Effects of Hormones on Behavior Through Evaluation of Prismatic Cases

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My Hormones Made Me Do It

By

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Cambridge Scholars Publishing

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FOREWORD

What is the message? Hormones can have profound effects on behavior in many different and striking ways.

How is the message delivered? The stories of patients are related in a manner understandable to those trained in the field of hormone medicine (endocrinology) as well to those naïve to this field of interest. Photographs as well as verbatim transcripts of interviews with patients let the reader appreciate examples of how hormones can affect behavior.

Why do hormones affect behavior? During fetal life, childhood, puberty and adulthood, hormones act on specific areas of the brain to influence behavior. This affect is influenced by multiple factors, including genetics, cultural environment, rearing as a child, exposure to family members, underlying talents, responses to stress, and peer pressure, to name a few. While the specific role that hormones play can often be difficult to sort out, in some instances, hormones are a dominant factor in determining behavior.

My personal experience: As a "hormone doctor" (endocrinologist) with nearly 45 years of clinical practice, I have observed patients whose hormones have affected their behavior in major ways, and this experience has given me a unique perspective. In my work at an academic medical center where patients with rare conditions are referred for evaluation, I have interacted with patients with a wide spectrum of problems.

Special role of a physician*:* Patients will often relate their innermost thoughts and feelings to their physicians as they view them as advocates who have their best interests at heart. For me, these unique interpersonal interactions provided a pathway to learn about some of the most unusual effects of hormones.

Key methods utilized: If given the time to express themselves, patients tell their own stories and relate the specific effects of hormones on their lives. Verbatim transcripts of interviews of patients provide dramatic examples of a variety of surprising and often disruptive behaviors.

Prismatic cases: The clearest examples of the effects of hormones on behavior are from patients that physicians call "prismatic cases," patients in whom certain, highly unusual features inform one about problems and often allow crystal-clear insight.

Why I became convinced about hormones and behavior: The book begins with a chapter on a "flasher" who convinced me that hormones can have a major effect on behavior.

Insight gained from research*:* The research method prepares the physician to think out of the box in an attempt to get to the essence of a medical condition. My research experience, as will be evident from discussion of some of the cases in this book, has allowed me to go into depth when trying to find out what the patient is experiencing.

Word of caution*:* The author is not a recognized expert in the study of behavior but draws conclusions from his observations of patients and application of what is known about hormones.

Source of Hormone	Name of hormone	Action of hormone
Anterior Pituitary	FSH (follicle stimulating hormone)	Stimulates the ovary to cause the eggs to mature in the female and sperm to be made in the male
" "	LH (luteinizing hormone)	Stimulates the ovary to make estrogen in the female and testosterone in the male
" "	GH (growth hormone)	Stimulates the body to grow prior to adulthood
" "	TSH (thyroid stimulating hormone)	Stimulates the thyroid gland to make thyroid hormones
" "	ACTH (adrenocorticotropic hormone)	Stimulates the adrenals to make hydrocortisone, aldosterone and male hormones
" "	Prolactin	Stimulates the breast to make milk
Posterior Pituitary	ADH (antidiuretic hormone)	Causes the kidney to hold on to water
Thyroid	Thyroxine (T4)	Increases body metabolism
	Tri-iodothyronine (T3)	Is a metabolite of T4 which binds to nuclei and is more potent than T4

Ovary	Estradiol	Stimulates breast development during puberty and controls menstrual cycles in women and contributes to libido in men
“ “	Progesterone	Stimulates the lining of the uterus (womb) and, when the levels drop, triggers menstrual bleeding
Testicle	Testosterone	Stimulates beard growth and body hair in men and contributes to libido in both men and women
	Dihydrotestosterone	Stimulates the growth of the penis in males during intra-uterine development
Parathyroid	PTH (parathyroid hormone)	Controls the levels of calcium in the blood
Pancreas	Insulin	Causes a decrease in blood sugar
“ “	Glucagon	Causes an increase in blood sugar
Adrenal	Cortisol	Regulates multiple steps in metabolism and can result in death if absent for any reason
“ “	Aldosterone	Causes the body to hold on to sodium (salt)
“ “	Epinephrine	Stimulates heart rate and heart output
“ “	Norepinephrine	Regulates blood pressure and increases both systolic (top number) and diastolic (bottom number) blood pressure
Body Tissues and Brain	Dopamine	Helps to regulate blood pressure and loss of sodium in the urine

LIST OF HORMONES

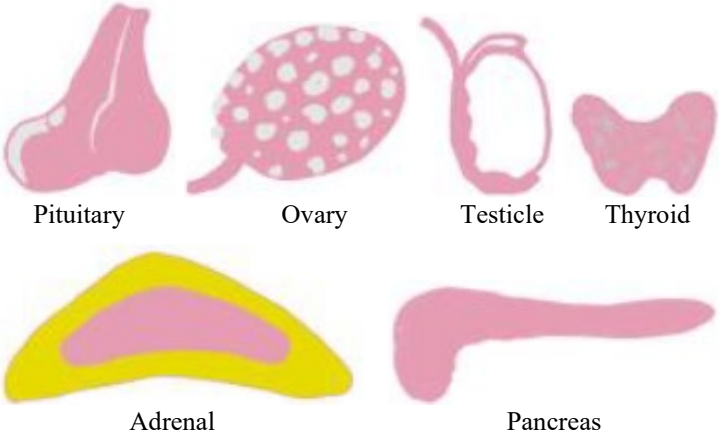
Some Examples of Behavioral Issues Influenced by Hormones

* Addiction to salt
* Addiction to licorice
* Addiction to water
* Compulsive urination
* Compulsive body building
* Compulsive eating
* Addiction to male hormones to enhance athletic performance
* Issues of gender identity
* Enhanced anxiety
* Exacerbation of paraphilias (attraction to unusual behaviors)
* Steroid rage
* Excessive aggression
* Abusive behavior
* Exaggerated libido
* Erotic dreams
* Enhanced marital discord
* Stress-related tremors and hyperthyroidism
* Hot flashes influencing behavior
* Psychotic response to thyroid hormone
* Low blood sugar and aggression
* Hyperthyroidism and overachieving
* Cortisol deficiency, stress, and president's behavior
* Hyperthyroidism and president's behavior

BACKGROUND

What are hormones and what do they do?

Before considering the possibility that hormones can play a major role in modulating one's behavior, we need to know a bit about hormones and what they do. Hormones are substances made by certain glands (endocrine glands) in the body. The most important are the pituitary, the master regulator gland; the ovaries, which make the female hormone; the testicles, which make the male hormone; the thyroid gland, which makes the thyroid hormone; the adrenal, which makes several hormones; and the pancreas, which makes insulin.



These glands release the various hormones into the blood where they can travel to distant parts of the body called target tissues. For example, the male hormone (testosterone) is released by the testicles (balls) and goes to the skin of the face where it stimulates beard growth. In the target tissues, the hormones bind to specific proteins called receptors. Hormones act like keys and receptors act like the locks into which the keys fit. Stated simply, the hormone (the key) binds to the receptor (the lock) and this unlocks certain body functions, such as the control of beard growth. Hormones provide a way for one part of the body to signal to another after being released into the blood stream, where they travel to distant tissues. Hormones can also be

made locally and act locally in the tissue. For example, breast tissue can make the female hormone in the breast itself and act there directly.

The key hormones affecting patients discussed in this book include testosterone, dihydrotestosterone, estradiol, thyroxine, hydrocortisone, adrenaline, aldosterone, antidiuretic hormone, prolactin, parathyroid, adrenaline (epinephrine), growth hormone, and insulin (see table). Dihydrotestosterone causes the external genitalia (penis and scrotum) to form during fetal development, while testosterone induces puberty and facial hair in boys and the sex drive in men. Estradiol induces puberty in girls, and is a key regulator of breast development and monthly periods. Thyroxine controls body metabolism, and hydrocortisone is needed for glucose production and is necessary for survival during stress. Aldosterone causes the body to hold on to salt, and the antidiuretic hormone (ADH) to hold on to water. Prolactin is needed for breast feeding after pregnancy, and the parathyroid hormone is to regulate calcium levels. Adrenaline is needed to handle stress, and the growth hormone regulates how tall one will grow. As you can imagine, a lack of these hormones or an excess can cause major problems, as discussed in later chapters. An important effect of these hormonal disturbances can be alterations of behavior, which at times can be very dramatic.

The amount of hormone made is generally regulated by what is called **negative feedback.** As a good way to understand this, the process of negative feedback is similar to how a heater for your house regulates temperature. Let's say that the thermostat in your house is set at a certain temperature, in this case 70 degrees.

When the heat in your house goes above the level set by your thermostat, let's say to 72 degrees, the heater turns off. This is negative feedback — as the heat goes up, the negative effect is to turn off the heater. When the heat in the house goes down, let's say from 70 degrees to 68 degrees, the heater goes on again to increase the heat to the temperature setting of 70. This allows the temperature in your house to remain within a fairly narrow range,

from 68 to 72 degrees. This negative feedback mechanism is how the levels of hormones are controlled in the body and why their regulation is very precise. For example, when thyroid hormone levels are too high, this shuts off the release of thyroid stimulating hormone (TSH) from the pituitary gland (negative feedback) and the levels of thyroid production by the thyroid gland go down. When the levels of thyroid hormone go down sufficiently, the body tries to compensate for this by increasing the level of TSH, which then increases thyroid hormone levels. This negative feedback mechanism allows for the precise control of thyroid hormone levels within a very narrow range. For several of the hormones, it is the pituitary gland where negative feedback occurs. For others, such as insulin, it is the pancreas, where high glucose (sugar) levels stimulate insulin and low glucose levels shut insulin off.

The underlying ways that hormones work are quite complicated, and it requires a lifetime of study to understand all of their effects in precise detail. Rather than attempt to describe all of this, I will concentrate on the specific effects of hormones on behavior and will attempt to use simple explanations which will be understandable to the lay public. The book will then give examples from real patients of the effects of excessive and low hormone levels and of the administration of hormones to patients. I have chosen to describe patients, primarily from my own practice, who illustrate very interesting but not always common behavioral changes that are due to hormones. It is often said that one learns more by personal experience than by lectures or reading textbooks The knowledge obtained can also be used to assess problems of public figures, as, for example, Presidents John F. Kennedy and George Herbert Walker Bush. My goal in this book is to share my experiences as a way of educating others about the power of hormones on behavior.

CHAPTER 1

THE "FLASHER" MADE ME A BELIEVER

1 The "Flasher" convinced me that hormones can effect bizarre behavior

Physicians learn best by listening to their patients and considering physical and behavioral manifestations. On occasion, a patient exhibits such extraordinary characteristics that insights arise from the very novelty of what is observed. The patient's story can often shed light on the underlying causes of the problem. This lesson became crystal clear to me from a patient who convinced me that hormones can markedly influence behavior and cause one to take unthinkable actions. This patient led me to the title of this book "My Hormones Made Me Do It".

This 52-year-old male patient was referred to me to find out how he could stay out of prison. He had been arrested for several episodes of exposing himself in public places. The lay term for this type of indecent exposure is flashing, and the person flashing is called a flasher. He related a complex story to me in precise detail.

He was born with one testicle (ball) that did not come down into the scrotal pouch at birth or later in life but remained in the abdomen. In medical terms, this is an undescended testicle. As this problem is associated with a two-to-eight-fold increased risk of developing cancer(Pettersson, Richiardi et al. 2007), he underwent surgery at age 30 to remove the testicle. At that time, he said that he was otherwise healthy and admitted to no emotional or behavioral problems.

Shortly after marriage at age 37, he and his wife wanted to have a child but his wife was unable to conceive. He was found to have a low sperm count and received treatment with a hormone, human chorionic gonadotropin (HCG). In men, HCG stimulates cells in the testicle to make increased amounts of male hormone (testosterone) and sperm. During the HCG treatment, the patient began to exhibit very bizarre behavior, and this was a radical change for him as he had been considered quite well behaved both by his wife and peers. Specifically, he would indecently expose himself to young women in public settings, mainly in coffee houses frequented by

female college students. Importantly, when the patient stopped the HCG treatment, the flashing episodes subsided completely.

After stopping HCG, his overall health and behavior were completely normal for another seven years until the age of 44. At that time, he developed testicular cancer in his remaining testicle, which was then surgically removed. As expected in a man with no testicles, he developed very low testosterone levels and accordingly began to receive testosterone injections. Shortly after that time, he again began repeated flashing. This was reported to the police, and he was charged with four different episodes of indecent exposure over a three-day period and imprisoned for several months.

After parole, the current referral was made to me to see if he might have some type of hormonal problem to explain his flashing. During the interview, he related to me that one year before, he had seen a psychologist, a certified sex- offender treatment provider. I read the detailed 10-page report, which described in graphic terms the inappropriate sexual behavior of his mother toward the patient during his childhood and that this likely influenced later behavior. The report also described very high testosterone levels after HCG and testosterone administration. Key sentences in the report stated

> "Based on the data derived from this assessment, it is clear the … inappropriate sexual behavior is clearly related to his very high testosterone levels. During each of the instances where he acted out by "flashing", his level of testosterone was significantly above what is considered to be normal (i.e. 300 to 1000 ng/dl) and his was at 2500 ng/dl.

I had never encountered this situation before, and it was not clear to me whether or not the flashing episodes were related to testosterone or not, although the suspicion was strong. I asked him to document the testosterone levels that he had recorded over the past several years. I wanted to correlate his testosterone levels with his episodes of flashing. I found that standard doses of testosterone, i.e., 200 mg every two weeks by intramuscular injections, caused his levels of testosterone in the blood to be 4-to-5-fold higher than I would expect, namely as high as 2500 ng/dl. One would expect levels of only 500-600 mg/dl. The correlations suggested that the episodes of flashing occurred when his testosterone levels were very high.

This information was puzzling to me and I asked myself the key question: **"Why did standard doses of testosterone cause the testosterone levels to be so high?"** The prepared mind can sometimes figure out problems that are opaque to those not so prepared. My prior research gave me an idea about this. I reasoned that his testosterone level was high because his body did not inactivate the administered testosterone

normally. Because of this, a standard dose of testosterone would cause extremely high blood levels. My prior research study had shown an 8-fold difference in the rate of inactivation of testosterone from one normal man to another(Santner,Albertson et al. 1998). From the results of my study, it seemed logical that standard testosterone doses could cause high levels because of slow inactivation and that might be the explanation for the highly unusual behavior.

I explained to him that I had never seen a problem with flashing related to high testosterone levels in my career and it was necessary to review the pertinent literature on this topic. I did this and found conflicting opinions (Grubin 1997, Weinberger, Sreenivasan et al. 2005, Maletzky, Tolan et al. 2006, Alexander BM 2011, Gooren 2011, Koo, Shim et al. 2013, Lee and Cho 2013, Carre and Archer 2018). My next approach was to consult with colleagues who were experts in giving male hormones to men whose testicles did not function correctly. As an academic endocrinologist, one gets to know both national and international experts in one’s field of interest. This made it possible to send emails to several experts in male reproductive endocrinology. including Drs. Henry Burger and David Handelsmann in Australia, Eberhardt Nieschlag in Germany, Alvin Matsumoto in Seattle, and William Crowley in Boston. None of them had experienced patients with this specific problem, but all agreed that the patient probably had an underlying psychological or psychiatric disorder which resulted in his episodes of indecent exposure. They all felt that this could be influenced secondarily by his high testosterone levels. Half of the experts cautioned against testosterone therapy, and the others suggested that I try to give testosterone but titrate the dose, starting at very low doses and increasing very carefully.

After this comprehensive evaluation, I wrote a detailed letter and explained all of this to the criminal court judge. After receiving my letter, he put the patient on probation but did not re- imprison him. I then discussed with the patient the conflicting opinions of the experts about continuing the testosterone and we jointly decided to do this. I lowered his dose from 200 mg every two weeks to 35 mg every week. As a consequence, his testosterone levels fell from levels of 1500-1900 to 320 ng/dl and he stopped further indecent exposure behavior. Interestingly, the patient noted that he still had the impulse to expose himself but on the lower doses of testosterone, he thought that he could control them. He had no further episodes of flashing over two years and the probation was dropped.

Was high testosterone really the explanation for his flashing? This seemed to me to be the case, but to get a highly informed opinion, I asked that he be evaluated by internationally recognized experts on the effects of

testosterone, Dr. Harrison Pope Junior and Dr. Martin Kafka, both from Harvard Medical School's McLean Psychiatric Hospital. Kafka's clinical and research interests include hypersexuality, the paraphilias, and paraphilia-related disorders (aka sexual addiction/sexual compulsivity). These psychiatrists explained to me that my patient's behavior very likely represented an underlying paraphilia (paraphilia is defined as an aberrant behavior, such as pedophilia). The fact that his mother had acted sexually inappropriately while he was growing up may have been a factor. They further noted that he might not have responded to impulses to expose himself until his testosterone had reached very high levels. When he had both testicles as a younger man, his testosterone levels were likely normal, and he exhibited no paraphilic behavior. It was not until he received HCG and, later, testosterone injections that the flashing began.

The patient was very grateful that we had a likely explanation for his high testosterone levels and that he had no more aberrant behavior. His wife, a very accomplished social worker who had accompanied him to the clinic, was very much relieved that perhaps we had found a solution to her husband's problem. However, then the plot thickened. The patient found out that the charge for a testosterone level test at our hospital was $400, and the charge at a local community hospital was only $45. For this reason, every time I ordered a testosterone level test to follow his therapy, he went to the local hospital to have this measured. Because all of these laboratory data had to be put into the chart piecemeal, it was not immediately clear that his testosterone level had begun to creep up over time. It had reached a level of 800 without attracting my attention. Again, he went to a coffee shop and exposed himself, just as he had done before.

In discussions with the parole officer and the court, we decided that he would have to be taken off of testosterone completely (i.e., the equivalent of a chemical castration). We did that, and he began to have hot flashes and depression but this ultimately resolved over time as he adjusted to the very low testosterone levels. Now he indicated that he no longer had impulses to flash. Over a period of an additional five years, he has had no more episodes of exhibitionism. As I got to know him better over these years, I learned that he was very successful in his work as a business consultant and actually adjusted well to a lack of testosterone.

With this experience, I began to ask myself how hormonal problems might affect behavior generally and specifically in prominent politicians. As discussed later in the book, two presidents, George H.W. Bush and John F. Kennedy, were affected by hormonal problems: a lack of adrenal hormones in John F. Kennedy and an overactive thyroid function in George

H.W. Bush. From these examples, I wondered whether hormonal effects might have altered history, as hypothesized later in the book.

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CHAPTER 2

ADRENAL

1 Interview of patient with Addison's disease

Background: Santen: One role of a professor in a medical school is to teach medical students, residents, and fellows about diseases in their specialty and how to manage those diseases. Fellows are the most senior trainees. They usually evaluate the patient without having the professor with them and then present the findings to the professor and discuss the management. One of my fellows was asked to interview a 71-year-old Caucasian patient and record the interview on videotape. The patient had been diagnosed with adrenal insufficiency just three weeks before and had been treated with hydrocortisone and a synthetic form of aldosterone called Fluorinef[R.] She had come back to the endocrine clinic for a follow-up to see about the response to treatment. The fellow interviewed the patient and recorded the responses.

Fellow: First of all, I know you've been sick for a long time. What was your main complaint?
Patient: Weakness, dizziness, nausea, and vomiting.
Fellow: Was it persistent, and were you feeling very nauseous just after meals?
Patient: More like 24 hours a day, and it was really bad.
Fellow: Was it relieved by anything or increased by anything?
Patient: No, but if I ate, sometimes it would stay down and sometimes it wouldn't.
Fellow: Were you feeling weak also, and were you able to get out of bed?
Patient: Yes, but that's about it.
Fellow: Did you notice any weakness when you tried to get up from a sitting position to a standing position?
Patient: Toward the last, yes; in the last month, it was that I couldn't do anything.
Fellow: Tell me what sort of dizziness did you have?
Patient: Whenever I tried to stand up, that's when it would act up.

Fellow: What exactly did you feel? Would it be lightheadedness or would it feel like the world is turning around?

Patient: Well, sometimes it would be so bad that I couldn't see anything and whenever I would try to get in the car to come down here, I was stumbling all over the place.

Fellow: Did you notice that you were eating more and more salt over the past two weeks?

Patient: No, I really didn't know that until I came here. Whenever I started getting better, I realized that I needed to eat more salt than I did before.

Fellow: But you did tell us before that that you had some kind of salt craving. and you were eating more and more potato chips and pretzels.

Patient: Yeah, yeah.

Fellow: Did you notice that your color was changing, or that anybody in the family commented on this and noticed that you are getting darker?

Patient: Yes, they kept telling me that I looked yellow.

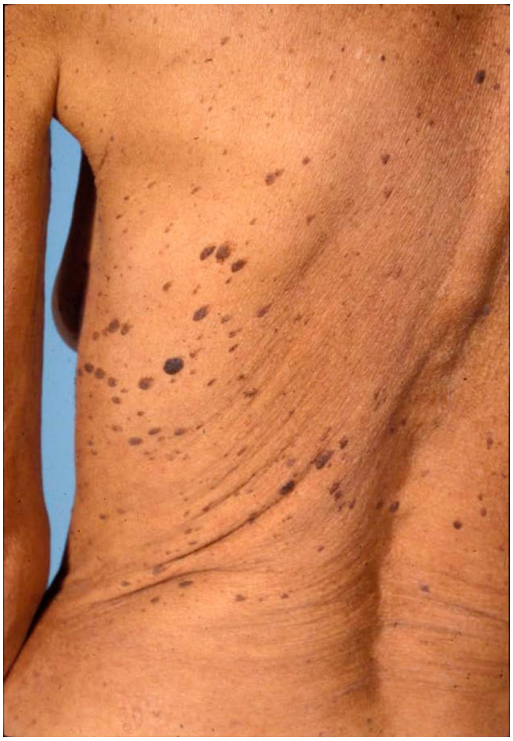

Fig. 2-1 Patient has hyperpigmented skin and hyperpigmented moles

Fellow: Did you notice anything specifically yourself?
Patient: I noticed some, you know, pigmentation in my mouth.

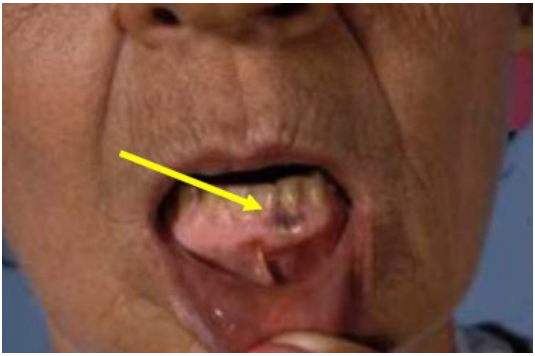

Fig. 2-2 Pigmentation of gums in mouth.

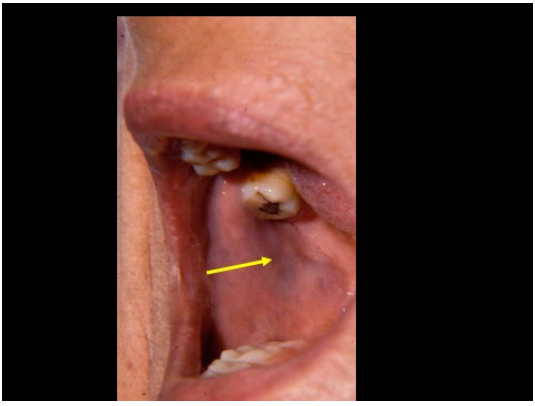

Fig. 2-3 Focal area of pigmentation on side of mouth.

Fellow: Did you notice that your tongue was getting darker?
Patient: Yeah.
Fellow: And how about your face, your changing color?
Patient: I really didn't recognize this myself. People just kept saying you are changing color, you are changing color, and I really just didn't pay any attention to that.
Fellow: Have you lost some weight over the past few weeks?
Patient: Yeah.
Fellow: How much weight would you think you've lost?

Patient: About 40 pounds, and that was over about a two-month period.
Fellow: It's important to recognize that the first time that we saw you, your blood pressure was only 60 systolic and you were very lethargic. We gave you some hydrocortisone intravenously in the hospital and your blood pressure did come up to 130/80 with a combination of fluid and steroids. This response is a sign of adrenal insufficiency and the response to therapy. You are now three weeks on steroid supplements. As we look at you, we can see the marked pigmentation, this is a most prominent around the knuckles.
Let me then ask you how you are feeling now since you've been treated and how is your nausea and vomiting after the replacement?
Patient: It's gone.
Fellow: Completely gone, and you think you're getting your weight back?
Patient: Oh yes.
Fellow: You're feeling much better now?
Patient: Oh yes.

Discussion with Santen in the presence of the patient: When we evaluate patients for Addison's disease, we look at certain blood tests that tell us about this. We have some values at the time of initial evaluation. One is an increase in potassium, and her level was 6.3, with normal being 3.5 to 4.5. The level of sodium in the blood goes down, and hers was 121, with anormal being 135 to 145. The patient had become somewhat acidic, and this is shown by the bicarbonate level of 18, which should be about 25. When the bicarbonate falls, this gives us an idea of the amount of acidity. Surprisingly the patient's calcium was 13.4. The blood sugar was also low at 64, as expected in a patient with low cortisol levels. With severe dehydration, the calcium levels go up, and this is a classical finding in Addison's disease. Further discussion continued to stress to the patient the need to continue the medication, increase the amount of hydrocortisone during stress, give herself an injection of hydrocortisone if she was vomiting, and order a bracelet indicating that she had Addison's disease.

Explanation of findings: Addison's disease is associated with several findings (Mitchell and Pearce 2012, Napier and Pearce 2014, Hellesen, Bratland et al. 2018, Barthel, Benker et al. 2019, Betterle, Presotto et al. 2019, Wolff, Kucuka et al. 2023, Lundholm, Ambalavanan et al. 2024). When ACTH goes up, a hormone called melanocortin goes up as well and causes hyperpigmentation on the gums (Figure 2), wall of the mouth (Figure3), and all over the body (Figure 1). The dizziness and weakness are caused by the lack of hydrocortisone, which causes low blood pressure. The low sodium in the blood results from the loss of sodium in the urine in

response to the decrease in aldosterone, the salt-retaining hormone. The salt craving is a behavioral change that develops as the body tries to maintain enough sodium in the body. That is why she learned to eat a lot of potato chips and pretzels. When treated with hydrocortisone and Fluorinef®, she began to feel better almost immediately.

Why does adrenal insufficiency happen? The adrenal gland can be destroyed by antibodies made by the patient, so called auto-antibodies, or by infections such as tuberculosis. Destruction of the adrenals causes the loss of the hormones hydrocortisone and aldosterone. Hydrocortisone controls body metabolism, blood pressure, and response to stress. Aldosterone controls the body's ability to hold on to salt. When the adrenals are destroyed, the disease is called Addison's disease. The symptoms, when severe, include nausea, vomiting, diarrhea, dizziness, fainting, confusion, and fatigue. Signs include darkening of the skin, low blood pressure, and weakness. The story told by this patient emphasizes how severe the illness may be.

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2 John F. Kennedy's Addison's disease and the Vienna Summit meltdown

The patient--President John F Kennedy: During his presidency, John F. Kennedy was living with Addison's disease, which had been clearly diagnosed by medical testing several years earlier (R Dalleck 2003, An Unfinsihed Life Boston).To manage this illness, he was receiving hydrocortisone, or its equivalent, daily by pill. He had the typical appearance of a patient with Addison's disease with darkening of the skin. As noted in the photograph, Kennedy always had an apparent suntan. However, rather than a suntan, this darkening of the skin resulted from increased MSH (melanocyte stimulating hormone), which is made in higher levels by the pituitary when the adrenals are wiped out by Addison's disease. MSH stimulates melanin cells in the body to produce pigment and this causes the apparent tanning. Interestingly, the media mistakenly commented on his tanned appearance as evidence of Kennedy as an "outdoorsy" man who was in excellent health.

Fig. 2-4 President Kennedy. The number 35 represents that fact that he was the 35th president of the United States.

President Kennedy and stress: The treatment of a sitting president with Addison's disease presents extraordinary challenges because of the intermittent episodes of stress associated with this office. Many times during his presidency, Kennedy experienced a great deal of stress, often documented by the media. A prime example was the Vienna summit, when he was under severe stress and was closely scrutinized by reporters and colleagues.

Let us closely examine what is known about this event. On June 4, 1961, Kennedy met with Nikita Khrushchev at the Vienna Summit just four months after assuming the presidency(Carlson 2011). We know from written reports that Kennedy wanted to be in his best form that day and he turned to a trusted physician, Dr. Max Jacobson, to help. Kennedy had been treated in the past by Jacobson and felt that the doctor's "miracle" injections markedly improved his energy and mood. He asked Jacobson to accompany him to Vienna so the doctor could inject him with his medicine before the young president sat down with the Soviet premier Nikita Khrushchev for their first summit meeting (Carlson 2011). Unbeknownst to his staff, Kennedy had flown Jacobson on a chartered Air France plane to Europe so that he could give the president this treatment if necessary. On the morning of the summit, Kennedy asked for and received a shot administered by Dr. Jacobson. Later it was found that the shot contained amphetamines, a strong, adrenaline-like stimulant.

Later that day, Kennedy complained of exhaustion. He appeared dazed and somewhat depressed, and was thought to have "melted down". **What had happened?** He was clearly severely stressed, and it is likely that he was not given a sufficient "stress dose" of hydrocortisone. Notably, his endocrinologist, Dr Eugene Cohen, had not come with him to Vienna to provide expert advice about Addison disease management.

Fig. 2-5 John Kennedy and Nikita Khrushchev, 1961

Assessment of Kennedy's stress level: How do we know how much stress the President was under? First of all, this young president was attending his first and very important summit meeting. Secondly, Khrushchev's behavior rattled Kennedy. The President himself stated that Khrushchev had been quite aggressive with him in their interactions. He commented, "He treated

me like a little boy, like a little boy" (Kempe 2011). A third and powerful stressor was the amphetamine shot. This drug, otherwise called "speed", causes major stress-like effects, particularly when injected. Taken together, it appeared that Kennedy experienced a triple-dose of stressors: the major international summit, Khrushchev's aggressiveness, and the amphetamines — clearly a very high level of stress in this young and as yet unproven president.

Kennedy's appearance: In his biography of Kennedy, Dallek stated: "Kennedy could not hide his distress over the harsh exchanges which promised worse future relations. Before cameras, as the two men left the Soviet embassy, Khrushchev put on a show of merriment but Kennedy was grim and unsmiling." A British journalist, who saw him as he escorted Khrushchev to his car (after the first session), thought Kennedy looked "dazed." During a stroll in the garden after lunch, Kennedy tried to establish a greater rapport with Khrushchev, but the Soviet premier was unrelenting.

> O'Donnell and Powers (Kennedy's advisors) watched them from an upstairs embassy window. Khrushchev was carrying on a heated argument, circling around Kennedy and snapping at him like a terrier and shaking his finger. (Dalleck R. An Unfinsihed Life Boston)

Later that day, while pacing the floor of his bedroom in the embassy, Kennedy asked Llewellyn Thompson, "Is it always like this?" The ambassador replied, "Par for the course." Thompson thought that the president was "a little depressed." Though he tried to comfort him by declaring that "the Soviets always talk tough," he believed that Kennedy had gotten "a little bit out of his depth" by being drawn into an ideologic debate (Kempe 2011).

In a conversation afterward, Kennedy told James Reston, the New York Times reporter, that he felt exhausted during the meeting with Khrushchev. Reston said that JFK came across as "very gloomy." Kennedy sank onto a couch, pushed a hat over his eyes, lit up like a beaten man, and breathed a great sigh. "Pretty rough. … Roughest thing in my life; he savaged me." (Carlson 2011, Kempe 2011). Later, while the exhausted Kennedy was soaking in a tub, Reston said, "You seemed pretty calm while he was giving you a hard time out there." They had been arguing over Germany and Berlin. "What did you expect me to do?" Kennedy said with some exasperation. "Take off one of my shoes and hit him over the head with it?"

Kennedy's own reaction: Kennedy was troubled by his own performance. His anger and frustration were as much with himself as with Khrushchev.

For the second time in three months, he believed he had acted unwisely, first in approving the Bay of Pigs attack and now thinking that he could reduce differences with Khrushchev by rational explanation. Other commentaries indicated that the one-on-one discussions were exhausting for Kennedy. He felt that he was not at his best during the later hours of the afternoon meeting.

Khrushchev's comments: Observing Kennedy's morose expression at the end of the summit, Khrushchev believed Kennedy "looked not only anxious, but deeply upset … I hadn't meant to upset him. I would have liked very much for us to part in a different mood but there was nothing I could do to help him. … Politics is a merciless business (Kempe 2011). However, historian William Taubman suggests that Khrushchev merely felt that he could "push Kennedy around" (Taubman 2003).

My assessment of Kennedy's behavior: Taking all of this into account, I believe that when the amphetamines and oral hydrocortisone wore off later in the afternoon of the summit, this caused Kennedy to have symptoms related to a lack of "stress doses" of hydrocortisone. This caused Kennedy to feel exhausted and appear dazed. Most experienced endocrinologists would believe that giving amphetamines to a patient with Addison's disease would be potentially dangerous. The resulting adrenaline-like stress might trigger symptoms of hydrocortisone deficiency when the shot wore off three to six hours later. In Kennedy's case, this risk would be doubly compounded by the stress that Kennedy was otherwise under at the summit. As an endocrinologist thinking about this, I believe that Kennedy should have been given stress doses of hydrocortisone under these circumstances, both because of the nature of the meeting and the effects of the amphetamines. On a practical basis, one stress dose was needed at the start of the meeting with Khrushchev, and another when the amphetamine effect wore off in the early afternoon. Dr Eugene Cohen, Kennedy's endocrinologist, was not at the summit to advise him, and it is possible that the President received insufficient stress doses of hydrocortisone.

Khrushchev's reflections: I learned that Khrushchev felt that he had the better of Kennedy during this summit interaction. After the afternoon meeting ended, Khrushchev told his comrades that JFK is "very young … Not strong enough; too intelligent and too weak." He further felt that Kennedy, while very intelligent, was young and inexperienced and perhaps reluctant to respond to Khrushchev with strong actions. Could this have influenced Khrushchev's later decision to place nuclear armed missiles in

Cuba? This is certainly plausible, but one can only look at the facts and speculate.

The assessment of others about the amphetamines: Several authors writing about the Vienna Summit were also concerned about the effect of the amphetamines. Robert Dallek stated

> A long day after much tension certainly accounts for most of Kennedy's weariness by the early evening, *but we cannot discount the impact of the Jacobson chemicals on him as well*. As the day wore on, and an injection Jacobson had given him just before he met Khrushchev in the early afternoon wore off, Kennedy may have lost the emotional and physical edge initially provided by the shot.

Barbara Lemming, another Kennedy biographer, wrote, "Kennedy did himself no favors by facing Khrushchev on speed" (Beschloss 1991, Carlson 2011). Dr. Hans Kraus commented, "No president with his finger on the red button has any business taking stuff like that" (Carlson 2011).

Michael Beschloss commented, in his book by quoting Peter Carlson (Carlson 2011)

> Jacobson injected Kennedy with his mysterious pick-me-up. It was risky. Even in small doses, amphetamines cause side effects such as nervousness, garrulousness, impaired judgment, overconfidence, and when the drug wears off, depression. What if Kennedy would have displayed those qualities in Vienna, when Khrushchev would be scrutinizing every aspect of his behavior, assessing his capacity, mettle and judgement? (Carlson 2011)

> There was no one who was in overall charge to anticipate or deal with the danger that an interaction of cortisone, procaine, amphetamines or whatever else Jacobson had in his syringe and could cause the president to behave in a way that could have had dire consequences.(Carlson 2011)

On June 11, 2011, Peter Carlson wrote an article entitled "How Dr. Feelgood almost drove John F Kennedy to the brink of nuclear disaster." The subtitle was "Previously secret medical records gave us a more authoritative answer to the question. So a summit intended to foster peace ended in war threats.(Carlson 2011)"

Proof that Kennedy had Addison's disease: In order to validly interpret Kennedy's behavior during the summit, it is important to have clear proof that Kennedy had Addison's disease. Kennedy, his family, and his close advisors carefully prevented the media and the public from knowing about

his illness, and it never became an important issue. Only later did the truth become firmly established.

Robert Dallek, who wrote a highly regarded biography of Kennedy ("An Unfinished Life"), obtained permission to review all of Kennedy's medical records after his assassination and refers on several pages to Kennedy's Addison's disease (pages 123, 152-153, 195, 399, 471-472, 576). Dallek describes the discovery of his Addison's disease in the fall of 1947. Kennedy was initially treated with the hormone, DOCA, which has some hydrocortisone-like properties. When it became available, Kennedy received cortisone, which the body converts into hydrocortisone. In 1951, while in Japan during his East Asia trip, Kennedy suffered a severe Addisonian crisis. He ran a temperature of 106°F, and the doctors feared for his life. The episode convinced him to be more fastidious about taking his medicine over the next two years, and his back problems became his principal complaint.

Dr Eugene Cohen, a prominent endocrinologist in New York City, usually managed Kennedy's Addison's disease. Cohen's therapy was standard and included two of the adrenal hormones Kennedy lacked, hydrocortisone and Fluorinef®, a hormone allowing him to hold onto normal amounts of salt (Brown 1992, LR 2009, Bennett 2013, Schwartz 2015). Dr. Lee Mandel delineated the treatment specifically to include daily doses of 10 mg hydrocortisone, 25 mcg liothyronine, 0.1 mg fludrocortisone, and 10 mg methyltestosterone, and 2.5 mg prednisone twice daily (Mandel 2009).

Definitive proof of Addison's disease was then documented from autopsy records that reported that Kennedy's adrenal glands were very small and were likely destroyed by anti-adrenal antibodies (Brown 1992, Dalleck 2003). Dr. J.T. Boswell, one of the pathologists present at the autopsy, confirmed that no adrenal glands were visible and that a microscopic exam of where they should have been revealed only a few individual cells (Brown 1992, Richard 2011, Lundholm, Ambalavanan et al. 2024).

About Dr. Max Jacobson: The story behind the amphetamine shot provides an interesting perspective on Kennedy, his interactions with physicians, and the effect on the Vienna Summit. Many months before the summit, Kennedy had heard from friends that Dr. Max Jacobson, a doctor in New York City, gave shots that made recipients less tired, improved their mood, diminished their levels of mild depression, and increased their energy. Many called Dr. Jacobson "Dr. Feelgood" or "Miracle Max" because of these shots and their spectacular effects (Carlson 2011, Schwartz 2015, Staff 2019).

When Jackie Kennedy developed mild post-partum depression, President Kennedy asked Dr. Jacobson to treat her with one of his shots.