Article

0021-972X/95/0505-0380$3.00/0
The Endocrinologist

A Case of Mistaken Identity: Occult Primary Adrenal Insufficiency in a Patient Taking Exogenous Glucocorticosteroids

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Adrenal insufficiency is an uncommon condition, and diagnosis is made difficult because of its variable and often nonspecific clinical presentation [1]. Exogenous glucocorticosteroids suppress the hypothalamic-pituitary-adrenal (HPA) axis, and secondary adrenal insufficiency may occur upon steroid withdrawal [2]. In contrast, in this report we describe a patient who was diagnosed with primary adrenal insufficiency while on chronic glucocorticoid therapy.

Case Report

A 50-year-old white retired male teacher on chronic glucocorticoid therapy was referred in March 1992 for evaluation of his HPA axis. From 1971 to 1979 the patient had nine admissions for fever (101–106°F) and vague gastrointestinal complaints without an identifiable infectious etiology. Treatment included intravenous hydration, antipyretics, and occasional intravenous glucocorticosteroids for hypotension. Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia were absent.

The patient was hospitalized in 1980 for acute pleuropericarditis, transient hypotension, and fever. His symptoms responded to intravenous glucocorticosteroids. Thereafter he was treated with oral prednisone for the presumptive diagnosis of seronegative systemic lupus erythematosus (SLE). His average prednisone dose was 10 mg daily from 1980 until 1985 and 5 mg every other day until 1991.

In 1991 he developed extreme fatigue, myalgias, and mild upper gastrointestinal discomfort. Prednisone was increased to 10 mg daily and rapidly tapered to 5 mg every other day because of newly diagnosed non-insulin-dependent diabetes mellitus. Despite excellent glycemic control, the patient became increasingly fatigued.

By March 1992 the patient had had a 10-lb weight loss over the prior 4–6 months without orthostatic light-headedness, hyperpigmentation, salt-craving, or symptoms of hypothyroidism or hypogonadism. Vital signs were normal without orthostatic changes. On examination he lacked vitiligo, hyperpigmentation, or asthenia. Laboratory data revealed normal electrolytes, calcium, and glucose. Serologic studies, including antinuclear, precipitin, and antinative DNA antibodies, were negative. A rapid adrenocorticotropin (ACTH) stimulation test was markedly blunted (Table 1), and the patient was placed on prednisone 5 mg daily for the presumptive diagnosis of secondary adrenal insufficiency, with symptomatic relief.

Over the next 6 months prednisone was tapered to 3 mg daily. Studies repeated March 1993 showed low basal cortisol and elevated ACTH levels (Table 1). Insulin-like growth factor-1, growth hormone, free- and total testosterone, free thyroxine, thyroid-stimulating hormone, and glycoprotein hormone α-subunit were normal. Magnetic resonance imaging of the hypothalamus and pituitary was normal.

In September 1993 cortisol and aldosterone responses to exogenous ACTH were blunted (Table 1). The

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The Endocrinologist 1995; 5: 380–381

Table 1
Laboratory data

	ACTH Stimulation Test		ACTH Level*
	Basal	Stimulated	
March 1992			
Cortisol†	80	100	
March 1993			35
Cortisol†	70		
September 1993			92
Cortisol†	50	80	
Aldosterone‡	<70	<70	

* ACTH normal range, 2–11 pmol/L.
† Cortisol normal basal range, 110–520 nmol/L.
‡ Aldosterone normal basal range, 220–430 pmol/L.

ACTH level was elevated further, and plasma renin activity was normal. Spiral computerized tomography revealed atrophic adrenal glands, measuring 2.0 × 1.0 × 0.3 cm, without calcification. Purified protein derivative was negative with normal anergy testing. Vitamin B_{12} level was normal.

Discussion

In patients taking exogenous glucocorticoids, adrenocortical suppression is common, although mineralocorticoid secretion is preserved [2]. Addisonian crisis has previously been reported in only three patients taking glucocorticoids for non-endocrine indications [3, 4]. We describe a patient taking exogenous glucocorticoids who presented with insidious, nonspecific symptoms without hyperpigmentation or electrolyte abnormalities. The diagnosis of primary adrenal insufficiency in this setting was made by measuring elevated ACTH levels and markedly attenuated cortisol and aldosterone responses following exogenous ACTH administration (Table 1). In retrospect, our patient likely had mild primary adrenal insufficiency in 1971 and was treated with glucocorticoids but not mineralocorticoids in 1980 for an incorrect diagnosis, SLE.

Clinical differentiation between primary and secondary adrenal insufficiency is usually based upon the presence or absence of hyperpigmentation and abnormalities associated with mineralocorticoid deficiency. Hyperpigmentation, which is present in 92% of patients with Addison's disease [1], was not apparent in our patient, likely because the secretion of ACTH and related peptides was partially suppressed by exogenous glucocorticoid therapy.

Electrolyte abnormalities are common in Addison's disease, with hyponatremia occurring in 88% and hyperkalemia occurring in 64% of patients [1]. Hyponatremia results from glucocorticoid deficiency, inappropriate secretion of antidiuretic hormone, and decreased renal free water clearance [5]. Hyperkalemia results from decreased mineralocorticoid-stimulated renal sodium-potassium ATP-ase activity [1]. Our patient had no electrolyte abnormalities; sodium homeostasis was maintained by replacement glucocorticoid therapy, and his marginal mineralocorticoid secretory capacity was evidently sufficient to maintain potassium homeostasis. Indeed, a minority of patients with Addison's disease are adequately maintained on glucocorticoids alone [6].

Primary adrenal insufficiency is diagnosed with a high degree of accuracy with a combination of rapid ACTH stimulation testing and the measurement of plasma ACTH, renin activity, and aldosterone levels [7]. As in our patient, low level exogenous glucocorticoid use does not interfere appreciably with this diagnostic endeavor.

Approximately 10 million patients in the United States are taking exogenous glucocorticoids for various medical indications (Maryland State Health Department, personal communication), whereas Addison's disease is a rare entity with an estimated prevalence of 60 per million [1]. One must consider the diagnosis of primary adrenal insufficiency in any individual with unexplained fatigue, weakness, and weight loss, regardless of exogenous glucocorticoid use. Early diagnosis and treatment may prevent life-threatening adrenal crisis.

Acknowledgements

I thank Drs. Howard Freeland and Baruch Friedman for their critical review of this manuscript and for their invaluable comments.

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Osteoporosis

By John A. Kanis, 254 pp. Cambridge, MA, Blackwell Science, 1994. $70.00.

Both reviewers thought that the nonspecialist would learn a lot about osteoporosis and that the specialist would certainly learn something. One reviewer noted some biases but that they were were in areas of controversy (as one might expect). The format was helpful to one and distracting to the other; let the reader decide! (ed.).

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Clinicians caring for patients with osteoporosis should welcome this introductory text. It is clearly written by an individual with an extensive background in clinical research in osteoporosis and metabolic bone disease. The author, who is Professor in Human Metabolism and Clinical Biochemistry at the University of Sheffield, has been a leader in helping us to define this disorder. Because it is an introductory text which focuses on clinical issues, clinical endocrinologists who are already well read in this field may find little that is new. Nevertheless, anyone working with osteoporotic patients is likely to find some material that is new and much that is presented in a way that clarifies and strengthens important concepts about the pathogenesis, prevention, and therapy of osteoporosis. However, those who want to learn more about some of the exciting new developments in bone cell biology, such as studies on the role of cytokines and other local factors and pathogenesis of osteoporosis, will be disappointed. Controversial areas such as the role of interleukin-1 in pathogenesis or of the vitamin D-receptor alleles in determining bone mass are not discussed.

One important feature of this book is the discussion of bone density measurements and the presentation of the concept that the diagnosis and preventive treatment of osteoporosis should be based on finding low bone density rather than waiting for a fracture to occur. Professor Kanis was one of the leaders in developing this concept, and it is not surprising that it is presented in a clear and forceful way in this text.

Individuals involved in caring for osteoporotic patients or helping women assess their risk of osteoporosis and develop prevention strategies would find much useful guidance in this book. This would include not only practicing endocrinologists, but also primary care physicians, whether they be in family practice, internal medicine or obstetrics and gynecology.

Given this positive recommendation, there are a few points about which I feel compelled to warn the reader. Professor Kanis has never been an enthusiast for the use of calcium to increase peak bone mass and prevent bone loss. His arguments are well presented, but the reader would do well to review some of the strong counterarguments presented by others at, for example, the recent NIH Consensus Workshop on Calcium.

In discussing the role of parathyroid hormone in pathogenesis, no mention is made of the studies that show that the PTH response to hypocalcemia, brought about by phosphate loading, is actually blunted in vertebral crush fracture patients (Silverberg et al., *New England Journal of Medicine* 1989; 320: 277). The section of biochemical assessment of osteoporosis is somewhat disappointing. The new methods for measuring markers of bone resorption and formation are not presented in any detail. For example, nowhere is it said that rapid immunoassays for these markers are now available. The section on testing symptomatic patients does not provide clear guidance. For example, there is a table of "Tests Commonly Used," which includes bone biopsy for osteomalacia and marrow aspiration for myeloma but does not mention serum or urine protein electrophoresis.

In line with Professor Kanis' lack of enthusiasm for calcium, it is not mentioned in the chapter on prevention, although it is covered quite adequately in a subsequent chapter on treatment. In the latter chapter we are provided with complete and balanced coverage of many therapeutic agents. There is also a section on the treatment of secondary osteoporosis and unusual forms of bone loss, including sympathetic algodystrophy, a disorder which is regularly diagnosed in the United Kingdom and Europe but less often recognized in the United States.

This text is typographically unusual. A 1½ inch column on the left-hand side of each page is largely blank, except for words or phrases in green which are supposed to highlight the text to the right; I did not find this very useful and wondered whether it was worth the 20% increase in the number of pages. There are also sections highlighted in green within the text, which presumably indicate important points that the author wished to cover; in some cases these points did not appear to be much more important than other portions of the text. The text includes a number of useful tales. There are relatively few illustrations but most are clear and effective, although I found a series of carpal radiographs intended to show focal osteoporosis after Colles' fracture uninterpretable. This book has clearly been edited quite carefully. There were few errors in the text, tables, or illustrations, although I did notice that not all the double bonds were put into the A ring of estrogens in one of the figures.

Overall, this is a worthwhile book. It is a readable and reasonably priced introductory text. I am certain that careful readers will learn a good deal about the management of osteoporosis and hope that they will be inspired to learn about the many new and exciting developments in this field.

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Despite its immense public health impact, osteoporosis has suffered from a certain lack of clinical focus. The large and rapidly growing body of knowledge about the disorder has sprung from diverse research roots (biochemistry and molecular biology, orthopedics, endocrinology, clinical nutrition, exercise physiology), and there have been few successful attempts to summarize those data in a coherent land practical form. Moreover, there are few individuals with a sufficient understanding of the whole to provide an appropriate perspective. Dr. Kanis has done it successfully.

In his preface, the author points out that the responsibility for the care of osteoporotic patients lies with both primary care and (in some countries) with subspecialty physicians. It is to this broad group of providers that his book is directed. The most salient tribute to the success of his effort is that it nicely provides a basic yet scholarly review which is eminently useful to a diverse, international medical community.

The book is organized to facilitate use at any one of several levels. For those less interested in detailed information, the most important summary points in each section are highlighted for quick consumption. For use as a reference book, the index is complete and subject words in the margins identify the topics of discussion for easy location. This feature also makes browsing for useful information straightforward. Obviously, the author and editors have taken some effort toward making this a user-friendly volume. The book is concise and well written, facilitating cover-to-cover reading.

The content is decidedly clinical and directed toward the provider facing practical patient-related issues. Dr. Kanis discusses clinical topics such as estrogen replacement therapy, calcium nutrition, and exercise by first examining their conceptual fundamentals in early chapters devoted to the basics of bone and mineral biology. He addresses such issues as dosing, adverse effects, and therapeutic decision-making in later sections. In most instances, important points are referenced but the book is not meant to be encyclopedic and is not burdened by a justification of each assertion. It is a quite personal approach to clinical osteoporosis; the author's opinions are presented as conclusions in a number of controversial areas (e.g., appropriate levels of calcium intake). On the whole, though, the book is well reasoned and quite balanced.

The major concern addressed is postmenopausal osteoporosis. There are major sections devoted to estrogen and to the management of menopause. Secondary osteoporosis and its management is discussed much more selectively. The osteoporotic man is mentioned but in a similarly abbreviated manner. Finally, the management issues considered are generally limited to currently available modalities. Up and coming approaches, for instance parathyroid hormone and estrogen analogues, are mentioned but not explored in depth. Perhaps these limitations are appropriate given the general attempt to focus on clinically relevant areas.

This is not a book intended for experts. It does not attempt in-depth evaluations, avoids esoteric topics, and does not discuss research methods unless there is a clinical point to be made. Nevertheless, it will be the rare academic who does not acquire both specific information and a better perspective. The book is a broadly useful addition to the literature and could as easily be added to the library of a university department as to the desktop of a primary provider.

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Alcohol and Hormones

By Robert R. Watson, editor, 339 pp. Totowa, NJ, Humana Press, 1995. $89.50.

Both reviewers felt there was little here for the clinician as most of the data presented were based on animal studies not yet translated to man. One reviewer hated it and felt the editor did not do justice to his writers, while the other reviewer thought one could dig out possibilities for future clinical application. On balance, a mixed review at best (ed.).

The strengths of this volume on alcohol and hormones emerge in the detailed, extensively referenced chapters by scientists personally involved in biomedical research and, to a lesser extent, clinical research in the area of alcohol, hormonal function, and related metabolic and human-developmental fields. A considerable number of the chapters read like the "background" and "work accomplished" sections of grant applications, with the results of the authors' laboratory studies providing the central core. These reviews represent important contributions to biomedical research and should provide excellent sources of information for investigators in this field.

The weaknesses of the volume are its seemingly minimal editorial input into topic selection (many key topics are not included), organization of chapters within the text (none is apparent), indexing (grossly inadequate), and cohesive or summary perspectives (none). With these deficiencies, this volume would appear to be of little use for the non-endocrinologist clinician, either in general medicine or in the field of alcoholism, and would not seem to be particularly useful for students, trainees, or educators attempting to gain concise, "textbook" knowledge regarding key interactions between alcohol use and hormonal function.

This volume clearly did not meet my expectations of providing an organized source of key data on alcohol-hormone interactions and the clinical relevance of these interactions for humans with varying drinking behaviors. In this regard, omissions from this text are glaring. There are no chapters or index citations for insulin, glucagon, parathormone, and the hormones of the digestive system. Alcoholic-thyroid interactions are "covered" in two chapters; one cogent review (Chapter 6) focused on the neuroendocrine effects of thyrotropin-releasing hormone (TRH) of relevance to alcoholism and a second (chapter 8), from the same laboratory but curiously separated in the text from their first chapter, described their research on the effects of TA-0910, a TRH analogue, on alcohol intake in alcohol-preferring rats. Hence, where clinical observations on alcohol and thyroid function are absent, the researcher in the field is

provided with intriguing data and speculations on potential blunting of TRH-induced thyroid-stimulating hormone (TSH) responses by alcohol and on potential neurobehavioral effects of TRH on alcohol-related behaviors.

The text is heavily weighted toward chapters on reproduction, growth, and pre-pubertal and pubertal development; seven of the eighteen chapters deal with these topics. Unfortunately, they are scattered through the text and there is no attempt by the editor to consolidate or discuss cohesive or divergent data or summarize the significance of these studies.

One of the more cogent and thoughtful presentations is that by T. J. Cicero and M. L. Adams on opioid-mediated control of neuroendocrine function, which cites evidence of specific opioid receptor regulation of luteinizing hormone (LH), prolactin, ACTH/corticosterone, and perhaps other hormone systems. This is somewhat ironic in that alcohol effects on these systems is not referred to at all, yet current clinical trials with the opiate receptor antagonist, naltrexone, suggest that opiate receptors may indeed modulate neurobehavioral responses to alcohol consumption.

Finally, returning to the editing, there appears to be no excuse for the failure to provide an adequate conceptual framework for the text and summary perspectives on individual or collected chapters, for the omissions of chapters on key hormone systems, or for the desultory indexing. The excellent investigators who contributed to the text and who presented key aspects of their scientific effort, and the reader, who will attempt to gain knowledge regarding alcohol use and hormone function, deserve a better effort.

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This book is a collection of 18 widely diverse research reviews most of which address the effect of ethanol consumption on various endocrine systems. It is the sixth volume of *Drug and Alcohol Abuse Reviews*, a series whose audience is mainly the addictive illness research community.

It is important at the outset to state that this is not a work intended for clinical endocrinologists. Almost all of the research discussed has been performed in non-human species, mostly the rat, and has been done to elucidate the mechanisms of alcohol-induced endocrine dysfunction. It contains very little information applicable to the solution of clinical endocrine problems, even those related to alcohol abuse. However, those with the time for careful reading of the sometimes dense text and a specific interest in the mechanisms of the endocrine consequences of alcohol consumption will find some stimulating and novel concepts presented.

Six reviews, fully one third of the volume, are concerned with the reproductive effects of alcohol consumption, particularly the mechanisms of testicular dysfunction. Anderson summarizes the effects of ethanol on rodent pubertal development and compares the changes caused by alcohol to those due to other factors, such as malnutrition and gonadotropin deficiency. He then goes on to summarize the data indicating that alcohol directly injures both Sertoli cells and the seminiferous epithelium in animal studies. Emanuele et al. present a thorough review of the effects of ethanol on the rat hypothalamic-pituitary-gonadal axis with many data on ethanol-induced changes in gonadotropin-releasing hormone (GnRH) and LH/follicle-stimulating hormone (FSH) synthesis and secretion. Adams and Cicero review the ethanol and endogenous opioids as mediators of reduced testosterone synthesis and testicular interstitial fluid secretion. They conclude that ethanol and opioids may share NO as a final common pathway in their common inhibition of testosterone secretion but have different mechanisms of suppression of testicular interstitial fluid formation. Dees, Nyberg and Hiney review ethanol's effects on female puberty in a rat model. Teoh, Mello, and Mendelson present a clinical review of the effects of ethanol on reproductive function in adult women and present data suggesting that alcohol consumption may be a more frequent cause of amenorrhea and hyperprolactinemia than usually appreciated. Gavaler, Rosenblum and Deal describe their work identifying and quantifying the phytoestrogens found in bourbon and beer.

Two reviews discuss the effect of ethanol on hepatocytes. Wands, Bhavani, and Sasaki examine the effect of ethanol on hepatocyte growth and proliferation. They found that ethanol reduced insulin-stimulated tyrosine phosphorylation in insulin receptor substrate 1 and epidermal growth factor (EGF)-stimulated phosphorylation of p36 protein and, consequently, reduced DNA synthesis and cell proliferation. Eagon and Lechner reviewed the effects of ethanol on the sexually dimorphic patterns of hepatic sex steroid metabolism and sex hormone dependent protein secretion in rats.

Two reviews, both from the same group, address the role of TRH and TRH analogs in the biology of alcoholism and their potential as specific treatments for alcohol craving. Garbutt, Silva and Mason summarize a number of studies indicating both reduced TSH response to TRH in individuals at risk for alcoholism and data suggesting that TRH has specific effects which antagonize the cognitive and habituating effects of alcohol consumption. Mason, Rezvani and Garbutt review their work with a TRH analog (TA-0910) on alcohol consumption in ethanol-preferring rat strains. Both reviews speculate that a central hyperdopaminergic state, which is moderated by ethanol or TRH in a reinforcing way, is part of the pathophysiology of the susceptibility to alcohol abuse.

Dopico, Lemos, and Treistman present an intriguing review of their work on the mechanism of ethanol inhibition of vasopressin and oxytocin secretion. They have chosen a model in which they have been able to explore ethanol effects on the activity of specific transmembrane channels and have found that ethanol most likely inhibits transmembrane calcium movement. Their work is producing a better understanding of one of the fundamental mechanisms of ethanol's biological effects.

Duester reviews the potential role of alcohol dehydrogenase (ADH) in the metabolism of retinoic acid. He speculates that ethanol may act as a competitive inhibitor of retinoic acid

synthesis by ADH and consequently impair neural tube development, resulting in some of the embryopathy of fetal alcohol syndrome.

Vogel and Evans discuss the effect of stress on the endocrine effects of ethanol and the converse effect of ethanol on the psychologic and physiologic manifestations of stress. They point out that stress changes the endocrine effects caused by ethanol and, consequently, studies done in resting unstressed individuals may not reflect the actual pathophysiology of alcohol abuse.

Other articles discuss interaction of ethanol and prostaglandins, and ethanol's effects on thermoregulation in animals. Two contributions are included that are not related to the principal theme of the book, presenting, instead, reviews of endogenous opioids as regulators of neuroendocrine function.

In conclusion, from the point of view of the clinical endocrinologist, there is little to offer here for our day-to-day practice. The range of material presented is striking and reflects the extraordinary spectrum of the biological effects of ethanol. Most of the data reviewed is derived from non-human species and much of the discussion is speculative and hypothetical. It is surprising and disappointing that we know so little about a substance to which so many are so routinely exposed. However, some of the best work discussed here is clearly on the threshold of important insights into the mechanisms of ethanol's actions; these insights will lead to useful therapeutic approaches.

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