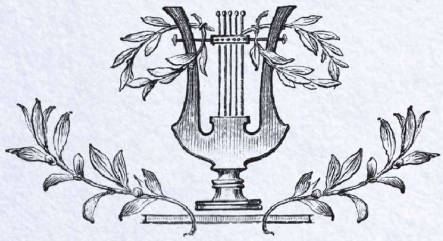
Cushing's Support & Research Foundation

cushing's newsletter

2019 the year in review

Develop enough courage so that you can stand up for yourself and then stand up for somebody else.

—MAYA ANGELOU



INSIDE THIS ISSUE

The 2019 CSRF Cushing's Patient Journey Summit: Defining the "New Normal"

Leslie Edwin

In 2019, there was a noticeable increase in validation of the rare patient voice across industry, government, and the medical community. The US Food and Drug Administration (FDA) has opened avenues for direct communication with patients, for example, and there has been a significant increase in quality of life research based directly on patient-reported experience and outcomes. CSRF recognizes that we patients are experts in our conditions, and the value of our experience is substantial—to learn from now to improve our care, and to make future outcomes better for other patients.

Everything about this event was special. The agenda was created by a steering committee of 36 patients, and the conversations about the agenda formed the basis for a 140-question survey that went out to membership via e-mail between January and the beginning of February 2020. After our last national conference in 2017, there were observations that many of us would like more of a "beyond the 101" program for everything that comes after the initial treatment, and that's how the name and concept were born.

Continued on page 3

AFFILIATIONS
American Association of Clinical Endocrinologists (AACE)
American Diabetes Association (ADA)
The Endocrine Society
European Society of Endocrinology
EURODIS (Rare Diseases Europe)
Global Genes
National Organization of Rare Disorders (NORD)
The Pituitary Society
World Association of Pituitary Organizations (WAPO)

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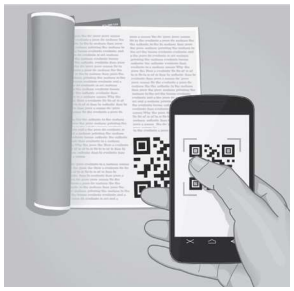
Message from the President

For me, 2019 was defined by the Patient Journey Summit in October and the many months of work it took to bring it to life. Aside from my children, it was one of the more meaningful things I've done with my time on this planet! Another big highlight was connecting with patients who are now becoming volunteers with CSRF as we build committees to expand our scope of support and research. This newsletter was a long time in the making, but for the most part it was for the best possible reasons.

In 2018 we began converting all memberships to free status—that process is complete. By the next issue of the newsletter (mails out end of June 2020), we will have updated our system to link donations to print subscriptions and will convert all other members to delayed electronic delivery of the newsletter. In basic terms—we would be honored to have your financial support, and a three-issue print subscription comes with every annual monetary gift. Anyone who has donated $1.00 or more since Spring 2018 is going to receive the next three issues (not including this one) in print. All other members will receive the newsletter via e-mail approximately one month after the print copy is mailed out. This might be a good time to contact CSRF to update your mailing and e-mail addresses if the newsletter is the only communication you get from us. All other membership benefits are the same regardless of donation.

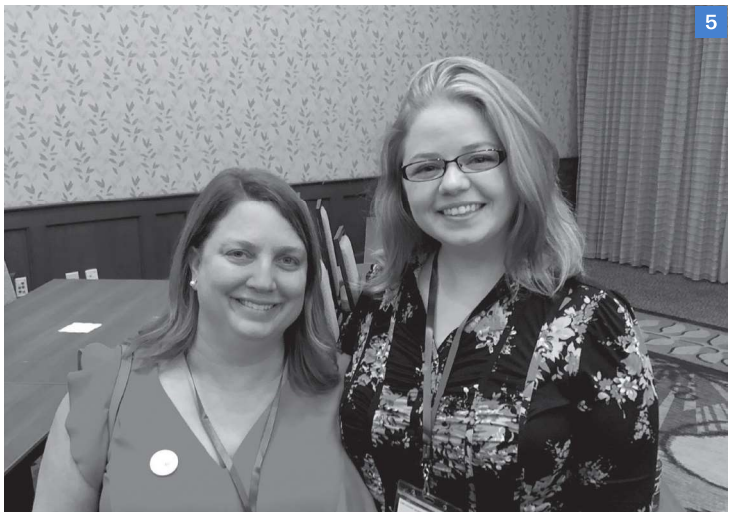
As this newsletter begins to arrive in your mailboxes, we will have entered the Spring conference circuit with a bit of uncertainty; COVID-19 is having a big impact. The Endocrine Society meeting has been canceled, and the World Association of Pituitary Organizations meeting has been postponed until October. We look forward to hopefully fulfilling the conference schedule that remains for May, because we have so much quality, patient-produced ammunition to share. Thank you so much for your involvement in and support of CSRF.

Leslie Edwin



Do you have a QR Code Reader on your phone or tablet?

Many articles in our newsletters contain QR codes to quickly link you to more information about the topics. If you do not already have a QR code reader on your device, there are several options in your app store.



1. Patient stories being captured on film

2. Laura Kapur and mom Geralyn Selzer

3. Dr. Maria Fleseriu, Dr. Lynnette Nieman, and Leslie Edwin

4. Dana Colon's "warrrior pose"

5. Amy Dahm and Heather Wickstrom

More 2019 summit photos can be viewed throughout this issue.

Continued from page 1

As a patient, I was excited to attend this event. I am still a bit starstruck to think about the presenters we had: my neurosurgeon and hero, Dr. Nelson Oyesiku, my other favorite health team member, Neuroendocrinologist Dr. Adriana Ioachimescu, plus 15 other experts in their fields who had prepared programming based directly on patient feedback. We held our meeting over multiple days on a warm weekend in early October in Atlanta at the Emory Conference Center, just a few blocks up the road from Emory University Hospital, home to a Pituitary Center of Excellence and also where I've received all of my care associated with Cushing's (neurosurgery, neuroendocrinology, neuropsychology, radiation oncologist, ENT, nephrologist, reproductive endocrinologist, etc.). Having it in my hometown was a blessing as the organizer because this was a hard year for me, and being able to drive 20 minutes to the site for planning was an adaptation I needed to incorporate to ensure success. If I tried to remember all the volunteers who gave hours of their time to pull this event off so smoothly, I would fail terribly, but I think you understand! Thank you again to everyone, so much. Special thanks to Marie Conley who added special touches that made the event better. We are currently taking suggestions for a location for our next biennial, international patient conference; please get in touch if you have ideas.

The meeting is well documented with videos, slides, and handouts at https://csrf.net/patientconference2019/ or scan the QR code. The patient story videos are on our YouTube channel at https://www.youtube.com/channel/UCcsLBoNnTSVu4SRsIcxS5Jg, or scan the QR code.

Editor's Note: *As of the publishing date of this issue, we had 178 responses to the survey mentioned at the beginning of this article. That's 78% more than the minimum I was hoping for, so thank you all so much! The survey is closed now for analysis. If you did not get the e-mail about the survey, please send us a message to update your e-mail address or consider joining as a member if you have not yet—it's free. There is a membership sign up form in this issue or you can do it on our website.*

patient journey summit meeting page

patient journey summit youtube channel

Patient Advocacy Leaders gathered for a pre-Summit meeting to discuss business and take this group photo at NORD.

2019 Conferences

Spring brings pollen, baby birds, short sleeve shirts... and endocrine conferences! We look forward to this time of year because it's a chance to hear about new science and technology that have become available. We share our resources and make new connections with doctors, nurses, researchers, and other stakeholders. We then translate some of the most relevant discoveries into educational materials and articles in the newsletter and on the website.

In 2019 we attended and/or exhibited at nine conferences and held one of our own:

- Pituitary Society International Pituitary Congress, March 20-22, New Orleans, LA
- Endocrine Society Annual Meeting and Expo (ENDO), March 23-26, New Orleans, LA
- World Orphan Drug Congress—USA, April 10-12, Oxon Hills, MD
- Memorial Sloan Kettering Update on the Treatment of Pituitary Diseases Symposium (MSK), April 12, NYC
- American Association of Clinical Endocrinologists Annual Scientific and Clinical Congress (AACE), April 24-28, Los Angeles, CA
- World Association of Pituitary Organizations Summit, May 17-19, Lyon, France
- European Society of Endocrinology European Congress of Endocrinology (ECE), May 18-21, Lyon, France
- American Association of Diabetes Educators Annual Conference (AADE), August 14-17, Houston, TX
- **CSRF Patient Journey Summit: Defining the "New Normal," October 4-6, Atlanta, GA**
- National Organization for Rare Disorders Rare Disease Summit, October 20-22, Washington DC

What follows is a summary of highlights from these conferences. Amy Dahm, Patient Advisory Committee member, wrote an article about her experience at the World Orphan Drug Congress and WAPO—you can find that following this article. The CSRF conference also has its own write-up in this issue.

Perioperative Management of Patients with Cushing's Syndrome (Pituitary Society)

Dr. Fleseriu and Dr. Elena Varlamov, both from the Oregon Health and Science University in Portland, discussed concerns of both patients and their medical teams at the time of surgery. Most of us who have had to spend five or more days in the hospital have probably asked every person coming in the room—"when can I go home?" It's worse when we get different answers from different visitors, but when it comes down to it, our endocrinologists are the ones to make that determination. They are the ones who have been tracking our cortisol, and they will be the ones we need to monitor us closely after surgery. When we have educated and experienced doctors, they are familiar with the "predictive value" of our blood numbers immediately following surgery and will be able to answer some of our more difficult questions regarding what we can expect of our health based on how the surgery went.

There are three areas of particular interest going into surgery:

- anticoagulation
- pre-operative management of hypercortisolism
- assessing remission post-operatively

Anticoagulation can be defined as treatment to prevent blood clots. More information is becoming available as time passes that there is a strong connection between hypercortisolism and hypercoagulability, and the highest risk comes at surgery. There doesn't seem to be a greater or lesser risk based on the source of Cushing's; we face an almost 18x greater chance of clotting than the general population.

There are known culprits for increased risk of blood clots—obesity, smoking, immobilization, and some drugs like estrogen and progesterone. There is conflicting data coming out that points to high urinary free cortisol tests (UFCs), abrupt drops in cortisol after surgery, and treating Cushing's with medication at the time of surgery as being other sources of increased risk. These findings have doctors' attention—should everyone be treated with anticoagulants at surgery? For how long? Who are the best candidates? What about for IPSS (inferior petrosal sinus sampling)? The answer, for now, is that they are working on it. Dr. Fleseriu and her team published an article that goes into much better detail titled **Hypercoagulability and Risk of Venous Thromboembolic Events in Endogenous Cushing's Syndrome: A Systematic Meta-Analysis** which you can find at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6360168/ or by scanning the QR code.

Pre-operative management of hypercortisolism's goal is to "stabilize" severe Cushing's and optimize dangerous co-morbidities like diabetes, hypertension, and low potassium. Research shows that adequate pre-treatment has been associated with a higher rate of long-term remission, and it may also reduce the occurrence of adrenal insufficiency (AI) in the immediate post-op periods. The downside is that it can also cause inaccurate early post-op numbers.

Data in the European Union-funded European Register on Cushing's Syndrome (ERCUSYN) shows that patients in Europe who received medical therapy for hypercortisolism prior to surgery were sicker overall at the beginning of therapy with higher blood pressure, more muscle weakness, and more skin changes than the "average". Unfortunately, there isn't any UFC data attached to that information to help evaluate. These patients more frequently reported having cortisol levels within the normal range immediately after surgery. However, patients in the registry who did not have pre-surgical medical therapy, most likely because their symptoms were not alarmingly severe, were more frequently reported to have low or undetectable cortisol levels immediately after surgery, cure and remission, and more robust clinical improvement of symptoms over the group that needed the medical therapy. Upon evaluation six months after surgery, there was no difference in remission rates or prevalence of post-surgical problems (like blood clots) between the two groups. The doctors agreed that it is reasonable to consider pre-treatment on an individual basis, but the data does not support an across-the-board recommendation for everyone to have it at this time.

Assessing remission post-operatively gets tricky. The doctors pleaded with their colleagues to stop using the word "cure". Recurrence rates are so high, this word could carry a huge psychological burden for patients who are called cured and then go on to experience recurrence. They recommend the word "remission" once biochemical numbers are stabilized and patient-reported data supports it.

Blood cortisol ranges immediately after surgery:

- if less than 2, there is a higher chance of long-term remission
- values between 2-5, which is most patients, will mostly also be in remission
- values greater than 5 usually indicate unsuccessful surgery but some will have a delayed remission
- looking at cortisol and ACTH together, if cortisol is less than 2 and ACTH is less than 5 after surgery, there is an almost 100% chance that the patient will achieve remission, but an ACTH higher than 15 is an 87.5% chance for persistent disease

All patients need long-term clinical follow-up! There is NO post-op number that will clear a patient from recurrence. **This is a lifelong disease.** Our input is needed constantly because problems don't fully go away. This cannot be emphasized enough.

The Challenge of "Pseudo-Cushing's" (Pituitary Society)

Dr. John Newell-Price, University of Sheffield, UK, discussed investigation of Cushing's syndrome at the mild end of the spectrum. "Pseudo-Cushing's" can be defined as some of the clinical features that resemble true Cushing's combined with some evidence of hypercortisolism, but he was quick to point out that the term pseudo-Cushing's is misleading. If a patient presents with persistent hypercortisolism that is not caused by a tumor, it is important to determine the cause and correct or treat it, if possible. Some conditions that cause high cortisol include pregnancy, chronic alcohol dependence, severe obesity, metabolic syndrome, poorly-controlled diabetes, major depression, anorexia, severe physical illness or stress, malnutrition, and chronic excess exercise.

Testing can be a challenge because some results will indicate the presence of hypercortisolism, but it is not from an autonomous source (tumor), so the question becomes how to address it with the patient. Questions remain about the best management practice for patients with non-Cushing's hypercortisolism. There are current trials for some drugs that could hold answers to some of these questions.

ENDO

The posters at ENDO are fascinating every year. While a poster is not a published, peer-reviewed, controlled piece of research, it is an eye-catching way to present work being done and provide opportunities to discuss the details in person with conference attendees. If you would like to see one of the posters mentioned, please e-mail Leslie at leslie@csrf.net. Some highlights and brief summaries, including title and institution:

Cushing's disease in men: a 20-year single center experience, *Emory University School of Medicine, Atlanta, GA:* The authors looked at records from 108 transsphenoidal surgeries done by one surgeon

Continued

in one location between 1994-2014. They were specifically looking for gender differences in presentations and outcomes, because there's very little research in this area, and what does exist can be conflicting. The authors concluded that more work needs to be done to look at differences, but their study noted distinctions between genders on age at surgery and co-morbidities like hypopituitarism and hypertension.

Safety and Efficacy of Early Postoperative Acetylsalicylic Acid for the Prevention of Thromboembolism After Transsphenoidal Surgery for Cushing Disease, *Brigham and Women's Hospital, Boston, MA:* This study looked at starting acetylsalicyclic acid (the compound in aspirin) within 48 hours of transsphenoidal surgery to prevent blood clots. As mentioned previously in this article, doctors are starting to address this serious post-operative risk. The conclusion here was that using this drug was well-tolerated and clotting was rare despite all the risk factors.

Racial distribution, presentation, and outcome in acromegaly and Cushing's disease: A tertiary referral center study in 220 patients, *Georgia Tech College of Sciences and Emory University School of Medicine, Atlanta, GA:* The US Central Brain Tumor Registry reports that African-American patients have a higher incidence of pituitary adenomas than non-Hispanic white patients, but some studies show that African-Americans are less likely to have surgery at high-volume centers. The authors of this study believe it is the first of its kind to look at race-specific patient characteristics in these two pituitary disorders. While African-American patients overall had more macroadenomas than non-Hispanic white patients, there were no real differences in long-term outcomes.

Peripheral Clock System Circadian Imbalance in Cushing's Disease, *Ribeirao Preto Medical School, Brazil:* The authors here identified that healthy cortisol circulation is the main driver of "circadian rhythm, controlled by the clock genes system." Because of that, Cushing's Disease may be associated with disruption of this system. Participants collected a salivary cortisol test at 9am and 11pm, then blood samples were taken four times throughout the day to assess seven "clock genes". In patients with Cushing's, the normal circadian rhythm was absent in six of the seven; in the final gene, variations were shown. The authors share that this is the first study looking at the circadian rhythm of clock genes and how they are ruined in hypercortisolism. This may contribute to the features of Cushing's. (Editor's Note: I didn't know what clock genes were before I saw this poster. If you're interested in circadian rhythm, I'd encourage you to read more on the subject! This publication does a great job of explaining it, or scan the QR code: https://www.unifr.ch/biochem/assets/files/albrecht/publications/AlbrechtRipperger.pdf.

Zebrafish to Humans: Translating Discoveries for Treatment of Cushing's Disease (AACE)

Dr. Shlomo Melmed, Cedars-Sinai Medical Center, Los Angeles, CA, opened this hugely popular session by addressing some of the most dangerous symptoms of Cushing's—depression, stroke, hypertension, infection, metabolic syndrome, thrombosis—and asking if we can "slow, stop, or reverse the inexorable decline by impeding cortisol production and action." If inadequately controlled, Cushing's Disease has a median survival rate of 4.6 years. That life expectancy is the same as it was in 1930.

There are challenges to the drive to understand how pituitary tumors come to exist: control tissue from healthy subjects is unavailable, the tissue removed during surgery is extremely small, it's difficult to do a biopsy, and there's just a very low prevalence of tissue available in general. In 2011, Dr. Melmed and his team published research about their transgenic creation of a zebrafish model that would rapidly develop pituitary tumors and serve as a model that could be used in place of readily available pituitary tissue. They experimented and discovered that a drug called roscovitine inhibits tumor growth and also suppresses ACTH production, which could mean it performs other functions that have not yet been determined. The end goal is to identify specific tumor drivers and personalize precision treatment. Roscovitine is currently considered an experimental drug candidate and even has a new name—Seliciclib. In December of 2018 Dr. Melmed became the Principal Investigator on a Phase 2 clinical trial out of Cedars-Sinai Medical Center in Los Angeles, CA looking at its use to treat Cushing's Disease: ClinicalTrials.gov Identifier: NCT03774446.

Mild Cushing's Syndrome (CS)—Does it Matter? (AACE)

Dr. Maria Fleseriu, OHSU, discussed how and why to diagnose mild Cushing's syndrome. She began by rejecting the term "subclinical Cushing's syndrome" in favor of "mild autonomous hypercortisolism". She then defined this as a condition of hypercortisolism in the absence of specific signs of cortisol excess such as striae, moon face, buffalo hump, muscle weakness, skin atrophy, and plethora. Criteria to diagnose mild hypercortisolism is currently 1) the presence of an adrenal incidentaloma (a mass found incidentally on scans intended to look at other conditions) and 2) a low-dose dexamethasone suppression test where:

- hypercortisolism is confirmed if result is 5 or above
- hypercortisolism is a possible diagnosis if result is between 1.8 and 4.9
- hypercortisolism is ruled out if the result is less than 1.8

There are caveats to this testing as well—if the patient takes oral contraceptives, is sick, has liver problems, takes antiseizure medications, or consumes alcohol, for example, the test results can be skewed. There are other tests to help with diagnosis: DHEA-S (dehy-

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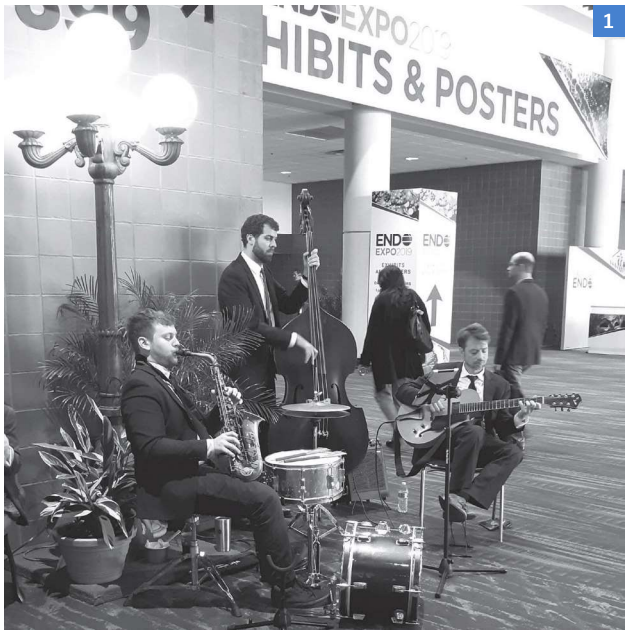
2019 Conference Highlights



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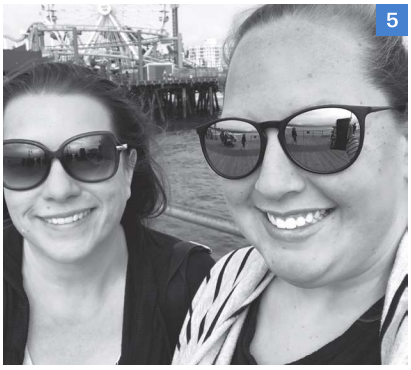

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1. *Jazz band at ENDO in New Orleans.*
2. *Diabetes Educators Niyati Hariyani and Jennifer Dyson, both from Houston, and CSRF members Ursula Henry and Blaire Boydston.*
3. *Patient Advisory Committee member Amy Dahm and Leslie Edwin "not serious" photo opportunity.*
4. *CSRF member Gena Tyner-Dawson and Leslie Edwin setting up the expo booth at ENDO in New Orleans.*
5. *Leslie Edwin and Danielle Reszenski take a break at the Santa Monica Pier after the close of AACE in Los Angeles.*
6. *Katherine Griffith and Diabetes Educator Mary Sikora Peterson (also a CSRF member!) meet at AADE in Houston.*
7. *CSRF's own Marie Conley (left) presenting on the Pennsylvania Rare Disease Advisory Council at NORD.*

More conference highlights can be viewed throughout this issue.

droepiandrosterone sulphate—suppressed in mild hypercortisolism), late night salivary cortisol, and adrenal scintigraphy (helps determine exactly what kind of mass is on the adrenal). The bottom line is that you need at least two positive tests of different methods to make a diagnosis. For incidentalomas, the low-dose dexamethasone suppression test is the best, followed by late night salivary, followed by UFC. The other tests can serve as "back ups".

Mild hypercortisolism, over time, can negatively impact a patient's metabolism, cardiovascular system, bones, and blood, so it needs to be addressed early for best long-term outcomes. Depending on the severity of the hypercortisolism, the patient has a number of options similar to those of a patient with a hormone-secreting adenoma.

Hypopituitarism and Pregnancy (AACE)

Dr. John Carmichael from the Keck School of Medicine at USC presented on the topic of fertility and hypopituitarism. It was such a great session, we had to do a break-out article with him! See the Doctors' Articles section for that.

Quality of Life Research: Dr. Susan Webb Award Lecture (ECE)

Dr. Susan Webb, Sant Pau Hospital in Barcelona, was awarded the 2019 Clinical Endocrinology Trust Award for her research on pituitary diseases—specifically on the persistent illness of supposedly "cured" endocrine patients, and on the patient perception of their own disease. Patients are very lucky to have Dr. Webb on their side because she has been instrumental in championing the patient voice and non-clinical variables as important to optimal outcomes.

She started by saying that the word "cured" does not always mean the same thing to the doctor and patient—for the endocrinologist, it means that hormones are normal and the tumor is stabilized, but for the patient it also means the ability to continue performing regular daily life tasks without pain or other limitations. Over the last two decades data has shown that despite "cure", Cushing's patients have more cardiovascular, skeletal, and neuropsychological problems than the general population.

In the brain alone, there are four types of abnormalities and neuropsychiatric disorders in Cushing's syndrome:

- **Structural Abnormalities:** brain atrophy, decreased cortical thickness, reduced grey matter volumes of cerebellum and anterior cingulate cortex, widespread reduction of white matter integrity
- **Functional and Biochemical Abnormalities:** reduced functional response during memory testing and emotional processing, altered connectivity between prefrontal cortex and posterior cingulated cortex, high levels of glutamate (causes cell damage) in the hippocampus, and widespread reduction of white matter integrity
- **Deficits in Cognitive Function:** memory, verbal learning, language, spatial information, and working memory
- **Psychopathology:** depression, anxiety, mania, maladaptive personality, and panic

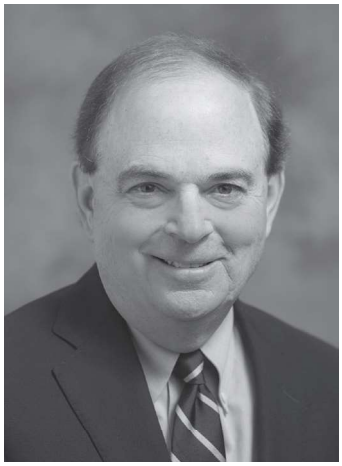
Dr. Webb has at least 150 articles listed on PubMed—we encourage you to scan through and read some to get a better feel for the expanse of knowledge this doctor has put into our community. https://www.ncbi.nlm.nih.gov/pubmed/?term=susan+webb or scan the QR code.

National Organization of Rare Disorders (NORD)

NORD holds an annual Rare Summit every October in Washington DC, and due to a scholarship program for member organizations, we have been able to attend many years in a row. The definition of a rare disease in the United States is one that affects less than 200,000 Americans. The FDA and other key policy-makers are extremely focused on advocacy and the patient voice right now—it is a good time to be a patient advocacy organization, because they seem to be listening more than ever. As you can read in Amy's article in this issue, the FDA has set up avenues to engage with patients to improve their drug development processes. It's such a simple and smart thing to bring patient experts in on all levels of decision-making because that's exactly what we are. We know parts of this disease that you can't learn anywhere else.

Attending the NORD Summit puts hundreds of patient advocates, many suffering from the diseases they represent, in the same room with teams of people from the FDA, CEOs, researchers, technology innovators, and others whose sole job it is to run the rare disease drug and access machine. On some scales, an organization like ours would get lost in the crowd, but at the NORD Summit we are amongst peers. NORD does an amazing job of supporting their member organizations with board management resources, access to scholarships for rare-related meetings, and general support. Just like with Cushing's, it feels great to get a chance to be around people who are in a rare position like you and understand what it's like to devote all your time to a cause you care fiercely about.

The theme for 2019 was "The Time is Now." In keeping with the theme of collaboration, there were many sessions that talked about bringing patients to the table at all points of drug development. Patient organizations in attendance were encouraged to set up patient registries; NORD and several companies in attendance have platforms for groups like ours to build registries. We're not quite at that point yet but it's good to start talking about it. If you're curious to learn more now, visit https://www.ncbi.nlm.nih.gov/books/NBK208643/ or scan the QR code.



Thank You!

Dr. James Findling of the Medical College of Wisconsin has been on our Executive Board of Directors as well as our Medical Advisory Board for many years and has contributed so much valuable insight to CSRF. In 2019 he stepped down from his role as Director, and we were only willing to let him do this because he agreed to stay on the Medical Advisory Board! In all seriousness, we thank Dr. Findling for everything he has done and continues to do for Cushing's patients every single day. We asked him to reflect on his time with CSRF, the "early days", and the Cushing's space today:

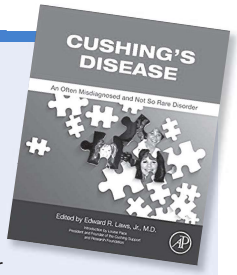
It has been gratifying to see the growth of the Cushing's Support and Research Foundation since its inception one-quarter of a century ago. Due to the inspiration and dedication of its founder, Louise Pace, and many others, CSRF has established itself as the most respected patient-oriented organization addressing the multiple medical, metabolic, and psychosocial issues associated with this complex disorder. I remember when CSRF was run on a shoe-string. The remarkable efforts of Louise and Karen Campbell kept it relevant and moving forward. I would always reassure them that the day the pharmaceutical industry became interested in Cushing syndrome the fortunes of the organization would improve. And that day finally came.

My interest in Cushing's syndrome began over four decades ago when an attending physician in internal medicine questioned my recommendation that an obese woman with diabetes and hypertension might have hypercortisolism. He scolded me for even considering such a rare diagnosis and dismissed my question. Since that time I have been searching for an answer to the diagnosis and management of this mercurial, life-changing endocrinopathy. Certainly CSRF has been on the forefront of awakening clinical endocrinologists to the importance of this diagnosis. The many, truly inspiring patient stories and their remarkable clinical improvement (pictures are worth a thousand words) after corrective therapy should serve as an inspiration to all of us. The newsletter has always been a tour de force and the CSRF website is the best resource for patients and families progressing through the challenges of diagnosis and treatment of Cushing's syndrome.

I have been honored and proud to serve as a member of the executive board of directors for many years, but I realize that it is now time for younger voices and new leadership on our board of directors. I enjoyed the opportunity to help start and grow CSRF and I am very encouraged by the new and creative leadership of Leslie Edwin, Elissa Kline, Dr Meg Keil, and Marie Conley. CSRF is in good hands.

Of course, I plan to stay active on the CSRF Medical Advisory Board. I continue to have a very busy practice seeing one or two new patients every week with Cushing's syndrome. I will remain dedicated to clinical research to help improve the diagnosis and management of this disorder and share my experience with clinicians so that patients will be diagnosed and treated in a timely fashion. Cushing's syndrome has been my passion for forty years. I'm looking forward to a very bright future.

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



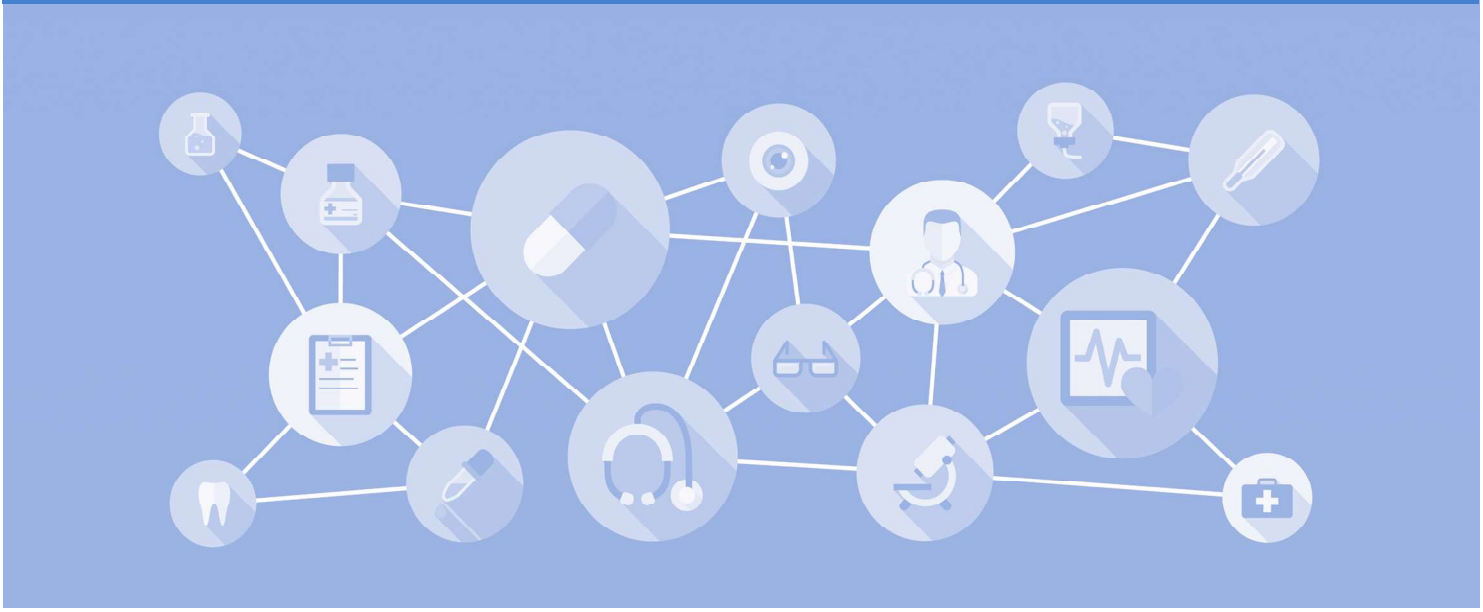
Edited by E. Laws, Jr., M.D., F.A.C.S., Professor of Neurosurgery, Harvard Medical School, Director—Neuro-Endocrine/Pituitary Program, Brigham and Women's Hospital, Boston, with an introduction by Louise Pace, Founder and President of the Cushing's Support and Research Foundation.

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)!*

Defining the "New Normal" 2019 Cushing's Patient Journey Summit, continued from page 3

Dana Colon and Michelle Nowalinski

Katie and Mindy Cohen



World Orphan Drug Congress USA 2019 & World Alliance of Pituitary Organizations (WAPO)

Washington, DC & Lyon, France, Spring, 2019
Amy Dahm

Two scientific conferences in Spring 2019 on opposite sides of the Atlantic showcased promising scientific breakthroughs and tools for Cushing's and adrenal insufficiency (AI) patients. Teams pitched four drugs under development designed to assist Cushing's and AI patients at The World Orphan Drug Congress USA 2019 in Washington, DC, while the World Alliance of Pituitary Organizations in Lyon, France, featured data from new quality-of-life studies and the first textbook for endocrine disorders written by endocrine nurses.

World Orphan Drug Congress USA 2019

New Drugs for Cushing's Patients

One of the most exciting parts of the World Orphan Drug Congress were the "pitches" delivered by the orphan drug development teams. Per Wikipedia, an "orphan drug" is defined as "a pharmaceutical developed to treat medical conditions which because they are so rare, would not be profitable to produce without government assistance... the assignment of orphan status is a matter of public policy and has yielded medical breakthroughs that might not otherwise have been achieved." Here were some of the most promising pitches aimed towards improving quality of life (QoL) for Cushing's patients (this is not an endorsement):

- **TBR-065 and TBR- 760:** Imran Babar, Chief Business Officer at drug accelerator Cydan II, pitched two drugs under development by portfolio company Tiburio targeted towards neuroendocrine disorders: TBR-065 for treating rare endocrine disorders including Cushing's Syndrome, and TBR-760 for treating non-functioning pituitary adenomas (NFPA).
- **ST-002:** Shortly thereafter, SteroTherapeautics CEO Manohar Katakam presented ST-002, a DHEA analog and anti-glucocorticoid that would address the hyperglycemia and non-alcoholic steatohepatitis (NASH: non-alcoholic fatty liver disease) affiliated with Cushing's. It is the only drug under development as a cortisol antagonist for Cushing's Syndrome, and has demonstrated anti-obesity properties in over 100 patients in multiple clinical trials. Mr. Katakam claimed that ST-002 does not lower cortisol levels, mitigating the potential for accidentally inducing adrenal crisis.
- **Cibinetide:** Joe Young, Chief Business Officer at Araim Pharmaceuticals, pitched a drug that would promote healing of damage in the cardiovascular and neural cells. Although the drug was designed for sarcoidosis and diabetic neuropathy, it could serve to enhance the recovery for Cushing's patients and perhaps mitigate damage to the cardiovascular and neurological systems.
- **OSSGROW:** Satyen Sanghavi, from Regrow BioSciences based in Pune, India, discussed the success rate of using live cultured osteoblasts for regenerating hip bone tissue lost to vascular necrosis, which is a side effect in 5% of Cushing's patients. Ideally, the osteoblasts can preserve the femoral bone from breakdown and hopefully avert the need for hip replacement surgery.

FDA Patient Advocacy

Several new tools are now available for Cushing's and rare disease patients to interact with the Food & Drug Administration (FDA). The FDA recently appointed a new Director of Professional Affairs and Stakeholder Engagement, CDR Eleni Anagnostiadis, RPh, MPM, at the Center for Drug Evaluation and Research in Silver Spring, MD. Over lunch, she discussed how she was overseeing the build out of

the patient outreach program and the March 2019 launch of the new FDA patient advocacy portal, www.fda.gov/RequestToConnect. The portal is designed to give patient advocates a single entry point to the FDA for questions and meeting requests, and routes requests to the appropriate internal FDA office. The FDA has a Twitter account, @FDAPatientInfo, and is available at 1-888-INFO-FDA.

During follow-up roundtable discussions with pharmaceutical representatives and scientists, participants had a heated exchange about the need for involving patients in every step of the development process. Although several pharmaceutical representatives debated the necessity of patient involvement (with one representative going as far as to comment that she did not want to "burden" the patients), the emerging consensus was that patient input is vital to the development process for both pharma companies and patients alike. Mr. Babar is actively seeking patient representatives to work with Tiburio on the development of its Cushing's drugs. For those who are interested, please contact Amy Dahm at a_dahm@yahoo.com. Dr. Nerissa Kreher, Chief Medical Officer for Tiburio, attended the CSRF Patient Journey Summit last year and presented a discussion about bringing a rare disease to market. We are glad that all Cushing's stakeholders seem to be on the same page as far as the importance of the patient voice at all points in drug and policy development.

Data

Data analysis is one of the new pioneering solutions for diagnosing Cushing's earlier and conducting vital research on patient populations. Two presentations in particular discussed innovations in data research and analysis for Cushing's patients.

- **HVH Precision Analytics & Diagnosing Cushing's Earlier** Oodaye Shukla, Chief Data & Analytics Officer with HVH Precision Analytics, discussed the methodology his company uses to analyze data to find potential patient clusters using symptomology. This allows HVH to inform doctors in the area about specific rare diseases and gives them a "heads up," leading to faster diagnoses. HVH has already conducted an initial survey about four years ago and is seeking to partner with patients and patient organizations to complete a full survey. If anyone is interested in helping to spearhead this project, please contact Amy Dahm at a_dahm@yahoo.com.
- **Rare Disease Registry Program (RaDaR)** There is a lot of debate in patient advocacy circles about patient registries and the best way to build them. Anne Pariser, Director of the Office of Diseases Research at the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health, discussed the launch of RaDaR, which is an online tool designed to help patient groups navigate and facilitate the process of setting up patient registries. RaDaR features best practices, lessons learned, and emphasizes data quality, standards, and sharing within registries. https://registries.ncats.nih/gov. It launched with new material February 2019. CSRF is in a "gathering more info" stage about a possible patient registry; stay tuned.

World Alliance of Pituitary Organizations (WAPO)

The 2019 gathering of the World Alliance of Pituitary Organizations (WAPO) in Lyon, France was the most dynamic yet and included:

- the first joint session with WAPO, the European Society of Endocrine Nurses, and the French Endocrine Nurses Group during the European Society of Endocrinology (ECE) on May 18;
- the unveiling of a revolutionary new patient-centered textbook for treating AI and other endocrine conditions;
- dynamic new research validating decades of patient feedback;
- and novel patient-centered approaches for dealing with endocrine conditions.

All of the sessions had simultaneous English and Spanish translation and delegates—including patients, researchers, doctors, and pharmaceutical representatives—converged from patient advocacy groups across North America, Europe, South America, and Asia to share best practices and experiences. This year's WAPO summit will be in Buenos Aires, Argentina, about the time this newsletter begins to mail out!

Andrei Andrusov, a Russian business man and math expert, founded WAPO five years ago after helping his brother navigate treatment for acromegaly. As someone who grew up in the USSR and attended university in the United States, Mr. Andrusov recognized that patients have varying levels of treatment, accessibility, and expertise across the globe, and that it is possible to save lives by setting patient-focused standards and sharing best practices. WAPO is truly a global organization—it has patient advocates from all over the world. It is run by Muriel Marks, a Dutch Cushing's patient affiliated with Dutch advocacy group Bijniervereniging and co-founder of AdrenalNET. Muriel attended and presented at our Patient Journey Summit in October.

Christine Yedinak

Ms. Yedinak, a patient advocate, gave a broad overview about AI. Although the causes are varied (genetic, autoimmune, infections, steroids, tumors, hemorrhages, and/or narcotics), the treatments are fairly streamlined, and include hydrocortisone, prednisone, and dexamethasone. Ms. Yedinak discussed the various problems patients with AI face, including individual needs, lifestyle and event variability, and variance in interpretation of current guidelines and availability and content of education. Data is absent regarding best practices, and there are no agreed-upon standards for education.

Launch of the First Patient Centered, Nurse-Authored Endocrine Text

At the first joint WAPO-ESE joint session, Dr. Sofia Llahana intro-

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duced the first endocrine book written by endocrine nurses, Advanced Practice in Endocrinology Nursing, endorsed by the European Society of Endocrinology. It has a full chapter on adrenal crises and how to handle them, and it goes into extensive detail on the rarest of endocrine conditions, including acromegaly, Cushing's Syndrome, and AI. It is designed for caregivers and patients, by carers. In addition to the book, individual chapters are available for download online at springer.com. (NOTE: CSRF's own Dr. Margaret Keil is one of the pediatric editors.)

New Comprehensive AI Study

In the same joint session, Dr. Llahana announced the creation, under the auspices of a European Society of Endocrinology, of a new, multi-year, patient-centered, comprehensive study about AI; she is actively soliciting input from rare disease patients and advocacy groups. Per Dr. Llahana, the project aims are two-fold: 1) to describe current service provision and patient education for patients with AI and identify gaps and needs; 2) develop a position statement on standards for patient education and care services in AI.

The first phase of the study will be comprised of an on-line survey of nurses, endocrinologists, and patients translated into different languages. It will cover demographics of AI; treatment approaches; barriers and facilitators to prevent and treat AI promptly; service delivery; and patient education and experiences. Any Cushing's patient with feedback, questions, or subject matter for Dr. Llahana to include in the study may e-mail her at: Sofia.Llahana@city.ac.uk

European Guidelines

Finally , Dr. Llahana discussed the formation of an ECE mission statement and an Endocrine Society Clinical Practice Guideline for AI. The ECE-approved guidelines recommend: annual patient monitoring, patient education for adjusting dosing on sick days, and most importantly for patients still debating with their doctors about the need for emergency injections: ALL PATIENTS SHOULD BE EQUIPPED WITH A STEROID EMERGENCY CARD AND A GLUCOCORTICOID EMERGENCY SHOT. [Note: in the United States, this would be the 100 mg shot of Solu-Cortef]

AI Patient App Soon to Launch in English

Co-founders Johan Beun and Muriel Marks of European patient advocacy group BijnierNET (AdrenalNET) run adrenals.eu, a website with the tagline "everything about adrenal gland disorders." The site covers adrenal-related illnesses and is in multiple languages, including Danish, Dutch, French, and German. The site offers various adrenal-related tools for free, including European Emergency cards in various languages, including French, Czech, and Icelandic. Per Ms. Marks, "all information is validated after the Dutch and EU countries and is kept up to date."

AdrenalNET will soon launch an adrenal app in English that provides "crucial medical information...any time of the day or night" and "helps to collect and access crucial information." It offers instruction for medical staff about how to treat a medical crisis and is also geared towards the loved ones of adrenal patients. Visit https://adrenals.eu/app/ for more information or scan the QR code.

New Research and Data

Quality of Life: Dr. Elena Valassi

During the course of the WAPO meeting, several new doctor and patient-led research initiatives and case studies were highlighted. Dr. Elena Valassi from the Hospital Sant Pau in Barcelona, Spain, presented groundbreaking QoL data gleaned from the national European patient registry (ERCUSYN: https://www.ercusyn.eu/ or scan QR code) that validate decades of patient feedback. Older age, female gender, hypopituitarism, AI, and brain structure are biological and physiological variables for recovery. She highlighted how depression, impaired physical functioning, bodily pain, and poor general health persist during remission from Cushing's. Symptom status, including depression/anxiety, lack of attention, sleep disturbances, weight gain, and muscle weakness are key determinants of quality-of-life. Her research showed that 19% of patients had to cease work altogether while 43% needed some sort of reasonable accommodation or working arrangements. And social and family life, sex life, relationships—not just work—impact patient's functional status. Her research also demonstrated that pituitary patients had a slightly more difficult recovery than adrenal patients.

Dr. Valassi noted that previous exposure to excess cortisol leads to persistent alterations in several target organs. Brain impact leads to persistent mood and cognitive problems; muscle damage leads to loss of strength, low performance, and tiredness; overall metabolic damage leads to increased risks of diabetes, hypertension, and negative body image; and bone issues lead to pain, osteoporosis, and fractures in many patients. There were structural and functional changes in the brain of Cushing's patients in remission for 11 years, including reduction of grey matter volume; increased cerebellum volume; reduced white matter integrity (associated with depression); and hypoactivation of brain areas during processing of emotions. Low muscle strength and impaired physical performance was associated with poor QoL even 11 years out, manifesting as pain, lack of vitality, and mood issues.

Even after a mean of 13 years of remission, subtle cognitive impairments, including issues with cognitive function, memory (concentration, verbal memory, visual memory), and executive function (information processing speed, cognitive flexibility) remained in the client population. Remarkably, increased prevalence of psychopathology and maladaptive personality traits remained after a mean of 11 years

in remission, including submissiveness, cognitive distortion, identity issues, affective liability, compulsivity, oppositionality, anxiety, conduct issues, suspiciousness, social avoidance, and insecure attachment.

European versus American Adrenal Protocols: AI for Life

There was a spirited audience discussion about European vs American protocols after a post-op AI patient, who had weaned off of steroids as part of her course of treatment for Cushing's, asked when she would be "in the clear." She mentioned having heard that some patients reported having adrenal crises over a decade after their remission. Her American doctors had told her to follow the "Sick Day Rules" for up to a year after she had successfully weaned off of steroids and her remaining adrenal gland started working. Unlike American protocols, many members of the European AI community are more conservative and believe that once a patient has AI, the patient is "AI for life" and susceptible to adrenal crises. When discussing these issues, one of the patient advocate experts spoke up and said that no one really knows, as no long-term studies have been performed on AI patients.

One of the facts that came up was that once a patient has experienced an adrenal crisis, they are THREE TIMES as likely to experience another. So prior adrenal crises is a risk factor in and of itself.

New Approaches: TPE, A Case Study

Dr. Aude Brac de la Perriere and Alexandrine Bost from the Federation d'Endocrinologie Groupemont Hospitalier Est in Lyon, France, presented a case study on the successes of Therapeutic Education in Adrenal and Pituitary Insufficiency (TPE). They defined adrenal crisis as the "mismatch between cortisol supply and demand, especially under conditions of physical and psychological stress." TPE has three different steps: educational diagnosis, sessions, and program evaluation. Their recommendations are:

- Carry an emergency kit (cards, tablets, and injection kit)
- Identify adrenal crisis: signs and risky situations
- Know to adjust steroid doses
- Know risk of overdose
- Know how to administer Solu-Cortef injection
- Know how to use relevant resources in the healthcare system

Two flagship teams in Lyon and Marseilles from the national reference center led the way, while the French Endocrine Society developed two different programs. Six nurses and two endocrinologists built the workshops and doctors selected patients. The workshops were held in a one day format and the trainers typically were one or two doctors or nurses. There were eight sessions. The agenda included workshops entitled:

- "Understand my Adrenal Illness"
- "Understand and Manage my Adrenal Treatment"
- "Prevent and Manage AI"
- "Know How to Do my Injection"
- "Manage the Effects of the Disease on a Daily Basis"

The education sessions included descriptive posters of the endocrine system as well as Role Play/ Scenario cards. Patients were sent home with models of emergency kits, booklets for adrenal crisis, and advice for patients re: high temperatures, jet lag over six hours, sports and training, pregnancy, and every day situations. Doctors received advice in cases of endoscopy; general anesthesia for surgery, trauma, and delivery; and dental care.

Life After Cushing's: A Case Study

Sammy Harbut from the UK is a Cushing's patient in remission. She turned to occupational therapy as a profession as part of her recovery from Cushing's, as she knows firsthand the benefits that can be reaped by patients. When she became ill with Cushing's, she knew that she could not return to her former position and started to consider other options. Working with patients with all sorts of different illnesses has been fulfilling and rewarding to her, and a major part of her own recovery. She did not ever expect to go into occupational therapy, but is extremely happy helping others and is eager to share the benefits with other Cushing's patients of something she considers an essential element of recovery.

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

Hypopituitarism and Pregnancy

Dr. John Carmichael and Leslie Edwin

Dr. John Carmichael, Co-Director of the USC Pituitary Center at the Keck School of Medicine, gave a presentation on hypopituitarism and pregnancy at the 2019 American Association of Clinical Endocrinologists conference in April. We hear from patients who are concerned about their chances of becoming pregnant after treatment for Cushing's Disease, so we hope that the information shared in the following summary of that presentation will be a good starting point for anyone in this position.

Causes and Categories of Infertility

Related to pituitary disease and surgery, there are several potential causes of pituitary failure that can lead to problems with fertility. Structurally, adenomas and other masses cause dysfunction. Functionally, diseases like obesity and chronic illness, hormonal excess or deficit, and certain medications can contribute to this as well.

Infertility can also be caused by a broad range of culprits outside of a pituitary source including intense exercise, eating disorders, stress, polycystic ovarian syndrome (PCOS), hypothyroidism, adrenal adenomas, and renal/liver impairment. While it is daunting to face these types of challenges, knowing what they are is a first step to a patient's best possible outcomes when the goal is a healthy mom and baby.

The World Health Organization (WHO) sorts ovulation disorders into three categories. Women with pituitary damage or dysfunction due to Cushing's Disease will usually find themselves in Class 1. Infertility treatment depends on the cause of the disorder:

- **Class 1:** Hypogonadotropic hypogonadal approximately 5-10% of cases fall under this category problems in hypothalamus and pituitary
- **Class 2:** Normogonadotropic normoestrogenic approximately 70-85% of cases problems in hypothalamus, pituitary, and ovaries
- **Class 3:** Hypergonadotropic hypoestrogenic approximately 10-30% of cases problems in ovaries

While a classification system is helpful, at this time there are still relatively few published studies to guide successful infertility treatment in women with hypopituitarism. Because the hormones required to become pregnant can be affected by having or treating pituitary Cushing's, most women will be affected by this, at least for a little while. Although women have been receiving hormonal infertility treatments since 1961, there isn't much data specifically about women who have chosen it due to pituitary deficiencies.

Two Studies in the Literature

In his presentation, Dr. Carmichael referenced a couple of studies. The first was done in England in 2002 looking at high-risk pregnancies in a group of nine women with hypopituitarism(1). Compared to the general population, these women experienced a high rate of miscarriage and maternal mortality. Amongst the nine there were 18 pregnancies with a live birth rate of 61%, a miscarriage rate of 28%, fetal death rate of 11%, and a 100% rate of C-section births. Half of the live births were at or below the 10th percentile for weight and the majority of the women were unable to breastfeed.

The next study came out four years later and had a total of 19 women with hypopituitarism including the nine from the earlier study. This study looked at pregnancies but also the fertility of the women(2). This group saw a 42% live birth rate, and seven out of 18 pregnancies ended in miscarriage.

Study 1

Hormone Replacement During Pregnancy

Optimization of existing hormone replacement therapy should be discussed before a woman with hypopituitarism becomes pregnant so that she has time to adjust to changes or additions to her dosing. Both mother and developing child must be monitored carefully throughout the pregnancy to ensure that dosing remains correct or is adjusted as necessary. Dr. Carmichael referenced the Endocrine Society Clinical Practice Guideline on hormone replacement in hypopituitarism in adults (3) that gives information on the interactions between replacement hormones and management during pregnancy:

Study 2

- **Glucocorticoids + Growth Hormone** = increased conversion of cortisol to cortisone, patient should have HPA axis tested before and after starting growth hormone in patients who do not take glucocorticoids
- **Glucocorticoids + Thyroid Hormone** = increased clearance of cortisol, patient should be evaluated for adrenal insufficiency (AI) prior to initiating treatment for hypothyroidism
- **Glucocorticoids + Diabetes Insipidus (DI)** = AI might mask DI, patient should be monitored for DI after initiating treatment for AI
- **Estrogen + Growth Hormone** = estrogen increases growth hormone resistance, women taking oral estrogen need higher doses of growth hormone for adequate IGF-1 production
- **Estrogen + Thyroid Hormone** = increased production of thyroid-binding globulin, patient needs to be reassessed for increased need for levothyroxine to stay in the normal range

Further, each type of hormone replacement has specific recommendations during pregnancy:

Adrenal

- hydrocortisone is preferred, with adjustments made as needed
- hydrocortisone is deactivated in the placenta
- patient must be monitored for over- and under-replacement
- stress dosing recommended for delivery

Thyroid

- levothyroxine is preferred with adjustments made as needed
- increased dose during first trimester, through delivery

Gonadal (estradiol and progesterone)

- discontinued during first trimester
- requires collaboration with OB/GYN

Growth

discontinuation during pregnancy is standard

Diabetes Insipidus (DI)

- pregnancy can bring out DI when previously it was not a problem for the patient
- patient should be treated with DDAVP (desmopressin) at bedtime with dosing adjusted as needed
- caution must be used to avoid overtreating

ENDO Hypopituitarism Guidelines

It is clear that fertility is impaired in patients with hypopituitarism. It's also an unfortunate reality that women who experience fertility challenges due to pituitary problems have poorer outcomes compared to women with other types of infertility. Making sure replacement hormones are at their best possible levels before conception seems to give the greatest chance to both mother and baby, and the patient needs to have her levels monitored throughout the pregnancy so deficits or excesses can be quickly adjusted.

It is encouraging to know that pituitary damage does not necessarily bar a person from becoming pregnant in the future. Knowing the challenges and the guidelines for best case scenarios could make a huge difference for a patient who might not be working with doctors who are very familiar with optimal conditions for patients with hypopituitarism trying to conceive. We had a few more questions for Dr. Carmichael:

Q: Do men with hypopituitarism experience fertility problems? If so, what can they do about it other than optimizing existing hormone replacement therapy?

A: Yes, quite commonly. In addition to optimizing other hormones, in most cases, there needs to be a transition from standard gonadal replacement with testosterone to hormones that directly stimulate testosterone and sperm production in the testes. As the goal of gonadal replacement shifts toward optimizing fertility, medications change from replacing testosterone to human chorionic gonadotropin (hCG) injections. HCG stimulates testicular production of both sperm and testosterone. In some cases, additional hormonal therapy is required to increase sperm production with human menopausal gonadotropin (hMG) or recombinant human follicle-stimulating hormone (rhFSH).

Q: Are there any current studies underway to look at fertility and pregnancy issues for patients with hypopituitarism?

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A: While pregnancy is tracked during many studies, including those with patients with hypopituitarism, searching clinicaltrials.gov for hypopituitarism and pregnancy yields no studies directly investigating the influence of hypopituitarism on pregnancy or fertility outcomes. There may be studies conducted locally that may not be listed, but these would usually not include anything interventional or prospective.

Q: What kind of impact would too much or too little hormone replacement therapy have on a developing fetus?

A: There are several concerns here. Firstly, too much glucocorticoid therapy can result in macrosomia, where the fetus becomes larger than normal, potentially causing issues with delivery. Over-treatment also may impact the mother with weight gain, gestational diabetes, and hypertension, among other systemic problems. Significant morbidity and mortality risk for the mother and fetus comes with adrenal insufficiency, especially at the time of delivery, most notably issues with hypotension. Effects on the fetus are rare though, due to placental regulation of maternal glucocorticoids and placental corticotrophin releasing hormone (pCRH) increasing fetal cortisol. The effects of hypothyroidism during pregnancy vary and may depend on the degree of hypothyroidism but include loss of the pregnancy, preeclampsia, low birth weight, cesarean delivery, postpartum hemorrhage, and neuropsychological and cognitive impairment in the child.

Q: I can find some research that points to maternal high cortisol and stress during pregnancy causing developmental delays in the young child. I also read that hydrocortisone does not cross the placenta. Is cortisol not needed for fetal development? Might there be some benefit then, if there is no or low natural cortisol and the replacement does not cross the placenta?

A: The research in this area shows correlation between these findings but does not distinguish between the association and the cause. Hydrocortisone is altered by the placenta, deactivating it to varying degrees, but some does cross, and fetal cortisol is driven by placental stimulating hormones as well, so cortisol is very crucial to the development of the fetus, and is equally as vital for the health of the mother.

Q: Do or would you recommend therapy or other mental health support for a patient with hypopituitarism who wishes to become pregnant? It seems like a very emotional, stressful experience to try to stay healthy and have a healthy pregnancy with hypopituitarism.

A: Absolutely, I think that there is not enough emphasis placed on the stress and challenge, both mentally and physically there is in going through this process. Most reproductive endocrinologists are aware of how their patients can benefit from a support system, which may include counseling from a mental health specialist.

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Defining the "New Normal" 2019 Cushing's Patient Journey Summit,* *continued from page 3

JD Faccinetti (PWN), Muriel Marks (WAPO), and Leslie Edwin

Dr. Nelson Oyesiku and Leslie Edwin

Health-Related Quality-of-Life (HRQoL) in Cushing's Syndrome (CS)

Adham Khalafallah, MD
Nicholas Rowan, MD
Debraj "Raj" Mukherjee, MD, MPH

Cushing's syndrome (CS) is a rare endocrine disorder caused by chronic exposure to excess cortisol, with an annual incidence of 10 –15 cases per million.1 CS manifests with many physical problems, including central obesity, hypertension, hirsutism, muscle weakness, gonadal dysfunction, and hyperglycemia, as well as psychiatric and psychological disturbances, such as major depression, mania, anxiety disorders, and cognitive impairment. As a result, CS can have a profound effect on patients' health-related quality-of-life (HRQoL). Even after achieving a hormonal cure, patients with CS may score lower on HRQoL measures of general well-being, anxiety, and depression relative to healthy controls.2 The potential long-term sequelae of this disease make the assessment of HRQoL outcomes in patients with CS paramount.

In an effort to better assess HRQoL outcomes in patients with CS, 2 disease-specific questionnaires, CushingQoL and the Tuebingen CD-25, were developed in 2008 and 2012 respectively. These validated disease-specific instruments improve our understanding of health dimensions most relevant to patients with CS and can help us identify areas for improved QoL management in patients with CS.

CushingQoL is a self-administered instrument consisting of 12 questions, each measured on a 5-point Likert scale, with a total score ranging from 0 to 100, and with higher scores indicating better quality-of-life. This instrument evaluates two primary sub-scales, namely physical problems and psychosocial issues.3 The Tuebingen CD-25 questionnaire consists of 25 items measuring the subdomains of depression, sexual activity, environment, eating behaviour, bodily restrictions, and cognition. 4 CushingQOL allows for a less granual assessment of domains affected by CS relative to the Tuebingen CD-25 questionnaire, but CushingQOL has been externally validated and mapped to other instruments, such as EQ-5D, allowing clinical researchers to measure cost-utility and other measures of cost-effectivness through use of CushingQOL.

Recent literature has demonstrated both clinically and statistically significant postoperative improvement in QoL scores following the endoscopic endonasal approach (EEA) for management of CS.5 This minimally invasive, endonasal approach has allowed for improved intraoperative visualization, decreased perioperative complications, shorter postoperative length of stay, and improved rates of surgical cure during its increased adoption over the past 20 years. Advances in minimally invasive, endoscopic techniques continue to evolve. For instance, at Johns Hopkins, we are rigorously studying the impact of the EEA on patient-reported QoL outcomes while seeking new, innovative ways to improve patient care. Two current intiatives are specifically focused on reducing potential sinonasal morbidities incurred with use of the endonasal corridor. We are actively investigating the use of a novel endonasal access guide in an effort to decrease intranasal trauma. Moreover, we are piloting use of mucosal grafts to enhance postoperative sinonasal healing while decreasing postoperative nasal morbidities, such as nasal crusting and nasal deformities, following the EEA for management of pituitary neoplasms.

The horizon continues to expand for clinicians and researchers seeking to improve HRQoL in CS. We at Johns Hopkins are excited to be working with the Cushing's Support and Research Foundation to maximize QoL in CS and provide truly personalized care to all our patients.

Editor's Note: EEA is technically the way most transsphenoidal adenectomies (TSA) are performed today, vs. the sub-labial approach (through the upper gums). Also, you can review and take the CushingQol and Tuebingen CD-25 surveys in the Questionnaire Appendix at the back of this issue.

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About the Authors:

Adham Khalafallah, MD is a Post-Doctoral Research Fellow in the Department of Neurosurgery at Johns Hopkins Medical Institutes. His research focuses on mining "big data" and developing novel patient-reported outcome measures in those with brain and skull base lesions, including Cushing's disease.

Nicholas R. Rowan, MD is an Assistant Professor of Otolaryngology-Head and Neck Surgery at Johns Hopkins University School of Medicine. He received his medical degree from Rutgers University, completed residency training at the University of Pittsburgh Medical Center and fellowship training in rhinology and endoscopic skull base surgery at the Medical University of South Carolina. Dr. Rowan performs a full complement of endoscopic sinus surgeries, including orbital and skull base procedures. He is actively involved in outcomes research and quality of life investigations in both patients with advanced rhinologic diseases and tumors of the skull base. His specific research interests include the senses of smell and taste, as well as improving patient quality of life. His research interests directly align with his clinical practice as Dr. Rowan also serves as the Department of Otolaryngology-Head and Neck Surgery Patient Experience Liaison in an effort to champion excellence in patient care.

Debraj "Raj" Mukherjee, MD, MPH is an Assistant Professor of Neurosurgery at Johns Hopkins University School of Medicine as well as Director of Neurosurgical Oncology at Johns Hopkins Bayview Medical Center. He completed a fellowship in open and endoscopic skull base tumor surgery at University of Pittsburgh Medical Center, and his clinical practice focuses on the treatment of patients with pituitary tumors, including Cushing's disease. His clinical work and research emphasize the development of individual treatment plans that optimize survival and quality of life in all patients. His work has been supported by the American Medical Association, National Cancer Institute, and National Institutes of Health.

Doctors' Answers

For this special issue, we wanted to ask some of our Medical Advisory Board members for their thoughts on several topics: What led them to work in endocrinology and specialize in Cushing's? When did they first learn about Cushing's and have their first patient? What are some challenges and inspirations? What changes in medicine and technology give you the best hope for the future of treatment? We got three endocrinologists and three neurosurgeons to share with us:

Dr. Martin Weiss

Professor of Neurosurgery, University of Southern California

These thoughts go back more than 50 years to the time when I was a student/resident when we (in the early 60s) were approaching the pituitary via the trans-cranial route and had little understanding about the physiology underlying Cushing's Disease. My career spanned the transition to sophisticated radio-immuno-assays, imaging technology, immunohistochemical pathological analysis and profound changes in surgical technique. I'm proud that we played a role in these processes.

As a medical student in the early 1960s, I was privileged to work with Dr. Bronson Ray, the undisputed premier pituitary neurosurgeon in North America, and Dr. Olaf Pearson, one of the first pituitary-fo-

cused endocrinologists. Dr. Ray stimulated my interest in pituitary surgery, and that was cemented during my residency when our program became one of the first in the US to adopt the transsphenoidal approach to the pituitary.

When I was subsequently recruited to USC in 1973, I found that there was no neurosurgeon in Southern California performing transsphenoidal surgery, and only Dr. Charles Wilson in San Francisco had similar significant experience with that technique. As a consequence, referrals for pituitary surgery allowed us to accumulate a series of greater than 4,200 transsphenoidal surgeries when I turned my practice over to my colleague, Dr. Gabe Zada, in 2017.

During our years at USC, we were privileged to introduce modifications of the standard sub-labial microscopic technique, publishing the first North American manuscript describing endoscopic pituitary surgery (JNS 1977) and the extended trans-sphenoidal approach (1987) that provided better access to the suprasellar and retrosellar areas. These techniques have now become part of the routine armamentaria of pituitary surgeons.

As I reflect upon this experience, it is apparent that patients with Cushing's Disease have perhaps been the most challenging of all pituitary tumor patients. Firstly, in the series that we published, we found that 26% of patients with both clinical and biochemical Cushing's Disease have normal high resolution (3T) MRI scans of the pituitary so that one has to rely upon studies of cavernous sinus/inferior petrosal sinus blood samples to confirm "central Cushing's." In such cases dependent upon dural sinus sampling for confirmation, the surgical cure rate is significantly lower than those cases in which a tumor is identified by MRI scan. Our new 7T MRI scanner has demonstrated increased sensitivity in identifying previously missed small tumors as recently reported in *The Journal of Neurosurgery.* When such equipment becomes generally available, our "yield" of surgical cures will hopefully correspondingly increase.

Secondly, the recognized delay in establishing the diagnosis of Cushing's Disease results in our patients frequently harboring life challenging co-morbidities such as severe hypertension, diabetes mellitus and morbid obesity. Hopefully, the persistent efforts of the CSRF will continue to alert both patients and physicians to consider the diagnosis before the profound co-morbidities arise.

Many years ago, Dr. Olaf Pearson coined the phrase "malignant endocrinopathy" to describe the consequences of unresolved Cushing's Disease. We sincerely hope that the work of the CSRF and its panel of scientific advisors will bring this problem to resolution.

Dr. Theodore Schwartz

Department of Neurological Surgery, Weill Cornell Pituitary Clinic

I have been taking care of patients with Cushing's Disease for over 20 years. It is truly a remarkable disease that such a small benign tumor can wreak such havoc throughout the body. The diagnosis is challenging and the treatment can be even more challenging. However, I look forward to seeing patients with Cushing's in my clinic. There is nothing more satisfying than curing a patient with Cushing's with surgery. Not only is the surgery itself minimally invasive and low risk, but the impact on the patients' lives is no less than astounding. Some patients come to me as a last resort after having had several surgeries from other surgeons. These are the most satisfying of all patients since a cure in this scenario is even more rewarding. I can see a future just around the corner where patients are given a specific radioisotope to label their tumors that can be seen on an imaging study and which fluoresces in the operating room to be seen by the surgeon. Cure rates will be rapidly increased with this new cutting edge technology.

Dr. Mary Lee Vance

Professor of Medicine and Neurosurgery, Division of Endocrinology and Metabolism, University of Virginia

What led you to want to work in endocrinology, and more specifically, to make a difference in the Cushing's space?

The exquisite beauty of the endocrine system, the intellectual challenges. Cushing's is such a devastating disease that goes unrecognized for a long time in many patients who need appropriate diagnosis and treatment(s).

When did you first learn about Cushing's, and what made it stand out to you above other specialties?

Medical School and Internal Medicine Residency. Stand out: the challenge of diagnosis and the difficulties regarding treatments.

How long have you been a Cushing's specialist?

For over 30 years

When did you have your first Cushing's patient?

As a Resident in Medicine in 1978 I saw a 12 year old girl with Cushing's. I saw more patients many times during my Endocrinology Fellowship.

What are the challenges you hope to help change?

Better and more effective drugs to control the disease. Development of a drug that actually cures Cushing's. Of course I can't change this, but have hope for the future.

What is it like to work with this difficult disease and its patients?

Exhausting, especially after successful pituitary or adrenal surgery (time for recovery is slow and frustrating for the patient), but well worth it when the patient has the correct diagnosis and successful treatment(s) and I don't recognize her/him with the remarkable changes with recovery (seeing the photos of what they looked like when they came to see me and after treatment(s) is amazing).

What keeps you inspired?

The need for these patients to receive a correct diagnosis and treatment(s).

Continued

What changes have you seen in medicine and technology since you first started that give you the greatest hope for better future outcomes?
Technology: more sensitive MRI development and inferior petrosal sinus sampling. Medications: currently not so much regarding efficacious and safe drugs.

Editor's Note: Dr. Vance has done a lot of research on recovery post-Cushing's. She has observed that a big roadblock to psychological recovery is difficulty in allowing oneself to be finished being a Cushing's patient. UVA is well-known for their Cushing's treatment program, so Dr Vance and her team frequently see patients who have been given the wrong diagnosis and in some cases unnecessary operations by doctors who did not understand or adhere to appropriate testing guidelines. It is an unfortunate reality but something that she has spent years trying to help patients set right when they reach her.

Dr. Eliza Geer
Medical Director, Multidisciplinary Pituitary and Skull Base Tumor Center, Memorial Sloan Kettering Cancer Center

I am drawn to Cushing's because cortisol affects basically every part of the body and brain, and there is still so much we don't understand. The more experience I have diagnosing and treating Cushing's, the more I realize how little we know! I am always learning from my patients. I am inspired, and rewarded, when I am able to make even a small difference for one of my patients. I hope to find ways to improve quality of life and long term outcomes for people with Cushing's, by focusing more holistically on mental and physical health, and establishing integrated treatment and support systems for patients during the recovery process.

Dr. Nicholas Tritos
Neuroendocrine Unit, Massachusetts General Hospital

Since my residency days, I have been touched by the health challenges that so many patients with pituitary tumors often face, especially those who have Cushing's disease. I have been inspired by our patients' courage and resilience and have celebrated their amazing recoveries in response to treatment. I have been always amazed at the enormous complexity of the pituitary gland, which beautifully orchestrates so many important functions in the human body despite its minute size.

Over the past several decades, substantial progress has been made in our understanding of the behavior of tumors that cause Cushing's disease as well as other pituitary tumors. As a consequence, we have better treatment strategies. Overall, our patients are doing better these days, which is very gratifying. However, significant challenges remain. For example, tumors of patients with Cushing's disease are often very small and hard to find by imaging tests (such as MRI) that are carried out before pituitary surgery, or even on direct inspection of the pituitary gland by the neurosurgeon during surgery. Although almost always benign, tumors that cause Cushing's disease may grow back after patients undergo initially successful surgery, thus requiring further treatment. These are some of the areas where more research can help us further improve the outlook for our patients.

Dr. Raj Mukherjee
Neurosurgeon, Johns Hopkins

What led you to want to work in endocrinology, and more specifically, to make a difference in the Cushing's space?
Cushing's disease severely impacts patients' and families' quality of life, and, as a surgeon, I have found it extraordinarily rewarding to cure these patients whenever possible.

When did you first learn about Cushing's, and what made it stand out to you above other specialties?
I first learned about Cushing's disease in medical school, nearly two decades ago. The complex underlying pathophysiology of the disease and its impact upon multiple organ systems throughout the body make it stand out to me.

How long have you been a Cushing's specialist?
I have been studying clinical outcomes and treating patients with Cushing's disease for ~10 years.

When did you have your first Cushing's patient?
I treated my first Cushing's patient in 2010.

What are the challenges you hope to help change?
Managing symptoms in patients with recurrent or residual disease are challenging, and I'd like to help create more patient-centered treatment options that maximize patient's quality of life while minimizing the morbidity of various treatments.

What is it like to work with this difficult disease and its patients?
I find it incredibly rewarding to work and support patients suffering from Cushing's disease. These patients are often incredibly knowledgeable regarding this condition and extremely grateful when we're able to provide them with a surgical cure.

What keeps you inspired?
Continuing to work with so many resilient patients with Cushing's disease continues to be an inspiration.

What changes have you seen in medicine and technology since you first started that give you the greatest hope for better future outcomes?
Advancements in adjunctive intraoperative visualization techniques with the endoscopic endonasal approach hold incredible promise, as do new devices that help maintain and improve nasal morbidity in Cushing's disease patients treated surgically.

CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

Efficacy of Repeat Transsphenoidal Surgery for Recurrent Cushing's Disease

William Burke; David L. Penn MD, MS; Caroline S Repetti BS; Edward R. Laws, Jr. MD FACS FAANS
School of Medicine, University of Louisville, Louisville, KY, USA
Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

BWH

Introduction

To systemically review indications and outcomes in patients undergoing repeat transsphenoidal surgery (TSS) for recurrent Cushing's disease (CD).

Methods

Retrospective analysis and a literature review was performed. The retrospective analysis was conducted on the 'Current Cohort,' occurring between 2008 - 2016, which consists of patients who have at least 24 months of post-op follow up after undergoing repeat transsphenoidal surgery (TSS) with senior author (ERL) for recurrent CD, performed at Brigham and Women's Hospital (BWH).

Patients were included for retrospective analysis if they underwent repeat TSS for clinical and/or biochemically recurrent CD with follow up at least 24 months post-operatively. Immediate post-operative remission was defined biochemically as serum cortisol < 5 microgram/dl or clinical adrenal insufficiency and remission on follow up was defined as normal 24-hour urine free cortisol or need for glucocorticoid replacement.

A 'Combined Cohort' was created which includes the Current Cohort pooled with a group of patients who underwent repeat TSS with senior author for recurrent CD at a different institution, obtained from prior publication, between 1992 – 2006. (1)

Results

Current Cohort

The current cohort included 12 patients. Pre-operative MRI showed evidence for tumor recurrence in 7/12 (58.3%) patients, and following TSS 5/12 (41.7%) patients had a pathology report that was negative for ACTH secreting tumor. Operations performed included: lesionectomy 3/12 (25.0%), hemi-hypophysectomy 2/12 (16.7%), subtotal hypophysectomy 6/12 (50.0%), and total hypophysectomy 1/12 (8.3%).

Remission was achieved immediately post-operatively in 11/12 (91.7%). Over an average follow up of 51.7 months (range: 24 – 96), 9/12 (75.0%) achieved continued remission. Two patients with initial remission had recurrence of CD at 24 and 50 months postoperatively.

Combined Cohort

When combined with the historical cohort, 33/48 (68.8%) had evidence of recurrent disease on pre-operative MRI and 17/48 (35.4%) patients had a pathology report that was negative for ACTH secreting adenoma. Operations performed included: 27/48 (56.3%) lesionectomy, 3/48 (6.25%) hemi-hypophysectomy, 12/48 (25.0%) subtotal hypophysectomy, and 6/48 (12.5%) total hypophysectomy.

Thirty-three (68.8%) patients went into remission immediately post-operatively and 29/48 (60.4%) had continued remission at most recent follow up averaging 40.1 months (range 2 – 126). Four patients had recurrence of CD after initial remission at 6, 11, 24, and 50 months postoperatively.

Endoscope vs. Microscope

All patients in the Current Cohort (n=12) underwent operations using endoscopy, while all patients from the previously published study (n=36) underwent operations with microscopy. Operations using endoscopy were significantly more likely to achieve immediate remission (11/12 vs. 22/36; p=0.047).

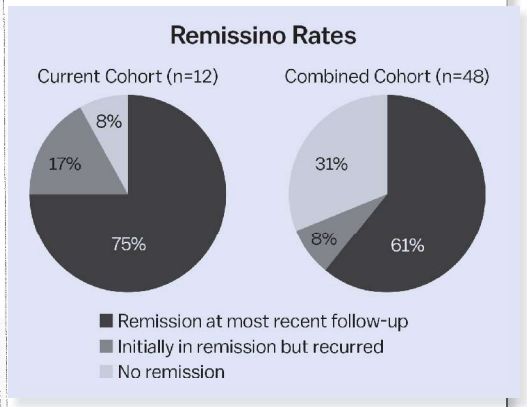
Conclusions

Recurrent CD recurrence can be a therapeutic challenge; however, these data demonstrate repeat surgery is an effective and safe next step prior to radiation or medical therapy.

The predictive value of tumor presence on pre-op MRI may be overstated, with 80% and 86.7% of patients with no identifiable tumors achieving immediate remission.

The predictive significance of ACTH tumor on patholgy report folowing TSS may be overstated, with 100% and 94.1% of patients with a negative pathology report achieving immediate remission.

Endoscopy use results in a more likely chance of immediate remission in this single surgeon study.



References

(1) Patil CG, et al., Outcomes After Repeat Transsphenoidal Surgery for Recurent Cushing's Disease. Neurosurgery. 2008 63:226-270.

Results

Potential Predictors	Current: Total Patients (12)	Current: Immediate Remission (11)	Combined: Total Patients (48)	Combined: Immediate Remission (33)
MRI Presence				
Positive	7	7 (100%)	33	20 (60.6%)
Negative	5	4 (80%)	15	13 (86.7%)
Final Pathology				
Positive	7	6 (85.7%)	31	18 (58.1%)
Negative	5	5 (100%)	17	16 (94.1%)
Extent of Resection				
Lesionectomy	3	3 (100%)	27	17 (63.0%)
Hemi-Hypophysectomy	2	2 (100%)	3	2 (66.7%)
Subtotal Hypophysectomy	6	5 (83.3%)	12	9 (75.0%)
Total Hypophysectomy	1	1 (100%)	6	5 (83.3%)

Medical Advisory Board member Dr. Edward Laws shared this poster that his team presented at the 2018 Congress of Neurological Surgeons meeting. It makes the case that a repeat transsphenoidal surgery can be an effective and safe option if a patient experiences recurrence.

Research Summaries

Patient-reported outcome questionnaires are frequently used across specialties to help patients explain how their illness or treatment is affecting them. We mention four of these questionnaires in this issue, so we decided to include two summaries of original research published when the questionnaires were created, and two summaries of research reviewing existing questionnaires to evaluate their continued efficacy. All four surveys can be found at the end of this issue in the Questionnaires Appendix; if you have a few minutes, why not grab a pencil and take one or two of them? If you'd like to read the full research, you can search by the doi number or scan the QR code for each.

The Center for Epidemiologic Studies Depression Scale: A Review with a Theoretical and Empirical Examination of Item Content and Factor Structure

R. Nicholas Carleton, Michel A. Thibodeau, Michelle J. N. Teale, Patrick G. Welch, Murray P. Abrams, Thomas Robinson, Gordon J. G. Asmundson. PLOS One. 2013; 8(3):e58067. doi: 10.1371/journal.pone.0058067

The CES-D scale is a commonly-used measure of depression. It was created in 1977, and since then there have been questions about the "robustness and suitability of the...CES-D model." This study aimed to test the validity of the survey. Researchers concluded that practitioners may indeed benefit from the structure of the CES-D and it is used to this day.

Screening for anxiety and depression: reassessing the utility of the Zung scales

Debra A. Dunstan , Ned Scott and Anna K. Todd. BMC Psychiatry (2017) 17:329. doi 10.1186/s12888-017-1489-6

The authors of this research start out by acknowledging that the gold standard for diagnosis of any mental illness is the clinical interview, but they give credit to self-report questionnaires because they are helpful for screening and measuring, and are also used quite a bit in research. In this article, the SDS is compared to two other scales to "re-examine its credentials". It holds up well; this scale is noted for its superiority in terms of sensitivity. The authors did feel that the cut-off levels could be adjusted with further research.

Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire

S MWebb, X Badia, M J Barahona, A Colao, C J Strasburger, ATabarin, M O van Aken, R Pivonello, G Stalla, S W J Lamberts and J E Glusman. European Journal of Endocrinology. 2008; 158: 623-630. doi: 10.1530/EJE-07-0762

The CushingQoL was developed by Dr. Susan Webb and her team to address the specific needs of patients with hypercortisolism. As you can read elsewhere in this issue, Dr. Webb has focused on quality of life research and used that expertise to design this questionnaire. It was found to be reliable, easy to do (it takes an average of four minutes to complete), and valid.

The development of the Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25). Part I: construction and psychometric properties

Monika Milian, Philipp Teufel, Juergen Honegger, Baptist Gallwitz, Guenter Schnauder and Tsambika Psaras. Clinical Endocrinology (2012) 76, 851–860. doi: 10.1111/j.1365-2265.2011.04191.x

A few years after Dr. Susan Webb created the CushingQoL, a team of researchers in Germany created the Tuebingen CD-25 to measure health-related quality of life (HRQoL) in patients with Cushing's. The final results showed high reliability and validity. They feel that more specific support can be offered to patients due to the expanded style of the survey.

If You Shop at Amazon....

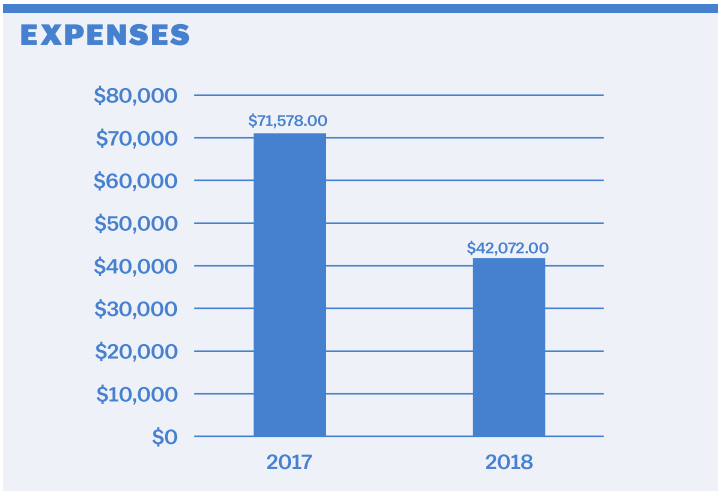
If you shop at Amazon.com, consider shopping through Amazon Smile, which lets you donate .5% of your purchase to your charity of choice. The link to shop at Amazon and support the CSRF is:
http://smile.amazon.com/ch/04-3271267

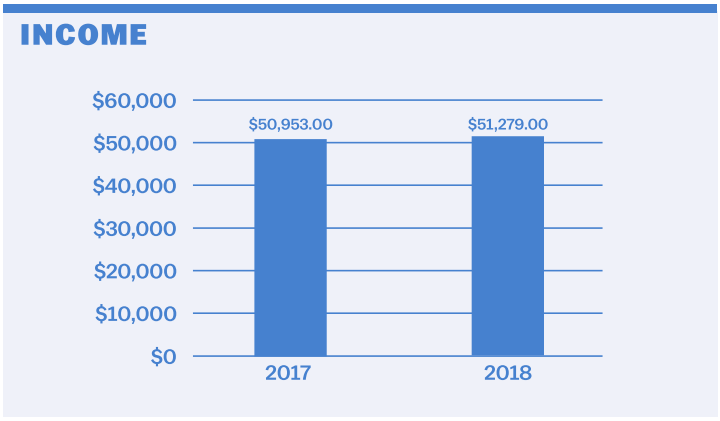
amazon.com

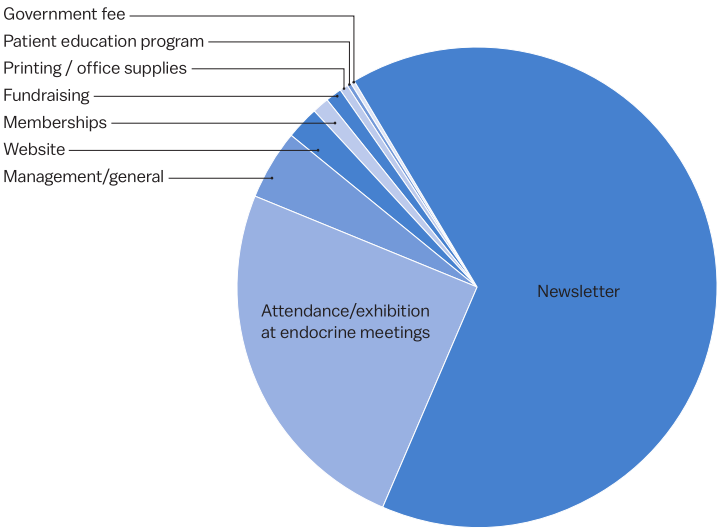
CSRF Finances: FY 2018

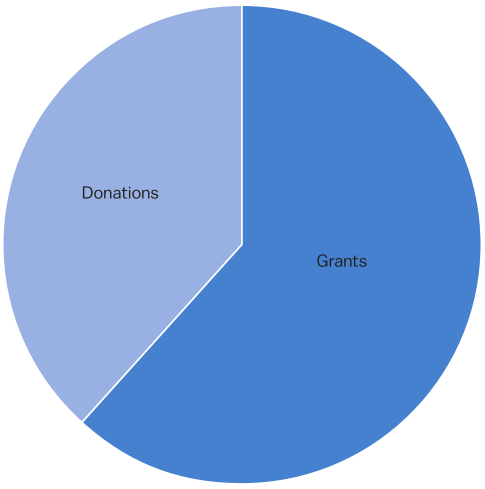
It would be difficult to compare 2018 to the year before; we held a Patient Education Day and invested in a national awareness campaign in 2017, both of which were large expenses not incurred on a regular basis. In 2018, our largest source of income continued to be grants—$31,730—followed by donations—$19,549. Overall income in 2018 was $51,279; in 2017 it was $50,953. A special thank you to our membership—donations increased about 13% in 2018 over the previous year!

Overall expenses in 2018 totaled $42,072; in 2017 they were $71,578. In 2018 our largest expense was the newsletter, which increased considerably in size and distribution over previous years. The next largest expenditure was attendance and exhibition at professional endocrine conferences—the amount we spent in this category is almost the same as in the previous year, but we cut some overall expenses and added a new conference to the rotation in 2018. **The FY 2019 finance report will be in the Summer 2020 issue.**









2018 Income

Grants	$31,730.00
Donations	$19,549.00
Total	**$51,279.00**

2018 Expenses

Newsletter (create, print, ship)	$27,368.00
Attendance/exhibition at endocrine meetings	$10,468.00
Management/general	$1,934.00
Website maintenance and hosting	$999.00
Memberships in related organizations	$481.00
Fundraising	$382.00
Printing and office supplies	$291.00
Patient education program	$114.00
Government fee	$35.00
Total	**$42,072.00**

Things We Wish We Had Known

It's virtually unanimous that Cushing's patients get past the immediacy of diagnosis and treatment and look back on the process and think "I really wish I would have / would have known..." about pieces of their journey that were particularly difficult in the moment. There are parts of the post-treatment "new normal" that only a patient—an expert in their disease—would know. This article was created by ten patients who want to share their experiences with others who may not have thought about these possibilities before. Above all else, we'd like to encourage you to be your own best advocate and health management team member.

A little about the contributors:

CB: Caz Brown from England is in her mid-30s and began to experience symptoms about five years ago. She was officially diagnosed in December 2018, but the tumor was not identified at that time so she was on medical therapy while waiting for a positive MRI. Her ENT surgeon ordered another MRI in late 2019, decided to move forward with surgery, and Caz has been in remission for four months as of February 2020.

DG: Dan Gaiek from Livonia, NY is in his early-60s and began to experience symptoms in early 2011. He was officially diagnosed in 2012 after severe blood pressure, back pain that turned out to be compression fractures, a prostate cancer diagnosis, and finding out he was one of a very small number of reported cases in the US to have what turned out to be an ectopic pituitary tumor in the sphenoid sinus (below the pituitary). Dan's case was so rare, there's a paper on it! Scan the QR code or visit https://doi.org/10.1016/j.inat.2014.04.003 if you would like to read that. Unfortunately, Dan had extreme difficulties after his initial diagnosis, including time spent in the ICU and a nursing home, recurrences in 2014 and 2015, additional surgery, radiation, and treatment for prostate cancer. As of 2017 his cortisol and ACTH levels began to level out somewhat. Dan is currently on medical therapy.

AD: Amy Dahm from Washington, DC is in her mid-40s and began to really notice ramped-up symptoms in 2012. It still took another year to get a conclusive diagnosis of cyclical Cushing's by her endocrinologist (who had been an NIH Fellow), to go to the Mayo Clinic for a second opinion, and ultimately to have a unilateral adrenalectomy at NIH in 2014. Amy currently remains in remission but is dealing with side effects and comorbidities brought on by exposure to hypercortisolism.

DR: Danielle Reszenski from Plymouth, MA is in her mid-30s and feels that she had symptoms throughout childhood that became worse after puberty. After two unsuccessful pituitary surgeries, Danielle had a bilateral adrenalectomy (BLA) in 2010 at age 24. A few years ago she was also diagnosed with Lupus.

KJ: Karrie Julian started noticing symptoms in 2012. An impossible string of medical mishaps over the next 5+ years ultimately led to a Cushing's diagnosis in early 2018 and pituitary surgery in April of that month. The past two years have remained difficult with mental health issues, extreme fatigue, and a dysfunctional thyroid.

LK: Laura Kapur from Marietta, GA is in her mid-30s and started noticing symptoms in approximately 2011. Prevalent symptoms were mood-related, so she was treated by a psychiatrist. A few years later symptoms got much worse and she saw multiple specialists. After

having gastric bypass in 2016 and seeing how the results caused Cushing's symptoms to become overt, she was diagnosed in 2017 and had transsphenoidal surgery in 2018. She remains tumor-free.

LW: Lisa Wollman from Boston, MA suspects she had symptoms going back before her second pregnancy about 20 years ago, but it was while pregnant that she really noticed symptoms. They were written off as consistent with pregnancy and sensitivity to body changes. After a first surgery 19 years ago and a recurrence 12 years ago, Lisa has remained in remission.

MM in North Carolina noticed weight gain and extreme reaction to sun exposure in her mid-20s back in 2003. By 2006 her weight had continued to climb and her blood pressure was very high. It was written off and doctors only agreed to additional labs 18 months later when she'd gained another 20 lbs despite running five miles a day and restricting her diet to 1200 calories per day. Testing at the end of 2007 supported the diagnosis and she had pituitary surgery in 2008. She remains in surgical cure to this day and takes no replacement meds.

PB: Pamela Barrows, 74, from Minnesota, feels that her symptoms began to be overt in the summer of 2017 with a period of excessive heart rate, weight gain and distribution, and hair loss a few months after a back fusion surgery. For the previous couple of years, she had developed paroxysmal atrial fib, and less manageable hypertension. A month later thyroid function tests came back abnormal and Pamela was referred to an endocrinologist who performed the standard tests for Cushing's. An MRI confirmed a pituitary adenoma, so she had surgery in February 2018. She developed adrenal insufficiency but was able to wean off steroids after a year.

TB: Tricia Borchardt from Whitewater, WI noticed symptoms starting in 2003, but it took until Fall of 2010 to be diagnosed with a pituitary tumor. She had surgery in January 2011 and remained on steroids for about six years to avoid adrenal insufficiency. Tricia is currently in remission and only takes Synthroid.

The questions we asked:

Which doctors were involved in getting you to diagnosis?

CB: podiatrist, general practitioner, endocrinologist, radiologist, and ENT surgeon

DG: general practitioner, urologist, nephrologist, and endocrinologist

AD: gynecologists, internist, neurologists, GI docs, radiologists, dermatologist, ophthalmologists, ENT, cardiologists, therapists, complementary doctors, and a team of endocrinologists at three different institutions

DR: somewhere in the range of 15 total doctors including five or six endocrinologists and a gynecologist

KJ: somewhere in the range of 13 doctors to diagnose and four new ones post-surgery to manage symptoms

LK: psychiatrists, dermatologists, gynecologist, primary care, neurologists, endocrinologist, nutritionist, sleep specialist, chronic fatigue center, nephrologist, cardiologists, and an orthopedist

LW: obstetrician, psychiatrist, endocrinologist, sleep specialist, cosmetologist, dermatologist, and podiatrist

PB: primary care and endocrinologist

TB: neurologist, internist, cardiologist, general practitioner, gynecologist, dermatologist, optometrist, endocrinologist, and a few nutritionists

When you left the hospital / after your first treatment, what kind of follow up or treatment plan was initiated for physical and mental needs?

CB: Was given a pack of info for sick day dosing, a sinus rinse, a number to call for emergency or information, and pre-scheduled follow up appointments with surgeon and endocrinologist.

DG: Followed a quarterly testing and appointment schedule and communicated through a patient portal when needed. Mental support was not offered / recommended.

AD: While receiving treatment at NIH, had access to a speech pathologist, rehabilitation doctor, acupuncturist, physical rehabilitation therapist, vocational therapist, occupational therapist, psychiatrist, nutritionist, reproductive endocrinologist, and chaplain. After NIH, built a three-pronged plan involving internist for daily needs, endocrinologist for AI management and endocrine issues, and the NIH team for monitoring. Worked with a psychiatrist and therapist to process the trauma of two major illnesses and adaptations to a new life. Several nutritionists were ultimately unable to address specific issues because they admitted they did not have access to much information about our conditions.

KJ: Nothing was initiated. I had to figure it out and ask for labs every five weeks. Boston surgeon and endocrinologist put me back in the hands of my local providers and it took awhile to get in with the endocrinologist at UW Madison who has actually seen Cushing's patients. She regulates pituitary and thyroid issues and my PCP handles antidepressants and blood pressure meds. I also see a psychiatrist for medication monitoring.

LK: I already had a mental health schedule and the endocrinologist scheduled regular follow up appointments.

LW: I did 24-hour UFCs every six months or so and saw my endocrinologist annually. MRIs were suggested but they never showed a lesion so I stopped having them. No mental support was ever offered or suggested, but I saw a private psychiatrist twice a month.

MM: Weekly check-in calls with a clinical nurse served as physical and mental health check-ins since I live four hours from my center. I

Continued

had a follow up MRI six weeks post-surgery, then annual follow ups for labs the next two years. I didn't ask for other support even though it was available. Looking back, I wish I had.

PB: Both of my doctors have been very good about working together on my case. Unfortunately, neither provided education nor monitored the impact of Cushing's on my brain. Also, neither was aware of some of the helpful modalities to help with my lack of stamina and my muscle weakness.

TB: Six week post-op appointment with the surgeon, I don't remember the endocrinologist post-op but do recall feeling like I was sent to surgery then forgotten about. I had no mental evaluation or suggestions to get any kind of mental or physical treatment.

Were you offered any clinical trials? If you were not offered a clinical trial, do you think you would have considered participating in one?

CB: I am participating in a general pituitary health research project at my hospital comparing healthy and unhealthy pituitaries.

DG: I would have considered a clinical trial if one had been offered to me.

AD: I was placed in the ongoing study at NIH.

DR: I tried getting into a trial for mifepristone but didn't meet the requirements. If going through the process today, I would absolutely consider medications and clinical trials.

KJ: No, but I would have loved to have participated in one.

LK: I was not offered clinical trials and I'm not sure I would have needed them.

MM: I wasn't offered a trial. With a confident surgeon, I was very optimistic about a surgical cure. It's hard to speculate, but I think if I had not been a candidate for surgery then I would have pursued clinical trials.

PB: No clinical trials were offered but I would have been very happy to participate in one. I did respond to an online questionnaire done in Germany (observational study collaboration between CSRF and Dr. Ilonka Kreitschmann, published 2018).

TB: No, I was not involved in any and I don't think I would have participated in any unless my tumor was inoperable.

Have you had to consider or take any of the medications available to us? Are you familiar with the Orphan Drug Act and "orphan drug" designation?

CB: Metyrapone

DG: Tried ketoconazole and it did not work. Currently on Metyrapone.

AD: No medication, but my advocacy work has exposed me plenty of times to the Orphan Drug Act and designation.

LK: I do know what orphan drugs are, but I have not needed one.

LW: I am familiar with the Act and designation but to date have thankfully not had to consider this.

PB: I am not familiar with the Orphan Drug Act. I did take ketoconazole for the last couple of months prior to my surgery.

Did you feel that your treatment team empowered you with all options or did they seem unsure about or unwilling to consider certain treatments?

CB: It took a repeat MRI requested by my ENT surgeon (after a first round of inconclusive scans) to make him comfortable to move forward with the surgery. My endocrinologist gave me a lot of information about the disease and what to expect/side effects.

DG: My Endocrinologist was great. She even came to the ER when I was admitted. She gave me options and asked other mentors for advice.

AD: My team presented all options but there was one clear path we all agreed on due to the variables.

DR: Due to the progression of my disease and severity of my symptoms, each time a decision needed to be made there seemed to only be one best option—surgery the first two times, then because I was young and very sick I decided against radiation (takes years to work) and opted for the BLA.

KJ: They all seemed unsure of the process. I would have benefited from having a champion who could have pulled all of this together.

LK: Absolutely! I had an excellent team that helped me with decisions. I had osteoporosis as a result of Cushing's. I was given many treatment options and felt like Emory was up to date on the latest and greatest options out there.

MM: I felt pretty informed, and they were very confident that the surgery was the best option for me. I was very reassured by being at a trusted center for pituitary disease.

PB: As a retired nurse, I did a lot of my own research and all the physicians I encountered were receptive to my inputs and requests.

TB: Surgery was presented as the only viable option.

What role has peer support (groups, social media, patient-to-patient communication, etc.) played in your understanding of the process and recovery?

CB: Huge! It's good to know what to expect, both good and bad, and to know there are others who understand what you are going through. It is reassuring to have other people who've had certain procedures tell you what to expect, as leaflets describing the process don't really help a huge deal.

DG: Cushing's Support & Research Foundation is a great support group. Patient's Day was extremely helpful.

AD: Huge. Each group has a different "flavor" and provides different types of support. After surgery, a friend with adrenal insufficiency (AI) gave me a copy of "Living with Addison's Disease" from the Addison's Disease Self-Help Group (https://www.addisonsdisease.org.uk, or scan the QR code) and talked me through a period of low cortisol. Peers provide valuable feedback about the day-to-day challenges of living with Cushing's and post-operative AI. In-person support groups and one-on-one meetings with other people with Cushing's might be the most valuable to me—there is no other feeling like being with someone who gets it. Their experiences validate mine, and when I face challenges they empathize and share their best practices with me.

DR: I feel like it's so validating to hear others' stories about going through this. I love talking to people and am active online. I sometimes think those groups had a bigger part than any doctor in my recovery. Any random question like "did you experience this too?" will be answered in minutes, at any time of day. It doesn't replace a call to your doctor, but it's useful.

KJ: It has made all the difference. Unfortunately I didn't find social support until after my surgery.

LK: I was fortunate to meet a former Cushing's patient who met with me to talk through how I was feeling. This helped me a lot. I think more real person connection would be helpful. I also joined social media groups that were great in the beginning, but I feel that they could become negative and spend less time looking at them.

LW: Initially peer support was very helpful. Talking to others at CSRF and online was a lifesaver. Later I found that support groups don't always tend to attract those with the good results and positive experiences, so I backed away.

MM: I can't put a value on peer groups other than to say I'm continuously humbled by each person's empathy for me. They were so kind when I was feverishly searching for info when my labs first came back abnormal. They were a source of feedback post-op that confirmed so many of my post-op struggles and emotions were normal.

PB: Very little. I had to find out about Cushing's support groups online on my own and the information is dated.

TB: Peer support has helped tremendously post-surgery during the recovery and post-recovery period. I had very little time between learning about the disease and my surgery but did find CSRF and have one person who had been through Cushing's call and mentor me pre-surgery. It was awesome!

How are you doing now after the time that has passed since your initial treatment? Have you had a recurrence or do you remain in remission? If before Cushing's you were at 100% physically and mentally, what percentage would you say you're at now on each of those?

CB: Have been in remission for four months as of February 2020. Walking is easier, pains have died down somewhat. Blood pressure massively improved, down 38 lbs. Physical appearance is much improved and sleeping through the night. Back to 80% mentally, about 30% physically.

DG: Recurrence and surgery in 2014, recurrence and radiation in 2015. Back to 90% mentally, 75% physically.

AD: I'm doing ok and still adapting to life post-Cushing's. I medically retired from my job in 2017. According to my doctors I am in remission, but I still have symptoms and issues that linger and impact my daily life in a profound way.

DR: I would say I'm not doing that well, but I know so many who are worse off. I survive. I've had many mental and other physical health issues that I've had to fight through which has been extremely difficult. I don't remember a time without Cushing's because it started so young.

KJ: I remain in remission and am at about 80% both mentally and physically. I struggle with insomnia, endocrine problems, upper back pain and stiff joints in my right hand, stiffness upon waking, and keeping spirits up. I'm still on hydrocortisone and take several other meds for thyroid and blood pressure.

LK: I am almost 2 years post-surgery and tumor-free. I am physically back to 90% (my osteoporosis, which caused most of my pain, has been cured). Mental is the harder part. I think at best I am 70% of what I was. I have a lot of short term memory problems and trouble multi-tasking.

LW: I've been in my second remission about 12 years now. It's hard to assign a percentage because I've had a baby and gone through menopause since my diagnosis. I would say that I am at 80% physically and mentally. I never got back to a totally normal stamina, sleep pattern, or body shape and weight. Mentally I have never recovered my ability to learn new complex things or remember names and references like I used to be able to do.

MM: I have been so lucky and blessed to remain in remission for over 11 years now. I am probably at 85% physically. I was never able to get back to the lean person I was pre-Cushing's. I lost a lot of weight, but the muscle wasting remained. My bones are also older than normal for my age. Mentally, I'm 95%. I'm not as quick or sharp, but I'm pretty close.

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PB: Frustrated that I am still limited in my physical ability to do the things I want to do because of the stamina and back muscles not fully recovering from the back surgery I had 10 months before my Cushing's surgery. I'm at about 50-60%. My low back, hips and thighs still bother me a lot. I also have a lot of stiffness when getting up after sitting.

TB: Eight years post-surgery, no recurrence, energy levels improving each year (especially since I've been able to wean off the steroids). I'd say I'm about 95% physically and 65% mentally. I still have memory issues, difficulty focusing, making decisions, feeling true emotions and finding words, holding conversations. I am easily irritated.

What have you discovered about the long-term effects of having Cushing's that you weren't told during treatment? What "surprises" have come up that you weren't prepared for?

CB: The mental side of things was very unexpected—the brain fog, stuttering speech, memory loss, and mood swings. I was not prepared for the damage it does to bones and mobility—I didn't expect to end up on crutches. The discomfort of withdrawal is a shock. Mental side effects remain—I thought I was ready to return to work but upon assessment it was determined that I needed a little more time. I'm still sick and I'm fed up with it, despite thinking I'd made peace with this journey. I've also developed a hernia because of the excess weight, and other unrelated conditions have gotten worse and now require surgical treatment (ex. cubital tunnel syndrome).

DG: I was surprised that Cushing's affects the brain and a full recovery will not happen. I also did not know that radiation takes two and a half years on average to kick in. Another surprise was the withdrawals. I had aches, joint pain, and did not want to eat or drink anything for around 4 months. Nothing tasted good, not even water.

AD: I didn't realize that Cushing's is the gift that keeps on giving, and that so many of the effects linger over time and actually produce new health issues. Patients who have experienced hypercortisolism are more susceptible to cardiovascular and autoimmune issues. I never thought I'd actually have to leave my job. I didn't think post-surgery could ever be harder than diagnosis or treatment, but it can be. I truly expected my symptoms to resolve once the cortisol was under control. Another aspect that I did not expect was how much time I would spend trying to validate my illness and experience to others, and the wide range of biases that doctors can have that can literally lead to a delay in or refusal of life-sustaining treatment.

DR: Mental health was a big one for me. I always assumed after treatment I would feel better, not just physically but mentally. That hasn't happened. It's been worse.

KJ: Living with replacements is NOT the same. I didn't expect the impact of cognitive decline, a shortened lifespan, and long-term bone density decline.

LK: I really thought my body would start producing cortisol again, but it has not yet and apparently that is a good thing. I'm also surprised about my mental capacity. This is a VERY hard part for me. My doctor said sometimes those parts don't come back and that was something I was not prepared for. Also, going through the life change of NOT being sick anymore is hard. You got so used to always feeling terrible, not socializing, because you were so exhausted, that it's almost like you have to start all over again with friends. Going back to work was hard too, and a therapist helped with that.

LW: Memory issues, PTSD, permanent body composition changes.

MM: The long-term inability to build and retain muscle is hard. I'm still 20 lbs heavier than I would like to be and I lack the energy and strength I had before Cushing's. They told me it would be different, but I just wasn't personally prepared for this. Hearing about and experiencing the post-op fatigue are not the same. I also had a lot of post-op itching. Discussion boards said it was normal but my medical team did not emphasize it.

PB: The length of time to start to feel like oneself. Other than depression, I was not aware of nor told about the potential cognitive and memory decline Cushing's might cause. As my body changed pre- and post-adrenal insufficiency, I regressed to almost my pre-surgery self and I don't think true recovery started until I was able to wean off the steroids.

TB: Recovery takes a long time. The mental and emotional damage aren't treated or acknowledged.

What advice would you give people who suspect Cushing's and are waiting for an appointment or conclusive testing?

CB: Only read official and scientific sites for information, and remember that patient stories are incredibly helpful but are just that, a patient's individual experience and will differ for everyone. Gather all your symptoms into a notebook, get before and after pictures with timelines and keep food/exercise diaries to prove weight gain isn't just being greedy or lazy. Above all, advocate for yourself and if something doesn't feel right then keep pushing.

DG: Be persistent, the process is slow and takes time.

AD: Educate yourself as much as possible. This is a case where you need to be more educated than your doctor. Only look at excellent, medically-vetted research such as that at CSRF. Also:

- Try to find a Cushing's expert that has prior experience with a wide range of Cushing's patients. You want a surgeon in a high-volume center who has done thousands of surgeries. Expertise and experience directly impact success and remission rates.
- If you are not gaining traction with a doctor, don't waste time. Switch. Confident doctors welcome second opinions.

- Create your own A-Team. This is a world-class illness and you need the best doctors and resources available to improve your chances of a successful recovery.
- There are resources available to help pay for transportation, diagnostic tests, medications, etc. Use them!
- Strive for balance, don't try to override your body. Re-draw your life to fit within the parameters of your "new normal" rather than trying to force yourself into a lifestyle.
- It's ok to "sample" an activity—don't stay four hours at the party, go for 20 minutes. People will respect boundaries if you vocalize them.
- When you can, give back to the Cushing's patients who are still struggling.

DR: Be persistent, the process is slow and takes time. It is good to have a caregiver go to appointments with you since your mind is not 100%. Speak up if your symptoms reoccur.

KJ: Educate yourself as much as possible and don't settle for a physician or surgeon who's only seen a handful of cases in their career. Take someone with you to appointments to help catch all the details.

LK: Find an endocrinologist with experience. Push doctors to run tests. Do not give up. You might see many doctors who do not immediately put all the details together, so you need to be your own advocate. They can only work with what you tell them. Keep a tracker of all symptoms. I also found it useful to bring my mother to appointments because I wasn't always good at explaining my symptoms. If you suspect Cushing's and testing does not support that, do not give up on finding out what IS causing your health issues!

LW: Be persistent with doctors—don't let yourself be dismissed. Keep a journal of symptoms and questions. Reach out for peer support! Trust your instincts.

MM: Don't panic—the worst case scenario is NOT the norm. Find an experienced center with a Cushing's-focused clinic. I am 100% convinced that it is the reason for my successful outcomes. Finally, embrace support and advice from your surgeon and endocrinologist, nurses, and other patients. The sources all add rich pieces of information that help you "complete the picture" of what to expect.

PB: Have a knowledgeable advocate and don't back down from demanding reasonable answers.

TB: Give yourself time, don't expect to "go back to normal". This is a life-changing disease. Life can be wonderful but it won't be the same. Request help with physical and mental issues you may have. What may work for one person may not work for you. Always get a second or third opinion if you don't like the answers you get.

with Cushing's Disease

with treatment

My Cushing's Story: Lauren Shelton

South Burlington, Vermont
laurenshelton55@gmail.com

My diagnosis of Cushing's Disease came in May of 2012, at the age of 57. I believe, however, that I had Cushing's for years, even decades, before my diagnosis. Starting in my 30s, I was routinely covered with bruises from minor bumps. Neither my primary care physician nor my hematologist had an explanation for this. I had a couple of serious hematomas, and I had an infection in my hand that required my rings being cut off because of sudden swelling.

In the fall of 2009, my hands became very swollen for no apparent reason. I remember the alarmed look on my primary care physician's face when she saw my hands; she didn't have a clue what was going on. I became very tired and sometimes nearly fell asleep while standing in line at the grocery store. I went to a rheumatologist and was told that I had rheumatoid arthritis and was promptly put on prednisone. That diagnosis got changed to polymyositis (a muscle disease that causes inflammation), and I was kept on prednisone. So far, I had only been seen at the University of Vermont Medical Center. I decided to go to Brigham and Women's Hospital in Boston, one of the Harvard Medical School hospitals, where I saw a team of doctors who spent the whole morning with me doing tests, ultrasounds and interviews. A medical student asked if I had recently travelled to a foreign country, and had other investigative questions. They later sent me a letter declaring that I had dermatomyositis, a rare, inflammatory autoimmune disease that was best treated with prednisone.

In an attempt to get treatment for myositis, I looked up experts in the field and started going to a rheumatologist at Dartmouth Medical Center in New Hampshire, in addition to seeing doctors at the University of Vermont. The diagnosis morphed into "We don't really know what you have. You want a name for it, but it doesn't matter

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because the treatment is the same" (more steroids). Methotrexate and azathioprine were added to my daily medications (both immunosuppressives).

For three more years, I continued to have a bizarre series of symptoms and ailments. Each time, specialists claimed a diagnosis in their field: for shortness of breath, the pulmonologist said I had asthma and gave me steroid inhalers. For incontinence, the urologist said I had weak pelvic muscles and recommended physical therapy. For insomnia, the neurologist gave me anti-depressants, which I took for three days until I thought I was going crazy an d I stopped. For hypertension, I started taking Lisinopril. Brain MRIs and other tests eliminated rheumatoid arthritis, multiple sclerosis, and lupus. To figure out my muscle weakness, I had a muscle biopsy and a series of tests where they give you specifically-placed electric shocks and monitor muscle reactions. I was told that my tissues were abnormal, and it stood that I had some kind of muscle disease.

I was exercising in the hopes of maintaining my muscles, but it was like pouring water into a sieve. I cried my way through yoga classes because I had lost my ability to balance my body. I couldn't stand on one foot, I couldn't jump and I couldn't run. I fell down countless times, just walking along; I was particularly vulnerable on uneven terrain. I broke my leg in one fall. In another, I broke three ribs, got pneumonia, had internal bleeding and contracted C-difficile infection. I fell on a sidewalk in Atlanta, slicing my face and breaking my cheek bone. I flew home the next day and burst an ear drum because of the swelling in my face. My skin had become as thin as that of someone in their 90s. I opened doors into my legs, peeling off the little bit of skin that was there; I asked doctors not to stitch my wounds because there wasn't enough skin. Despite my claim, an ER doctor insisted on suturing a cut with 15 stitches, and within a few days, they all fell out. I carried rolls of gauze with me everywhere because I was constantly cutting my arms and I couldn't use band aids because they would pull the skin off. I had bursitis in my elbows. I had cysts on my feet that would appear suddenly and then go away; one determined surgeon removed one on sight and was baffled by the biopsy because they couldn't identify what it was. My face was red and round. I gained 30 pounds. The bones in my right hip "died;" I was on crutches for five months until I had a hip replacement in 2010. The surgeon was puzzled by the gelatinous state of the "bone." I was told I had "vocal cord dysfunction" and was sent to a speech therapist, who was perplexed at both the diagnosis and what she might do to help me. I was experiencing some classic cognitive issues from elevated cortisol levels, such as foggy brain, short term memory loss, fatigue, anxiety, depression, nausea, trouble sleeping and lack of energy.

My doctor at Dartmouth insisted that I was "stable" and told me to continue taking prednisone, methotrexate and azathioprine. When I described my symptoms, I was told that they were a result of taking steroids. I said that I had these symptoms before I started taking steroids, but I wasn't heard. One healthcare professional told me my shortness of breath meant that I was getting old. (I was 55.) I knew that I was seriously ill and I needed a clear diagnosis.

My dermatologist refused to give up on me. She challenged my Dartmouth rheumatologist for not considering the possibility that I might have Cushing's Disease, not Cushing's syndrome from taking steroids. My neurologist at UVM started questioning the diagnosis of an autoimmune disease. He had done several rounds of muscle function tests with me and had printed out and read a stack of papers detailing my complex medical history. He said, "It is possible that you don't have a muscle disease." I looked at him and cocked my head to the side. "What are you saying?" I asked. He shrugged. Eventually, my endocrinologist looked at my red, swollen face and my "abdominal obesity" and wondered quietly if I had Cushing's Disease.

I was able to convince doctors to let me stop taking the steroids so we could get an accurate reading on my cortisol level, which of course, was "off the charts." Yet another MRI showed some questionable areas around the pituitary, and a subsequent closer look indicated a pituitary tumor, about 1.6 centimeters, a macroadenoma as opposed to a microadenoma.

I had the tumor removed in July of 2012 and within a couple of months, I was almost back to normal. A year later, I had lost 30 pounds and eventually, all 21 of my symptoms went away. I went back to work part time, teaching workshops and classes in Early Childhood Education. I was able to care for my young granddaughter for the first time. Her sister was born in 2015 and I became vigorously involved in their lives on their farm, still my favorite place to be. In 2016, I celebrated my recovery with a 10-day, 100-mile walk on the Camino de Santiago in Spain. (You can watch my YouTube video called "10 Days on the Camino.") I felt great. I was Rip van Winkle, waking up after a very long time asleep. I was alive again!

Alas, my Cushing's symptoms returned in the fall of 2018. I was gaining weight, 30 pounds again, having trouble sleeping, suffering mild incontinence, feeling weak in the legs and fat in the face. A general, familiar feeling of Cushing's Disease silently descended on me. My husband had been urging me to get a cortisol test for months, but I didn't see the point since it hadn't occurred to me that the tumor could come back. As it turns out, my Boston doctor said that there is a 20% chance of recurrence for a macroadenoma. My cortisol level tested even higher than it had been the first time. Alone at home when the news came, I was hysterical for 45 minutes. I could only imagine what might be ahead for me.

A subsequent MRI did not detect a tumor, but the doctors at the endocrine clinic at Massachusetts General Hospital said that there was without a doubt a return of the tumor. A second surgery was not recommended because chances are the tumor would keep coming back. The best route would be proton beam radiation, and the results

would take one to six years, maybe longer, for the pituitary to regain its normal function. I would first need to get my cortisol level down, so I started taking ketoconazole. Two months later, in March of 2019, I had the one-time radiation treatment. Having radiation so close to my brain and my eyes was the scariest thing I have ever done, but I made it through without passing out or throwing up. I am extremely grateful for the opportunity to have this treatment, and I am grateful to my husband for his support, and for his health insurance. As I was leaving the radiology department, I asked an attending nurse, "How am I different now?" She said with a smile, "You will be able to beam purple light and see through buildings!" I was radiated and empowered. Now I needed to be patient.

I am still taking ketoconazole, 1200 mg/day, to keep my cortisol in the normal range. I have lost 25 of the 30 pounds that I had gained. I never got the bone necrosis, thin skin, muscle weakness, shortness of breath or the other myriad of symptoms that plagued me the first time, but I have struggled with some of the cognitive issues, like tiredness, short term memory loss and anxiety. The hypertension came back, so I am taking two medications for that. I experience nausea from the ketoconazole. I sometimes feel like I am on a roller coaster ride caused by an artificially regulated endocrine system.

I am waiting for signs that my cortisol production is normalizing. It has been 12 months since my radiation treatment. The earliest recovery my doctor reports is six months, with an average of one to two years, so I am reaching the potential range of seeing results. In the meantime, I work with my re-invented self. I write in my Gratitude Journal. I take pleasure in being with my granddaughters, who are five and eight now. I garden, sew, swim, walk, read, listen to music, play ukulele. I started teaching early childhood education classes again, part time, which has helped my cognitive functioning and my sense of purpose. My family and friends have been wonderfully supportive. As one friend told me, I "present well," which allows me to continue relationships and activities with minimal distractions. I am very grateful for the medical procedures that have saved me from the scary downward spiral that results from untreated Cushing's Disease, and I am optimistic about a full recovery.

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.

Patient Story: Melissa Clauson

Idaho, m.clauson@hotmail.com

My name is Melissa and I am 54 years old and live in the Boise, Idaho area. I am 11 months post op adrenalectomy due to a functional tumor that caused my Cushing's syndrome. I have a 20-year career in the military followed by work as an Occupational Therapist. I was adopted by a loving family, so entered my Cushing's journey with no medical history. Thankfully I have a wonderful supportive husband. I was also recently diagnosed with a pituitary tumor (prolactinoma) causing increased prolactin and growth hormone. My pituitary tumor is being treated with a medicine called Cabergoline.

In the past 30 years I have had every female hormone problem I could imagine. Fibrocystic breasts, benign breast lumps, ovarian cysts with one ovary removed, uterine fibroids, severe endometriosis, polyps, hysterectomy, frequent urinary tract infections, and surgeries needed to remove adhering scar tissue on numerous organs and a twisted colon from them.

In the last 10 years I started developing chronic fatigue, frequent infections in the form of shingles on my arms and legs only, severe hot flashes and night sweats (menopausal), hypothyroidism, losing my hair, high blood pressure, high cholesterol, hepatic hemangiomas (non-cancerous liver masses), pre-diabetes A1C number 5.8, and peripheral neuropathy in my toes. I was put on estrogen, thyroid, and blood pressure (diuretic form) medicine. I gained about 20-25 pounds, but I wouldn't say I had the moon face or excessive weight gain like some.

In 2018, I had my first ER visit. My blood pressure elevated to 174/108, and I was having a visual disturbance in my left eye seeing color patterns like a sideways rainbow. They did a retinal ultrasound and EKG, which were normal. I was referred to an ophthalmologist who said I had a migraine with a visual aura without the headache. He actually showed me the picture I had seen in my eye. He said it was probably related to high blood pressure and from all my hormone imbalances. In the same year I had the shingles 4x, started getting more urinary tract infections, poor sleep, and unbearable hot flashes/ night sweats. I had just finished Cipro for a UTI when I started developing extreme symptoms such as headaches, vertigo (dizziness), panic attacks, excessive fear, loud heartbeat in my head, racing thoughts, inability to calm myself, crying, no sleep, no eating, difficult getting water down, nausea, blurred vision, worsening numb toes and feet, tingling down arms and legs, and chest pain.

In January 2019, I ended up at the ER and urgent care twice in one weekend. My diagnoses were generalized anxiety disorder, non-specific chest pain, low potassium, and vertigo. I was given anti-anxiety meds, taken off the diuretic blood pressure medicine (supposedly causing loss of potassium), and referred to a cardiologist. I was in

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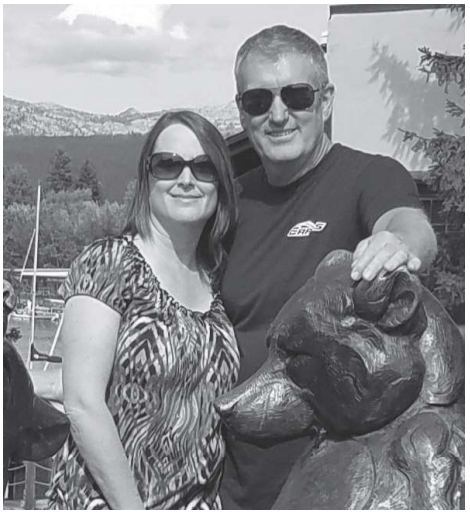
Melissa before Cushing's

with Cushing's



after Cushing's

panic mode every day. I had a hard time in enclosed spaces, offices, buildings, and at church. Fear of future, and an overwhelming dread that I just couldn't explain. I couldn't concentrate and was pacing a lot. Blood pressure would elevate throughout day causing my heart rate to get louder. I felt panicked and anxious around people and did not feel normal. I hadn't been able to eat much and during this time lost 25 pounds before diagnosis. Go figure? I kept saying something is wrong with me.

A little note about me concerning the anxiety—this was not me and never had been me. I am 20 years retired military and worked on jet airplanes, flew in Air Force jets/helicopters, jumped out of planes sky-diving, retrained as an EMT in the emergency room, traveled all over Europe, and river rafted many Class 4 rivers. Now I am diagnosed with a sudden anxiety disorder with no apparent reason. NO!

The cardiologist had me wear a halter monitor taped to my chest for two weeks, and I had a stress test/echocardiogram. I passed with excellent results. My Primary Care doctor on the other hand said I was too low on my estrogen and my menopause was worsening. She increased my estrogen, adjusted my thyroid medicine, changed my blood pressure medicine, and gave me anti-anxiety medicine with a recommendation to see a psychiatrist for counseling.

I was able to get a same-day cancellation with a psychiatrist and counselor who increased my anxiety medicine. The counselor taught me breathing techniques, but it was a battle keeping the anxiety and racing thoughts in check. I would look at her like this was a monumental task. I didn't know if I could do it. She would tell me I have to get this under control, or it would get worse. I'm that military girl who follows directions, but at the same time crying out to the Lord with such desperation assuming I now had an anxiety disorder. My meds were barely helping, and I was fighting to not take more than recommended. I couldn't sleep and I honestly wished I would not wake up when I did sleep. I know that it's not Gods plan for me or anyone, but I now understand what a struggle this is for some in the mental health network. I just had to endure the 4-6 weeks until the medicines kicked in I guess.

At one point I literally wanted to be admitted for psychiatric treatment. I had the back of my car packed with my wonderful scripture quilt, meds, bible, worship music and therapeutic coloring books ready to be admitted. I couldn't take it anymore, but my husband talked me out of it and helped calm me down. My brother helped a few nights to calm me being a substance abuse counselor, for which I will be forever grateful. I had my Lord Jesus, family, tons of prayers, and church support. I was an open book and I didn't care.

I prayed and sought the Lord which prompted me to make an appointment with an endocrinologist while this was all happening, and without my family practitioner knowing. I was to wait over a month. My symptoms continued to increase, and I was still in panic mode. I was struggling to follow up with doctors, and to go out in the public for family and church events. I would take long walks praying trying to keep my anxiety and fears at bay, hoping I wouldn't lose my husband and sanity. My poor husband didn't know what to do for me. I remember thinking how could he put up with this and what if he leaves me. I probably wouldn't blame him. I would too, but Lord willing he was there for me.

God was watching over me and guiding me, and again I was prompted to call every day for a cancellation to the endocrinologist. The first day I called they had one rare cancellation that very afternoon. She was so wonderful—I did lots of blood tests and 24 hour urine tests, which started to reveal pituitary and/or adrenal malfunctions. My doctor even called me over the weekend to tell me I had failed the overnight dexamethasone test miserably, and referred me for a CT scan. The results were two left adrenal gland nodules. One of the nodules became functional causing excess cortisol. I was in continuous fight or flight mode. You are so right when you feel overjoyed to the point of crying to get a diagnosis that there was something going on, and you aren't just a crazed human being.

I was referred for surgery. I remember my surgeon telling me that some people get psychotic symptoms with this diagnosis. I said yes that was me. Unfortunately I had to wait a month for surgery, but the day finally came in April 2019. They removed my adrenal gland and the benign tumors. I was put on hydrocortisone meds until my other adrenal kicks back in. It has been a rollercoaster. I have been tapering down on my steroids for the last 11 months. I still get similar symptoms, especially crying and emotional instability. Of course I get the sore joints and muscles with difficulty waking up and moving in the morning. Mostly hip, lower back, and knee pain. I still need meds for sleep and the hot flashes/night sweats. My cortisol and ACTH are still very low. Also, I cannot get my thyroid regulated.

Unfortunately, we also discovered I have a pituitary tumor. My prolactin and growth hormone levels had been elevated. MRI revealed a 6mm microadenoma (prolactinoma). Thankfully Cabergoline is a medicine that can reduce its size and lower these hormones. I am hoping this was my missing link that was affecting my continued mental issues.

On a positive note my blood pressure has been normal without medication. I am not pre-diabetic anymore. My A1C went from 5.8 to 5.4. I haven't had shingles or a UTI for over a year, and I'm not wearing glasses anymore. My cholesterol is still slightly high, but my endocrinologist wants me to wait before taking statins.

One special surprise this diagnosis brought about was that it prompted me to search for my biological parents and medical history, since I was adopted. I now have new relationships with my birth father and two new half-sisters that I am enjoying getting to know. God is good.

God amazes me with how our complex bodies work, and how our hormones are connected to every system. You just have to have the right balance to function. Cushing's and hormone imbalances are real, unexplainable at times, more common then we think, and very hard to go through. But yes you can get through. It requires patience and endurance, and a diagnosis. I also have a huge empathy now for people who struggle with unbalanced mental and hormonal health. I was so scared at times that my only hope was in my Lord and Savior Jesus who was my refuge and who held me together. I am still a work in progress and am hoping and praying I will come out of this with few scars, but I am preparing for God's will either way.

Please email me if you need support or encouragement. I would also love to speak with others who understand what I have gone through—there are little support services or others to talk to in person where I live. Email: m.clauson@hotmail.com. Thank you for listening and God Bless.

Need to talk? Local support contacts and groups

Going through Cushing's is isolating, and sometimes we need to talk with someone who understands. The members listed below are support contacts in their respective cities and in some cases there are active support groups meeting. Don't see your city listed and want to discuss being a point of contact in your area? Email Leslie at leslie@csrf.net and we'll see if it's a good fit. Thank you!

Phoenix, AZ*
Barrow Neurological Institute
Maggie Bobrowitz
(888) 726-9370
margaret.bobrowitz@dignityhealth.org

Phoenix, AZ
Elaine Thobe
(949) 285-8612
elaine.etc@zoho.com

Atlanta, GA
Leslie Edwin
(404) 791-5483
blueofnoon@hotmail.com

Chicago, IL
Barb Gallagher
(630) 832-9047
bmgallagher@sbcglobal.net

Florence, KY
Heather Wickstrom
(513) 818-6102
unicorn_zebra@hotmail.com

Boston, MA
Heather Shaw
(617) 372-6880
heathershawdesign@gmail.com

Houston, TX
Katherine Griffith
(713) 683-6241
kgelberg@yahoo.com

King of Prussia, Hershey, Harrisburg, PA*
Marie Conley
marie@kickcushings.com

Western MA, Capital Region & North Country NY, Southwest VT, and Northwest CT
Mark Navin
(413) 822-3808
navin.mark@yahoo.com

Maryland & Washington DC*
Dr. Georgie Eddins
(703) 298-4414
georgie@georgieeddins.com

Amy Dahn
a_dahm@yahoo.com

New York City, NY
Miriam Klein
(347) 631-9837
Miriamklein90@gmail.com

Tampa, FL
Linda Weatherspoon
(843) 213-7127
Linda@jwxspoon.com

Seattle, WA
Ellen J Koretz
(206) 789-8159
ellen.j.koretz@gmail.com

Canadian Pituitary Patient Network
info@canadianpituitary.org
canadianpituitary.org

Alberta, Canada
Alberta Pituitary Patient Society
info@albertapituitary.org

**support group*

QUESTIONAIRES APPENDIX

Throughout this issue we have mentioned several self-reporting questionnaires—the Zung Self-Rating Depression Scale (SDS: 1965), the Center for Epidemiologic Studies Depression Rating Scale (CES-D: 1977), the CushingQoL (2008), and the Tuebingen CD-25 (2012). These surveys are the result of decades of efforts to find effective tools to measure mental health and quality of life. We encourage you to grab a pencil and take one or more of them! Our mental health is just as important as our physical health. If you find that your results point to signs of depression or a need for support, please reach out to a trusted healthcare provider. Summaries of research related to these questionnaires can be found in the Research section of this issue for more background information.

Zung Self-Rating Depression Scale (SDS)

This survey aims to assess the level of depression in patients diagnosed with depressive disorder.

SCORING: There are ten positively worded and ten negatively worded questions. Each is scored on a scale of 1-4. The positively worded questions (2, 5-6, 11-12, 14, 16-18, and 20) should be scored inversely (4 for the first column, 3 for the second, etc.). Scores range from 25-100: 25-49 Normal Range, 50-59 Mildly Depressed, 60-69 Moderately Depressed, 70 and above Severely Depressed.

Zung Self-Rating Depression Scale (SDS)

For each item below, place a check mark in the column which best describes how often you felt or behaved this way during the past several days.	A little of the time	Some of the time	Good part of the time	Most of the time
1. I feel down-hearted and blue.				
2. Morning is when I feel the best.				
3. I have crying spells or feel like it.				
4. I have trouble sleeping at night.				
5. I eat as much as I used to.				
6. I still enjoy sex.				
7. I notice that I am losing weight.				
8. I have trouble with constipation.				
9. My heart beats faster than usual.				
10. I get tired for no reason.				
11. My mind is as clear as it used to be.				
12. I find it easy to do the things I used to.				
13. I am restless and can't keep still.				
14. I feel hopeful about the future.				
15. I am more irritable than usual.				
16. I find it easy to make decisions.				
17. I feel that I am useful and needed.				
18. My life is pretty full.				
19. I feel that others would be better off if I were dead.				
20. I still enjoy the things I used to do.				

Center for Epidemiologic Studies Depression Scale (CES-D)

In the past week, how often have you felt each of the following ways?

SCORING: Zero for answers in the first column, 1 for answers in the second, 2 for answers in the third, 3 for answers in the fourth. Questions 4, 8, 12, and 16 will get a reverse score (a check in the first column is 3, second column is 2, etc.) Possible range of scores is zero to 60; the higher the score, the more likely you should consider taking a next step.

Center for Epidemiologic Studies Depression Scale (CES-D)

Below is a list of the ways you might have felt or behaved. Please tell how often you have felt this way during the past week.	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with help from my family or friends.				
4. I felt I was just as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people disliked me.				
20. I could not get "going."				

Cushing's Quality of Life (CushingQoL)

These sentences refer to how you have felt about your Cushing's in the last four weeks. Answering this questionnaire helps your doctor understand how you perceive your quality of life (QoL).

SCORING: Rate each sentence on a scale of 1 (Always / Very much) to 5 (Never / Not at All). Scores range from 12-60, with a lower number indicating a more negatively impacted QoL.

Cushing's Quality of Life (CushingQoL)

For each item below, place a check mark in the column which best describes how often you felt or behaved this way in the past four weeks.	Always/Very Much ←------→ Never/Not at All				
	1	2	3	4	5
1. I have trouble sleeping (I wake up during the night; it takes me a long time to get to sleep, etc.)					
2. I have pain that keeps me from leading a normal life.					
3. My wounds take a long time to heal.					
4. I bruise easily.					
5. I am more irritable, I have sudden mood swings and angry outbursts.					
6. I have less self-confidence, I feel more insecure.					
7. I'm worried about the changes in my physical appearance due to my illness.					
8. I feel less like going out or seeing relatives or friends.					
9. I have had to give up my social or leisure activities due to my illness.					
10. My illness affects my everyday activities such as working or studying.					
11. It's difficult for me to remember things.					
12. I'm worried about my health in the future.					

Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25)

This survey covers issues related to depression, sexual activity, environment, cognition, and other restrictions to look a little more in depth at our daily routine and how Cusihng's affects it.

SCORING: Each question gets a score of zero (strongly disagree) to four (strongly agree) points, with a max score of 100. The higher the number, the more negatively impacted the QoL of the respondent.

Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25)

Place a check mark in the column which best describes how you feel about each item below.

Because of my Cushing's disease....	Strongly Disagree (0)	Somehow Agree (1)	Sometimes Agree (2)	Mostly Agree (3)	Strongly Agree (4)
DEPRESSION					
1. I am dissatisfied with my life.					
2. I have the feeling that I am in a desperate situation.					
3. I have the feeling that my life is unfulfilled.					
4. I have the feeling of being observed by other people.					
5. I do not have any impulse to change anything in my life.					
6. I am not able to enjoy things as much as I could in the past.					
SEXUAL ACTIVITY					
7. I am dissatisfied with my sex life.					
8. I feel bad when I am naked in front of my partner.					
9. I have the feeling that I am ignored by the opposite gender more often than other people.					
10. I am afraid to disappoint my partner sexually.					
ENVIRONMENT					
11. I rarely get compliments because of my appearance.					
12. It is difficult for me to socialize with someone new.					
13. I do not have the same possibilities in my life compared to other people.					
14. I have given up many of my activities and interests.					
15. I am lacking the impulse to go out.					
16. I have the feeling that I am uncharismatic.					
EATING BEHAVIOR					
17. I do not feel I have had enough food even after an adequate meal portion.					
18. I do not have the feeling that I have my eating behavior under control.					
19. I eat more when I am on my own rather than in company.					
20. Although I am eating considerably less than other family members, I am still gaining weight.					
BODILY RESTRICTIONS					
21. I am afraid to fall and suffer a bone fracture.					
22. I watch out not to crash into things because I get bruises easily.					
23. I feel overstressed when I perform my daily activities.					
COGNITION					
24. I am slowed in my mental and motor activity.					
25. I suffer from concentration disorders.					

Clinical Trials

Surgery is the first line of treatment for endogenous Cushing's syndrome (caused by a tumor), but sometimes there are delays, and sometimes a first surgery is not successful. Especially in the latter case, suddenly there are several options for the patient to consider—repeat surgery, radiation, medication, and clinical trials (if available). Trials tend to have slow recruitment because there just aren't that many Cushing's patients and there can be barriers to enrollment, usually geographic. However, successfully completed clinical trials over the years have led to our small collection of pharmaceutical choices, and new trials will investigate potential options for the future. A significant bonus is that enrolled patients receive all trial medication and treatment at no cost and frequently are eligible for extended no-cost access to the drug after the trial has concluded.

We will focus more on clinical trials in our next issue, but there is a current trial that will potentially finish recruitment before that goes to print so we are including information about it now. The Grace Study, run by Corcept Therapeutics, is a Phase 3 trial for their drug Relacorilant (following several earlier successful phases, this phase involves more participants across the intended patient population at different dosages, measuring safety and efficacy—it is the "last step" before FDA approval). Rather than working at the pituitary or at the adrenal, this medication binds with cortisol receptors throughout the body to block cortisol uptake. A popular misconception about this type of action is that there is no way to "pull out" of a scenario where "too much" cortisol is being blocked and the patient could experience adrenal insufficiency; dexamethasone counteracts the effect of the drug. The best two people to advise you on every decision in your journey, including whether or not to participate in a clinical trial, are YOU and your doctor. Read everything you can… from a scientific source. Read the listing on clinicaltrials.gov (the Grace Study is Identifier: NCT03697109). Discuss your concerns with your doctor.

The Grace Study is currently recruiting in 20 states (AZ, CA, CO, DC, FL, GA, IL, IN, LA, MI, MS, MO, NY, NC, OH, OK, PA, SC, TX, and WA), Bulgaria, Israel, Italy, Netherlands, Poland, and Spain. For more information visit cushingresearch.com or scan the QR code.

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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?

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