a false signal that the patients were over-treated, when in fact they were undertreated.

Results of the Fraser study should alert all physicians to the potential for harming their patients through following the practice guidelines of the endocrinology specialty. Basing their dosage decisions on TSH and free  $T_4$  levels instead of clinical assessment will leave many patients undertreated—a condition that is hazardous to the patients' health (see following section).

### CONSEQUENCES OF THE PRESUMPTION THAT $T_4$ -REPLACEMENT IS INVARIABLY SAFE AND EFFECTIVE

As I wrote above, the endocrinology specialty maintains that if patients with hypothyroid-like symptoms have “normal” TSH levels, their symptoms must be caused by something other than a thyroid hormone deficiency. It is precisely this false belief that has led to the “new diseases” of the past 30 years. Prominent among these are so-called “fibromyalgia” and “chronic fatigue syndrome.” Considerable evidence indicates that inadequate thyroid hormone regulation is the major underlying causative factor in these supposed new disorders. For example, the only studies in which patients with these diagnoses have fully and lastingly recovered are those in which they underwent thyroid hormone therapy.<sup>[10][11][12][13][14][45][71][72][73]</sup>

As I have argued with substantial documentary evidence,<sup>[44][50][51]</sup> the disorder underlying most patients' fibromyalgia is inadequate thyroid hormone tissue regulation. Our data indicate that the fibromyalgia symptoms and signs of approximately 90% of patients are features of hypothyroidism and/or thyroid hormone resistance. In most cases, patients' thyroid disease is complicated by low physical fitness levels, nutritional deficiencies, the dysglycemic and proinflammatory effects of poor diet, and the adverse metabolic effects of various medications other than thyroid hormone prescribed to control symptoms of hypothyroidism and/or thyroid hormone resistance. The number of patients with chronic, widespread pain (a classic symptom of hypothyroidism) increased in the mid-1970s to a point that rheumatologists began to take notice. This occurred shortly after endo-

crinologists, in 1973 and 1974, recommended cutting hypothyroid patients' thyroid hormone dosages in half. This reduced patients' dosages from the equivalent of 200-to-400 mcg of  $T_4$  to 100-to-200 mcg.<sup>[74][75]</sup> The purpose was to raise the patients' TSH levels. (The new TSH test had recently come into widespread use.) The rheumatologists unquestioningly accepted the endocrinologists' pronouncement that the patients' reference range TSH levels ruled out thyroid hormone deficiency as the cause of their chronic, widespread pain. Eventually, the rheumatologists gave this classic hypothyroid symptom the name “fibromyalgia.”<sup>[76]</sup>

The numbers of patients with overwhelming chronic fatigue steeply increased in the late 1970s. Eventually, researchers named this classic hypothyroid symptom “chronic fatigue syndrome.” As standard practice at this time, physicians had come to adjust patients' thyroid hormone dosages to keep their TSH levels within the reference range.<sup>[77]</sup> As Dr. David Derry wrote in the *British Medical Journal*, “In 1973 thyroidologists officially endorsed the newly designed TSH test for thyroid function . . . The TSH test caused the appearance six years later of chronic fatigue and fibromyalgia.”<sup>[78]</sup>

The endocrinology specialty has been completely deaf to our reports that inadequate thyroid hormone regulation is the major cause of symptoms diagnosed as fibromyalgia and chronic fatigue syndrome.<sup>[44]</sup> The reason for the deafness is the belief expressed in the quotes above by Guttler and Surks—that symptoms of patients who have “normal” TSH levels can't possibly be due to too little thyroid hormone regulation. Our reports that this is false, and that the symptoms of fibromyalgia and chronic fatigue syndrome are those of inadequate thyroid hormone regulation, are supported by a growing body of evidence.

**Continued Suffering of Many Patients on  $T_4$ -replacement.** Three survey studies have shown that many patients on “adequate  $T_4$ -replacement” continue to suffer from symptoms and signs of hypothyroidism. As one would expect, these patients were dissatisfied with their thyroid hormone therapy.<sup>[52][53,p.153][54]</sup>

In a study of 37 patients with subclinical hypothyroidism,  $T_4$ -replacement improved patients' memories. But the patients had no measurable improvement in other symptoms or their health-related quality of life.<sup>[38]</sup>

Results of the survey studies and the study of subclinical hypothyroid patients are backed up by three of the four studies at issue.<sup>[1][2][3]</sup> Patients who still had hypothyroid symptoms despite being treated with  $T_4$ -replacement were included in the studies. Neither  $T_4$ - nor  $T_4/T_3$ -replacement relieved their symptoms. In another

of the studies, researchers compared the psychomotor development of infants who had congenital hypothyroidism to that of infants who had normal thyroid function. The hypothyroid infants had impaired psychomotor development. Neither  $T_4$ - nor  $T_4/T_3$ -replacement relieved the infants' impairment.<sup>[4]</sup>

Psychiatric researchers reported that patients taking antidepressants often remain depressed when they are on  $T_4$ -replacement—even TSH-suppressive dosages. Adding  $T_3$ , further depressing the TSH level, then relieves the patients' depression.<sup>[30]</sup>

Researchers recently reported measuring changes in weight of two groups of patients after they had therapeutic destruction of their thyroid glands. The first group, thyroid cancer patients, used TSH-suppressive dosages of thyroid hormone after the destructive therapy. They didn't gain weight. The second group, Graves' disease patients, used  $T_4$ -replacement after destructive therapy. They did gain excessive weight. The researchers concluded, "The excessive weight gain in patients becoming hypothyroid after destructive therapy for Graves' disease suggests that restoration of serum TSH to the reference range by  $T_4$  alone may constitute inadequate hormone replacement."<sup>[55]</sup>

**Increased Incidence of Disease and Medication Use Among Patients on  $T_4$ -replacement.** Researchers recently conducted the first large, community-based study in the U.K. of the health status of hypothyroid patients using  $T_4$ -replacement therapy.<sup>[37]</sup> Compared to matched control patients, hypothyroid patients on "adequate" dosages of  $T_4$  had a higher reported incidence of four diseases: depression, hypertension, diabetes, and heart disease. Hypothyroid patients on inadequate  $T_4$ -replacement (their TSH levels were elevated) also had a higher incidence of strokes. In addition, hypothyroid patients chronically used more prescription drugs, especially for diabetes, cardiovascular disease, and gastrointestinal conditions.

We've recently been consulted by many hypothyroid patients whose physicians have reduced their  $T_4$  dosages to extremely low amounts, in some cases as low as 25 mcg. The patients report to us that their physicians refer to reports by endocrinologists that TSH suppression increases the risk of atrial fibrillation three-fold. As I explain in Addendum 4, this is an unjustified generalization from a study of elderly (60 years of age and older) sedentary people. This misguided practice by physicians is likely to increase the patients' incidence of coronary artery disease and cardiac fatalities.

The dosage of  $T_4$  that suppresses the TSH level varies considerably, but may be as much as 171 mcg or as

little as 50 mcg.<sup>[56][57][58][59][60][61][62]</sup> Hypothyroid patients should be concerned when their physicians restrict them to lower-end dosages of  $T_4$ . In one study, researchers used coronary angiography to assess the progression of coronary atherosclerosis in elderly hypothyroid patients. In 5 of 6 patients who kept their  $T_4$  dosages at 150 mcg or more, the disease didn't progress. But in all 6 patients whose dosages were 100 mcg or less, the disease had progressed.<sup>[63]</sup> This study suggests that elderly patients whose TSH levels are suppressed by fairly low dosages of  $T_4$ , and whose physicians insist on keeping their TSH levels within the reference range, may, as a result, have increased progression of coronary artery disease, leading to strokes and/or heart attacks. In that the incidence of atherosclerosis is high even among young individuals in modern societies, younger hypothyroid patients should be concerned over the possibility of lower dosages of thyroid hormone inducing or exacerbating atherosclerosis.

#### **DILEMMA FOR THE ENDOCRINOLOGY SPECIALTY**

The four studies that are the subject of this document clearly show that neither  $T_4$ - nor  $T_4/T_3$ -replacement is effective for many hypothyroid patients. The ineffectiveness of the two replacement therapies translates into three likely adverse consequences for these patients with inadequate thyroid hormone regulation: continued suffering from symptoms, susceptibility to potentially disabling or lethal diseases, and increased use of drugs to control the symptoms and diseases. The endocrinology specialty sets and maintains practice guidelines for the diagnosis and treatment of hypothyroidism; that it does so imposes upon it an ethical and humanitarian responsibility to expediently act to protect hypothyroid patients from the three adverse consequences. That responsibility is the compelling reason for the endocrinology specialty to promptly reform its incorrect official position that  $T_4$ -replacement is safe and effective for all hypothyroid patients.

Many researchers, physicians, and patient advocates believe that the endocrinology specialty has been curiously obstinate in its advocacy of  $T_4$ -replacement. Its obstinacy is evident in its disregard for the protests of thousands of patients and a growing number of doctors that  $T_4$ -replacement is ineffective and harmful for many patients.

The specialty's obstinacy may be sustained by financial incentives from corporations that profit from the practice of  $T_4$ -replacement therapy. This suspicion of fi-

nancial motivation is reinforced by the specialty's standard method of enforcing the practice of T<sub>4</sub>-replacement among doctors: political tyranny rather than scientific argument and debate. The suspicion will only mount if the specialty—despite the recent studies showing replacement therapies to be ineffective<sup>[1][2][3][4]</sup> and harmful<sup>[3][7][63]</sup> for many hypothyroid patients—sidesteps the issue now at hand. How safe and effective is T<sub>4</sub>-replacement compared to alternate approaches to thyroid hormone therapy now in widespread use? For its own credibility, it is imperative that the specialty immediately address this issue free from prejudicial preconceptions.

## ADDENDA

**Addendum 1: Inaccurate Statements of the Endocrinology Researchers.** In some statements, the researchers accurately reported what they found in their studies. In other statements, however, they quite inaccurately reported what they found. I've illustrated this below with specific excerpts.

In their abstract, Walsh et al. accurately wrote: "We conclude that *in the doses used in this study*, combined T<sub>4</sub>/T<sub>3</sub> treatment does not improve well-being, cognitive function, or quality of life compared to T<sub>4</sub> alone."<sup>[1,p.4543]</sup> (Italics mine, showing proper qualification.) At the end of their published paper, they accurately wrote, "In conclusion, we found no evidence that combined T<sub>4</sub>/T<sub>3</sub>-replacement (*in the dosage regimen used in this study*) resulted in improved well-being, cognitive function, quality of life, or increased thyroid hormone action on peripheral tissues compared with T<sub>4</sub> alone."<sup>[1,p.4549]</sup> (Italics mine, showing proper qualification.)

However, they titled their published report with an invalid conclusion: "*Combined thyroxine/liothyronine [T<sub>4</sub>/T<sub>3</sub>] treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone . . .*"<sup>[1,p.4543]</sup> (Italics mine, showing lack of proper qualification.) The title of their article will function as an advertising banner providing a memorable and quotable sound bite implying that no approach to T<sub>4</sub>/T<sub>3</sub> therapy works better than T<sub>4</sub> alone.

Sawka et al. accurately wrote at the end of their published paper: "In conclusion, our data do not support the routine use of T<sub>3</sub> in addition to T<sub>4</sub> *to maintain euthyroidism* in hypothyroid patients who are receiving stable doses of levothyroxine hormone [T<sub>4</sub>], but who complain of depressive symptoms." (Of course, "to maintain euthyroidism" means to keep the TSH, free T<sub>4</sub>, and free T<sub>3</sub> levels within their reference ranges, the very definition

of "replacement" therapies.) And they accurately wrote, ". . . there is insufficient evidence to support changing the current approach of routinely using T<sub>4</sub> alone *to maintain euthyroidism* in hypothyroid individuals."<sup>[2,p.4555]</sup> (Italics mine, showing proper qualification.)

These accurate statements of Sawka et al., however, are buried within the text of their published paper. Precious few doctors, patients, or science reporters will ever read them. At the end of their abstract, however—which many doctors, patients, and reporters will read—Sawka et al. quite inaccurately wrote: "In conclusion, the current data do not support the routine use of combined T<sub>4</sub> and T<sub>3</sub> therapy in hypothyroid patients with depressive symptoms."<sup>[2,p.4551]</sup>

Cassio et al. gave their readers a better chance—albeit little better—for an accurate understanding of their study finding. In their abstract, they wrote, "The combined treatment with T<sub>4</sub> plus T<sub>3</sub> seems not to show significant advantages, *at least in our experimental conditions*, compared with the traditional treatment with T<sub>4</sub> alone in early treated [congenitally hypothyroid] infants."<sup>[4,p.1055]</sup> (Italics mine, to show their vague qualification. One would have to carefully read the rest of the authors' abstract or parts of their full report to understand that "*in our experimental conditions*" refers to their testing of only replacement therapies.) In the conclusion section of their full report, the authors make the same error as all the other researchers: "These preliminary data," they wrote, "seem to indicate that the combined treatment with T<sub>4</sub> plus T<sub>3</sub> does not show any significant advantage, at least in the short-term, compared with traditional treatment with T<sub>4</sub> alone in early treated [congenitally hypothyroid] infants."<sup>[4,p.1059]</sup>

Clyde et al. failed to accurately state anywhere in their abstract the result of their study. They worded their conclusion so that readers are almost guaranteed to mistake their study of replacement therapies as an all-inclusive study of T<sub>4</sub>/T<sub>3</sub> therapies compared to T<sub>4</sub> alone. To wit, "Compared with levothyroxine [T<sub>4</sub>] alone, treatment of primary hypothyroidism with combination levothyroxine [T<sub>4</sub>] plus liothyronine [T<sub>3</sub>] demonstrated no beneficial changes in body weight, serum lipid levels, hypothyroid symptoms as measured by a [sic] HRQL questionnaire, and [sic] standard measures of cognitive performance."<sup>[3]</sup>

**Addendum 2: Endocrinologists' Advice to Continue T<sub>4</sub>-replacement.** Based on the studies showing that replacement therapies—including T<sub>4</sub>-replacement—are ineffective for many patients, the endocrinology researchers and other endocrinologists have recommended that T<sub>4</sub>-replacement remain the treatment

of choice for most (Kaplan et al.<sup>[19,p.4541]</sup>) or all (Walsh et al.,<sup>[1,p.4549]</sup> Sawka et al.,<sup>[2,p.4555]</sup> and Clyde et al.<sup>[3]</sup>) hypothyroid patients. Below are the specific quotes.

Walsh et al. wrote, “Unless beneficial effects of combined T<sub>4</sub>/T<sub>3</sub> treatment over T<sub>4</sub> alone can be convincingly demonstrated by others, T<sub>4</sub> should remain the standard treatment for hypothyroidism.”<sup>[1,p.4549]</sup>

Sawka et al. wrote, “. . . there is insufficient evidence to support changing the current approach of routinely using T<sub>4</sub> alone to maintain euthyroidism in hypothyroid individuals.”<sup>[2,p.4555]</sup>

Kaplan et al. wrote in their editorial concerning the Walsh and Sawka studies, “. . . evidence is fading that adding T<sub>3</sub> to T<sub>4</sub> is beneficial in the long-term treatment of hypothyroid patients with autoimmune thyroiditis . . . We do not believe that the current evidence supports the use of T<sub>3</sub> for these patients, who are probably the largest group of hypothyroid patients.”<sup>[19,p.4541]</sup>

Clyde et al. wrote, “This study supports these guidelines [of the American Association of Clinical Endocrinologists and the National Academy of Clinical Biochemists] by providing sound evidence that levothyroxine [T<sub>4</sub>] alone continues to be the most appropriate therapy for patients with primary hypothyroidism.”<sup>[3]</sup>

These endocrinologists, then, recommend that T<sub>4</sub>-replacement should remain the treatment of choice for hypothyroid patients. The four studies at issue, however, are an admission that T<sub>4</sub>-replacement is ineffective for many hypothyroid patients. None of the endocrinologists’ recommendations based on the studies, however, contain any allowance for the needs of these patients for symptom relief and preemption of potentially lethal pathology. This obvious disregard for these patients’ needs raises serious ethical and humanitarian concerns.

**Addendum 3: Persistent Symptoms Among Patients Using Replacement Therapies.** In the Clyde study, hypothyroid symptoms and/or their severity decreased about equally in patients treated with T<sub>4</sub>-replacement and those treated with T<sub>4</sub>/T<sub>3</sub>-replacement.<sup>[3]</sup> The improvement is inexplicable. It’s *highly* unlikely that the improvement was caused by T<sub>4</sub>-replacement. This is indicated by the fact that the patients, throughout the study, simply continued taking the dosage they’d been taking for at least six months before the study began. Cooper attributes the improvement to a placebo effect.<sup>[20]</sup> The replacement therapies, then, weren’t effective for the patients. Were it not for a placebo effect, natural variations in symptom intensity, or some unknown factor, the patients’ symptoms wouldn’t have improved at all.

The outcome of the other three studies shows that

replacement therapies weren’t effective for most or all patients studied. In the Cassio study, for example, the researchers treated infants who had congenital hypothyroidism with either T<sub>4</sub>- or T<sub>4</sub>/T<sub>3</sub>-replacement. Testing showed that regardless of the type of replacement used, hypothyroid infants had lower neuropsychological scores than did control infants who weren’t hypothyroid.<sup>[4]</sup> Replacement therapies, then, through their ineffectiveness, retarded the neuropsychological development in these infants.

To take part in the Sawka study, patients had to have test evidence of depression. The researchers showed through their study that replacement therapies weren’t effective for these patients and left them depressed.<sup>[2]</sup>

In the Walsh study, typical symptoms suffered by patients—despite their use of T<sub>4</sub>-replacement for at least six months—were “tiredness, impaired well-being, or weight gain.” Patients’ test scores were “worse” for somatic symptoms, anxiety, and insomnia.<sup>[1]</sup> The study showed that replacement therapies were ineffective for these patients and left them suffering from their symptoms.

**Addendum 4: Endocrinologists’ Warnings of Harm From TSH-Suppressive Dosages of Thyroid Hormone.** Endocrinologists warn of three potential adverse effects from dosages of thyroid hormone greater than replacement dosages: decreased bone density, acute adrenal crisis, and atrial fibrillation.

**DECREASED BONE DENSITY.** Some eight years ago, I was surprised when bone density radiologists told me that a prevailing belief of endocrinologists was wrong: that TSH-suppressive dosages of thyroid hormone significantly reduce bone density. The available research literature confirmed that the radiologists were right. As they said, the evidence is that for most people, TSH-suppressive dosages of thyroid hormone *don’t* significantly reduce bone density or increase the risk for fractures. They were emphatic that there was *no evidence* that such dosages cause osteoporosis.

Considerable evidence, however, shows that decreased bone density is not a likely adverse effect from TSH-suppressive dosages of thyroid hormone. Psychiatric researchers reported that “supraphysiologic” (TSH-suppressive) dosages of T<sub>4</sub> for one year and longer didn’t significantly reduce bone mineral density in pre- or post-menopausal women with mood disorders.<sup>[32][33]</sup> Similarly, reviews of studies of thyroid cancer patients taking TSH-suppressive dosages of thyroid hormone show that the patients don’t have reduced bone mineral density; the studies included men and pre- and post-

menopausal women.<sup>[17]</sup> But still, despite overwhelming evidence to the contrary, some endocrinologists today continue to issue their warning.<sup>[27][36]</sup>

**ACUTE ADRENAL CRISIS.** Some endocrinologists also still warn that TSH-suppressive dosages of thyroid hormone may cause acute adrenal or Addisonian crisis, leaving a patient in shock and possibly dead. These warnings are based on a few published case reports.<sup>[80][81][82,p.872][83,p.813][85][86][87][88][89][90]</sup> For the most part, the cases involved patients in extraordinary circumstances. To extrapolate from these few reported cases to hypothyroid patients in general cannot be justified logically or scientifically.

My colleagues and I have observed hundreds of hypothyroid patients whose impaired adrenocortical function was unveiled by thyroid hormone therapy, resulting in acute cortisol deficiencies. The worst symptoms most patients experienced were weakness and fatigue. *We've not seen a single case of acute adrenal crisis.* To protect patients from potential harm, of course, we should always err on the side of safety, especially with patients who have Graves' disease.<sup>[82,p.872][83,p.813]</sup> But we err on the side of potential harm by keeping a patient's dosage of thyroid hormone too low from fear of this extremely rare adverse effect. (See section above titled "Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T<sub>3</sub>, and the Safety and Effectiveness of T<sub>4</sub>-replacement.")

**ATRIAL FIBRILLATION.** Today, the most often repeated warning against TSH-suppressive dosages of thyroid hormone involves the cardiac rhythmic disorder called atrial fibrillation. Researchers have conducted several studies and found that patients with the lowest TSH levels had an increased incidence of atrial fibrillation. The warning from the endocrinology specialty that has followed reports of this finding is that no patient taking thyroid hormone should have a suppressed TSH level. This warning, however, is based on an unjustified extrapolation from several studies. As I wrote in 2003:

Recently, endocrinologists have warned that TSH-suppressive doses of thyroid hormone increase the risk of atrial fibrillation three-fold. A number of studies showed that a certain set of people who had low TSH levels had a higher incidence of atrial fibrillation.

But don't conclude from this finding that if you take a dose of thyroid hormone that suppresses your TSH level, you'll have atrial fibrillation. What endocrinologists—the main doctors who warn of this risk—don't bother to

tell you is that these studies were done on elderly, sedentary individuals. In fact, in some of the studies, the patients were bedridden in nursing homes. In none of the studies did the researchers control for a heart-protective diet, nutritional supplements, or cardiovascular exercise to tolerance. The patients appear to have been in such poor health that they may have developed atrial fibrillation if they drank too much coffee each day. It's ludicrous and outrageously wrong to conclude that the results of these studies apply to healthier people using TSH-suppressive doses of thyroid hormone.<sup>[48,p.164]</sup>

Other endocrinologists and medical writers have reported less than a three-fold increased risk of atrial fibrillation, but they also violate the rule of accurate scientific reporting by extrapolating from the specific study population to a population with distinct relevant differences. In a 2004 issue of the *Annals of Internal Medicine*, for example, Helfand wrote: "About one fourth of patients receiving L-thyroxine for primary hypothyroidism are maintained unintentionally on doses sufficient to cause an undetectable TSH level."<sup>[22][64]</sup> Data from the Framingham cohort suggest that 1 excess case of atrial fibrillation might occur for every 114 patients treated with doses of L-thyroxine sufficient to suppress TSH.<sup>[64][65]</sup>

The implication of Helfand's two sentences is that a suppressed TSH level from excess thyroid hormone predisposes patients to atrial fibrillation. However, some of the patients in the Framingham study may have had low TSH levels because of pituitary hypothyroidism. Among those patients, atrial fibrillation may have resulted from too little thyroid hormone rather than too much. Because of this, we can consider his calculation an unjustifiable inference from the Framingham study. In addition, Helfand failed to note that the people in the Framingham study were, as the authors of the study specified, "elderly," and they weren't classified according to cardioprotective practices. His calculation, then, is illogical in that, as it's written, it extrapolates from one class of people prone to cardiovascular disorders to all patients who have low TSH levels. Helfand's statement constitutes inaccurate science reporting, and it is a disservice to the cause of scientific truth and quality patient care. (See section below titled, "Previous Atrial Fibrillation Studies: Possible Irrelevance to Hypothyroid Patients Taking TSH-Suppressive Dosages of Thyroid Hormone.")

**Patients with heart-protective factors not studied.** The endocrinologists' warning of atrial fibrillation is unbalanced in terms of scientific evidence. In warning of atrial fibrillation, the specialists refer to no studies in which researchers controlled for factors known to increase resistance to atrial fibrillation. For example, in no studies have researchers controlled for heart-protective factors such as a non-atherogenic diet, cardiovascular exercise, or cardioprotective nutritional supplements.

Studies must be conducted to assess any adverse cardiac effects of TSH-suppressive dosages of thyroid hormone in patients whose hearts are protected by these factors. On principle, whether individuals do or don't avail themselves of these factors determines to a great degree their susceptibility to cardiac abnormalities such as atrial fibrillation. With a high degree of probability, the outcome of such studies will provide a more balanced view. Some hypothyroid patients with suppressed TSH levels are, of course, susceptible to atrial fibrillation. But cardioprotective factors render most patients more resistant to cardiac abnormalities. The incidence of atrial fibrillation with TSH-suppressive dosages of thyroid hormone will be strikingly lower than in people in general, and especially lower than in the sedentary elderly patients included in the previous studies.

What's needed is a study of a large population of people—both those protected by these factors and those not protected by them. If we include enough individuals, we're likely to find a bell curve distribution of cardiac responsiveness to TSH-suppressive thyroid hormone dosages.

On the right flange of the bell will be a diminishing percentage of people whose hearts are progressively more responsive to a particular TSH-suppressive dosage of thyroid hormone. Correspondingly, that diminishing percentage of people in the right flange will have a progressively higher susceptibility to cardiac abnormalities in response to that dosage.

On the left flange of the bell would be a diminishing percentage of people whose hearts are progressively less responsive to the particular TSH-suppressive dosage. Correspondingly, that diminishing percentage of people in the left flange would exhibit a progressively lower incidence of cardiac abnormalities in response to the dosage.

In other words, people on the right side of the curve would be progressively more susceptible to cardiac abnormalities, and those on the left would be progressively more resistant to abnormalities. The current method for establishing the reference range for the TSH and

thyroid hormone levels ignores this mathematical and practical phenomenon dictated by the central limit theorem, which has accurately predicted anything and everything human beings have measured enough times in the past 270 years. To continue to ignore it—as do those who establish the reference ranges—is to doom practicing physicians to an unnecessarily high failure rate in the diagnosis and treatment of hypothyroid patients.

From consideration of the central limit theorem, some diminishing percentage of hypothyroid patients clearly have some relative degree of tissue resistance to a particular dosage of thyroid hormone that most other patients are more responsive to. Normal metabolism in these patients is possible *only* with dosages of thyroid hormone that are overstimulating to most other patients. To deny them those dosages is to consign them to lifelong hypometabolism with all its attendant adverse health effects. This is truly inhumane. They are thusly consigned, however, when restricted to replacement dosages (which for them are clearly inadequate) to protect them from the atrial fibrillation that only patients on the right flange of the bell curve would experience.

**Previous atrial fibrillation studies: possible irrelevance to hypothyroid patients taking TSH-suppressive dosages of thyroid hormone.** Aside from the bell curve phenomenon, a methodological issue may render the studies of atrial fibrillation irrelevant to patients taking TSH-suppressive dosages of thyroid hormone as a medication. The studies involved patients whose TSH levels were suppressed without the use of thyroid hormone. These patients, as a group, may differ in some relevant way from patients taking thyroid hormone from an external (exogenous) source. If they do differ in a relevant way, they may *not* share an increased risk of atrial fibrillation with patients who have endogenously suppressed TSH levels.

I anticipate the criticism that this distinction isn't important. My retort is that such distinctions are often made in defense of T<sub>4</sub>-replacement therapy. Recently, for example, Kaplan et al. noted that from using higher-end thyroid hormone dosages, thyroid cancer patients' mood and cognitive dysfunction improved more than that of autoimmune thyroiditis patients.<sup>[19,p.4540]</sup> The cancer patients were taking higher dosages of thyroid hormone than the thyroiditis patients; in fact, about half of the cancer patients were using dosages that suppressed their TSH levels. As in other studies,<sup>[23][24][25][28][29][30][31][34]</sup> the thyroid cancer patients undoubtedly improved more because of their higher thyroid hormone dosages. Kaplan et al. conjectured, how-

ever, that thyroid cancer patients improved more—not because of their higher dosages of thyroid hormone—but because they differed in some relevant but undetermined way from autoimmune thyroiditis patients.<sup>[19,p.4540]</sup> Methodological issues remain relevant no matter who draws attention to them.

**CONCLUSION REGARDING WARNINGS.** Available scientific evidence shows that the endocrinology specialty's sweeping warnings against TSH-suppressive dosages are unwarranted. Scrutiny of the evidence shows that the specialty has exaggerated the warnings in the extreme, and it has generalized them into invalid universal propositions. The specialty's failure to show equal concern about the adverse effects of patients taking too little thyroid hormone suggests that its major concern is not protection of patients, but instead, perpetuation of the widespread practice of T<sub>4</sub>-replacement.

**PATIENT SAFETY MUST BE BASED ON EVALUATION OF THE INDIVIDUAL'S TISSUE RESPONSES TO THYROID HORMONE.** I want to emphasize that *the responsiveness of different patients' tissues to a particular dosage of thyroid hormone varies widely*.<sup>[18,p.16]</sup> A particular dosage for some patients is overstimulating, while for others, it regulates metabolism perfectly—yet for still others, it is understimulating. In short, for any particular dosage of thyroid hormone, we'll find a predictable bell curve of tissue responsiveness in the population, if we test enough subjects.

In view of this, the only rational approach to safe and effective thyroid hormone therapy is a highly individualized one, based on how each patient's tissues respond to a particular dosage. This cannot be accomplished by deductions based on levels of TSH or thyroid hormone, as the endocrinology specialty implies. The TSH level does change in response to changes in thyroid hormone dosage, but not within a range considered clinically relevant. In contrast, the resting metabolic rate, calculated from patients' resting VO<sub>2</sub> consumption, is a measure of tissue responsiveness that is *highly* sensitive to slight changes in thyroid hormone dosage.<sup>[79]</sup> Therefore, compared to the resting metabolic rate and other measures of tissue response, TSH levels are inferior as a method of fine-tuning thyroid hormone dosages.

**Addendum 5: About Dr. Hutton.** Dr. James H. Hutton was the author of the 1966 book titled *Practical Endocrinology*. At that time, he was consulting endocrinologist at the Illinois Central Hospital. He had been professor of endocrinology at the Chicago Medical School, and past president of the Chicago Medical Society.

Two physicians wrote introductory comments about

Dr. Hutton in *Practical Endocrinology*. Dr. Ernest Olson wrote, "The author has been a consultant in endocrinology to the Illinois Central Hospital since 1920. It has been my privilege to observe the development of this specialty in our hospital since 1923 under his direction."<sup>[18,p.v]</sup>

Dr. Chester Guy wrote, "The author's long and rich experience in this field [endocrinology], together with his ability as a teacher, prompted the request that he prepare a series of lectures for the house staff of the hospital. These proved so interesting and practical that he was urged to incorporate them in book form under this appropriate title. It is believed that this volume, with its historical and humorous observations, and *its directions for proven therapies*, will merit a place in the libraries of those whose practices involve problems of the endocrine glands."<sup>[18,p.v]</sup> (Italics mine.)

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