Management of Patients with Pseudo-Endocrine Disorders

A Case-Based Pocket Guide

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Editor

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This book is dedicated to Libby, whose strength, courage, and love of life are a daily inspiration, and to Katie Cohen, Emily Cohen, Hayley McDermott, and Henry McDermott, for making life fun.

Preface

"Pseudo-endocrine patient" is a term that can be applied to many different types of patients that we see in our practices every day. They are those who believe they have an endocrine or metabolic disorder, despite previous normal testing, because of the misleading information they have gotten from a health-care provider, a personal trainer, a friend, a book, or the Internet. They may even have been given a diagnosis of a disorder that has not been scientifically proven to exist. They are those who may have true endocrine disorders but continue to have symptoms despite adequate treatment and normal on-treatment tests. They are patients who have been treated with excessive hormone doses or unproven and even dangerous treatments. They also include those whose conditions have been incorrectly diagnosed by lab testing interference or other assay issues.

We have all seen these types of patients. Many of us are trained in traditional medicine and practice evidence-based medicine, whenever there is evidence available. And we have very good tests and treatments for many of the maladies our patients suffer from. Yet we all see patients that have conditions or complaints, as described above, that challenge our ability to find evidence-based diagnostic tools and/or evidence-based treatments. We all deal with these patients and these situations in our own self-taught ways because there has been little or no organized effort to provide education during fellowship or thereafter regarding the best ways to evaluate and deliver good care to these patients. We would all like to do better.

The purpose of this book is to initiate an ongoing dialog about these issues and to begin to develop a framework for

training, research, expert opinion, and eventually evidence-based guidelines to assist providers in dealing with this very important aspect of their practices. I have asked experienced colleagues from around the country, in academic institutions and in private practice, to contribute chapters describing, in case-based formats, their approaches and opinions regarding the optimal evaluation and management of patients with "pseudo-endocrine" disorders.

I did not attempt to suggest or encourage the authors to adopt any specific point of view. I asked them to write about the pseudo-endocrine disorders they most commonly see and that they think are the most important for us to recognize and discuss. Because some authors felt very strongly that they wanted to write about certain topics, you will see that there is some overlap among chapter titles and content. Rather than being repetitious, I found their various points of view on these topics to be interesting and enriching.

As you will see, these seasoned professionals vary significantly in their philosophies and opinions about the optimal evaluation and management strategies for these patients. Some believe in a straightforward scientific and evidence-based approach that emphasizes the robustness of our current testing paradigms and the safety and effectiveness of the currently available FDA-approved treatment modalities. Others prefer a modified approach that utilizes both evidence-based diagnostic and treatment recommendations and variable degrees of alternative medicine strategies in areas where no solid evidence base exists. All recommend honesty and compassion.

I greatly appreciate the time and effort these colleagues have devoted to their chapters and their dedication to forge ahead to develop guidance in this challenging area of endocrinology. I have learned a great deal by reading their chapters, and I hope that all our readers will similarly benefit.

Aurora, CO, USA Michael T. McDermott, MD

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Chapter 1
Pseudo-Endocrine Disorders: Definitions, Examples, and Considerations

Michael T. McDermott

What Is a Pseudo-Endocrine Disorder?

The term "pseudo-endocrine" disorder does not yet have a clear and distinct definition. The term could be used in reference to people who believe they have an endocrine or metabolic disorder because of information they received from another health care provider, a personal trainer, a family member or a friend and, despite previously appropriate normal testing, they request further unwarranted testing of their endocrine system or their hormones. It may apply to patients who have read about endocrine disorders (real and unproven) in books or on the Internet and may have even ordered hormone or metabolic testing online. It also refers to those who have been given "endocrine" diagnoses by providers based on symptoms alone without validated hormone testing. It can also be applied to patients who have true endocrine disorders for which they are being treated but continue to have

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symptoms despite appropriate therapy and normal on-treatment tests. And it also refers to patients with endocrine or metabolic conditions that were diagnosed correctly (or not) by other providers and who are treated for these conditions with excessive hormone doses or with unproven, inappropriate, and even dangerous medications. Alternatively, an endocrine diagnosis may have erroneously been made as a result of lab assay error due to supplements and other conditions that adversely affect the accuracy of various tests.

In this introductory chapter, I will show multiple case examples and patient emails that illustrate many of the issues regarding pseudo-endocrine disorders that I have regularly encountered throughout my many years in practice. Following these, I offer some thoughts about the complexity of the endocrine system and further considerations for the evaluation and care of these patients. I do believe that our current diagnostic tests provide a very good evaluation of the endocrine and metabolic milieu. However, I pose some honest questions about whether our current diagnostic armamentarium is sufficient to evaluate all aspects of our various multi-layered systems of hormone synthesis, secretion, transport, action, and feedback homeostasis.

My personal approach to the management of these issues in individual patients will be the subject of the next chapter. In the following chapter, I will address the more general issue of rogue practitioners and practices, reproduce two letters I have received from colleagues, and offer suggestions about what we might do as a community of professionals to curb these unethical practices. The subsequent chapters by my esteemed colleagues will then describe and discuss multiple specific topics and the authors' individualized approaches to evaluation and management of patients with these conditions.

Case Examples

Case 1

A 32-year-old woman has been experiencing fatigue, depression, and difficulty losing weight for 2 years. Thyroid tests that

she ordered online have been normal except for a moderately low reverse T3.

PMH: Negative Meds: Multiple supplements

PE: BP 122/84 P 80 Ht 5′6″ Wt 172 lb.

Complete exam normal

Lab Report: TSH 1.2 mU/l (nl: 0.45–4.5)

Free T4 1.3 ng/dl (nl: 0.8–1.8)

Free T3 3.1 pg/ml (nl: 2.3–4.2)

Reverse T3 9 ng/dl (nl: 10–24)

She has read that thyroid tests don't accurately evaluate thyroid function. She requests more thorough thyroid testing and treatment to raise her reverse T3.

Case 2

A 47-year-old woman has been experiencing fatigue for about 15 years but complains of "total exhaustion" progressively over the past year. She does not sleep well but does not snore. Her appetite is poor. Mild weight gain (5 lb.) has occurred in the past year. She cannot exercise due to severe fatigue.

PMH: Mononucleosis at age 18 Meds: Occasional prescription pain medication

PE: BP 128/70 P 80 Ht 5′8″ Wt 157 lb. (Orthostatic vitals negative)

Complete exam normal

Lab: Full-day salivary cortisol profile – diagnostic of "Adrenal Fatigue"

She requests to be treated for Adrenal Fatigue for which she says she has tested positive.

Case 3

A 53-year-old man complains of muscle weakness, exercise intolerance, fatigue, lack of motivation, increased need for sleep, and difficulty concentrating for about 5 years, all following a motor vehicle accident with "whiplash injury." He read about post-traumatic hypopituitarism and has had online tests done. Thyroid and adrenal tests were normal but his growth hormone (GH) level was low and his Insulin-like Growth Factor 1 (IGF-1) level was low normal.

PMH: GERD, Colon Polyps	Meds: None
PE: BP 140/85	P 76 Ht 5′11″ Wt 208 lb.
	Complete exam normal
Lab:	Growth Hormone 0.05 ng/ml (nl: 0.05–3.0)
	IGF-1 82 ng/ml (nl: 60–220)

He requests treatment for Growth Hormone Deficiency.

Case 4

A 38-year-old woman is self-referred for hormone evaluation because of chronic progressive fatigue. She began feeling fatigued at age 28, about 1 year after the birth of her second child. She also endorses hair loss, inability to lose weight, and persistent "brain fog." She has read extensively on the Internet and is convinced that this is a hormone disorder and is adamant that this is not due to depression. She has ordered some tests online (cycle day 4) and several are abnormal.

PMH: Negative	Meds: Vitamins
PE:	BP 129/74 P 74 Ht 5′7″ Wt 158 lb. BMI 24.8 kg/m^2
	General: Normal Thyroid: Normal Skin: Normal

Tests from Online Orders (Cycle day 4; 10:00 AM):	
TSH 2.1 mU/l (nl: 0.45–4.5)	Free T4 1.0 ng/dl (nl: 0.78–1.81)
Free T3 2.4 pg/ml (nl: 2.3–4.2)	Reverse T3 23 ng/dl (nl: 10–24)
TPO Antibodies: Negative	Tg Antibodies: Negative
Cortisol 12 µg/dl (nl: 10–20)	ACTH 19 pg/ml (nl: 10–50)
Testosterone 27 ng/ml (nl: 30–95)	Estradiol 101 pg/ml (nl: 27–123)
Progesterone <1.5 ng/ml (nl < 1.5)	DHEA 188 µg/dl (nl: 145–395)
GH 0.04 ng/ml (nl: 0.05–3.0)	IGF-1 57 ng/ml (nl: 60–220)

She is concerned that she has Wilson's Low T3 syndrome, Reverse T3 syndrome, and Growth Hormone Deficiency and requests advice and treatment for all of these conditions.

Case 5

A 51-year-old man is referred by his PCP for exercise intolerance, muscle weakness, excess sweating, and difficulty concentrating for the past 4–5 years. He is a former college athlete. He eats a well-balanced diet, exercises regularly, and sleeps fairly well. Libido and sexual function are normal. He has five alcohol drinks/week and doesn't smoke. A general evaluation, including serum TSH and Testosterone, was normal. A naturopath advised thyroid support and adrenal support supplements, but he has not yet started these.

PMH: Colon polyps Meds: Vitamins, minerals

PE: BP 140/85 P 76 Ht 5′11″ Wt 208 lb. BMI 29 kg/m^2

General: Normal Thyroid: Normal Skin: Normal

Labs: TSH 2.3 mU/l, Free T4 1.4 ng/dl (nl: 0.8–1.8)

Testosterone 390 ng/dl (nl: 275–1075)

IGF-1 132 ng/ml (nl: 60–220)

He would like a more complete hormone evaluation and consideration for testosterone therapy because he is a former athlete and believes that this testosterone level, while in the normal range, is low for him.

Case 6

A 42-year-old man is referred for persistent hypothyroid symptoms despite LT4 therapy. Hypothyroidism was diagnosed 6 months ago. He still experiences fatigue, mild depression, and difficulty losing weight. He requests further thyroid testing and medication adjustment.

PMH: Hypothyroidism Meds: Levothyroxine 150 μg/day

PE: BP 122/84 P 76 Ht 6′1″ Wt 203 lb.

General Exam: Normal Thyroid: Enlarged, granular

Lab: TSH 1.6 mU/l (nl: 0.45–4.5)

Free T4 1.4 ng/dl (nl: 0.8–1.8)

You say: "It's not your thyroid."

He says: "I was told you'd say that. But I believe it is. What else could it be? My previous doctor said that my TSH does not reflect my actual thyroid status but that my symptoms do. I want to take a natural thyroid hormone."

Case 7

A 46-year-old woman is self-referred for hormone evaluation because of obesity and an inability to lose weight. She weighed 118 lb. at high school graduation. She gained 30 lb. with each of two pregnancies and retained ~15 lb. after each. She has gradually gained weight since then despite intermittent dieting and exercise programs. She also endorses fatigue, dry skin, and constipation.

PMH: Negative Meds: Vitamins, supplements

PE: BP 138/76 P 82 Ht 5′5″ Wt 194 lb.

General: Generalized obesity, mild buffalo hump, rosy cheeks

Thyroid: Normal size/consistency Skin: Non-violaceous abdomen striae

Lab: TSH 1.9 mU/l (nl: 0.45–4.5), Free T4 1.1 ng/dl (nl: 0.8–1.8)

24 h Urine cortisol 29 μg (nl < 55 μg/24 h)

Serum cortisol <1.8 μg/dl after 1 mg Dexamethasone at bedtime

She is convinced that her weight gain and inability to lose weight must be a hormone problem.

Case 8

A 33-year-old man complains of progressive fatigue and lack of motivation. His sleep habits are poor because he brings his work home with him and works until late at night. His interest in sex has waned but is still present. Erectile function is normal. His primary care provider evaluated him for these complaints but all lab tests, done in the afternoon on the day of his visit, were normal. However, because his testosterone level was in the lower one-third of the normal range, he visited a local "Low T" clinic. Additional testing was not done but he was given an injection of testosterone pellets. He noted some subjective improvement after this. The testosterone pellets were not covered by insurance. He presents to his local endocrinologist to verify that he has an ongoing need for these pellets so that insurance will cover them. He also asks if his low testosterone levels will cause him to be infertile. His serum testosterone level is 1173 ng/dl (nl: 300–1000).

Case 9

A 55-year-old woman complains of hot flashes, insomnia, fatigue, and depression. Her naturopath recently prescribed a compounded hormone replacement product containing estrogens, progesterone, and testosterone. She has recently noted dark hair growing on her chin, which has never happened before since she is red-haired and fair-skinned. Her serum testosterone is 2129 ng/dl (nl: 20–80).

Case 10

A 60-year-old woman was diagnosed with chronic fatigue syndrome 26 years ago. She was told that her thyroid and adrenal glands were underactive, but she is not sure exactly what tests were done. At that time, she was started on dexamethasone, levothyroxine, and liothyronine. Because of worsening symptoms, dextroamphetamine, modafinil, and midodrine were later sequentially added and various antidepressant medications were tried over the years. Despite these interventions, her symptoms worsened: she developed severe insomnia and she intermittently began considering suicide. She is referred to endocrinology for management of her hormone issues. Current medications: dexamethasone 0.5 mg every morning, levothyroxine 100 μg daily, liothyronine 15 μg in the morning and 10 μg in the afternoon, modafinil 200 mg BID, dextroamphetamine 5 mg BID, midodrine 5 mg TID, Zolpidem 10 mg HS, Bupropion XL 300 mg daily, cyclobenzaprine 10 mg TID, Lamotrigine 150 mg daily, linaclotide 145 mg daily, estradiol patch 0.1 mg/24 hours, and micronized progesterone cream 50 mg BID. Her fatigue continues to worsen, and her insomnia persists. She says: “Something has to be done about this. I can’t go on feeling this way.”

Email/Phone Questions (Unedited)

- Phone call from a 47-year-old woman with active severe Graves' disease for whom Methimazole treatment was recommended. "I don't want to take that medication because it might make me gain weight. A friend recommended that I try Naturethroid. Please send a prescription for Naturethroid to my pharmacy."
- For about a month, I have been having this sensation of bugs crawling on the right side of my head in my hair. Last night when I Googled, I was surprised to find that this is more common than I knew and can be caused by hypothyroid. Since it has been a long time since I have had my thyroid checked, it seems that it is time. So, might you be able to order the test and then prescribe as needed?
- Dr. McDermott ... I have just been diagnosed with conjunctival chalasis (the film that covers the eyeball) becomes very loose and wrinkles up causing discomfort and irritation as if there is something continually in your eye? One prospective study found that the prevalence of conjunctival chalasis in patients with autoimmune thyroid eye diseases was as high as 88%. I may have to have surgery. Would it help me to change to Armour? A shortage of T3 is supposed to contribute. Thanks,
- Dr. McDermott, I continue to struggle with exhaustion constantly and maybe that is just parenthood and need to improve my sleep habits. It is frustrating. I feel my best when pregnant honestly. What are your feelings on celiac connection with thyroid levels?! I have been having a lot of dizzy spells lately, more than just the feeling when you stand up too quickly and my menstrual cycles are heavier and take me down for a few days. My levels and labs were fine, so I guess it is a mystery. I have not been taking supplements as regularly and looks like my vitamin D could stand to be increased. Thanks for ordering them!

Questions for Insightful Endocrinologists to Consider

The hypothalamic–pituitary–thyroid axis, hypothalamic–pituitary–adrenal axis, hypothalamic–pituitary–gonadal axis, hypothalamic–pituitary–GH–liver–IGF1 axis, calcium–PTH–Vitamin D homeostasis, total body–energy balance, and overall nutrient metabolism and distribution are all highly complex systems. Hormone synthesis, secretion, transport through the circulation and other fluids, receptor binding, second messenger generation, gene expression, post-transcriptional modification, ultimate hormone action, and feedback regulation are all discreet processes that are unique and critical components of each individual hormonal and metabolic system.

Most of us delighted in learning about the intricacies of homeostatic regulation within these systems. We have diligently pursued further understanding how disease processes can affect these systems and how our static and dynamic endocrine tests and imaging modalities can dissect apart the individual components of the systems to pinpoint where the pathology exists so that the best possible treatments can be developed for endocrine and metabolic disorders. As a result of the work of dedicated scientists and devoted clinicians, we have developed testing platforms that are remarkably accurate and treatment strategies that are safe and highly effective.

Nonetheless, all of us who are involved in caring for patients with known or possible endocrine disorders must continue to be innovative thinkers, who are eager to make, understand, and apply new discoveries that will push our knowledge, diagnostic skills, and treatment options to even higher levels. So, we must ask: Based on our current clinical endocrine testing and imaging capabilities, do we really understand, without a doubt, every aspect of the function and dysfunction of the very complex endocrine and metabolic processes within our patients? Is it possible that some symptoms a patient suffers could result from inherited or acquired abnormalities (genetic, epigenetic, or other) at any of these

multiple steps of hormone and metabolic physiology for which we currently do not have adequate tests?

Are we ready to declare that we now know everything there is to know about hormone secretion, transport, and action, that our tests can evaluate every aspect of endocrine and metabolic function, and that there is no need for improvement in the options we currently offer patients to treat their endocrine diseases? Should we not acknowledge instead that we don't know everything and that we eagerly await new research discoveries to help us take better care of our patients?

I am not suggesting that all or even many patients with "pseudo-endocrine" disorders have an actual endocrine or metabolic disorder and that, if we just order enough tests, we will identify them; nor do I believe that when additional tests of the endocrine system become available, all or most of these patients will be found to have a previously undiagnosed endocrine disorder. However, I do believe we should acknowledge our current diagnostic and therapeutic limitations and support innovative research to overcome these limitations. We should practice evidence-based medicine but be open to novel ideas when they are based on solid science, and that we should always strive to develop compassionate and supportive relationships with all of our patients, regardless of whether or not they prove to have identifiable endocrine or metabolic disorders.

Additional Important Considerations

Endocrinologists are the acknowledged experts in the diagnosis and treatment of disorders of hormone secretion, transport, and action and of numerous metabolic diseases. It is an honor that a person respects our expertise and entrusts their healthcare to us. Every patient deserves our respect and compassion. When patients say, "Fix my thyroid, adrenal, pituitary, or metabolic condition," what they are really saying is "Please help me." The patient's quality of life is poor, and she/he is frustrated. Can we play a role in improving this patient's quality of life? Can we help this patient even if there is no apparent endocrine disorder? We should consider it an honor

and privilege that he/she entrusts us with an opportunity to help her/him. Therefore, we should listen attentively, examine our patient, offer additional testing if appropriate, admit that current testing options have some limitations and always provide honesty, encouragement, and compassion.

It's an exciting time to be an endocrinologist. There is still so much to learn, and so many people we may be able to help.

Suggested Reading

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Chapter 2
Pseudo-Endocrine Disorders: My General Approach to Management of the Patient

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We all have our own individual approaches to the evaluation and management of patients with challenging medical conditions, including those with pseudo-endocrine disorders. I have discussed this with many seasoned colleagues, including several of the authors of other chapters in this book. These are useful learning experiences for me. Each provider should approach patients with these issues in their own natural way, using their knowledge of Endocrinology, their well-honed personal instincts, and always their highest degree of humanism, respect, and compassion. In the discussion below, I describe the approaches that I have found most useful in providing the best possible care and assistance to patients with pseudo-endocrine disorders.

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Listen Attentively

I ask the patient to describe their symptoms and then listen attentively, without interruption. This helps to validate for the patient that I hear them, that I believe they are having these symptoms and that the symptoms are seriously affecting their quality of life, that I understand their concerns and frustrations, and that I am willing to be part of the solution. I maintain eye contact, if the patient is willing, and avoid typing in the electronic health record as much as possible. If I must type in order to accurately capture and remember key details, I periodically ask the patient to look at my monitor to make sure that I have recorded the details and their concerns accurately. I then ask for clarification of any parts of their description that I did not understand and ask additional questions to probe further into their major concerns. I also ask questions about lifestyle issues, such as their diet, exercise, and sleep habits (including if they snore) and about their use of tobacco, alcohol, marijuana, and other legal or illegal drug use. I carefully ask about their family life and their employment situation and satisfaction. I ask about their level of stress and their coping mechanisms. I rarely use the word "depression" on a first or second visit, unless the patient is forthcoming about this issue, but I get a good idea about this from the discussion described above. I avoid allowing the patient to spend much time describing their frustrations about previous providers and prior evaluations. All of this must be done, of course, within reasonable time constraints because we all have busy practices and our subsequent patients that day also deserve to be seen on time and to have adequate time devoted to their issues and concerns. Therefore, it may be beneficial to have the patient return for a second visit to continue the discussion. My emphasis throughout this time is attentive listening.

Perform a Thorough Physical Examination

The value of a thorough physical examination cannot be overstated. True endocrine disorders are often associated with distinct physical findings, which can be readily appreciated by the