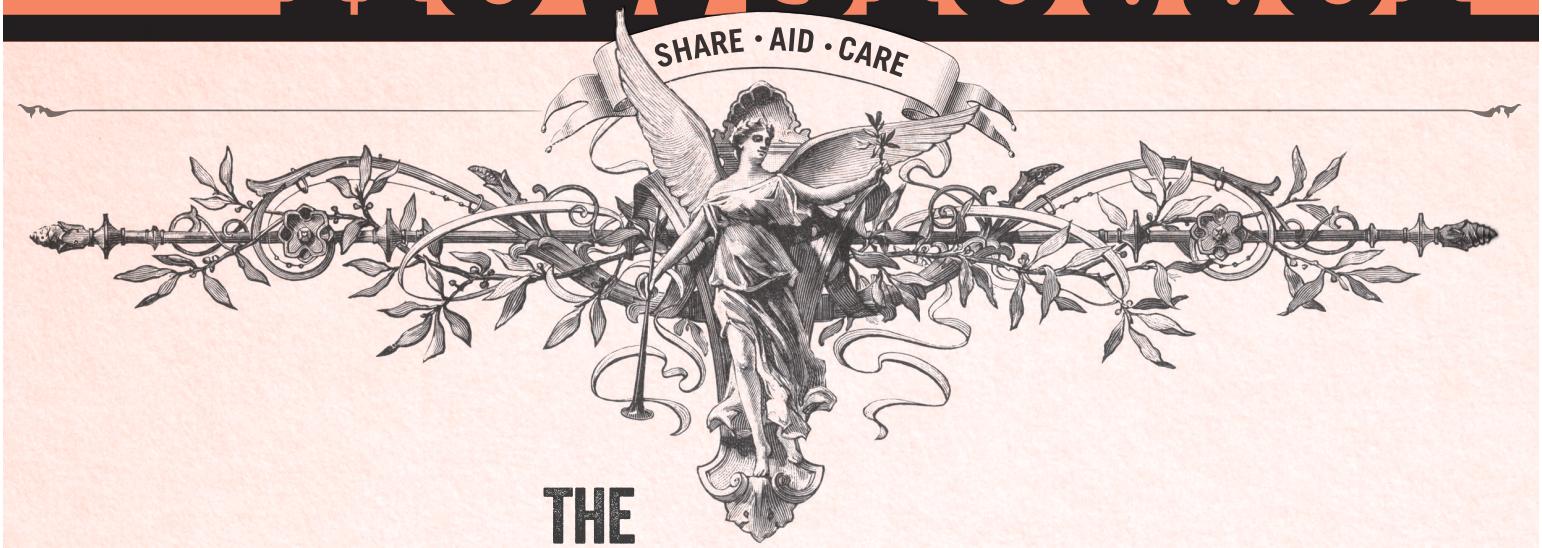
Cushing's Support & Research Foundation
Summer 2018

cushing's newsletter



THE SCIENCE ISSUE

INSIDE THIS ISSUE

Tour meetings between March and May of this year provided a treasure chest of new research about Cushing's, Adrenal Insufficiency, and everything in between. In March we exhibited and attended sessions at ENDO2018, the Endocrine Society's annual meeting in Chicago. Later that month we attended Adrenal Insufficiency United's first-ever conference in Kansas City, MO and met up with about a dozen other Cushing's patients including Associate Board Member Danielle Reszenski and Marie Conley of the Conley Cushing's Disease Fund. In the middle of May we had representatives on two continents attending presentations and talking to attendees: at the American Association of Clinical Endocrinologists (AACE) conference in Boston and the European Society of Endocrinology (ECE) annual meeting in Barcelona, Spain. It is exciting to see all the emerging breakthroughs regarding issues of the Endocrine System.

We returned with notes, slides, memories of conversations, and a lot of anticipation about sharing everything with our membership. Our goal with this issue was to translate the knowledge that we absorbed into a language that makes sense. When specific numbers, percentages, or details are listed, the data came directly from the doctors' presentations. Articles and research are cited when used. We hope that we are accurately communicating the volume of work being done that directly affects our community. We also hope to provide some tools that will help you search for more information and to educate yourself on what science is doing right now.

Continued on page 2

CSRF Newsletter Design: Heather Shaw
www.heathershawdesign.com

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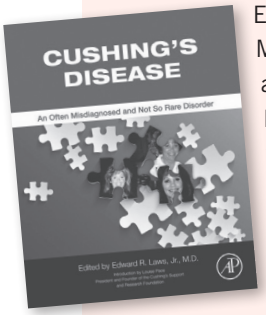
https://twitter.com/CSRFnet

Continued from page 1

Dr. Lynnette Nieman of the NIH (and our Medical Advisory Board) recommends the following website for a comprehensive listing of fact-based research and resources: *https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines.* The Hormone Health Network at *https://www.hormone.org* is an excellent source for easy-to-understand patient material that can help you have better conversations with your health care providers.

Thank you Sabrina, Elissa, Joanie, Danielle, and Sandra for taking time out of your schedules to represent CSRF! *Leslie Edwin*

Cushing's Disease: An Often Misdiagnosed and Not So Rare Disorder



Edited by E. Laws, Jr., M.D., F.A.C.S., Professor of Neurosurgery, Harvard Medical School, Director — Neuro-Endocrine / Pituitary Program, Brigham and Women's Hospital, Boston, with an introduction by Louise Pace, Founder and President of the Cushing's Support and Research Foundation.

This comprehensive guide to Cushing's disease describes the functions of pituitary, adrenal and other hormones, lists the typical and atypical symptoms of Cushing's disease and its subtypes, outlines the causes of elevated cortisol and explains how clinicians can test for, diagnose and treat Cushing's disease. Physicians will find this concise book detailed, thorough and well-referenced. Patients will also find clear and helpful information in this important book. *Published in 2017 by Elsevier Inc — an excellent resource for physicians (and patients)!*

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ENDO 2018

ENDO, March 2018, Chicago IL: Elissa Kline, Joanie Kilbride, Sabrina Whitt, Leslie Edwin

Sabrina Whitt and Leslie Edwin

This year marked the 100th anniversary of the Endocrine Society's Annual Meeting and Expo. The event was held over several gorgeous days in Chicago from March 17–20. Endocrinologists, scientists, nurses, medical students, and other stakeholders gathered in the mutual pursuit of the latest theories, research, and developments in endocrinology. As in previous years, the CSRF reached out to attendees and sponsors on the exhibition floor, welcoming them into our booth for education and discussion. CSRF volunteers Leslie Edwin, Elissa Kline, Dr. Meg Keil, Joanie Kilbride, and Sabrina Whitt promoted awareness and the Foundation's patient resources. This year's conference did not disappoint, offering almost three dozen Cushing's-related presentations in addition to more than 100 related endocrine study and discovery posters.

The following is a summary of scientific information that was presented in nine sessions and four posters related to the Cushing's journey. Presenting doctors are listed as well as any specific research or trial references.

REEXAMINING THE DIAGNOSIS AND MANAGEMENT OF HYPERCORTISOLISM

Dr. Ty Carroll, Medical College of Wisconsin, Menomonee Falls, WI

Increased cortisol frequently causes a number of symptoms that are likely familiar to readers: muscle weakness, vertebral fractures, blood clotting disorders, cognitive and psychological changes, diabetes, and osteoporosis. We know the diagnosis of Cushing's, but a patient can have sustained, elevated cortisol (hypercortisolism) caused by sources other than tumors or steroid use. Hypertension is another frequent symptom of hypercortisolism, but there is a greater issue of cardiovascular health that can sometimes get put on the back burner while treating the more immediate threats of high cortisol. Dr. Carroll stressed the significant effect of cortisol's disruption of the natural circadian rhythm of our bodies, which is an essential regulator of everything from sleeping and feeding patterns to adequate management of glucose and insulin.

It is an unfortunate fact that untreated Cushing's leads to about a 50% mortality rate over five years. According to Dr. Carroll's research, there is a direct correlation between results of the dexamethasone suppression test (DST) and mortality — if a patient's cortisol level suppresses on the low-dose DST with a reading of <1.8 mcg/dl, there is an average 91.2% survival rate; a reading of >1.8 mcg/dl drops the average survival rate to 57% as related to the patient's hypercortisolism. An individual with an adrenal adenoma that is ≥2.4 cm in size is three times more likely to have a cardiac event, and even those with non-secreting adrenal nodules have been found to have a much higher rate of developing diabetes than patients without adenomas of any type present. This research was done on patients who presented with some signs of hypercortisolism but without a diagnosis of Cushing's.

Continued on page 4

The dangers of hypercortisolism-related cardiovascular damage are enough to warrant careful consideration in patients where testing has indicated elevated cortisol. On average, 4-7% of ALL imaged adults have an adrenal incidentaloma (defined as an adenoma, nodule, or "spot" found while doing a scan for another reason). This number increases with age. From this set of patients, an estimated 5-30% of those adenomas turn out to be cortisol-secreting. According to the European Society of Endocrinology, all patients with adrenal nodules should be screened for hypercortisolism. This is not standard procedure in the US yet, and we cannot stress enough that choosing an experienced, educated physician can make a big difference in the care you receive. Physicians experienced with hypercortisolism tend to be more aware of less-commonly discussed screening and diagnostic standards. Even without overt clinical signs of hypercortisolism, the presence of an adenoma and any Cushing's-like symptoms are directly related to an increased risk of health problems.

Dr. Carroll encourages use of the low-dose DST and shared a word of caution against depending too heavily on the urinary free cortisol (UFC) test due to its low sensitivity in mild cases of hypercortisolism. As for blood tests, he prefers testing dehydroepiandrosterone-sulfate (DHEA-S) as opposed to adrenocorticotropic hormone (ACTH) because the level of DHEA-S in the blood remains relatively steady while ACTH is easily disrupted and varies throughout the day.

Editor's note: Interestingly, the percentage of adrenal incidentalomas discovered during abdominal scans for other reasons seems to be higher in the U.S. (4-7%) than the 2% currently reported in a European trial mentioned by Dr. Carroll (NCT02364089 — clinicaltrials.gov).

DIAGNOSIS AND TREATMENT OF "SUBCLINICAL CUSHING'S SYNDROME": WHO, WHY AND HOW?

Dr. Antoine Tabarin, CHU Bordeaux, France
Dr. Irina Bancos, Mayo Clinic, Rochester, MN

The lecture began with a dissection of the word "subclinical" when referring to mild cases of Cushing's with an adrenal source. It can be useful for physicians with little experience dealing with hypercortisolism because it is a term that has been around for a long time and is easily understood to differentiate from overt or pituitary cases. There was unanimous agreement on a recent panel of physicians to instead use the term "autonomous cortisol secretion".

The doctors made the case that diagnosis of autonomous cortisol secretion can be problematic because UFC testing seems to be useful in only about 30% of adrenal cases, and there is a general lack of agreement among the various tests. Their philosophy is to avoid overdiagnosis and overtreatment without missing relevant diseases and to establish a diagnosis at the time an adrenal mass is found. They felt that the 1mg DST was the best tool for diagnosis of possible cortisol secretion in adrenal incidentalomas: a result under 1.8 mcg/dl excluded, above 5 mcg/dl confirmed, and the area in between was a solid "possible". Additional investigations can help to confirm, especially if repeated over a period of 3-12 months depending on the severity of the patient's condition (if they can tolerate the wait). The presence of comorbidities (simultaneous presence of two or more chronic conditions) and the age of the patient are relevant in making the decision on how to proceed.

Some patients are ready to head straight to removal of one or both adrenals when high cortisol is present. There are a lot of potential problems with this approach when the source of high cortisol is not clear and might be something other than a secreting tumor. As rote as it might seem, aggressive lifestyle changes that reduce weight, reduce A1C, and improve hypertension can sometimes lower cortisol in a patient with an adrenal incidentaloma that has questionable cortisol secretion. Medication can sometimes help manage mild hypercortisolism. Unfortunately there are few comparative studies of patients who have adrenalectomies vs. those who opt in favor of other interventions (lifestyle changes, medication, etc). Post-adrenalectomy management is also a matter up for serious debate — there's still quite a bit of "what now?" from both the patient and the physician, and this is not a condition that is beneficial to a person who just had surgery and frequently has other comorbidities to manage.

The take home message from this session was that there is no cut and dried method to ensure success for a patient without clear symptoms and targets. All options must be considered and tests must be repeated. Patients sometimes do not want to wait and will change doctors during the testing process out of frustration. It is vital that the communication between doctors and patients improves so both understand the other's needs, limits, fears, and desired outcomes.

Studies have shown that patients with mild hypercortisolism cross in and out of "normal" and "high" cortisol states if tested over a period of time. We hear patients discuss strategies to "catch highs" to prove they have Cushing's, but this might be misleading with potentially adverse effects if the patient is pursuing a diagnosis that is not appropriate for their condition. Also, one high or low test does not prove anything definitively. Some patients with borderline, intermittent, or self-described "cyclic" cortisol excess have successfully changed their habits (diet and exercise) and seen their DST results return to and stay in a normal range. It's imperative for patients to understand that multiple tests over a period of time are essential to getting the diagnosis correct. It is just as important for doctors to find better ways to make their patients feel that they are heard, believed, and recognized as an active partner in their journey to diagnosis and healthy outcomes. It was encouraging to see so much interest in this subject that the presentation was given twice, in the ballroom (biggest session room), with at least 90% of the chairs filled.

RECENT PROGRESS IN ADRENAL TUMORS

Dr. Constantine Stratakis, National Institutes of Health, Bethesda, MD
Annabel Berthon, PhD, National Institutes of Health, Bethesda, MD

Researchers are expressing special interest in adrenal tumors, their origins, and ways to prevent their formation early in development. Ms. Berthon presented her work with Dr. Stratakis and his team on Kisspeptin, the Kisspeptin Receptor, its role in adrenocortical development, and how that development affects the adrenal gland's secretion of cortisol. Kisspeptin is a hormone made in the hypothalamus and is involved in general endocrine function and puberty. There is some evidence it is also involved in age-related hormone decline.

Studies have looked at the complexities of manipulating various proteins and receptors in their attempts to determine what causes an adrenal tumor to form and why it begins to oversecrete cortisol. It has been determined that damage to the process involving the kisspeptin receptor can lead to hyperaldosteronism, which is the overproduction of aldosterone in the adrenal glands. This condition can lead to hypertension and low potassium / high acidity in the blood.

Kisspeptin and Kisspeptin Receptor May Be Involved in the Regulation of Adrenocortical Development and Steroid Hormone Secretion, Annabel Sophie Berthon, PhD1, Nikolaos Settas, PhD1, Andreas Giannakou, MD1, Angela Delaney, MD2, Fabio Rueda Faucz, PhD3, Constantine A. Stratakis, MD, PhD4. 1NIH, Bethesda, MD, USA, 2National Institutes of Health, Bethesda, MD, USA, 3NIH/NICHD, Bethesda, MD, USA, 4NICHD/NIH, Rockville, MD, USA

CHALLENGING CUSHING'S

Dr. John A Wass, Oxford University, UK

Dr. Wass chose to do the majority of his presentation town hall style — with a brief presentation of data and then the floor opened up for questions and conversations with the physicians in attendance. He described cases of patients who presented in clinic with a few Cushing's-like symptoms and a request for testing. Symptoms ranged from florid to patient-reported but clinically undetectable. He asked attendees to tell him how they would proceed. There were subtle differences in approach and speed, but the audience seemed committed to following established diagnostic guidelines. Still, not everything was as it seemed initially with the patients, which is no surprise.

Dr. Wass shared concerns about the typical symptoms and challenges of Cushing's. He highlighted the fact that patients are more susceptible to infections, psychiatric problems, and clotting tendencies during and after treatment. He feels that most patients need anti-clotting protection for surgeries and exploratory procedures such as the inferior petrosal sinus sampling (IPSS). Dr. Wass was also very insistent that patients be allowed to benefit from a multidisciplinary approach to their symptoms (Dr. Harvey Cushing initially discovered "polyglandular syndrome", which clearly lays out that Cushing's is not a single narrow diagnosis). Outcomes are optimized when specialists get involved and apply their expertise. Centers of Excellence are offering better chances for patients who can use their services because specialists are "under the same roof" and share records. A patient who is treated across the spectrum of specialties will have a much better prognosis.

Another highly debatable topic is cyclical Cushing's. All available evidence points to cyclic being a rare form of an already rare disease. Cushing's is probably more prevalent than currently reported, but it is rare. It is difficult to diagnose because many common factors can lead to intermittent high cortisol readings, and there is a growing knee-jerk reaction in patients to determine they have cyclic Cushing's based on a single high test and online encouragement to fight for that specific diagnosis. Frustration grows when further testing is done and does not back up the single, or occasional, high cortisol test(s). In all cases, the patient can identify at least a few "Cushing's symptoms" because they are so non-specific. There is much work to be done in this area. The following is verbatim from one of Dr. Wass's slides:

> "Cyclic Cushing's: A small group of patients with Cushing's syndrome have alternating normal and abnormal cortisol levels on an irregular basis. All causes of Cushing's syndrome may be associated with cyclical secretion of cortisol. Clearly, the results of dynamic testing can only be interpreted when the disease is shown to be active (elevated urinary cortisol secretion and loss of normal circadian rhythm and suppressibility on dexamethasone)."

Dr. Wass concluded with the bold statement that Cushing's is one of the most challenging conditions for an endocrinologist to treat. Treatment in experienced centers is practically mandatory for a successful outcome, as is long term follow-up of the patient. This follow-up is intended to diagnose and treat recurrence, hormone deficiency, and psychological and other consequences of the disease as early as possible.

ADRENAL INSUFFICIENCY: IMPACT OF PATIENT EDUCATION AND CHOICE OF REPLACEMENT OPTIONS

Dr. Stefanie Hahner, Wurzburg Medical School, Germany

Dr. Hahner began with a patient example — a 38 year old female with adrenal insufficiency (AI) who complained about being tired and having to give up her love of flamenco dancing. She asked the audience how they would proceed, and most agreed that they would individualize the patient's replacement steroid dosing to ensure she was taking a small extra amount ahead of the intense physical exertion required of a flamenco dancer. The patient did this and resumed her passion but still had reduced energy and eventually had to cut back on work hours.

Continued on page 6

What next? The patient was switched to Plenadren, a once-a-day extended release form of hydrocortisone (Plenadren is not licensed for use in the US but has obtained orphan drug status). She would then take a dose of hydrocortisone before her strenuous activity. She felt more stable but still unable to work full time. Her doctor added DHEA treatment — studies show moderate positive effects on depression, anxiety, and the way a patient feels overall when they take DHEA. The patient reported acne and greasy hair about 10 weeks into treatment with DHEA, so the dose was reduced and the negative symptoms resolved. Over the next six months the patient reported slight improvements in sexuality and mood, but she was still only working half time.

Unfortunately, this is a reality for a lot of people with AI. In fact, it could be a best possible outcome for some when compared to the limitations and challenges they experience personally. Not all doctors are comfortable adjusting doses of life-saving hydrocortisone, but this seems to be getting more attention and will hopefully evolve to benefit all patients with AI who do not feel that the standard two doses a day fit their particular life. In the meantime, the squeaky wheel may very well be the one that gets the grease — there is enough research and information available so that patients who want to consider individualized dosing of their replacement cortisol should be able to discuss this approach with their endocrinologist.

In addition to individualized dosing, there are benefits and drawbacks to each of the types of cortisol replacements that are available in the US like prednisone, hydrocortisone, and dexamethasone. In choosing the type of replacement a patient takes, factors like age, ability to remember to take doses regularly, and presence of diabetes should be taken into consideration. If the patient takes a medication that accelerates the metabolism of hydrocortisone (ex. carbamazipine, phenobarbital), that is also very important to factor into replacement choice and dosing.

One last related note, and there is no way to state this too often: there is a high prevalence of psychiatric disorders and metabolic comorbidity in patients with AI. It is vital that all aspects of the patient's health are put under the spotlight and followed when they become adrenally insufficient.

DIABETES INSIPIDUS: CHALLENGES IN DIAGNOSIS *and* MANAGEMENT AND VASOPRESSIN, FALLS & FRACTURES

Dr. Daniel Bichet, Universite de Montreal, Canada
Dr. Joseph Verbalis, Georgetown University, Washington DC

Although diabetes insipidus (DI) is a fairly common occurrence after treatment for Cushing's, providers face some surprising challenges in its management. DI is not related to blood sugar but rather to the water balance involving the kidneys and vasopressin, the anti-diuretic hormone (ADH). Vasopressin affects cells in the collecting ducts of the kidneys. The synthetic replacement for vasopressin can quickly become a deficient patient's best friend, as it helps prevent fluid loss from the body by reducing urine output and helping the kidneys reabsorb water into the body.

As soon as we become comfortable with a synthetic form of vasopressin to help us maintain our bodies' fluid balances after damage to or removal of the pituitary, we find that this very medication has been shown to play a role in increased numbers of falls and fractures. Desmopressin, or DDAVP, can be a very effective and extremely useful drug, but this replacement hormone is powerful. Too little DDAVP can lead to DI. Too much can lead to congestive heart failure, cirrhosis of the liver, and syndrome of inappropriate ADH (SIADH).

Dr. Verbalis explained the danger behind a less common side effect of taking the drug: hyponatremia, or the condition of having an abnormally low concentration of sodium in the blood. Excessive vasopressin affects the body's sodium levels and can cause a condition in which the brain develops an area of edema (swelling) because of sodium imbalance. The patient will often develop gait instability because hyponatremia affects nerve conduction and leads to loss of muscle strength.

Since the body is an efficient user of its own resources, when it experiences chronic sodium deficiency, it can actually break down bones for nutrients. In the persistent absence of enough sodium, the body will send bone-dissolving osteoclasts (similar to white blood cells) out of its bone marrow to do their job and free up sodium, which is found in bones along with calcium and Vitamin D. Due to this breakdown, the patient can experience bone weakness that often leads to falls and a sharp increase in fractures and breaks. The standard for diagnosis of hyponatremia is the Bone-Micro CT scan with treatment focused on targeting the underlying cause of the excessive ADH dosage.

UNCONVENTIONAL CAUSES AND TREATMENTS OF ADRENAL INSUFFICIENCY

Dr. John Achermann, University College London,Great Ormond Street Institute of Child Health, UK
Dr. Peter Kuhnen, Institute of Experimental Pediatric Endocrinology, Berlin, Germany

Although the following information discusses causes of adrenal insufficiency (AI) that are not related to Cushing's, it is still very encouraging that scientists are looking into the ways this condition develops on a microscopic level. Advances in genetics can lead to better understanding and beneficial outcomes for all AI patients - the researchers are attempting to understand what causes AI in the hopes that they may eventually develop a way around that mechanism and prevent it from happening in the first place.

Three mutations can contribute to symptoms of AI in adults and children. These gene variants are present and detectable as early as four

weeks post-conception and can accurately predict the incidence of primary AI. AI that starts later is often a result of deficient genetic mutations in CYPIIA1 and the STAR gene. A third mutation, an endocrine regulator called SAMD9, leads to a progressive chromosome loss that ignites a series of events that will also cause AI.

Another uncommon cause of AI is a deficiency of the proopiomelanocortin (POMC) gene, which is synthesized in the pituitary. A lowered level of POMC leads to low ACTH in addition to problems with obesity and achieving satiety. POMC deficiency also affects the body's melanocortin, frequently leading to pale skin (https://ghr.nlm.nih.gov/gene/POMC). Further research has focused on treatment that might restore the action of POMC, ultimately returning the body's ability to feel full and more effectively utilize its energy.

DEBUNKING THE INTERNET MYTHS: WHAT IS THE BEST APPROACH?
Dr. Jonathan Leffert, North Texas Endocrine Center, Dallas, TX

The internet is an amazing resource — what CAN'T you find online these days? You never come up short, even with the most obscure search topics. According to a recent study, 60% of the public uses the internet for health information and 35% is actively engaged in "online diagnosis." (J Med Internet Res. 2017 June 13;19(6):e202)

As with everything in life, there is a dark side to this stunning collection of information: misleading advice, disinformation, and opinions stated as facts. You could say it is human nature to want to share our personal truths, even if we don't realize that subtle methods to our storytelling can end up being detrimental to some of our audience. Cushing's patients and those pursuing a diagnosis are vulnerable in so many ways — just one example is the list of more than 30 symptoms that can accompany this disease. A huge portion of the population could claim at least a few of those symptoms on a regular basis. Does that mean that everyone has Cushing's? Of course not.

Dr. Leffert noted that in the early years of his practice (from 1991 until a few years ago), patient referrals usually came from another physician or the insurance company. In the last few years, many referrals have come from internet self-diagnoses, online ratings websites, and other online sources. This is awesome in a way: expanded access to specialists you'd never know about without the internet is a priceless resource. Helpful advice from patients who have come before you can comfort you throughout the excruciating period of diagnosis and provide wisdom for the "after".

The downside is that patients desperate for an answer to what ails them frequently do not do thorough research to understand the functioning of the larger systems of the body. Endocrinology is a perfect example. Symptoms of endocrine disease are often vague and nonspecific. Lab tests may be assay- or time-dependent, resulting in "abnormal" results when easy-to-confuse instructions are not followed precisely. Agreeing to the wrong treatment at the patient's insistence does not fix the underlying symptoms because the underlying disease is not addressed.

Doctors must strike a delicate balance between appropriate testing and the patient's expectations. If the two are not aligned, it's going to be a difficult time for everyone involved. Dr. Leffert advised the packed room to empathize with the patient but to stand firm in the conviction not to perform unnecessary tests or prescribe medications that are not clearly indicated. Most important, physicians must remember that patients come to them out of a need to feel better. They need help. There may be therapies that can help with some symptoms while the patient begins a lengthy testing period.

There is a lot of work to be done to help patients and doctors communicate and understand one another, to get the right tests done the first time, and to help the patient understand the process, especially in the case of hypercortisolism / Cushing's.

Prescription Assistance

There are many prescription drug cards that can be found by searching the internet. The CSRF does not endorse any specific card. One that has recently come to our attention is **UNA Rx** card which can be used nationwide. More information is available at *http://www.unarxcard.com/index.php*

Rx Hope is another program with discounted prescription pricing: *https://www.rxhope.com/*

PAN has programs for some of the medications specific to Cushing's including Korlym and Signifor: *https://www.panfoundation.org/*

NORD also provides help with medication costs as well as travel and other medical expenses: *http://rarediseases.org/for-patients-and-families/help-access-medications/patient-assistance-programs/*

Call: 1-800-999-6673 x 326
Email: Cushings@rarediseases.org

ENDO2018: Poster Highlights

Hundreds of posters representing recent research and case studies looking into various clinical aspects of Cushing's were presented. Some highlights:

- **Dr. Elena Valassi** (Universitat Autonoma de Barcelona, Spain) and colleagues examined quality of life (QoL) in patients with Cushing's Disease versus patients with adrenal Cushing's Syndrome using European registry data. They found that the single most important predictor for quality of life was achieving remission, rather than the origin. There was sufficient data to conclude that patients with a pituitary source vs. an adrenal source had lower QoL at long-term follow up. **(Patients With Cushing's Disease Have Worse Long-term Quality of Life Than Patients With Cortisol Producing Adrenal Adenoma. Data From The European Registry On Cushing's Syndrome (ECUSYN),** Elena Valassi, MD, PhD, Universitat Autonoma de Barcelona, Barcelona, Spain et. al.)
- **Dr. Irina Bancos** (Mayo Clinic, Rochester, MN) and colleagues have been investigating expression of the FKBP5 gene and its potential future use as a biomarker for measuring cortisol activity. Increases in glucocorticoids in the body lead to increased expression of FKBP5. This correlation can be used not only for diagnosis, but also for monitoring response to medical or surgical treatments in patients with hypercortisolism. After successful surgical treatment, FKBP5 gene expression has been found to be comparable to gene expression in healthy subjects. It was their conclusion that FKBP5 gene expression could potentially be used as a clinical biomarker for evaluation and diagnosis in patients with Cushing's. **(FKBP5 Gene Expression Biomarker In ACTH-dependent Cushing Syndrome Patients Pre- and Post-curative Surgery,** Irina Bancos, MD1, Betul Ayse Hatipoglu, MD2, Kevin Choong Ji Yuen, MD, FRCP (UK), FACE3, Andreas Moraitis, MD4. 1Mayo Clinic, Rochester, MN, USA, 2Cleveland Clinic, Beachwood, OH, USA, 3Swedish Pituitary Center, Swedish Neuroscience Institute, Seattle, WA, USA, 4Corcept Therapeutics, Menlo Park, CA, USA)
- **Dr. Pejman Cohan** (Specialized Endocrine Care Center, Beverly Hills, CA) and colleagues gave a case presentation of a patient believed to have spontaneously entered remission following treatment with mifepristone (Korlym), a glucocorticoid receptor antagonist. The 23-year-old woman experienced three recurrences, each time with symptoms of rapid excessive weight gain, hypertension, and depression along with multiple other conditions. She was repeatedly treated with transsphenoidal surgery, each time achieving only a temporary remission. It is believed by some that spontaneous nonsurgical remission of hypercortisolism in Cushing's Disease patients can be a result of a sudden obstruction to the blood supply in the pituitary (apoplexy or infarction). The authors postulate that mifepristone may have played a role in this spontaneous remission of a non-visible pituitary tumor. **(A Curious Case of Biochemical and Clinical Remission After Treatment with Mifepristone, a GR Antagonist,** Pejman Cohan, MD1, Daniel Kelly, MD2, Precious J. Lim, PhD3. 1Specialized Endocrine Care Center, Beverly Hills, CA, USA, 2Pacific Neuroscience Institute, Santa Monica, CA, USA, 3Corcept Therapeutics, Menlo Park, CA, USA)
- **Dr. Jennifer Cheng** (Jersey Shore University Medical Center, Neptune, NJ) and her colleagues presented their endorsement of a combination treatment for the management of mifepristone-induced hypokalemia (low potassium) in a case study. The combination of potassium-sparing diuretics amiloride and spironolactone helped their subject lose weight, control his blood pressure, and also maintain his potassium level. He was able to significantly decrease or discontinue all of his previous medications. The patient reported improvements in mood, depression, and anxiety, and he no longer experienced suicidal ideations. Muscle strength improved, abdominal girth decreased, and striae greatly improved. **(Combining Amiloride and Spironolactone to Manage Hypokalemia and Edema in Patients with Cushing Syndrome,** Jennifer Cheng, DO1, Rachel Bunta, MBA2. 1Jersey Shore Univ Med Center, Neptune, NJ, USA, 2Corcept Therapeutics, Menlo Park, CA, USA)

If you'd like to browse the summaries for all posters presented, and there are a LOT on Cushing's-related issues, visit https://www.endocrine.org/endo-2018 and click the link for "Abstracts Presented" under the topic "View the ENDO2018 Abstracts".

AACE, May 2018, Boston MA: Leslie Edwin and Danielle Reszenski

Sandra Marques at the ECE conference in Barcelona, May 2018

CSRF in Barcelona

In May 2018 CSRF was represented at the European Society of Endocrinology's 20th annual conference in Barcelona, Spain by member Sandra Marques from the UK. Sandra reports that traffic at the CSRF table was much heavier this year than last, with 80% of our business cards gone by the end of the meeting; many doctors took several to share with their patients. One doctor from Russia spent time discussing Cushing's with Sandra and ended with a request that we stay in contact and see what we can do to help patients like hers in St. Petersburg who do not have access to resources like ours. Medical Advisory Board member Dr. Maria Fleseriu from Oregon stopped by to say hello, as did Anne Marie Bergevin, a volunteer from Quebec who translated many of our pamphlets into French with review from Dr. Andre Lacroix, CHUM, Montréal, Canada.

Sandra's experience at this event has energized her to want to do more to help spread patient support and education in Europe. She has offered to translate some of our materials into Portuguese — thank you, Sandra! She noted that CSRF sponsor HRA Pharma was also presenting on the exhibit floor and there are many companies in Europe who seem to be interested in supporting patients in the rare disease community. We are excited to see how this all unfolds.

Emotional Health in Adults with Cushing's and Adrenal Insufficiency

A summary of the AIU meeting presentation by Kyle Gillett, PhD, LMFT, Asheville, NC

We need to broaden and never pause in the conversation about mental health, depression, and neuropsychological changes due to excess or deficient cortisol. There is no room to consider them any less important than our other symptoms. The average risk of depression in the general population is about 9.5%, and the average risk for anxiety is 18%. Add a chronic illness to the equation and the likelihood of depression or anxiety jumps to 28%. Specify Cushing's and the risk goes up to a staggering 50-90% for depression and around 79% for anxiety. It is the norm, not the exception. Patients report guilt, anger, loss, and feelings of rejection by friends and family who don't understand. Too many of us struggle silently, afraid to burden our loved ones with yet another aspect of our disease. We would be doing ourselves a favor to seek professional help from someone who has the tools and experience to hear what we are saying and help us work through it. Occasionally or regularly, why shouldn't it be considered part of our specialist appointment routines?

Emotional stress also hits hard on the low end of the cortisol spectrum: it is the third leading cause of adrenal crisis, preceded only by gastrointestinal issues and fever. From a neurological perspective, when faced with a stressor, if the body's normal ability to bring stress back down to normal level isn't well regulated, the stress can become a trauma. When your body is deficient in the hormone that controls stress response, efforts to "deal with" the stress don't do anything to replenish the diminished hormones and steroids in your body and can lead to the crisis.

It would be great if the issue was solved by simply taking replacement hormones and steroids. Unfortunately, research suggests that depression still exists in about 35% of patients six months after starting hormone replacement therapy. After a year of treatment, that number is still too high at 25%.

Why so prevalent? Among more obvious reasons, hormones impact how neurotransmitters work and thus directly impact psychological and emotional functioning. Things we do repeatedly in life create "superhighways" of heightened connections in the brain. Dr. Gillett hypothesizes that patients with Cushing's and/or adrenal insufficiency (AI) are more likely to be and stay depressed and full of anxiety because our brains have repeated the stress response so often that they have become trained to exaggerate it with every single thing that comes our way in life.

It is an easy segue to address post-traumatic stress disorder (PTSD) and the high prevalence of its existence in relation to Cushing's or Addison's:

- *re-experience symptoms* — bad dreams, frightening thoughts
- *avoidance symptoms* — staying away from things that remind, emotionally numb, strong feelings of guilt, depression or worry, loss of interest in previous enjoyments
- *hyperarousal symptoms* — easily startled, quick to respond

Many pieces of news we get on the Cushing's journey are sad. The way we feel makes us sad. If we also have a little (or a lot of) depression going on, it might be difficult to always tell the difference. The following are examples of feelings that are not just sadness:

- it is hard to still enjoy things you like
- your emotions are about a specific event or thing rather than general
- you are not maintaining normal eating and sleeping routines
- you have self-punishing or extremely self-critical thoughts
- you have self-harming thoughts

Stress and anxiety often dress like each other but have some basic differences:

- anxiety is internal, stress tends to be external
- stress eventually comes to an end, anxiety is still there after the problem is resolved
- in stress the worry is justified, in anxiety the worry is distorted and amplified
- unlike stress, anxiety can bring on a panic attack (reported to feel like a heart attack, difficult time breathing, tightening of muscles, increase in heart rate and pulse, and flushing of the skin which is often hot and sweaty)

Other types of anxiety include but are not limited to OCD, panic disorder, and specific phobias. Other challenges include but are not limited to substance abuse, the inescapable drag of "why me?", and suicidal thoughts. It isn't easy, and if you already showed up to the game with some baggage, you have that many more reasons to create the softest landing spot for yourself when the burdens of these diseases really make themselves known in your life. Please PERSIST and find a professional who can partner with you on your mental health.

Thank you for your support!

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Cushing's Patient Pamphlets

Pamphlets include *Understanding Cushing's, Diagnostic Testing, Recovery, Prevention and Treatment of Adrenal Insufficiency,* and *Why Replacement Medications are Needed.*

ENGLISH TO SPANISH TRANSLATION

Thanks to the efforts of Dr. Marta Araujo Castro, an endocrinologist at the Puerta de Hierro's Hospital, in Madrid, Spain, the Cushing's Patient Pamphlets have been translated into Spanish and are posted to our website!

ENGLISH TO FRENCH TRANSLATION

Thanks to the joint efforts of Anne Marie Bergevin and Dr. Andre Lacroix, French versions of some pamphlets have been posted to our website.

Pros and Cons of Surgical Interventions, Radiation, and Medical Therapies

By Leslie Edwin

Dr. Beverly MK Biller gave a fascinating presentation on some of the treatments available to Cushing's patients at the American Association of Clinical Endocrinologists meeting in May. I had intended to write about all of the options for this issue, so listening to what Dr. Biller had to say was a great start. I also consulted two research articles on pituitary- and adrenal-focused treatments done by Dr. Maria Fleseriu as well as a previous article in our newsletter by Dr. Ty Carroll about medical therapies. Please see *Author's Note* at the end of this article for references.

When a patient presents with obvious signs of Cushing's that are confirmed with testing, treatment options can be fairly easy to choose. Surgery is still the preferred first line of treatment to remove a tumor. Having a patient whose case is clear to start with doesn't necessarily mean they will get a one-and-done treatment though. Research shows that recurrence rates are as high as 27% if patients are followed long enough, and this data comes from expert centers with highly trained doctors who have treated thousands of patients. Based on that statistic alone, it would not be a waste of time to think about and develop a flexible plan for all the things that could happen after a first surgery.

The majority of patients reach remission and most have low cortisol after surgery for approximately 12 months, but many still recur. This is concerning because even though patients in remission don't seem to have a higher-than-normal mortality rate, those who experience recurrence see their chance of death increase almost five-fold. In these cases, the next line of treatment is trickier and more of a complex decision — will the benefits outweigh the risks, and are the risks worth taking? This is a highly individualized decision that can have a range of consequences for the patient.

One factor to highlight is the importance of credible, science-backed sources of information to guide your decision-making process. Personal reasons for choosing one (or two) approaches over the others are never exactly the same for any two patients, and yet the good advice from our peer group can remind us to consider certain real-life scenarios that might not always get addressed when discussing "what next" with a doctor. We strongly encourage you to consider yourself in your world, as recommended by Dr. Harvey Cushing himself, and proactively become a partner in your healthcare to ensure your best outcome.

The following is pro and con information for some of the treatments available to us. There is no way to accurately describe these in full detail without writing a book, so please explore each as it interests you. Look things up online but try to stick to links that come from places of science, education, and medicine such as the NIH, Mayo Clinic, Endocrine Society, UCLA, Harvard, etc.

REPEATED TRANSSPHENOIDAL SURGERY

Pros: seems to be well-tolerated for those who can have it, effects tend to be immediate, provides the only chance for permanent tumor removal

Cons: as with a first operation, steroids are usually required afterwards, patient might become hormonally deficient, surgeon might miss tumor cells, patient might not achieve long-term remission

BILATERAL ADRENALECTOMY

Pros: immediate remission from cortisol, usually permanent, well-tolerated, especially when done laparoscopically

Cons: risks of abdominal surgery, lifelong need for glucocorticoids (hydrocortisone) and mineralocorticoids (fludrocortisone), complications from Addison's Disease and possibly Nelson's Syndrome, recurrences rare but possible

RADIATION

Conventional radiation is typically given over 5 days a week for 6 weeks. Stereotactic radiosurgery is a single, high dose treatment that is given on just one day. There are three different types of stereotactic surgery that can be used: linear accelerator (LINAC), Gamma Knife or Proton Beam. Over many years, radiation seems to have a spectrum of 28-86% success rate for biochemical control, with tumor control at a higher rate of 80-100%.

Pros: well-tolerated, possibly a single treatment, tumor and cortisol control

Cons: delayed effectiveness, medication needed until radiation begins working, long-term risks such as pituitary deficiencies, damage to nearby tissue, and secondary tumors, possible but rare recurrence

Things get trickier when you consider the small number of available medical therapies. Each has a unique personality and it's likely that more than one will not be a good fit. The patient and doctor must

Continued on page 12

consider a number of things: severity and urgency of the illness, overall treatment goals, medical history and patient factors, drug-drug interactions, oral vs. injectable delivery, the side effect profile, and cost and availability of the drug.

MEDS THAT WORK AT THE PITUITARY LEVEL

Cabergoline (generic) is fairly well-tolerated but does not seem to be effective in people with very high cortisol levels. Cabergoline is mainly used for the treatment of prolactin-secreting pituitary tumors, but it has been shown to normalize cortisol levels in 20-40% of patients with Cushing's. Unfortunately, the effects of cabergoline tend to wear off over time and cortisol levels rise despite continued treatment in about a third of patients who take it.

Pasireotide (Signifor, manufactured by Novartis) is an injectable medicine originally developed to treat Acromegaly, another type of pituitary tumor disease. Trials were done with Cushing's patients and showed a lot of promise — weight, blood pressure, lipids, and other symptoms improved and cortisol declined. Based on this data, the FDA approved Signifor as a therapy for Cushing's. An updated, once-monthly version of the original drug just completed an extension study for patients who had success with pasireotide from the original study (see info on Dr. Maria Fleseriu's late-breaking poster information in our Research Summaries section). Signifor causes adrenal insufficiency (AI) in only about 8% of users. Most frequent side effects are gastrointestinal. This drug can cause hyperglycemia or worsen already-existing diabetes in the patient, but this effect can potentially be managed with additional meds.

MEDS THAT WORK AT THE ADRENAL LEVEL

Ketoconazole (generic) is an antibiotic used in the treatment of fungal infections and is one of the most, if not the most, commonly used medications in patients with Cushing's. About 50-75% of patients treated with ketoconazole have their cortisol levels normalized. However, its effectiveness may be limited by side effects including liver damage. This damage can occur at any dose, and the liver injury may be irreversible even after stopping the drug. The US Food and Drug Administration (FDA) recommends weekly blood testing to monitor liver function for the duration of treatment with ketoconazole. This drug works by inhibiting several enzyme steps in cortisol production. Studies have shown cortisol control ranging from 49-99%. A Phase 3 trial studying a new formulation called levoketoconazole (Strongbridge Biopharma) that hopes to address some of the pitfalls of traditional ketoconazole treatment is almost complete. Ketoconazole has a lot of drug-drug interactions.

Metyrapone (Metopirone, manufactured by HRA Pharma and available via DSI Pharmacy in the U.S) is currently approved in the US only as a diagnostic drug to test for ACTH function. It can be used off-label to decrease and stabilize cortisol levels. Metopirone is currently approved for treatment in Europe. It inhibits the last enzyme step in cortisol synthesis, with cortisol control reported in about 75% of patients across three studies running from the 1970s-1990s. Gastrointestinal issues and adrenal insufficiency are the most common side effects in about 25% of patients taking the medication. This medication has been available for a long time, so the safety profile is well known. Although no drug is approved for use in pregnancy, there has been successful use of Metopirone in a pregnant patient who then went on to deliver a healthy baby.

Mitotane (Lysodren, manufactured by HRA) is primarily used in patients with adrenal gland cancer, but it can also be used to lower cortisol levels. Like ketoconazole, Lysodren blocks production of cortisol, but in higher doses it may also cause destruction of adrenal cells. Studies show it is effective in more than 80% of patients, but nearly as many patients have side effects that can be significant. Many patients may have gastrointestinal problems and some develop problems with confusion and impaired mental function while taking Lysodren.

Etomidate (generic) is an intravenous drug usually used for anesthesia, but it is also used for seriously ill patients with severe hypercortisolemia who cannot take oral medication. There are only a few cases of its use reported in scientific literature. Some studies have shown it to inhibit cortisol fairly rapidly at a dose low enough to avoid sedative effects. The most common side effects are hypnotic effect, hypotension, nausea, and vomiting. This medication can cause AI.

MED THAT WORKS ALL OVER

Mifepristone (Korlym, manufactured by Corcept Therapeutics) is the first FDA-approved medication specifically for the treatment of high blood sugar in patients with Cushing's. Korlym works differently than the other medications — it blocks the action of cortisol in the body rather than reducing it. An impressive 60-90% of patients taking Korlym achieve improvement in blood sugars and many of the clinical features of Cushing's. Most common side effects include nausea, headaches, swelling (edema), and low potassium levels. Women taking this drug may also have vaginal bleeding, and Korlym should never be taken for the treatment of Cushing's in women during pregnancy because of its antiprogestin activity. In that same vein, it should not be confused with Mifeprex, a different mifepristone drug made by Danco Laboratories for other purposes.

Some doctors are not familiar with prescribing Korlym and have reservations because cortisol cannot be accurately measured to assess the dangers of AI. Although Korlym and hydrocortisone cancel each other out, the cortisol blockage effect of Korlym can be reversed with dexamethasone. There are many potential drug-drug interactions with Korlym, so it is important to tell your doctor about all of the medicines you take including prescription and non-prescription meds, vitamins, and herbal supplements.

Although this list is rather short and full of unfortunate side effects, it is a solid start. Many rare diseases have zero medical options. It took a long time to get to the point where there were ANY therapies identified, targeted, or approved for treatment of Cushing's. It is encouraging that updated versions of several of these drugs are in Phase 2 or 3 trials now with promising data and fewer adverse effects and/or better cortisol control.

Author's Note: this article was based on a lecture given by Dr. Beverly MK Biller (Mass General, Boston, MA) at the AACE meeting. All clinical information comes from her presentation, the information in the review articles ***Pituitary-Directed Therapies for Cushing's Disease*** *(Langlois F, Chu J, Fleseriu M. Front Endocrinol (Lausanne). 2018 May 1;9:164. doi: 10.3389/fendo.2018.00164.) and* ***Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies*** *(Fleseriu M, Castinetti F. Pituitary. 2016;19(6):643-653. doi:10.1007/s11102-016-0742-1), and some direct passages about medical therapies from Dr. Ty Carroll's Doctor's Answer to the question, "What medications are used to treat Cushing's?" in the Winter 2013 issue of our newsletter.*

Adrenal Insufficiency in Adults, Stress Dosing, and Adrenal Crisis

Leslie Edwin

Dr. Anthony Heaney, Co-Director of the UCLA Pituitary and Neuroendocrine Program and President of the International Pituitary Society, presented two sessions titled "What are the causes of adrenal insufficiency in adults and when do I need to stress dose?" and "What is Adrenal Crisis?" at the AIU conference. This is my interpretation of his presentations and the accompanying slides.

ADRENAL FUNCTION AND INSUFFICIENCY

Knowing when to stress dose and what to do in an adrenal crisis are two of the most important questions that must be addressed when a patient enters adrenal insufficiency (AI). The patient is suddenly tasked with trying to adequately mimic the essential stress response that is unique to each of us with cortisol replacement while simultaneously becoming aware of conditions that can cause them to need more than just their maintenance dose to avoid becoming sick. Best case scenario has us quickly able to access our medicines at all times and avoid crisis, but worse case sees an AI patient become very ill, unable to take oral medication, using an emergency injection, rushing to the ER, and/or worse.

It is helpful to think about stress as acute vs chronic. Our adrenal glands are built to handle both types of stress events, but that fact isn't very useful if our adrenals are not working properly or have been removed. During acute stress, mechanisms in the brain send signals rapidly to nerves in the spinal cord that connect with the medulla (lowest part of the brainstem). This releases epinephrine (adrenaline) and norepinephrine. Within 30-40 seconds, heart rate and blood pressure go up, the liver produces glucose to deal with the event, and the lungs dilate.

Cortisol, metered and chronic in its approach, arrives on the scene when your brain anticipates an extended challenge. This entire process is mediated by hormones throughout your endocrine system. It causes retention of sodium and water in the kidneys, increases glucose production, and reduces insulin response to keep the glucose in the blood stream.

Dysfunction among the glands of the endocrine system impacts these processes. In primary AI, the adrenal itself is damaged. In secondary AI, something else was damaged and caused problems in the adrenal.

In primary AI, there is an absence of cortisol and aldosterone, a hormone that regulates sodium and potassium. An example of primary AI is Addison's Disease, which affects women and men equally at a ratio of about 1:100,000 people in the US. Symptoms of Addison's can include extreme fatigue and weakness, salt craving, nausea and vomiting, low blood pressure and blood sugar, decreased appetite and weight loss, body hair loss, GI disturbances, and bronze pigmentation of the skin.

The origin of secondary AI frequently involves the pituitary: removal of an ACTH-secreting pituitary tumor or radiation to the pituitary, for example. There are other, less frequent causes including tuberculosis and gene mutations.

TREATMENT FOR AI DEPENDS ON THE TYPE:

- Primary AI patients replace cortisol with hydrocortisone, cortisone acetate, or prednisone and replace aldosterone with fludrocortisone. Sometimes they replace androgens (testosterone or estrogen) with synthetic DHEA or Prasterone. If possible, it is optimal to treat the underlying cause of the AI.
- Patients with secondary AI brought about by damage to the pituitary replace cortisol with hydrocortisone, cortisone acetate, or prednisone. They sometimes replace other hormones such as thyroid, growth, and anti-diuretic. They do not have to replace aldosterone because their adrenals are intact and still performing this function which is not affected by the damage to the pituitary.
- Patients with steroid-induced AI are advised to work with their doctor to safely wean off the steroid, reduce intake of the steroid, and/or switch to a different medication.

Continued on page 14

For all patients with AI, it is important to work with your doctor to fine-tune your personal best dosage for daily maintenance and stress dosing. Your doctor needs input about your lifestyle so they can really understand you in your natural environment. Are you a couch potato or a marathon runner? Do you do better with two daily doses or a more personalized three or four? The challenge is to find the proper balance that keeps your cortisol from becoming too low but also protects against adverse effects of too much steroids: mood and sleep disturbances, weight gain, high blood pressure and blood sugar, osteoporosis, and other symptoms of high cortisol.

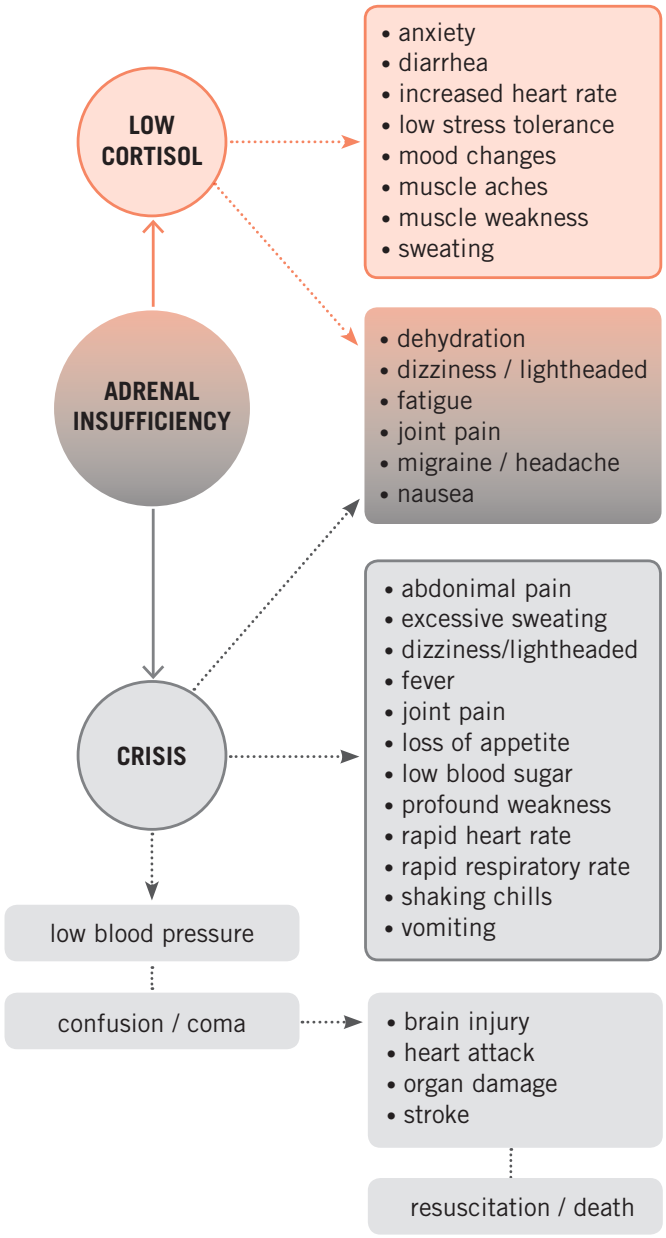
STRESS DOSING

There is a spectrum of stress, and usually an adrenal crisis is brought about by more than just one thing. A catastrophic event could do it, but more commonly it's due to trauma or illness. It's important to recognize the difference and not get into a situation where steroid doses are being increased too often, because that can lead to symptoms of hypercortisolism. There is always an exception to the rule — under certain circumstances of acute high stress, such as caring for a terminal parent, short-term sustained increased dosing can help, but it's extremely important to return to your normal dose as soon as possible. This highlights the value of helping your doctor determine the appropriate individualized dose for your life and what you're experiencing.

Increasing hydrocortisone can present two types of effects: dose-dependent and duration-dependent. Dose-dependent effects are from large doses taken for short periods of time and can include temporary high blood sugar, psychosis and peptic ulcer disease. Duration-dependent effects appear when higher-than-needed doses are taken for long periods of time. Examples of this are high blood pressure, Cushingoid physical changes, frequent infections, and osteoporosis.

Osteoporosis is especially concerning because we only make bone until about age 22. That's it for the rest of our lives. Bones don't get better with time. It is recommended that we Cushing's and AI patients have our bone density checked about every two years, preferably on the same machine. This can be challenging due to moving or insurance, but bone health should not be ignored.

SPECTRUM OF ADRENAL INSUFFICIENCY



ADRENAL CRISIS

We know our bodies best, but some of us are particularly good at giving the outward appearance that everything is ok when it's not. AI and adrenal crisis do not have time for that nonsense. Prompt action is required to prevent dangerously low cortisol levels. Signs that you might be heading into an adrenal crisis include:

- fatigue, lack of energy, weight loss
- low blood pressure, dizziness, possible collapse
- abdominal pain, tenderness, nausea, vomiting
- fever
- confusion, sleepiness, in severe cases delirium or coma
- back and leg cramps and spasms

If you think you are heading into an adrenal crisis, hopefully you have rescue medicine and are trained and ready to give yourself an emergency injection of hydrocortisone if you cannot keep an oral rescue dose down. The next step is to be seen by or in touch with a doctor immediately. The life-threatening qualities of an adrenal crisis dictate that there are no adverse consequences to initiating life-saving treatment with hydrocortisone. Diagnostic measures should never delay swift treatment of a suspected adrenal crisis — they can be safely established once the patient is stable. Typically, after a patient is stabilized, they will continue to receive high doses of hydrocortisone and

rapid rehydration for a short period of time, after which they will be tapered off the high doses with the guidance of their endocrinologist.

PUTTING IT ALL TOGETHER

Managing AI is a delicate balance that requires control and attention to many moving parts. At the AIU conference, two things puzzled me in the beginning: it seemed like there were a lot of people who forgot to set their alarms to silent because they kept going off during the presentations, and everyone was very enthusiastic about the electrolyte samples being given out. I discovered that the alarms weren't random — they were alerting that it was time to take a dose of hydrocortisone. The electrolytes address the lack of aldosterone in primary AI patients. One presenter had a box of broth with a straw sticking out — she called it her adult juice box. In her severe case, this is her solution to the problem of low sodium. This information is very timely for me personally because all signs point to secondary AI in my near future after radiation and removal of my pituitary gland in my ongoing effort to beat Cushing's. I feel lucky to have spent a weekend witnessing the adaptive behaviors of people who manage AI in their lives.

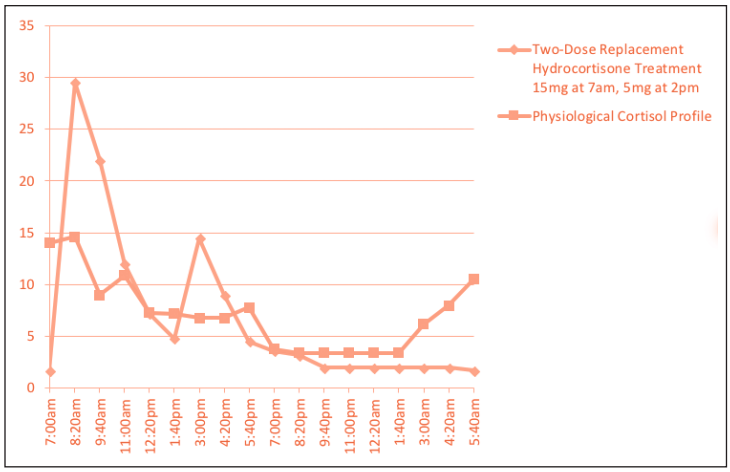
Adrenal Insufficiency United *is a volunteer-run patient organization focused on helping patients safely and successfully find solutions for their lives with AI. Some patients reach remission from their Cushing's and are able to avoid AI, but for those who have no choice but to integrate it into their "new normal", support and advice from others with the same affliction can be just as important as clinical treatment from your doctor. If AI is an issue for you, we highly recommend that you visit AIU's website at aiunited.org or find them on Facebook.*

New Approaches and Treatments in Adrenal Insufficiency

Adapted from a presentation at the AIU conference by Dr. Mitchell Geffner, Children's Hospital of Los Angeles, CA

The structure of cortisol was discovered in the 1930s. By the next decade scientists had developed a way to create a synthetic replacement, a substance known as cortisone. The 1950 Nobel Prize in Physiology or Medicine went to Drs. Edward Kendall, Tadeus Reichstein, and Philip Hench for "their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects" (www.nobelprize.org/nobel_prizes/medicine/laureates/1950). By 1955, hydrocortisone as we know it today was presented to the world.

Traditional treatment in temporary and permanent adrenal insufficiency (AI), regardless of the source, tends to be twice-daily hydrocortisone (with the addition of fludrocortisone if the patient has primary AI). Doctors have historically preferred hydrocortisone over others like prednisone and dexamethasone because it is the most physiologically similar to natural cortisol, it is not as strong as the other choices, and it clears the body quickly. The graphic below shows why the two-dose regimen tends to work for the majority of patients who need replacement — it does a satisfactory job of mimicking the natural profile of cortisol in the body.



That being said, Dr. Geffner expressed approval of three doses spread every eight hours to avoid a period of time overnight where a patient would not have any cortisol coverage. Many patients in the audience shared how they split their total daily quantity of hydrocortisone into three or four doses based on experience, activity levels, and to avoid lows or "crashes" in the evening.

There are three hydrocortisone products in development out of the UK that address some of the issues patients can have when hydrocortisone, prednisone, and dexamethasone still leave something to be desired.

Plenadren (manufactured by Shire) is a modified dual-release hydrocortisone with immediate and sustained absorption through its immediate-release coating and extended-release core. In adults, the single morning dose gives similar cortisol exposure to a thrice-daily regime of immediate-release hydrocortisone, although Plenadren tends to provide higher concentrations of cortisol in the late morning and lower concentrations in the late evening than a conventional hydrocortisone schedule. The expectation is that a once-daily dose will improve adherence and quality of life, although this remains to be demonstrated in trials.

Chronocort (manufactured by Diurnal) is a modified-release hydrocortisone that differs from Plenadren in that it has a "delayed and sustained" rather than an "immediate and sustained" absorption profile. Chronocort aims to replace physiological cortisol concentrations

Continued on page 16

by dosing at morning and night. The nighttime dose provides release of hydrocortisone in the early hours of the morning providing a pre-waking rise in cortisol levels. A study of Chronocort in 16 adults with Congenital Adrenal Hyperplasia showed that a twice-daily regimen of Chronocort provided a similar cortisol rhythm and early morning peak to physiological cortisol concentrations in healthy volunteers. Whether these short-term effects can be sustained and what effect on overall health status this has in patients is the subject of an ongoing Phase 3 study in the UK. **(Is physiological glucocorticoid replacement important in children?** Archives of Disease in Childhood 2017; Porter J, Blair J, Ross RJ, 102: 199-205)

Lastly, there is the **Hydrocortisone Pump.** This technology was pioneered by Professor Peter Hindmarsh of Great Ormond Street Hospital in the UK and is similar to an insulin pump. The scientific community is currently looking at this treatment through trials, but it's not expected that this will become a common treatment anytime soon. Several patients who use the pump have written blog posts and other first-hand accounts of why they sought it out, the difficulties of getting it, and pros and cons of using a pump vs. more traditional therapy. AI patients who would benefit most from a cortisol pump are:

- those who have rapid metabolism of cortisol in whom adequate control cannot be achieved with conventional replacement, even at 4-5x daily dosing
- those with severe stomach irritation from glucocorticoids
- those for whom life-threatening conditions are a reality because they don't take their meds on a regular basis, as scheduled

Ultimately, the pump was designed and intended for those who experience extremely diminished quality of life because of their inability to achieve an acceptable level of success with oral cortisol replacement. The pump ensures 100% absorption because the medicine goes straight from the fat into the vein. Users can still stress dose with oral meds for illness.

Doctor's Answers

Q I get frustrated when my doctor says there's no science to back up certain symptoms I am convinced are part of Cushing's — either I have had them or I know someone who has. I feel certain that in time, lots of things that have no science behind them now WILL have science behind them. Why do these patient-reported symptoms not get treated seriously sometimes?

A Because of the tremendous amount of overlap with other conditions, and the unfortunate inability of some physicians to put it all together, symptoms alone are not enough. So we try to depend on laboratory tests to clinch the diagnosis, and avoid dangerous and fruitless medical or surgical therapies. The lab tests, however, are difficult to perform properly, vary in accuracy from one lab to another, and may not be conclusive, either. We need to be sure that there is excess cortisol being excreted, and that it is coming from excess ACTH. Dexamethasone suppression is not totally reliable, salivary cortisols may be variable, and fasting blood cortisol and ACTH are really important, along with 24 hr UFCs which can also be difficult to perform with total reliability. The symptoms should trigger a consideration of the diagnosis of Cushing›s Disease, and a referral to an endocrinologist with experience with pituitary and adrenal disease.

This question was answered by Dr. Edward Laws, Brigham and Women's Hospital, Boston, MA

Q What is the best way for a patient to convince you to test them for Cushing's? I spent three years getting worse while my endocrinologist would only test every six months. I live in a small town and don't have easy access to Cushing's specialists. After gaining almost 70 lbs and having many classic symptoms, I finally had a series of high enough tests for my doctor to refer me to a specialist several hours away who diagnosed me and sent me to surgery. I'm frustrated about all the wasted time feeling horrible when I knew in my heart all along that I had it. I wish I had been more aggressive in the beginning.

A The feeling of a need to convince someone is not a good one, and we all sympathize with this problem. It would be best to copy a list of the symptoms and signs of Cushing's Disease from an authoritative paper or book chapter or book on the subject. Then check them off, and if you see that they really fit, request a referral to an endocrinologist who is familiar with pituitary and adrenal disease, and also with PCOS and its differential diagnosis. The endocrine testing should fully support the diagnosis and is necessary to avoid ineffective and potentially dangerous medical or surgical treatment.

This question was answered by Dr. Edward Laws, Brigham and Women's Hospital, Boston, MA

Q I recently attended a meeting with other adrenal insufficiency patients and was surprised to find out that some of them had personalized dosing of hydrocortisone and were taking smaller but more frequent doses, some 4x a day. I've been taking two daily doses for years but the idea of having a small third dose to potentially avoid my semi-frequent crashes in the evenings sounds very appealing. Is this a generally accepted practice amongst Endocrinologists? My doctor has never mentioned doing it that way, but then again, I haven't asked. I want to discuss personalizing my dosing without him thinking I'm trying to get more steroids. Is there anything I should be especially concerned about if I try adjusting my dose on my own?

A There are many variations in the ways that doctors prescribe glucocorticoids (cortisol-like medicines) — sometimes based on what they have learned and what other colleagues do, and sometimes based on the patient's response. I like to use hydrocortisone because it is cortisol, and doesn't last as long in the blood as do other glucocorticoids, like dexamethasone. If we give two or three doses a day we can very roughly mimic the normal circadian rhythm of cortisol in the blood. Theoretically, it seems a good idea to give a replacement that is as close to normal as possible. However, some patients don't want to take more than one (or two) doses each day, and seem to do fine on just one or two. Others complain of nighttime "crashes" (as in the question) and seem to do better with a third dose. In the US, most endocrinologists seem to give two doses a day, divided roughly 2/3 in the morning and 1/3 in the afternoon. In Europe, and especially in the UK, three doses are given about as often ("thrice daily dosing") as are two, and one or four doses is very uncommon.1

In deciding how to split the dose, there are a few principles to use: First, the total daily dose should remain the same. I generally use 10 – 12 mg/M2 body surface area, and not just weight. The amount decreases over the day: 2/3 – 1/3 for two doses; 50-35-15 for three, and so on. Since it is hard to prescribe less than 2.5 mg dose, the amounts will vary depending on the number of doses and body size. Second, it is important to give the first dose as early as possible in the morning, but the timing of the afternoon dose can be varied by the patient. The evening dose timing can also be varied but generally should be given early enough so that there is a perceived effect, and not so late that it disrupts sleep.

So for a more specific answer to the question, it is important to figure out the best total daily dose, and modify that number as needed. Then it can be split up in different ways, always with the highest dose on wakening, and the timing of subsequent doses can be varied by the patient.

1 Murray RD, Ekman B, Uddin S, Marelli C, Quinkler M, Zelissen PM; the EU-AIR Investigators. Management of glucocorticoid replacement in adrenal insufficiency shows notable heterogeneity — data from the EU-AIR. Clin Endocrinol (Oxf). 2017 Mar;86(3):340-346.

This question was answered by Dr. Lynnette Nieman, NIH, Bethesda, MD

Q My pituitary gland was removed, so now I replace a lot of hormones. I didn't have a period for awhile, but once I changed my doses of estrogen and progesterone, now I have one like clockwork every month. I'm still in my 30s. Is it possible for me to become pregnant?

A The pituitary hormones FSH (follicle stimulating hormone) and LH (luteinizing hormone) direct the ovaries to grow eggs each cycle and promote production of estrogen and progesterone. They are most likely deficient in this patient, as she is taking estrogen and progesterone. These hormones can be given as injections as a substitution therapy to induce egg growth and hormone production. This is generally done by gynecologists who specialize in reproductive endocrinology and infertility and perform in vitro fertilization. Because there are some risks, these artificial cycles should be followed closely under the care of such a specialist.

This question was answered by Dr. Lynnette Nieman, NIH, Bethesda, MD

Q Depending on what you read, some sources think the 24 hour urine is the "gold standard" test for Cushing's, while others think it's the dexamethasone suppression test. Some doctors will only start with a blood cortisol test, and a lot of resources I've read say that this is an almost worthless test. How can Cushing's patients feel confident when the literature and different doctors don't agree on the best test for Cushing's? There are countless examples of people who had normal cortisol on their first test but did end up having Cushing's.

A With regard to current laboratory testing, we all agree that it is imperfect in many cases, and can be misleading and very frustrating for the patient and the Physician as well. One test is not enough to send the patient on a course of therapy that may not work and may have side effects and/or complications. All of the treatments are designed to lower circulating cortisol levels, so unless we can be sure they are elevated, and that there is a good chance that they are the result of a pituitary source, it may not be wise to recommend treatment, especially surgery, before being certain. It is well known that in some cases repeated testing may be needed to pin down the diagnosis with security.

This answer provided by Dr. Edward Laws, Brigham and Women's Hospital, Boston, MA

A Current guidelines recommend three tests for the diagnosis of possible Cushing syndrome: Late-night salivary cortisol, low-dose dexamethasone suppression test, and urine cortisol. All 3 of these studies probe different aspects of abnormalities seen in patients who have either pituitary or adrenal Cushing syndrome. Although urine cortisol was considered a "gold standard" in the 1980s and 1990s, it has become increasingly obvious to experienced clinicians that urine cortisol may lack adequate sensitivity in some patients. In other words, some patients with pituitary and many patients with adrenal Cushing syndrome have normal urine free cortisol and a normal level should never be used to exclude the diagnosis.

Late-night salivary cortisol is the most sensitive means to detect patients with pituitary Cushing syndrome. Virtually all patients who have pituitary Cushing syndrome will have elevations of late-night salivary cortisol — albeit sometimes intermittently. Consistently normal late-night salivary cortisol levels exclude the diagnosis of pituitary Cush-

Continued on page 18

ing syndrome. Low-dose dexamethasone suppression test is always abnormal in patients with adrenal Cushing syndrome and abnormal in the vast majority of patients with pituitary Cushing syndrome. Unfortunately, both late-night salivary cortisol and low-dose dexamethasone suppression testing have a 10-20% false positive rate and can be misleading. Therefore, abnormal results should ALWAYS be interpreted and evaluated by an endocrinologist. However, normal levels of dexamethasone suppression testing and late-night salivary cortisol exclude Cushing syndrome of any type. Consequently, many of us believe that these two studies should be the initial tests utilized in the screening of patients with possible Cushing syndrome.

This answer provided by Dr. James Findling, Medical College of Wisconsin, Menomonee Falls, WI

The hunger for knowledge and fact-based science about Cushing's has steadily grown in recent years. If you're not familiar with the process of looking for research and deciphering what you've found, we hope this section will be helpful. We patients can use published research kind of like lawyers find case precedents to support their actions in court – when our doctors are unknowledgeable or have a limited grasp of our condition, providing backup from the scientific community could make a difference in helping them understand. Even if your doctor has all the tools he or she needs to diagnose and treat you, the ability to access this research remains an amazing resource for patients who are curious about their condition, want to know about new developments on drugs they are considering, or want to quell (or confirm) suspicions they have about aspects of the disease or standards of care.

The U.S. National Library of Medicine at the NIH makes research available through PubMed at https://www.ncbi.nlm.nih.gov/pubmed/. PubMed is easily searchable by key word, title, or researcher. Most of the studies and articles are published in scientific journals that hold rights of distribution, so you won't always find the full text available for free although it's not uncommon to find a link to the full text in the online version of a publication. In PubMed this availability will be indicated in the upper right section of the page.

Each of the following examples begins with a citation for the literature. This "address" gives you the title, authors, journal, and date of publication. Some citations contain a digital object identifier (DOI), a permanent reference to a location where the work can be found for as long as it exists. URLs and other markers might change over time, but the DOI system provides continuity of access. Keyword, DOI, or title searches, even in Google, are usually successful in finding specific research.

Value of pituitary gland MRI at 7T in Cushing's disease and relationship to inferior petrosal sinus sampling: case report. Law M, Wang R, Liu CJ, Shiroishi MS, Carmichael JD, Mack WJ, Weiss M, Wang DJJ, Toga AW, Zada G. *J Neurosurg.* 2018 Mar 23:1-5. doi: 10.3171/2017.9.JNS171969. (epublished ahead of print)

In March we came across an article in the news about a patient who had Cushing's symptoms and received both a 1.5T and 3T MRI that were negative for tumors, but an IPSS pointed to a pituitary source. Drs. Meng Law and Gabriel Zada and their team at the Keck School of Medicine at USC in Los Angeles successfully found the tumor on a 7T MRI. This is the first time this machine has been used to detect a previously-undetectable pituitary tumor. The patient went on to have a successful surgery. Drs. Law and Zada were happy to share the full case report and we hope to hear a lot more from them. Only the abstract is currently available online.

Pituitary-Directed Therapies for Cushing's Disease. Langlois F, Chu J, Fleseriu M. Front Endocrinol (Lausanne). 2018 May 1;9:164. doi: 10.3389/fendo.2018.00164. eCollection 2018.

This review article looks at all the drugs currently available and in trial that address pituitary sources of hypercortisolism. The full text of this article is available for free.

Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies. Fleseriu M, Castinetti F. *Pituitary.* 2016;19(6):643-653. doi:10.1007/s11102-016-0742-1.

This review article looks at all the drugs currently available and in trial that address adrenal sources of hypercortisolism. The full text for this is also available online for free.

Long-Term Efficacy and Safety of Once-Monthly Pasireotide in Patients With Cushing's Disease (CD): A Phase III Extension Study. Maria Fleseriu, Stephan Petersenn, Beverly MK Biller, Pinar Kadioglu, Christophe De Block, Guy T'Sjoen, Marie C Vantyghem, Libuse Tauchmanova, Shoba Ravichandran, Michael Roughton, André Lacroix, John Newell-Price

This study is summarized on the next page and was not yet published as of the date we went to print with this newsletter. Dr. Fleseriu shared the summary after presenting the poster in May at the ECE meeting in Barcelona. The abstract is available online at http://www.endocrine-abstracts.org.

Long-term efficacy and safety of Pasireotide LAR in Cushing's disease, poster tour presentation at ECE 2018, Barcelona, Spain

Summary by Dr. Maria Fleseriu, OHSU, Portland, OR

INTRODUCTION

Many patients with Cushing's disease require long-term medical treatment to manage their disease. It is therefore necessary to understand the long-term efficacy and safety of pharmacotherapies in these patients. Here, we report the efficacy and safety of long-acting pasireotide in patients with Cushing's Disease following a long-term extension to a large Phase 3 study.

METHODS: STUDY DESIGN

Patients were eligible to enter the extension if they had normal mUFC levels (the mean of three 24-hour urine test results over a period of two weeks) or were achieving clinical benefit from pasireotide at the end of the 12-month core study.

RESULTS: PATIENT DISPOSITION

81 patients entered the extension phase; of these, approximately half completed the extension, with the other half discontinuing treatment (most commonly as a result of consent withdrawal). Median exposure to pasireotide for these patients was 24 months (maximum duration: 55 months).

Long-term efficacy of pasireotide

Most patients who remained in the study at month 24 and month 36 had normal mUFC levels at these time points. Median mUFC levels decreased rapidly during the core study and remained suppressed throughout the extension, with similar patterns seen for serum cortisol and late-night salivary cortisol.

Changes in clinical signs

Biochemical changes were accompanied by sustained improvements in the clinical signs of hypercortisolism, including blood pressure, body weight and waist circumference.

Changes in tumor volume

Clinically meaningful reductions (defined as ≥20% decrease from baseline) in tumor volume were seen in over 60% of patients at months 24 and 36, including those with a macroadenoma at baseline.

Safety of long-acting pasireotide

All patients who received at least one dose of pasireotide were included in the analysis of adverse events (AEs), irrespective of whether they entered the extension. Most common AEs that were reported throughout the study were consistent with the known safety profile of pasireotide. The majority were hyperglycemia-related, reported in 77% of patients; however, only six patients experienced a new hyperglycemia-related AE after the cut-off date for the core study. While median fasting blood sugar levels and A1C increased soon after initiation of pasireotide, levels then stabilized over long-term treatment. A1C remained within the goal of <7% set for the management of diabetes throughout the study.

Conclusions

In this study, long-acting pasireotide provided sustained biochemical and clinical improvements in patients with Cushing's Disease who remained on long-term treatment and showed a similar safety profile to that reported during the core study. Long-acting pasireotide appears to be an effective long-term treatment option for some patients with Cushing's Disease.

AIU, March 2018, Kansas City MO: Cushing's patients unite

Need to talk?

Turn to page 27 for CSRF local support groups and contacts.

Another resource offered by the U.S. National Library of Medicine is the database of interventional and observational studies that can be found at http://www.clinicaltrials.gov. Interventional studies are also commonly called clinical trials, while observational studies do not involve any sort of intervention or treatment. Studies in all stages are listed on the website for anyone to view. At the time this issue went to print, there were 44 returns to a search for clinical trials with the keywords "Cushing's Disease". If there was a way to search for every instance of cortisol-related issues, that number would be in the hundreds. If you are interested in finding out if a particular type of trial might be available in your area, there is an advanced search option under "Find a Study" where you can get as specific as you want with your parameters. Even if you don't find an exact match, you can tweak your search terms and probably change the outcome of the search. Along the way you will be offered many links to studies with titles that give you a glimpse into the world of science and proof that "someone" is most definitely "doing something"!

Trials occur in phases, or stages, based on study objectives, participants, and other factors (observational studies do not operate in phases):

- **Early Phase 1:** exploratory studies conducted before the traditional trials begin, involve very small doses of the drug and make no claims of therapy or diagnosis of any disease
- **Phase 1:** studies focused on the safety of a drug, usually conducted with healthy volunteers, main goal is to study adverse events, their frequency, and how the body breaks down and gets rid of the drug
- **Phase 2:** studies focused on gathering preliminary data in patients with the disease, frequently involve some patients receiving a placebo, measuring safety and adverse events still a priority
- **Phase 3:** studies that receive the benefit of data from the first few phases of trials and involve more participants across specific populations at different dosages, measuring safety and efficacy of the drug still a priority
- **Phase 4:** trials that occur after FDA approval of the drug that continue to gather safety and effectiveness data to ensure optimal use of the drug

Here are a few results to a query for currently recruiting U.S. trials on "Cushing Syndrome":

Collecting Information About Treatment Results for Patients With Cushing's Syndrome, an observational study consisting of many questionnaires and profiles that aims to track patients before, during, and over time after surgery, radiation, and/or medical therapy. Dr. Eliza Geer at Memorial Sloan-Kettering Cancer Center in New York, NY (and a Medical Advisory Board member) is the contact on this study. **(NCT03364803)**

A Study of ATR-101 for the Treatment of Endogenous Cushing's Syndrome, a Phase 2 trial using a drug that works at the adrenal level by inhibiting an enzyme that transforms free (circulating) cholesterol into the basis for making cortisol. Without its "base," steroid production in the adrenals is reduced and the investigators hope to see a ≥50% reduction in patients' UFC numbers. Dr. James Findling (Medical College of Wisconsin, Menomonee Falls, MI), also a CSRF Medical Advisory Board member, is the Principal Investigator on this trial being conducted in multiple US and UK centers. **(NCT03053271)**

Study to Evaluate Relacorilant (CORT125134) in Patients With Cushing's Syndrome, a Phase 2 trial assessing safety and efficacy of relacorilant, a drug from Corcept Therapeutics. It is an "updated version of Korlym (mifepristone)" without the antiprogestin effects that can cause termination of pregnancy, thickening of the uterine lining, and/or irregular vaginal bleeding. Outcome improvements sought are glucose and/or blood pressure control. This study is taking place in several US states and European countries as well as the UK. The Study Director is Dr. Andreas Moraitis at Corcept. Dr. Moraitis will also direct the Phase 3 trial, which is expected to start later in 2018. **(NCT02804750)**

A Study to Assess the Safety and Efficacy of Levoketoconazole in the Treatment of Endogenous Cushing's Syndrome (LOGICS), a Phase 3 trial assessing efficacy (decrease in cortisol), safety, tolerability, and action of the drug in the body. Strongbridge Biopharma, maker of levoketoconazole, is conducting this trial in several US states plus several other countries. **(NCT03277690)**

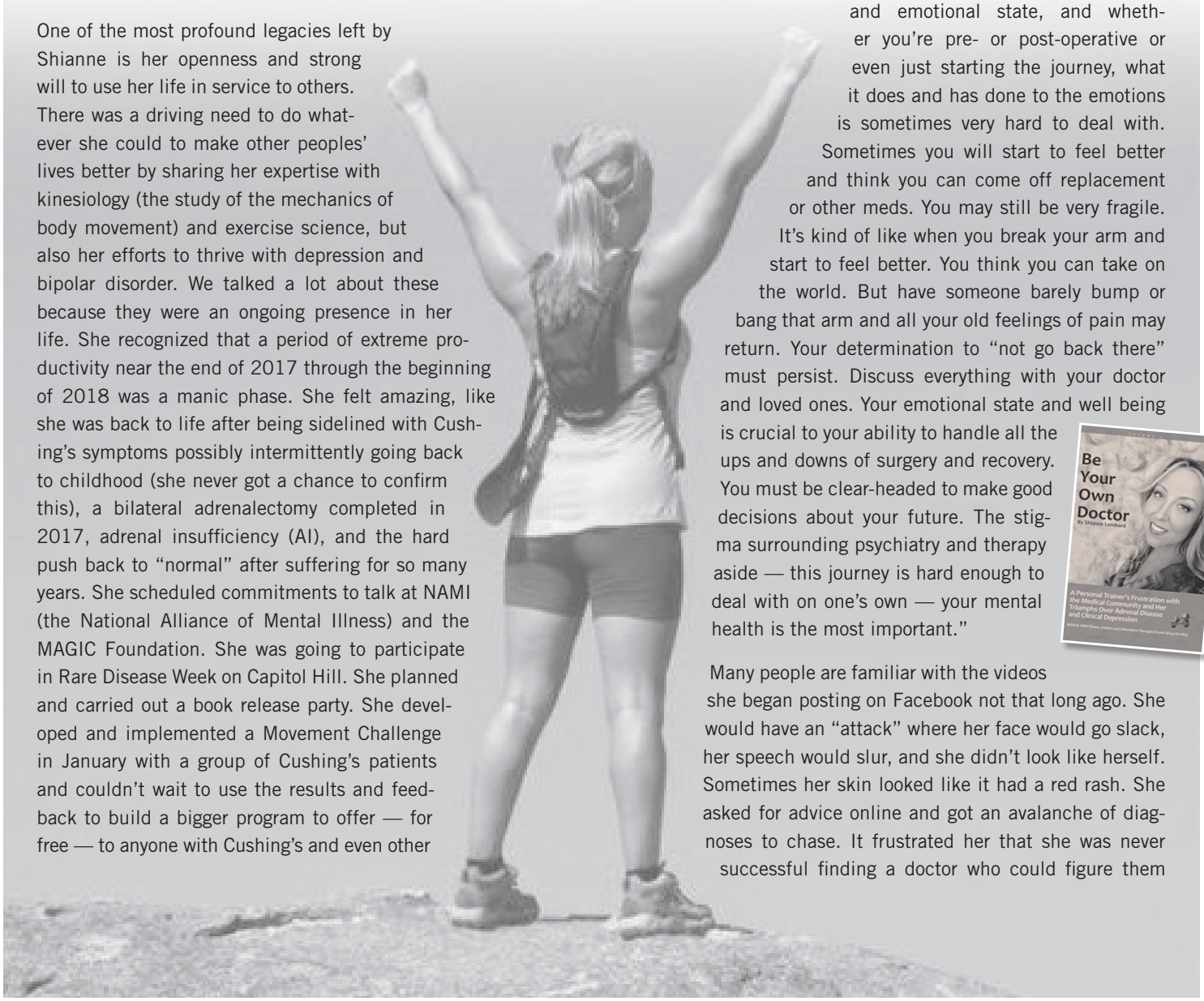
Efficacy and Safety Evaluation of Osilodrostat in Cushing's Disease (LINC-4), a Phase 3 trial conducted by Novartis Pharmaceuticals in 32 locations around the world. Osilodrostat binds to and inhibits the activity of a couple of adrenal enzymes - CYP11B1 and CYP11B2. These genes catalyze the final steps of cortisol and aldosterone synthesis, respectively. **(NCT02697734)**

In Memoriam: Shianne Lombard-Treman

Leslie Edwin

My friend Shianne Lombard Treman was a complex, deep person who had enough life stories for someone twice her age. The first time you met her, you were struck by her beauty and exuberance. She was goofy but smart and really tuned in when you talked to her. Her personality made people comfortable. Cushing's impacted her so intensely that it caused a pivot in her goals; it made her want to help people protect their bodies and minds as they went through the drawn out diagnostic process, treatment, crash, and "new normal" afterwards.

One of the most profound legacies left by Shianne is her openness and strong will to use her life in service to others. There was a driving need to do whatever she could to make other peoples' lives better by sharing her expertise with kinesiology (the study of the mechanics of body movement) and exercise science, but also her efforts to thrive with depression and bipolar disorder. We talked a lot about these because they were an ongoing presence in her life. She recognized that a period of extreme productivity near the end of 2017 through the beginning of 2018 was a manic phase. She felt amazing, like she was back to life after being sidelined with Cushing's symptoms possibly intermittently going back to childhood (she never got a chance to confirm this), a bilateral adrenalectomy completed in 2017, adrenal insufficiency (AI), and the hard push back to "normal" after suffering for so many years. She scheduled commitments to talk at NAMI (the National Alliance of Mental Illness) and the MAGIC Foundation. She was going to participate in Rare Disease Week on Capitol Hill. She planned and carried out a book release party. She developed and implemented a Movement Challenge in January with a group of Cushing's patients and couldn't wait to use the results and feedback to build a bigger program to offer — for free — to anyone with Cushing's and even other limited-mobility patients. Her findings were intended to be the basis of at least one webinar with CSRF. This is just a partial list of all the things Shianne wanted to do — and would have done extremely well — while also tending to a fairly new Addison's diagnosis and continuing her career as a personal trainer at The Sanctuary, a gym in Baltimore, MD.



At the end of a video she made several months ago, Shianne read some very personal excerpts from the book she wrote. It was so important to her that people understand how vital mental health is, especially when dealing with a nightmare like Cushing's and a challenge like Addison's:

"I encourage anyone who deals with emotional instability to please get help. Do not hesitate. Cushing's messes with the mind and emotional state, and whether you're pre- or post-operative or even just starting the journey, what it does and has done to the emotions is sometimes very hard to deal with. Sometimes you will start to feel better and think you can come off replacement or other meds. You may still be very fragile. It's kind of like when you break your arm and start to feel better. You think you can take on the world. But have someone barely bump or bang that arm and all your old feelings of pain may return. Your determination to "not go back there" must persist. Discuss everything with your doctor and loved ones. Your emotional state and well being is crucial to your ability to handle all the ups and downs of surgery and recovery. You must be clear-headed to make good decisions about your future. The stigma surrounding psychiatry and therapy aside — this journey is hard enough to deal with on one's own — your mental health is the most important."

Many people are familiar with the videos she began posting on Facebook not that long ago. She would have an "attack" where her face would go slack, her speech would slur, and she didn't look like herself. Sometimes her skin looked like it had a red rash. She asked for advice online and got an avalanche of diagnoses to chase. It frustrated her that she was never successful finding a doctor who could figure them

Shianne and Amy Dahm doing a radio spot on Cushing's in Baltimore, MD in November 2017

out once and for all, and they became so debilitating that she had to stop seeing clients at the gym. Advocacy was a huge new part of her life, but personal training was her original passion and career. I still don't know a lot about bipolar depression, but I know the pendulum can swing hard in either direction. The attacks increased and Shianne started letting go of commitments one by one. I noticed longer periods of time in between our communications, but I mistook that for a full schedule — that was one of the things we had in common. We can't ever focus on just one thing. She was also very good at controlling her outward appearance to give the impression that everything was going ok.

There is no substitute for Shianne. There are no feel-good words that make it alright. I can't randomly text her anymore, and we will never again have marathon phone sessions talking about crazy advocacy ideas. These are selfish thoughts, but Shianne was a very unique person with amazing intentions and the skill and ability to make them all happen. Above that, she was a loyal friend who made me feel special. She hoped to inspire self-care and healthy change in all aspects of the lives of people living with Cushing's. At the same time, she had a chemical imbalance that she suspected was exacerbated by Cushing's and then AI. She questioned her medication. She would talk about moving out of the manic phase in the other direction. It sounded like she knew exactly what was going on and was doing anything and everything that seemed worth pursuit in her attempts to get better. It bothered her that the period of feeling elated with life and full of purpose evaporated with the intensifying of her health issues.

Depression and mental illness are not shameful, and they very much need to be addressed as part of your overall care as you go through and emerge from the hormonal whirlwind of hypercortisolism. Even without a previous diagnosis of depression or mental illness, the stress, anxiety, fear, pain, insecurity, and loss of "normalcy" that come with Cushing's and AI can lead to unhealthy or even dangerous behaviors. I am grateful for the time I got to have Shianne in my life. Please nurture yourself, and support and look out for each other.

Psychiatric Problems after Remission from Cushing's

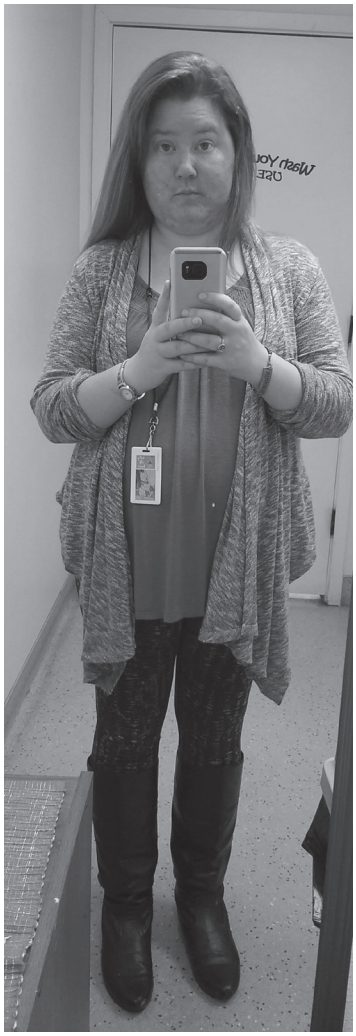
There is a mutual benefit to the ongoing clinical trials for Cushing's at the National Institutes of Health (NIH): patients receive excellent treatment from experts at no cost, and researchers gather data to analyze for details to explore further with additional studies. Dr. Meg Keil and her team collaborated on one such study looking at a group of pediatric patients who suffered significant psychological effects after successful surgery. Within her report, Dr. Keil states the following:

> "There is substantial evidence that adults with CS suffer a high incidence of psychopathology, most commonly depression or affective disorder, with gradual improvement of symptoms after remission and recovery of the HPA axis. However, many patients do not achieve a premorbid level of functioning and experience persistent impairment of QoL and cognitive function. Brain morphologic changes, including cerebral atrophy and decreased hippocampal volume associated with cognitive decrement and depressive symptoms, have been reported in adults with active CS and are partially reversible after cure. These data highlight the need for prospective research to investigate the long-term psychological and cognitive morbidities.
>
> In adults with active CS, suicidal ideation has been reported in ~17% of subjects, and although psychopathology was associated with elevated cortisol levels, it was not uncommon for a delay in resolution of psychiatric symptoms for months or years after resolution of the hypercortisolemia. Also, there is evidence that adults and children endorse compromised QoL measures for many years after resolution of CS. Experimental models have demonstrated long-term changes in neuronal function caused by excess glucocorticoid exposure, and this mechanism has been suggested as a possible cause of neurocognitive sequelae *(conditions that are caused by previous disease or injury)*."

Although there is not yet a large volume of research completed on this subject, we are glad to know it is getting attention.

Cases of Psychiatric Morbidity in Pediatric Patients After Remission of Cushing Syndrome. Keil MF, Zametkin A, Ryder C, Lodish M, Stratakis CA. Pediatrics. 2016;137(4):e20152234. doi:10.1542/peds.2015-2234.

Before Cushing's



With Cushing's

I started having serious health issues after my freshman year of college. I was 18 years old and extremely active with two jobs and in college with upper division courses. Physically, emotionally, and mentally I was working overtime. My symptoms started with a 20 lb weight gain and a significant case of acne. I was put on Accutane by my dermatologist for five months which did not fix the acne. My face got worse and I continued to gain weight. For years I exercised like crazy, tried different things, and ate healthy; still no change. In fact, I continued to gain weight. It felt like I was constantly going in for bloodwork and had multiple tests and ultrasounds. I also saw numerous specialists including my primary care doctor, a kidney and nutritionist specialist, my gynecologist, etc. They all kept telling me that things were normal, and I just needed to lose weight, go on a low sodium diet, etc.

I went a total of 4½ years being misdiagnosed. Eventually I was referred to an endocrinologist by my gynecologist for something I thought was unrelated, but now I'm not so sure. Before even giving him my list of symptoms and issues he knew by my appearance that something wasn't right.

I met my endocrinologist on June 26, 2017. Repeated testing confirmed his initial suspicion, and we scheduled an MRI to find the tumor. They confirmed a 17mm tumor on my pituitary gland; this is extremely large compared to an average Cushing's case where the average tumor is more like 6-8 mm and is frequently so small that it can't be seen on an MRI. My doctor told me that surgery to remove the tumor was the only way to get relief from the symptoms of high cortisol, so the next step was to see a surgeon.

"I have Cushing's... but Cushing's will NOT have me!"

A little over a month later, on August 1, I met with the neurosurgeon; he was extremely taken aback by what he saw. My case is one of the most extreme cases he's seen, especially because I'm only 22 years old and suspect that I have had this disease and tumor for about 4½ years now. He's never seen a Cushing's case with this size of tumor reach this point over this amount of time when it comes to this disease. He said once the tumor reaches past 10mm it becomes complicated and creates a challenge for surgery because it has to be approached in a different way. He also said there was a chance they would not be able to get all of the tumor. He said that it is treatable and can be maintained but may not be 100% cured.

We couldn't schedule the first surgery until August 31 due to the surgeon's availability, which meant that I had to wait a month before being able to have surgery. My symptoms had gotten so extreme and unbearable that I could not leave the house and I had to go to the ER due to some of my symptoms. On the images my doctor showed me how my large tumor stretched and invaded areas that were going to make surgery difficult and not likely to produce 100% success. He felt he could get a portion of the tumor but there was a significant portion above the sella turcica, which is the thin bone surrounding the pituitary gland. Before the first surgery we discussed the second, because he was certain there would be one. What type would depend on how much tumor he could get the first time and how the remainder behaved. I had my first surgery on August 31.

As expected, my cortisol level did not drop after surgery. We waited six weeks before dong an MRI on October 12 which confirmed that he'd only removed about a third of my tumor. Unfortunately the more

invasive option for the second surgery was the only one that offered a 98-99% removal rate, so I headed into a craniotomy on October 23. The surgeon went in to remove the remaining tumor through a small round hole in my skull.

The next step was to attempt to stabilize the residual tumor that is still there through five days of radiation in December. Benign tumors take on average 2-3 years to begin to respond to radiation, so while waiting we discussed medicine to control the cortisol that was still too high.

At the end of December I met with my endocrinologist for a post-radiation follow up and to discuss medication. My bloodwork showed mildly abnormal liver numbers, so my doctor ordered an ultrasound to make sure it was not a situation that would keep me from being able to take some types of cortisol-controlling medicine. Thankfully it was not, so I started on ketoconazole in January 2018. I responded fairly well to the keto but my cortisol and ACTH remained high, so we moved up in dosing to the maximum by the beginning of May of this year even though suddenly one of my liver numbers was a bit elevated. After three weeks of this high dose we decided I would taper off and try Korlym because the keto doesn't seem to be working as hoped for me.

All throughout this process, I have had various specialist appointments: the ophthalmologist in March for vision issues, the orthopedist in April for complications related to a broken foot from March of last year (the fracture never healed and I currently have strict movement restrictions and use a cart and handicap parking designation), the nephrologist in May for low potassium and bacteria in my urine.

Cushing's has complicated my life in ways I could never imagine. I'm not even 25 and I am a MASTER at dealing with a debilitating, chronic illness. It may not look like it because I am currently unable to even attempt any exercise thanks to my unhealed foot! I have accepted intensely invasive procedures in my attempt to live, and the persistent high cortisol has been damaging my body 24/7. I am hopeful that the Korlym will work for me and buy me the time that I need to see the radiation work without having to consider additional invasive treatments.

Meanwhile, I went back to school at the University of Arizona in January 2018 after missing the Fall semester. I just finished with As and Bs and many of my instructors have commented about how amazing it is that after everything I have gone through up to this point that I am back in school so soon and still working hard for my education. I still have a hard time with my energy, focusing and other cognitive issues, though.

I also still experience night sweats, cramping, sleep issues, anxiety, irritability, mood swings, sores everywhere, temperature sensitivity, inflammation, and many other symptoms that I have had since I began this Cushing's journey. Every day is different depending on how high my cortisol is. I was also having a lot of problems with my job due to appointments and my school schedule. This stress is not good for my health. Trying to balance the great aspects of life with the difficult challenges is not easy. Sometimes it feels like I take two steps backwards for every step forward, but I am trying to stay as positive as I can that this WILL get better and I will beat this. I tell myself that I won't let this disease control my life or win. I have Cushing's… but Cushing's will NOT have me!

Danielle Lawrence
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Tucson, AZ

My name is Wendy Moses and I was diagnosed with Cushing's Disease at the age of 10 in 2009. I had been dealing with weight gain, growth suppression, headaches, muscle weakness, and insomnia since 2007. A couple of nurses at our church said the weight gain would be solved with a growth spurt and we should just wait for that. However, a few months turned into a year which turned into two years and there was still no growth spurt, so we made an appointment with a doctor.

I was diagnosed after only one appointment at my general practitioner's office. An adenoma was found on my pituitary and I had surgery to remove it in August of 2009. However, that did nothing to stop the Cushing's. Suddenly I went from having a rare disease to being the patient that nobody knew what to do with. I was referred to the National Institutes of Health and after just one visit a tumor was found on my pancreas. After measuring hormone levels and looking at multiple scans the doctors were sure that the tumor was the cause of my Cushing's. I had a distal pancreatectomy in March of 2010, removing the tumor and about a third of my pancreas with it. I was so happy to finally be beyond this disease and start my recovery.

All that came crashing down when a nurse walked into my room and casually mentioned that "because the surgery didn't work…" It was like time stopped. Nobody had told me or my parents that the surgery was unsuccessful. That was the single worst day of my life. I don't remember a whole lot about the next few days. I remember that I cried a lot and ate little (extremely unusual for somebody with Cushing's).

My mom took me on walks outside but I rarely wanted to go. It was as if for a few days the fight had left me and I had to really refocus myself before I came out of that fog.

We found out that during the surgery microscopic baby tumors (tumorlets) were found all throughout my pancreas. I was given maybe a few months to live. I also had multiple complications to deal with, the worst of which was a cyst on my pancreas that caused extreme pain and took three attempts to drain. After more testing it was confirmed that I had a genetic mutation (MEN-1) that caused the cancerous tumors (G-PNETs) that caused the Cushing's. Those diagnoses left me with the title "the only one". I am the first person ever documented to have MEN-1 first show up as G-PNET, which first showed up as Cushing's. To further complicate things, both my parents underwent genetic testing and neither of them have the genetic abnormality. (MEN-1 — multiple endocrine neoplasia — is a condition that causes many tumors, benign and/or malignant, to appear on more than one gland of the endocrine system. G-PNETs are malignant gastro-pancreatic neuroendocrine tumors.)

The summer of 2010 was horrifying for me. I was in such a daze from the pain and the medication to control the pain that I barely remember anything about it. The few memories I have are all medical — having three appointments with three different doctors in one day, driving to the ER after experiencing severe abdominal pain, and waking up from the first attempt to drain my cyst. There is one memory I have of 2010 that is good — I was granted a wish by the Make-A-Wish Foundation. This was one of the only things that could get me really happy during those months of pain. After a lot of tests, appointments, failed medications (including a chemotherapy pill), and the prayers of thousands of people, I had a last-minute semi-emergency bilateral adrenalectomy in September of 2010.

In January of 2011 my family and I experienced a magical trip to Disney World. The trip was amazing. I was able to spend a whole week free from anything medical except for a back brace I had to wear due to compression fractures. It was, however, easy to forget that I was wearing the brace when I was seeing my dreams come true before my eyes. I felt great the whole time, almost as if I was in perfectly good health and none of the past four years had happened. My wish trip was truly a turning point in my recovery, and it also sparked an interest in volunteering for Make-A-Wish. On my 19th birthday, November 4, 2017, I was honored to be a Wish Ambassador at the Wish Ball in Michigan. My only duty was to talk to the other attendees about my wish and how it impacted my life. I was so happy to finally be able to give back to those who had given so much for me. I still volunteer for Make-A-Wish during special events and it is an honor to do so!

Now I am trying to finish recovering from Cushing's while also battling an incredibly rare cancer caused by a one-in-a-million genetic mutation. This fight includes a surgery in 2013 to remove my spleen, gall bladder, and an inactive adrenal tumor. I have a 13-inch scar from that surgery. However, I have seen the hand of God in all of this. Being diagnosed after only one appointment was a miracle in itself. Surviving long enough to have the bilateral adrenalectomy was another wonderful miracle. A third incredibly important miracle is that I am truly at peace with all of this. I lost my childhood to multiple diseases, one of which will cause health issues my whole life, yet I know that God knitted me together in my mother's womb just the way He wanted me, genetic abnormality and all. It is incredibly humbling to be proof that God still performs miracles!

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Dr. Stratakis would like to point out that Ms. Moses is an example of how MEN1 can present first with Cushing's Syndrome, an association that is not well known.

Changes to Membership

Starting July 1, 2018, all memberships will be converting to FREE status. This will be rolled out over several months with completion sometime near the end of this year. You do not need to do anything!

We are currently updating our operating documents and looking at the definition of membership — what we offer to you but also ways you can get involved if you have the desire and some time to spare, from small tasks to more detailed projects. A "good" thing about a rare disease is that one person making moves really can effect change for the whole community. Please know that even a one-time offer of a few hours of your time would make a big difference to us.

- If you receive the print newsletter now, you will receive one more print copy after this one before the new membership structure becomes permanent.
- **Starting in 2019, the print newsletter will be mailed out for one year (three issues) as a thank you for an annual contribution of whatever amount is best for you.** We are working on adding a couple of options for "microgiving" such as Two-Dollar Tuesdays and monthly automatic donations and hope to have those available by the end of the year. **If you prefer to receive your newsletter electronically,** we will be happy to oblige with immediate delivery via e-mail when the print issue goes out.
- **All donations or funds received between July 1, 2018 and January 31, 2019 will ensure continued delivery of all three print issues in 2019 unless you choose the electronic format.**
- Beginning with the first issue of 2019, all other memberships will receive the newsletter in electronic format via e-mail approximately one month after the print issue mails out. If you decide you miss the timely print issue and want it back in your mailbox, we are serious when we say that any annual donation will trigger a 3-issue subscription to the print copy beginning with the issue immediately following your donation.

We hope these changes will remove any financial barriers to membership in addition to preserving resources by printing less. Your donations enable us to do everything we do. Thank you!

In addition to donations, another way you might consider supporting our mission is through sponsorships. Perhaps you own or work for a business that sets money aside for charitable causes. We have established guidelines to partner with us on some of our endeavors:

PROJECT-SPECIFIC SPONSORSHIPS

Actual cost of the project; examples would be an outreach mailing to doctors and attendance/exhibition at a professional endocrine meeting.

GENERAL SPONSORSHIPS

Silver: $5,000+
Gold: $15,000+
Platinum: $25,000+

General sponsorships support our bottom line and enable growth.

NEWSLETTER SPONSORSHIPS

$5,000+

Our newsletter brings support, research, and other valuable information to an international audience of over 2000 and growing. Thrice-annual issues are currently displayed in several dozen doctors' offices across the country. We plan to increase these numbers annually.

Special Events like Patient Education Day will have separate sponsorship opportunities.

To recognize your financial partnership, we offer benefits to all the levels of sponsorship:

Project-Specific: a post on our social media with information about the project and inclusion of sponsor involvement in project materials if possible.

General: increasing levels of recognition in the newsletters and on social media with bulk copies mailed to your destination of choice. Platinum and Gold include participation in or planning and hosting of educational events at your destination of choice.

Newsletter: recognition in one or more issues, bulk copies mailed to your destination of choice, and a social media post.

Send us an e-mail at leslie@csrf.net if you would like more information on sponsorship.

We need your patient and recovery stories!

If you are interested in having your story in the CSRF newsletter, please email it to cushinfo@csrf.net or use Share Your Story under the Quick Links on our homepage.

Need to talk? Local support groups and contacts

Many of you have expressed interest in local support groups and contacts. If you don't live in one of the following areas, consider starting a group in your area! Email the CSRF if you are interested. In particular, we have an existing group in the Los Angeles / Orange County area without an organizer.

San Francisco Bay Area, CA
Danielle Ziatek
(925) 548-1148
dziatek@yahoo.com

Sacramento, CA
Bethany Frederici
(916) 798-6165
Bfrederici@outlook.com

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Atlanta, GA
Leslie Edwin
(404) 791-5483
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Boston, MA
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King of Prussia, Hershey, Harrisburg, PA
Marie Conley
marie@kickcushings.com

Western Massachusetts, Capital Region and North Country of New York State, Southwestern Vermont, and Northwestern, CT
Mark Navin
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Maryland and Washington DC area
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reneebrooks302@comcast.net
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Stacy Hardy
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Seattle, WA
Ellen Whitton
(206) 789-8159
ekwhitton@earthlink.net

Want to be on the CSRF mailing list?

If you aren't already on our mailing list, you can join through our web site at www.CSRF.net — Member Services, or just return this form to: CSRF, 4155 Lawrenceville Highway #8130 Lilburn GA 30047. **All memberships are free.**

Name

Address

City *State* *Zip*

Phone

Email

Suggested donation is $30.00 or whatever is best for you. All donations are tax deductible. Please make checks payable to CSRF. Memberships without associated donations will be automatically converted to electronic newsetters in 2019. An annual donation in any amount will trigger a 3-issue print subscription.

Are you a Cushing's patient?
☐ YES ☐ NO

Did you have:
☐ pituitary tumor ☐ adrenal tumor ☐ other

Would you like to discuss publishing your story in a future issue of the newsletter?
☐ YES ☐ NO

What would you like to see addressed in future issues?

CSRF Share. Aid. Care.
CUSHING'S SUPPORT & RESEARCH FOUNDATION

4155 Lawrenceville Highway #8130
Lilburn, GA 30047

The CSRF Medical Advisory Board

Corcept THERAPEUTICS

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