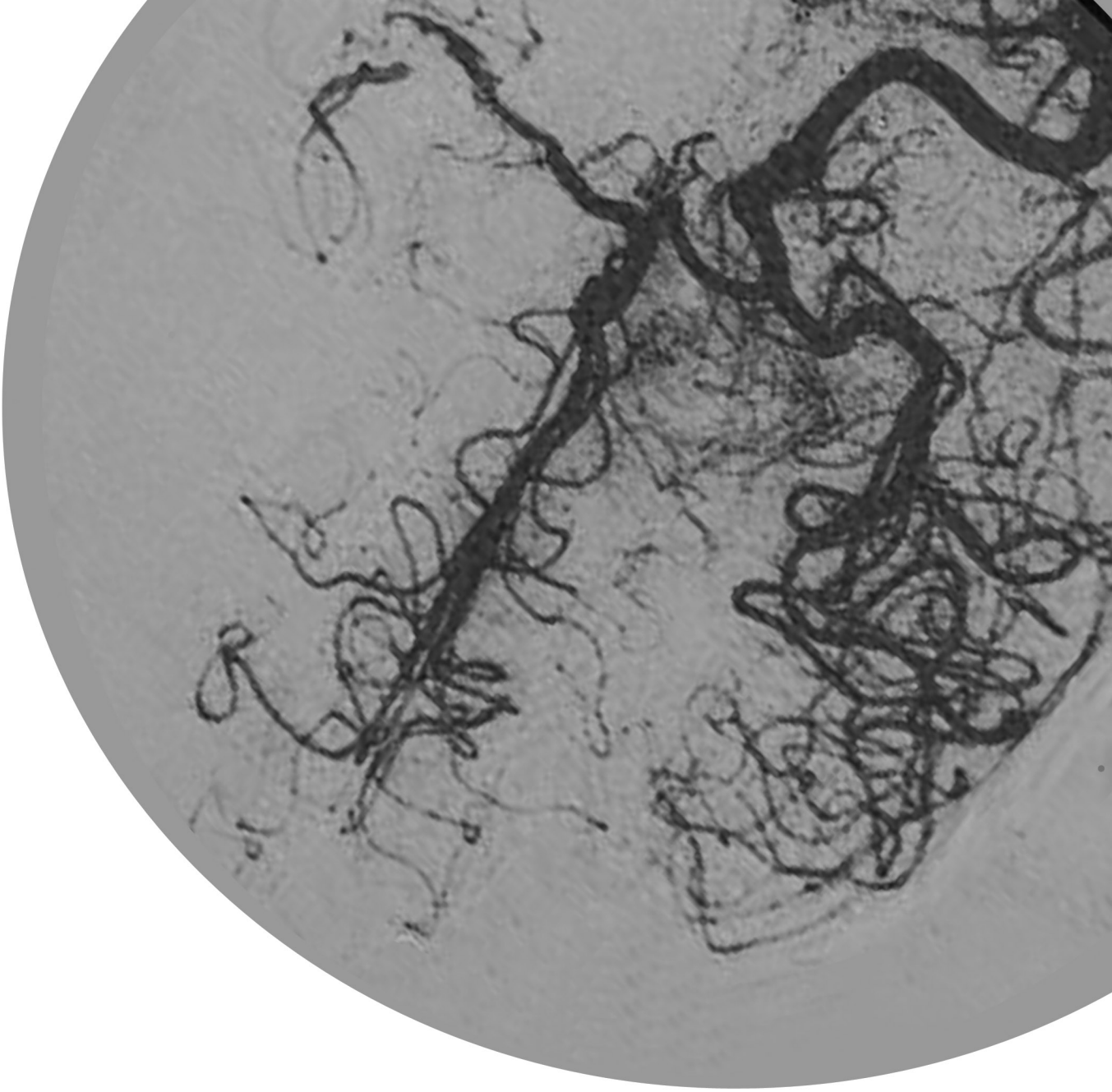


COLUMBIA

Medical Review

FROM THE EDITOR

Dear Reader,

Thank you for picking up this inaugural copy of the *Columbia Medical Review!* This is a student-run and peer-reviewed medical journal that publishes articles focused on healthcare and written by the students and faculty of the Columbia University Medical Center. We hope that you will find something enjoyable and informative in its pages. In fact, we hope that everyone in the Columbia medical community finds something of interest in our journal. Our goal is to publish a wide variety of articles that examine issues in healthcare from diverse perspectives. This issue contains original scientific research, scientific reviews, a travel narrative, a personal reflection, and a book review.

The *Columbia Medical Review* has three principal purposes:

- To allow students to experience the process of critically reviewing, editing, and publishing scholarly articles.
- To give students and faculty a forum in which to develop and share their ideas.
- To increase the intellectual connectedness of the CUMC community.

We also intend, in future issues, to publish the results of scholarly projects performed by students of the College of Physicians and Surgeons. Starting with the class of 2013, all medical students at Columbia will complete such projects.

The idea for a student-run medical journal at Columbia is not new. The *P&S Medical Review* was a similar journal published over nine volumes from 1993 to 2003 by Columbia medical and public health students. We have changed our name to the *Columbia Medical Review* in order to encourage students and faculty from schools other than P&S to read and contribute to the journal. However, it is out of deference to the many excellent issues published by our predecessors that we are starting our journal at Volume 10, Issue 1.

We encourage you to send your suggestions, questions, letters to the editor, and original submissions to us at *columbiamedicalreview@gmail.com*. We also invite you to visit the online journal at *juno.cumc.columbia.edu/psreview*.

Sincerely,
Clement Marshall
Editor-in-Chief

Top (L to R): Mariel Kozberg, Mahesh Madhavan, Joshua Cook, Noam Rudnick, Andrew Chan, Avery Miller, Anna Janas
Bottom: Obi Emeruwa, Michael McDowell, Clement Marshall, Sheila Rajagopal, Neil Pfister
Not pictured: Britton Kreiner, Camila Mateo, Lisa Roth, Jacob Tulipan, Mimi Zhang
Photo by Lauren Orr

COLUMBIA
Medical Review

Editor-in-Chief: Clement Marshall (P&S 2013, MD)
Layout and Design: Sheila Rajagopal (P&S 2013, MD)
Website: Noam Rudnick (P&S 2016, MD-PhD)

TABLE OF CONTENTS

ESSAY

The increasing role of silence in my ongoing medical education

By **Britton Kreiner**
College of Physicians and Surgeons, 2013

At our white coat ceremony, my classmates and I were presented with a pin and lecture from the Arthur P. Gold Foundation to honor the spirit of Humanism in Medicine and foster its growth. It is in this spirit that I share with you a couple of experiences that have taught me to better appreciate a crucial idea that may never make it to a chart or prescription pad: the ability to be quiet inside.

During my first year of studies at Columbia, I was assigned to a small group that held role-plays and discussions related to sensitive areas in healthcare, with an emphasis on delving into both social and individual perspectives. Throughout the course, we dealt with topics such as abortion, the right to die, delivering bad news, and taking a sexual history. On one such occasion, we were asked to choose a partner and share a story of personal emotional significance. I partnered with Dr. R., our preceptor, who happened to be sitting next to me. After I shared my own story, Dr. R. paused for a moment and then began to tell the story of his father, a highly respected dean in our institution, who was battling amyotrophic lateral sclerosis (ALS, Lou Gehrig's Disease) and was deteriorating. He spoke fondly of his father's resilience and dedication, having continued to serve as dean until a few months earlier. It was not until the preceding couple of weeks that Dr. R. and his family had begun to take the inevitable step of bringing themselves to accept and cope with the imminent likelihood of his father's death. In doing so, they had managed to enjoy a few intimate, love$filled moments in the hospital room that were no doubt priceless for his father in his final days. One such example that I found especially touching was how his mother would come to play her harp at his bedside, moments that had undeniably deep significance for Dr. R.

As his story wound down, I realized that I had developed a sincere intimacy with Dr. R. The exercise in class had intended to emphasize listening. As our presenting classmates had reminded us, "The average doctor interrupts a patient every seven seconds." Neither Dr. R. nor I had really interrupted each other during our stories, and as a result, we both felt appreciated and were more trusting of each other. I did not interrupt him with even a private thought, and this in retrospect, made such a special interaction possible.

Looking back on that moment, I learned that listening and being quiet did not simply mean not talking, but also not thinking. Usually when I am listening I am also usually rehearsing, preparing to answer, preparing to help – I am thinking. But sitting with Dr. R. that day, I was in no rush to helpfully instruct him or offer my own similar story. I knew that I had no memory of my own that would allow my words to be of help to him. I knew I was hearing something sincere and unique, and I listened. As a result, the usual stream of possible answers gave way to a naked receptivity that allowed me to provide a truly therapeutic space to my preceptor, and both of us were able to benefit from that space.

Later, during my second year clerkship, I was assigned to see patients at Stamford Hospital in Connecticut to learn the art of physical diagnosis and history taking. It was the most extensive patient interaction yet in my education, and our site preceptors found a wide variety of patients and clinical situations from which we could learn. One day in late October, my site partner John and I walked into a hospital room to meet our patient, a man in his late fifties who came to Stamford with a chief complaint of leg pain. After a series of standard questions about the pain, we examined at his leg and saw what he referred to as "pork red" skin bearing a number of ulcerative surface lesions.

When we then asked him what medications he was taking, he brought up an Excel spreadsheet on a nearby laptop and read off a list that included broad-spectrum antibiotics for the skin infection as well as cortisone and Avastin (a drug that blocks blood vessel formation in an attempt to starve fast-growing tumors). We discussed the possibility that his steroids were suppressing his immune system and providing a window for opportunistic infections of the skin, and then asked him to clarify his need

for Avastin. He began to tell us that he had a grade 4 astrocytoma of the spinal cord, which was initially diagnosed at spinal level T1, and had since spread as far down as T3 and as far up as C3. As soon as he finished describing the tumor, he began to well up with tears. "You see, I'm probably going to be a paraplegic, and later, a quadriplegic. I have a wife, a daughter. No one knows what to do to fix this," he told us.

John and I were crushed. Our patient had a wife, a college-aged daughter, and, until the tumor invaded his spinal cord, many years of life ahead of him. He was an engineer, just like my own father, who would also no doubt use an Excel spreadsheet to track his medications. Seeing him cry openly in front of two strangers at the thought of losing his body and ability to provide for his loved ones was deeply moving. At that moment, our giving this man a receptive space to emote became more important than gathering information on his allergies and history of kidney disease. As second-year medical students, we were thankfully not subject to the time pressure that would otherwise prevent us from offering that space.

The gravity of this man's plight both devastated and inspired John and me. Having participated in the emotional reality of the situation, we found a personal significance that we could use as motivation to become better doctors, but it was more than that. Our patient felt cared for; as we were only medical students, he did not expect us to cure him, but he sensed our desire to help. In a way, that was enough. It was beautiful.

I reflect on this case when my energy seems exhausted. This kind of clinical experience makes the hours spent memorizing Greek- and Latin-derived terminology more than worthwhile. There is no lecture that could have replaced this moment with a patient. The memory I have is one of a tangible emotional energy, and I am thankful that John and I as fresh, naïve students were able to be open to it.

I do not want to lose this openness, but rather strengthen it as I mature in my medical training. I do not want to wall myself off from emotional situations, but rather develop the ability to relinquish my own stress in order to make room for the needs of my patients.

My observation is that some health professionals tend to become somewhat accustomed to the fact of their patients' suffering, and while they may not lose true empathy, they may lose the ability to fully express it in lieu of a more efficient routine. Some prefer to wear the thick husk of emotional distancing in order to accomplish their daily business with a minimal amount of emotional stress and intensity, and this can come across to patients not as simple hurriedness but instead as true insincerity or brusqueness, which can later hinder physician–patient trust and even adherence. There are those doctors who have too many patients and nowhere near enough time, and then there are doctors who simply feel that they should avoid getting involved in most patients' emotional needs to "keep sane" on the job. The latter is the particular attitude that I hope to avoid in my own career.

In searching for a way of improving my ability to relate to the emotional and attentive needs of others without wearing myself out, I have realized that there are techniques that, when practiced regularly, can strengthen my ability to give full attention to every situation. Pursuing this goal will strengthen relationships, improve rapport in hospital rooms, and allow people like me to intuit hidden emotional needs in others. I have found it helpful to practice moments of austere silence on a regular basis. The regular practice of physical and mental peace reduces the intensity and frequency of the frantic, habitual thinking that plagues many members of today's stressed out culture. This layer of thinking—of personal tasks, goals, and desires unrelated to the present situation—is that callous husk that prevents us from connecting deeply to others in the present. Because we cannot help but keep thinking of our own business, we cannot fully appreciate the emotive expression of others. It is as though the mind were talking during the movie. Relaxing the busy mind for a period each day teaches it to loosen its grip on our attention when we might need it for someone else.

There are many times that I wish true meditation or contemplative prayer—and the utility of such practices in keeping our minds attentive—were taught to medical students as a tool to foster enthusiasm for healing others. This is one reason why I jumped at the chance to participate in the new Narrative Medicine component of our curriculum. It gave my classmates and me a chance to think outside the walls of hard data, to work beyond the current limits of our own knowledge, and to create. Meditation, art, and philosophy courses are offered as options for seminar study. This represents an innovation in medical education at Columbia that will hopefully continue to advance.

For me, however, there remains a greater need to teach methods of developing mental silence as a basis for forming healing relationships with others. I would propose that techniques to bring this inner quietude, such as meditation, are much less about a particular cultural identity and more about the subjective sciences of thought, sensation, and human relationships. It is after all, in silence that we hear the most.

Summer Reading and Synchronicity

Reviews by **Michael J. Devlin, MD**
Professor of Clinical Psychiatry, College of Physicians and Surgeons
Associate Director of the Eating Disorders Research Unit, New York State Psychiatric Institute

Kitchen Table Wisdom by **Rachel Naomi Remen, MD**
Riverhead Trade Publishers, $16.00

Zeitoun by **Dave Eggers**
McSweeney's Publishing, $24.00

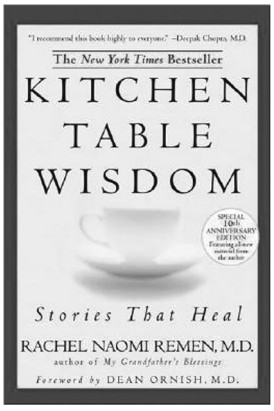
Switch: How to Change Things When Change is Hard by **Chip and Dan Heath**
Crown Business Publishers, $26.00

One of the great satisfactions of practicing and teaching at a medical school is the opportunity to hear my colleagues and students' stories from the trenches even as I live and tell my own stories from my own trenches. Likewise, one of my greatest pleasures when not at work is to read other stories, some about medicine, but also others with little overt relationship to what I do by day. With all these stories in play, I've become a great believer in synchronicity, a Jungian concept that roughly translates as meaningful coincidence. Sometimes, the stories just seem to speak to one another in unexpected and revealing ways and seem almost uncannily suited for one another.

When I was recently reminded to get going on the brief review of *Kitchen Table Wisdom* that I'd promised to write, I happened to be reading two other books, neither of which is particularly related to medicine. Somehow, though, the juxtaposition of the three books in the context of the summer season made my synchronicity bells go off. Well, not really bells – more like a sneaking suspicion that turns into a conviction that there's some important commonality, some bit of wisdom that lies just out of reach.

Wisdom from a Book

When I asked my clinical medicine seminar students whether they would rather receive a book that would increase their knowledge or one that would increase their wisdom, one responded that she was not convinced that it was even possible to receive wisdom from a book (but she took the leap of faith anyway). Fair enough— wisdom comes from experience, and it's reasonable to question whether vicarious experience, such as that conveyed in a book, can do the trick. However, if you can get past the folksiness of the first part of the title and the hubris of the second, I think that *Kitchen Table Wisdom. Stories That Heal* may change your mind. In the interest of full disclosure, I had the opportunity to attend a training workshop with Rachel Remen in 2005 and have been a fan ever since. Trained as a pediatrician, Dr. Remen became a counselor, particularly working with individuals who have life-threatening illnesses. The vignettes in *Kitchen Table Wisdom* are mostly just a few pages long, easy to read in just a few minutes, and they encompass Dr. Remen's experiences as family member, trainee, pediatrician, counselor, and patient. They are grouped by meaning—big topics like Life Force, Self-Judgment, Freedom, and Mystery and Awe. Each section is preceded by a brief written reflection, and these are some of my favorite parts of the book. For example:



"The most important questions don't seem to have ready answers. But the questions themselves have healing power when they are shared. An answer is an invitation to stop thinking about something, to stop wondering. Life has no such stopping places; life is a process where every event is connected to the moment that just went by. An unanswered question is a fine traveling companion. It sharpens your eye for the road." (p. 293)

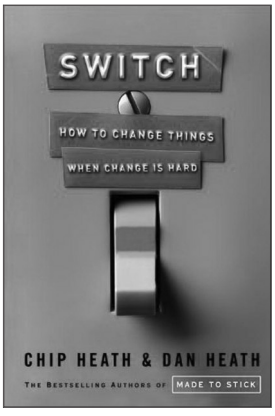
As I type this, I realize that, particularly taken out of context, passages like this, and the stories that illustrate them, can hit you in different ways at different times. They can be as generic – or cryptic – as a fortune cookie, and they can also seem as if they were written just for you and just for this moment. It all depends on the context. Which is what's great about *Kitchen Table Wisdom* — you can pick it up at different times and different passages or stories will jump out at you. Can you get wisdom from a book? It's clear where I stand, but I don't expect that to convince anyone. You just have to take the leap of faith.

No Going Back

Having recently returned from a conference in New Orleans, I was inspired to pick up *Zeitoun* and immediately realized that this is a book you cannot put down once it gets going. *Zeitoun* tells the story of Abdulrahman Zeitoun, a contractor originally from Syria now living with his wife Kathy and family in New Orleans, and his experiences during and following Hurricane Katrina. Initially inspiring, then horrifying and enraging when Zeitoun is arbitrarily arrested and imprisoned with no opportunity to demonstrate his innocence, the book keeps you turning the pages in the hope that somehow this will all be straightened out. And – I can say this without a spoiler alert, as it's clear from the start – it does. And it doesn't. The gut punch is the gradual realization that, even when Zeitoun is reunited with his wife and kids, there's really no going back. The experience has changed all of them, and the trauma and loss is something they will live with forever. The image of the released Zeitoun going back to find the dogs he'd been feeding after the storm now dead from neglect is one that continues to haunt me. There's no going back for Zeitoun and no going back for New Orleans. Which is not to say that there's no hope of recovery or of moving forward. Zeitoun, like his adopted city, is remarkably resilient and the book ends on an optimistic note of regeneration. But life as it was pre-Katrina has been swept away, never to return.

Does any of this sound familiar? Serious illness, of the sort Rachel Remen writes about, follows a similar pattern. Arbitrary and even discriminatory suffering – check. Irreversible change with no hope of going back to life as it was before – check. Finding ways to move forward given changed realities – check. And there's one other level that's explicit in Remen's book and implicit in Eggers'. That is the essential role of the witness. What Remen writes articulately about, and what seeps out from the pages of *Zeitoun*, is the healing that comes from having someone listen, understand, and tell your story. As a writer, Eggers creates a kind of therapeutic space, and as a reader, you become a part of the process.

When Change is Hard



When a group reflection session begins to spiral downward, it's painful to behold, much less facilitate. But there's an interesting pattern in play. Much of the time, this sort of derailment signals that the group has stumbled upon a system-level problem, i.e. something so large and so ingrained that it seems impossible to change. These discussions are high stakes: too many experiences of dysfunctional systems, excruciating injustices, and good intentions defeated by senseless realities can leave a person jaded and embittered, focused only on getting out as quickly as possible. A book like *Switch* can help.

Reading *Switch* had a perceptible antidepressant effect on me as I contemplated the next several challenging tasks that lay ahead. Right out of the starting gate, the Heath brothers hit you with some lessons, backed up by narrative and scientific evidence that both academics and medical students can use. For example, self-control is an exhaustible resource – obvious, perhaps, but so easy to forget in the high-pressure environment in which we live. The authors then outline a simple framework and provide a myriad of examples, many of which involve individuals who are in the middle or even near the bottom of the power hierarchy – even surgical interns in one case – who are faced with the need for change. They compare the challenge to that of influencing the course of a rider atop an elephant ambling along (Note: Freud got there first with his metaphor from *New Introductory Lectures on Psychoanalysis* (1932) of rider and horse for ego and id). The major strategies for change are to direct the rider, motivate the elephant, and shape the path. This may sound like so much millennial business school babble, but the Heaths transcend the usual level of advice-giving motivational books by filling their book with rich and even inspiring examples of ordinary individuals using creative strategies to begin to nudge those

dysfunctional systems or overwhelming challenges in the right direction. I particularly enjoyed the story of a pediatric oncology team that succeeded in increasing chemotherapy adherence rates via a video called *Re-Mission* featuring a nanobot zapping cancer cells. Although there were plenty of educational messages embedded in the game, it became clear that its most powerful effect was not on knowledge, but on the self-perception of teens for whom the meaning of taking medication was transformed from a reminder of being a "sick kid" into a sign of being a fighter capable of winning the battle against cancer. In the Heaths' scheme, this is an example of the "find the feeling" principle as a way of motivating the elephant. Another medical example is the use of simple checklists and systems that facilitate adherence to these checklists, which profoundly decrease the occurrence of intravenous catheter infections in the intensive care unit (in the Heaths' lingo, an example of using the "build habits" principle to shape the path).

Even as I write this review, I find myself using some of the recommended strategies for guiding the elephant: shrink the change (just spend an hour on this and then move onto something less taxing), find the feeling (I am psyched that I was asked to do this, I love thinking about this stuff, so why not just write it down), and build habits (develop an action trigger for writing first thing in the morning). Maybe the most important aspect of all this, beyond the useful specifics, is the genuine empowerment that it provides. Regardless of the enormity of the challenge, having a systematic approach to change that allows for and even encourages the strokes of genius, of which the authors provide many examples, somehow makes it possible to get up and face the brick wall day after day.

So where is the common thread in all of this? As I write this book review, it is early July. These are the longest days of the year and the sunlight abounds. This brings forth a couple of different associations. On one hand, the harsh light of day reveals realities that we may wish to avoid, but cannot: illness and loss are inevitable, sometimes there's no going back, and change is indeed hard. On the other hand, the sunlight brings energy and hope: maybe stories really can heal, sometimes there's a way forward when there's no way back, and perhaps there are lessons to be learned about creating change even when the strongest rider can't steer the elephant. All three of these books have at their core both a harsh reality and an essential optimism about surviving and moving forward. You can't bottle sunlight, but you can read a book, listen to a friend, or tell a story. And maybe that's enough.

If you would like to submit work to the Columbia Medical Review

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or visit
juno.cumc.columbia.edu/psreview

INFORMATION FOR AUTHORS

We welcome submissions written by students and faculty of Columbia University on topics broadly related to healtcare and medicine. In particular, we are seeking original research articles and pieces written about the relationship of medicine to other disciplines. Works are reviewed by student editors who provide feedback to authors and vote on acceptance. Accepted works are submitted to at least one member of the faculty review board for final approval. All submissions are screened for plagiarism using the Turnitin program.

Dr. Jeremy Mao

DDS, PhD, Edward V. Zegarelli Professor of Dental Medicine and Senior Associate Dean for Research, College of Dental Medicine

By **Mariel Kozberg**
College of Physicians and Surgeons, 2013

Osteoarthritis is the leading cause of chronic disability in the country, affecting over 27 million adults in the United States. [1] Dr. Jeremy Mao's laboratory at Columbia University Medical Center is on the cusp of developing a new, long-lasting solution to this problem. In osteoarthritis, the hyaline cartilage at the ends of bones in joints wears down, and the resulting friction causes significant pain. The process begins with small holes forming in the cartilage, which in turn progress to larger, increasingly painful lesions. The standard treatment of severe osteoarthritis is joint replacement surgery, in which the joint is refitted with a metal and plastic implant. Despite years of advances, biomechanical implants wear down over time and often damage surrounding tissues.

The structural nature of these problems has attracted the attention of professionals in a variety of biology and engineering fields. Tissue engineering is particularly important in the development of novel materials for human implantation because it aims to regenerate tissues rather than relying on prostheses. Tissue engineers propose that a more effective treatment for cartilage degeneration is to replace the worn cartilage with the patient's own, regenerated cartilage, thereby creating the ultimate biocompatible material. Constructing a new articular surface from the patient's own stem cells avoids immune rejection as well as wear associated with metal and plastic implants.

Instead of repairing small cartilage defects, Dr. Mao's lab operates under the assumption that all of the cartilage in a degenerating joint will eventually wear down, whether a patch is performed or not. His group is now working toward developing biocompatible scaffolds that can be implanted to enable full cartilage replacement. In a recent project described in a paper published in *The Lancet*, his lab removed all of the cartilage in the knee joints of rabbits and replaced it with biocompatible scaffolds composed of poly-ε-caprolactone and hydroxyapatite that were printed using computer-assisted design and a 3D printer. [2] The shape of the implant was determined precisely from MR and CT images of each rabbit's knee, and the implants were printed with microchannels to act as conduits for recruitment of the host's endogenous stem cells. In this design, the scaffold acts as a support structure on which host stem cells can grow. The pivotal molecule that induced recruitment of host stem cells is transforming growth factor β3 (TGF-β3). TGF-β3 was injected into the custom-fitted scaffold, acting to promote the regeneration of a new joint by attracting the host's own stem cells. Within just three to four weeks, the rabbits were able to fully bear weight on their new joints and did not favor the replaced knees. After four months, the scaffolds were completely covered with new cartilage and the properties of the regenerated cartilage were on par with those of native cartilage in terms of compressive and shear properties. The high biocompatibility of these scaffolds may prolong the lifetime of the implants far beyond what metal- and plastic-based options currently enable. The next phase in this study will be to apply the system in animal models followed by a clinical trial.

By avoiding the need to harvest stem cells and inject them back into the patient, this product could appeal to orthopedic surgeons, who would prefer readymade implants that do not require cell culturing.

In addition to the research described above, Dr. Mao's laboratory work ranges from the engineering of artificial teeth to the construction of breast implants from a patient's own adult stem cells isolated from adipose tissue. Although Dr. Mao's interests may be broad, a common theme is that his work is never far from clinical application. Dr. Mao was an oral surgeon for four years before he decided that he wanted to have a larger impact on society than his practice allowed. He went back to school to earn his PhD and has been integrating the knowledge gained from two degrees ever since to produce high-

impact, tissue-engineered products. He has over 60 patents with Columbia and two biotechnology startup firms. In fact, approximately half of the graduate students and postdoctoral fellows in his lab go on to work in the biotechnology industry, while the other half remain in academia. Although Dr. Mao no longer sees patients, he continues to draw inspiration for his research from the problems that they face.

1. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58(1):26–35.

2. Lee CH, Cook JL, Mendelson A, et al. Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study. Lancet 2010;376(9739):440-8.

Jenny Yuan

MD-PhD student
Department of Biomedical Engineering

By **Mariel Kozberg**
College of Physicians and Surgeons, 2013

Ms. Jenny Yuan began her research career in cartilage tissue engineering after her freshman year of college. Now entering the fourth year of her MD/PhD at Columbia, she is working on meniscus tissue engineering in Dr. Gordana Vunjak-Novakovic's Laboratory for Stem Cells and Tissue Engineering. In this laboratory, researchers work on the engineering of tissues ranging from heart cells to bone and cartilage. The lab also focuses on building microbioreactors to help direct the differentiation of stem cells. In the field of osteochondral tissue engineering, researchers in Dr. Vunjak-Novakovic's laboratory have been using human mesenchymal stem cells cultured in custom-built bioreactors to seed silk scaffolds produced by Dr. David Kaplan's laboratory at Tufts University. Because mechanical competence is essential to the functioning of a bone or cartilage graft, the bioreactors play a key role in creating useful tissue by modulating the environment in which the stem cells grow, specifically the shear stresses to which they are exposed and the delivery of nutrients.

Like Dr. Mao, Ms. Yuan finds inspiration in the large number of people affected by cartilage pathology as well as the dramatic effect on quality of life that cartilage problems can have. Meniscus tears are common sports injuries, and frequently co-occur with other knee injuries such as anterior cruciate ligament (ACL) and medial collateral ligament (MCL) tears. [1] Each knee has two menisci (one lateral and one medial) that lie between the femur and the tibia. These cartilaginous structures distribute weight evenly across the knee joint. Ms. Yuan is fascinated by the unique dynamic characteristics of the meniscus. At birth, the meniscus is fully vascularized, but over time it undergoes a transition to acquire a peripheral vascular layer as well as an internal avascular layer. This modification is unique to the cartilage found in joints, which forms after the primary cartilage of the body (hyaline cartilage). Hyaline cartilage receives nutrients by diffusion and may progress to bone if vascularized; therefore, tissue engineers generally grow hyaline cartilage from stem cells in hypoxic environments. In contrast, in menisci, lack of vasculature leads to a loss of the meniscus's ability to heal. Surgeons currently address this by drilling small holes through damaged menisci to help increase blood flow and promote the regrowth of cartilage. However, this invasive process is imperfect, as it leads to formation of significant scar tissue.

Ms. Yuan is studying the contribution of vascularization to meniscus repair in order to understand how to apply current engineering principles to the repair of meniscus tissue. Her first steps involve implanting dissected bovine meniscal tissue from both avascular and vascular regions into highly vascularized environments, such as subcutaneous pouches in mice. Post-implantation, she will study the degree to which the surrounding vasculature is able to infiltrate the meniscal matrix. Furthermore, she creates gaps in some of the implanted menisci in order to study the formation and integration of repair tissue. Previous studies from other labs have focused on the repair of meniscal tissue *in vitro*, and with these studies Jenny hopes to help lead the way to better clinical solutions to meniscus tears. Whether Jenny will choose orthopedics as a medical specialty remains to be seen, but it is safe to predict that her current work will have an impact in the field.

1. Peterson W, Pufe T, Stärke C, et al. Locally applied angiogenic factors--a new therapeutic tool for meniscal repair. Ann Anat 2005;187(5-6):509-19.

Dr. Helen Lu

Associate Professor of Biomedical Engineering, Associate Professor of Dental and Craniofacial Bioengineering

By **Jacob Tulipan**
College of Physicians and Surgeons, 2013

Dr. Helen Lu's Biomaterials and Interface Tissue Engineering Laboratory encompasses research into both intercellular communication at bone-soft tissue interfaces and the design of tissue-seeded scaffolds that mimic or promote that communication. Overall, the lab studies bone-cartilage, bone-ligament, and bone-tendon interfaces. These are characterized in terms of cell morphology, mechanical properties, and chemical signals.

The Lu lab is split into a few interconnected divisions. The first focuses on basic science, looking at cell-cell communication in combined cultures of two and three cell types (e.g. different populations of chondrocytes). This aspect of the lab's work was showcased in a 2007 paper in *Osteoarthritis and Cartilage*. [1] The paper describes an experiment in which deep-zone (near the bone) and surface-zone (near the joint) chondrocytes were co-cultured and stimulated with thyroid hormone. In the co-culture, parathyroid hormone-related peptide (PTHrP) from the surface-zone chondrocytes inhibited the mineralization of deep-zone chondrocytes. This can be replicated by adding PTHrP to a monoculture of deep-zone chondrocytes, which mineralize without the added signal. This mineralization is important in the formation of the osteochondral interface, but also deleterious in osteoarthritis, as it appears to be responsible for the loss of lubricating cartilage in the joint. The ability to inhibit mineralization and measure this inhibition is thereby important for future attempts at engineered cartilage replacement as well as potential osteoarthritis therapies.

The laboratory's second division uses this information—elucidated by the first—to design multiphasic scaffolds with different regions that have different mechanical properties. These scaffolds, often made out of biodegradable materials such as the polyester PLGA [poly(lactic-co-glycolic acid)], hydrogels, or bone-like ceramics, encourage the growth of the proper cell type at the intended section of the scaffold. A 2006 *Tissue Engineering* paper from Dr. Lu [2] describes a triphasic scaffold intended for anterior cruciate ligament (ACL) repair. The scaffold consists of three distinct segments, mimicking in whole the gradient in mechanical properties of tendons while simultaneously providing specific growth environments (based on pore size and shape and scaffold composition) that encourage the growth of fibroblasts and osteoblasts in their respective correct locations. This selective growth was accomplished without the use of scaffold-embedded growth factors, which add cost and complexity to the scaffold construction process. In the end, both cell types formed the relevant extracellular matrix in their specified areas, and the interface between the two, in the scaffold's center, did indeed begin to form. The resulting structure, with ligament fibroblasts, then fibrocartilage, then bone, looks and behaves much like a ligament, and holds promise as a possible replacement for injured structures.

Further studies have gone on to implant these scaffolds in animals, and observed the effects of the implantation on the scaffold's mechanical properties and its seeding with cells. [3] Once animal testing has determined the optimal means of seeding the scaffolds and implanting them into their intended positions, it is likely that similar multiphase structures will see use in humans.

While this is by no means a complete view of Dr. Lu's laboratory, her laboratory provides a clear example of what it means to be involved in translational research in biomedical engineering. Each of the projects in the Lu laboratory has a clinician involved, lest the downstream clinical utility be forgotten. This model, in which basic science gives way to engineering, which moves to testing and then the clinic, is an example of "bench-to-bedside" research, and we expect to see more labs following it in the future.

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Project Medshare: Haiti Earthquake Relief

By **Tanya Lam, MD**
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It has been over ten months since an earthquake devastated Haiti, where much of the destruction was concentrated in the capital Port-Au-Prince. An estimated 230,000 people were killed and one million people displaced. In March, 2010, Ayesha Siddiqui, MD, a family medicine fellow, and I volunteered with Project Medishare, an NGO affiliated with the University of Miami.

Due to its longstanding presence in Haiti's health care and community development sectors, the Haitian government asked Project Medishare to set up an emergency field hospital in Port-Au-Prince. Together with the US military and the Haitian Ministry of Health, an emergency and trauma hospital was set up on the outskirts of the city's airfield within 24 hours of the earthquake. The hospital initially had 300 critical care beds, four operating theatres, and an intensive care unit. In February, it transitioned to an emergency and rehabilitation hospital. Physical therapy and prosthetic services were added to help amputees. The field hospital relies on volunteers staying for eight-day rotations, with new arrivals each Monday and Saturday. The composition of incoming volunteer staff is highly variable, meaning at times there may be no obstetrician, a very understaffed neonatal intensive care unit (NICU), or a shortage of anesthesiologists.

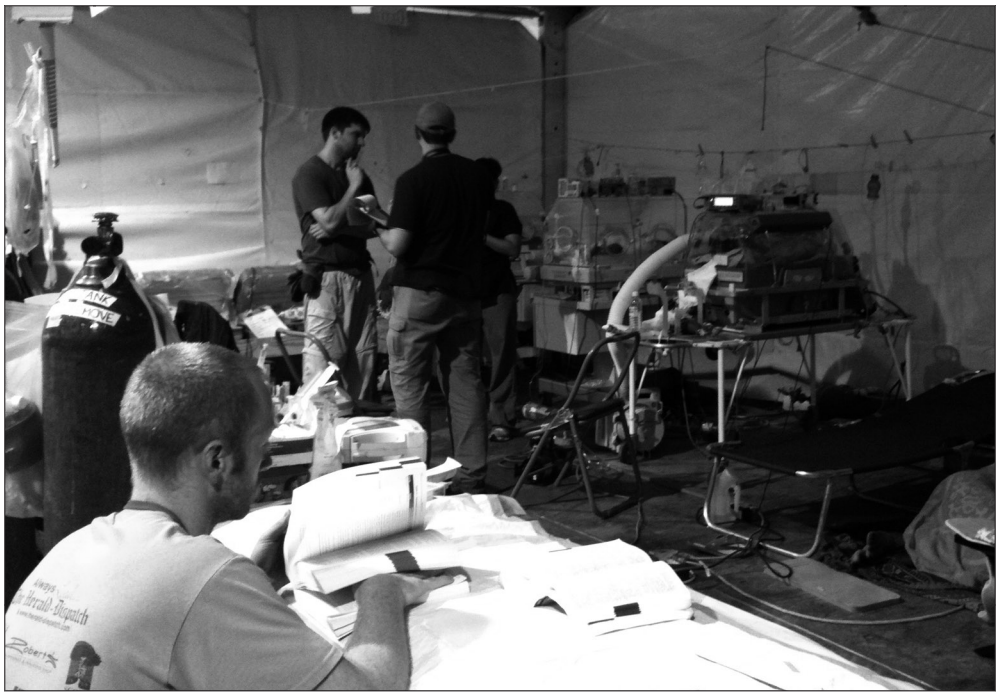
Project Medishare

Project Medishare was established in 1994 by two doctors from the University of Miami. Barth Green, MD, FACS, is a professor of neurosurgery and orthopedics and Arthur Michael Fournier, MD, is a professor of family medicine and community health. They assembled a team from the schools of medicine and nursing to assess the health care situation in Haiti and explore ways in which it could be improved. Project Medishare has since conducted a range of programs.

The school health program provides vaccination, nutrition, de-worming, vitamin supplementation, health education, and basic medical care for children. Since 2003, community health programs have been conducted in conjunction with the Ministry of Health. These have involved home visits, vaccinations, and nutrition and education programs. Project Medishare's agriculture program trains farmers in sustainable farming and women in food processing and home economics. In conjunction with nutritionists, it also coordinates agricultural production at the Akamil Production Facility. Here, grains and crops are bought from farmers and fortified with essential vitamins and nutrients such as zinc, vitamin A, and iron. The products are then sold at a reduced price to women merchants who distribute them to the wider Haitian community.

Project Medishare also runs the Ministry of Health's clinic in the town of Lahoye. The earthquake caused large-scale displacement; this has increased pressure on existing services. For example, the town of Thomonde has seen a 29% increase in population. Here, Project Medishare built a Maternal Health Center and provides a full spectrum of reproductive care including education, antenatal care, screening, and prevention of mother-to-child transmission.

A fourteen year old girl with a champion smile presented with bilateral foot deformities which were severely infected and eventually needed a below knee amputation.



The NICU/PICU area within the pediatric tent at Medishare's field hospital in Port-au-Prince.

An integrated community development program based on the Millennium Village Project model is currently in the stages of data collection and will be coordinated with multiple cross-sector partners. The construction of a nutrition and training center began in 2007 to provide nutrition to malnourished women and children.

Specialty surgical training programs involve teams from the University of Miami and Emory medical schools, which provide services and training in both Port-Au-Prince and Hinche. The aim of the program is to provide treatment and build sustainability. Project Medishare also has plans to train Haitian surgeons in neurosurgery over a period of three years.

Arriving in Port-au-Prince

On our arrival in Haiti, two months had passed since the earthquake and the relief effort was in a transitional phase. Commercial flights into Haiti were just starting to resume. We took an overnight flight from New York to Miami and then waited for a chartered flight into Port-au-Prince. Although we had anticipated a small propeller plane to take us from Miami, a large 200-seat plane full of medical and logistical personnel flew us in.

The hospital consisted of four main tents: a supply tent, a medical tent with a single X-ray machine and pharmacy, a combined pediatric, NICU, intensive care unit (ICU), and operating room (OR) tent with an additional pharmacy and pathology area, and the staff sleeping tent. There was also a smaller logistical tent and a rehabilitation and physical therapy tent. There was one source of potable water at the back of the camp and a set of shower stalls. We were encouraged to use as little water as possible. Sharing the area with us was the NGO ShelterBox, which provided tents to the Haitian population as part of the relief effort. For safety reasons, we were discouraged from leaving the enclosure, which was guarded from the main road and throughout the camp. Security guards carried batons and there was often a presence of military and army personnel because they were also based at the airfield.

The week before we arrived, triage had processed up to 400 patients a day, in a four by five meter area covered by a piece of tarpaulin. Cases were a mix of emergencies and chronic illnesses that had not been adequately addressed because of the poor existing health system. The pediatric ward had approximately 40 patients. The NICU/PICU (pediatric intensive care unit) had eight beds, a resuscitation area, and its own pharmacy. The pathology area had a single microscope, where basic blood investigations and Gram stains could be performed. Strikingly, the OB-GYN area consisted of a corner of the triage area separated by a tarpaulin and an ultrasound machine in the walkway of the pediatric tent. The ICU area had room for four patients, and the operating room could run two cases at a time. Being in a tent, operating conditions were not truly sterile, as there was always the possibility of outside contamination entering the tent. The pharmacy was surprisingly well stocked, with a large range of medications available, including sophisticated drugs such as gamma globulins. However, some essentials, such as misoprostol, were absent. Overall, women's health appeared to be somewhat neglected, which is a common scenario in emergency settings.

Staff were predominantly US trained, although there were volunteers from several countries as well as local Haitian nurses. Patients spoke predominantly Creole, occasionally French, and rarely English. We worked together with translators one to one. Some of the translators were Haitian medical students who hoped for progress in the rebuilding, without which their studies could not resume.

Working in the Field Hospital

Working in the pediatric ER, we saw a

range of acute infections, malnutrition, burns, and trauma. There were several cases of hydrocephalus, including a six-year-old girl who had only recently decompensated. There was much talk of the need to transfer patients to the US for definitive surgery. We also had a number of patients with severe burns from campfires, who were undergoing grafting. Several children presented with severe malnutrition. Some came from orphanages that were overwhelmed and under-resourced. I had a long conversation with the head nurse at an orphanage who implored me not to return the children to the orphanage, as "only the strong would survive" there. Malnutrition became a difficult issue when our calorie-dense nutrition supply went missing from the supply tent. Air force personnel offered their MREs (Meals Ready to Eat) and staff pooled their own food supplies, mostly energy bars.

There were many homeless children who came to the clinic and stayed in need of placement. It was difficult to accept that we were discharging most patients and their families to live on the streets. The more fortunate families had relatives away from the capital whose houses were still standing. Others had tents that had been donated; many were simply living under tarpaulins by the side of the road. We explained the need to breast-feed, particularly under the conditions they were facing. It was a struggle though, as many preferred to bottle-feed. A colleague explained to me that when bad things occur, mothers are reluctant to breast-feed because they do not want any bad luck to be passed onto their children. Parents would ask for clothes or infant food, of which there was little available. An obstetrician and I were on the verge of making an asthma inhaler spacer out of a water bottle, when we finally found the last box of pediatric spacers.

Port-au-Prince was a challenging environment to work in. The temperature was routinely above 100°F, with high humidity and only partial shade in the triage area. Although the monsoon season was yet to start, there were several days of downpour, where even the staff tent was flooded and everyone needed their knee-high rubber boots. The downpour reminded us of the many thousands in the overcrowded camps, which would also be flooded, but without even the simple comforts and equipment we had. Nights in the hospital were unpredictable. Pregnant women would present well into labor, on several occasions delivering in front of triage. A 16-year-old boy presented febrile, agitated, hydrophobic, and with new-onset seizures. We were concerned he had rabies, but he recovered overnight after a clear lumbar puncture and starting a course of IV antibiotics.

> "It was difficult to accept that we were discharging most patients and their families to live on the streets."

On the adult side, many patients presented with complications of amputations that had been performed in the immediate aftermath of the earthquake. This was largely due to poor hygiene and subsequent infection. Surgical revisions were required, as below-knee amputations became above-knee amputations. Also common was the reopening of wounds for debridement, wound care, IV antibiotics, and physical therapy. Discharge planning was particularly difficult as these patients were minimally mobile or, in the case of spinal cord injuries, immobile. Many had almost no family and no home. The adult ICU was populated by patients with decompensated chronic illnesses, such as diabetic ketoacidosis and pneumocystis pneumonia in HIV patients. Many patients were beginning to exhibit signs of depression and anxiety. Psychiatric services were minimal and no referrals for ongoing care were available.

Conditions in Port-au-Prince

The family medicine and internal medicine doctors also spent time working in the general hospital in the city. The hospital treated patients under tents as well, because most buildings that had survived the earthquake were considered unsafe. There was no air conditioning in the tents and the few local doctors there worked under sweltering conditions. Pharmacy stock was very limited and patients had to pay for medications before they were administered. The repercussions of gender-based violence in the setting of the crisis were evident. An entire tent was filled with female rape victims, many of them teenagers.

On our final afternoon, a group of us took a brief guided drive through the city. For the first time we saw the fields of tents and tarpaulins, the dilapidated old buildings, and finally, in the city center, block after block of rubble. Although most of the roads had been cleared, there remained crumpled buildings, some of them half standing, with their rooms and wallpaper visible. We drove past the shattered stained glass windows of a cathedral, where the congregation was singing under a tent in the courtyard. Throughout the city, people were living in the rubble, selling their wares in front of where primary schools and ministry

buildings used to stand. Throughout the whole drive, we saw only a single bulldozer that sat empty in the middle of a half-cleared lot. Between collapsed buildings were individual ones that remained standing. The shiny, silver multistory tower of the network provider Digicel stood gated and unaffected by all around it, a testimony to the importance of standards in building construction.

We continued over the hillside and drove through markets, where children were playing on the streets and a crowd gathered around a TV watching soccer. Occasionally we saw a row of portable toilets and we also drove past a water bladder holding 10,000 liters of water for the nearby community. UN guards were present outside the presidential palace and along the outskirts of the camps, but we wondered about the safety within the camps where so many women and children were unaccompanied.

> "A consequence of working in resource-poor settings is that the returns for people who have little access to health care is greater."

Reflections

Working in Haiti with an excellent team of health professionals was rewarding. Colleagues from all disciplines were committed and tireless in physically and mentally challenging circumstances. When we had time, staff would ride on the back of a SUV to the UN compound, where the cafe made much appreciated "real food." The tables were filled with an international mix of staff in scrubs and UNICEF shirts and UN soldiers, all with their unique roles in the relief effort.

Since our time in Haiti, doctors who have recently returned have described how the torrential rains of the monsoon season flooded much of the field hospital. Thankfully, the Medishare hospital has been relocated into the Hospital Bernard Mevs in Port-Au-Prince and is now working together with local doctors to continue offering medical care and training staff. In particular, volunteer staff are helping train local nurses to care for the children in Haiti's only NICU/PICU and physical therapists are training physical therapy assistants. Patients and their families continue to face a great amount of uncertainty in their lives. Likewise, Project Medishare continues to rely on volunteers to provide much-needed health services to the Haitian people.

One consequence of working in resource-poor settings is that the returns for people who have little access to health care are greater. The economic principle of diminishing marginal returns has been shown to apply to health care, and certainly, whether one is contributing in the form of clinical, logistical, or policy work, the results in such a setting are much more dramatic than in the environments in which we normally work.

Working in the field hospital highlighted the vast amount of coordination required to establish a relief effort. As clinicians, we deal with the patient interface. In a way, we take for granted the supply of medicines, equipment, and infrastructure. Working with Project Medishare made us acutely aware of the logistics, diplomatic negotiations, and fundraising that were essential to our work.

This experience also highlighted the importance of one's colleagues in a challenging setting. In contrast to the young pediatric doctor in the Doctors Without Borders documentary "Living in Emergency," who was alone in a remote part of Africa, the support and teamwork at our field hospital was invaluable and shaped our experience, making the difficult circumstances much more bearable.

The concerns we faced over nutritional supplies and basic obstetric medicines such as misoprostol are not unique in the developing world or the emergency setting. Enterprises with vastly more resources and staff in developed countries still at times have overlooked areas. While it was difficult knowing that supplies were being stolen, we also acknowledged that the people stealing them were themselves desperate.

Clinical problems were compounded by concerns over housing and the safety of our patients, issues beyond the realm of clinical medicine but the consequences of which we treated. As in all instances of disaster and emergency, broader issues were pertinent to the population's outcomes and future.

There were over 375 NGOs in the health sector in Haiti following the earthquake. The coordination of roles in such a setting became a priority to prevent the overlap of services and to optimize efficiency. There was some debate as to the role of intensive care facilities in such a setting. However, the field hospital was initially set up as an emergency and trauma service, filling a vital gap in Haiti's health service. Project Medishare's aim of transitioning to an integrated and sustainable health care system in Haiti reflects its previous work in the country, which in addition to medicine was focused on development and education.

The fight for children with spinal muscular atrophy

By **Anna Janas**
College of Physicians and Surgeons, 2013

Spinal muscular atrophy (SMA) is a devastating neurodegenerative disease with a prevalence of 1 in 6000, making it the most common genetic cause of death in infancy. [1] It is characterized by a loss of motor neurons and progressive skeletal muscle atrophy. SMA is classified as types 1 through 4 depending upon the age of onset and clinical course. (Table) In SMA type 1—the most severe form—onset is before 6 months of age, and patients never achieve the ability to sit. This is by far the most common presentation of the disease. Patients with SMA type 2 with onset between 6 and 18 months are wheelchair bound, while those with SMA type 3 have disease onset after 18 months and gain the ability to walk. The least severe form, SMA type 4, encompasses patients with adult onset SMA who reach the ability to walk. [2]

Although SMA type 1 typically presents in neonates and infants, the most severe cases can be recognized as early as late pregnancy by a loss of fetal movement. These infants usually die before one year of age from respiratory failure. Although otherwise neurologically and cognitively intact, children with less severe types of SMA go on to develop a chronic, progressive disease and suffer from diffuse muscle weakness (especially in the lower limbs) and absent or markedly decreased deep tendon reflexes. Most patients develop respiratory muscle weakness that ultimately progresses to respiratory failure and death. [3-5] Currently there is no cure for SMA and the treatment options available are palliative.

Columbia University Medical Center is at the forefront of elucidating the molecular mechanisms involved in SMA, and multiple labs are searching for a cure. The Motor Neuron Center (MNC), established in 2006 and co-directed by Chris Henderson, PhD, Darryl DeVivo, MD, and Serge Przedborski, MD, PhD, is home to about 40 researchers and clinicians engaged in the study of the biochemical and cellular aspects of neurodegenerative diseases that affect motor neurons, including SMA. Tapping into the resources of one of the strongest neuroscience programs in the country, the MNC brings together experts in the hope of discovering new insights into the biology of both healthy and diseased motor neurons. The laboratories of Livio Pellizzoni, PhD and Umrao Monani, PhD among others focus specifically on the molecular mechanisms of SMA and translate this knowledge into experimental therapeutic interventions in both cell culture and animal models.

The cause of SMA was a mystery until about 15 years ago when a group of French researchers linked the SMA-determining gene to a locus on chromosome 5 termed 'Survival Motor Neuron' or SMN. [6] SMN is expressed ubiquitously in all cells and is required for the biogenesis of small nuclear ribonucleoproteins (snRNPs)—the integral components of the spliceosomal machinery, which removes introns from precursor mRNAs. [7] One intriguing (and still unanswered) question in SMA research is why the disease is motor neuron-specific if the affected protein is expressed in all cells

The vast majority of patients with SMA have an inactivating mutation or deletion of both copies of the SMN1 gene. However, because total loss of SMN protein is not compatible with life, all patients retain at least one copy of the closely related (and human-specific) SMN2 gene, which differs from the SMN1 gene by a single base substitution. [8] Approximately 80% of the time, this substitution causes alternative splicing of SMN2 pre-mRNA with exclusion of the critical exon 7, which encodes the C-terminal domain of SMN. Without the C-terminal domain, SMN protein does not oligomerize efficiently and is rapidly degraded. The remaining 20% of transcript makes a fully functional protein (so-called full-length or FL-SMN). Interestingly, the increased number of copies of the SMN2 gene in the patient's genome leads to greater levels of fully functional SMN protein, less severe SMA type, and, ultimately, better patient outcomes. [9] Consequently, current research on potential therapeutics aims to identify a drug (or a class of drugs) that would increase transcription of SMN2 (by enhancing SMN2 promoter activity) and/or exon 7 inclusion (by

altering the splicing pattern of SMN2 pre-mRNA).

In recent years, several new drugs have emerged as potential therapeutics. Among them is a class of drugs known as histone deacetylase (HDAC) inhibitors, which includes valproic acid (an FDA-approved anticonvulsive drug used to treat epilepsy and bipolar disorder), phenylbutyrate (an FDA-approved treatment for urea cycle disorders), sodium butyrate, M344, and SAHA (currently approved for the treatment of cutaneous T cell lymphoma). [10] *In vitro* studies have suggested that HDAC inhibitors can increase SMN2 gene expression by stimulating transcription and/or restoring the splicing pattern and thereby can increase FL-SMN protein. Unfortunately, promising *in vitro* studies often do not translate into *in vivo* systems. When HDAC inhibitors were introduced into mouse models of SMA and then SMA patients, their relative effects did not live up to expectations. For instance, two open-label clinical studies with valproic acid showed conflicting results and highlighted a major drawback of nonspecific HDAC inhibitors: unwanted side effects, such as the depletion of total or free plasma carnitine (which plays a role in fatty acid metabolism) and an associated increase in muscle weakness. [11]

An alternative, more promising strategy involves a newly developed class of molecules called antisense oligonucleotides (ASOs), which have already successfully completed phase II clinical trials in the treatment of Duchenne muscular dystrophy. In the context of SMA, ASOs, which are chemically modified single-stranded RNA molecules (typically 20 base-pairs in length) complementary to a chosen sequence, bind to splicing sites on SMN2 pre-mRNA and modify exon 7 inclusion in SMN2 mRNA. Initially, the major difficulty facing ASOs was selective delivery to target tissues—for example, into spinal motor neurons that are affected by SMA [12]. Recently, however, it was shown in a mouse model of SMA that ASOs can be effectively delivered to the central nervous system (CNS) via intracerebroventricular injection. Moreover, ASOs directed against SMN2 transcript increased FL-SMN protein levels and partially corrected the phenotype. However, there are several challenges facing the introduction of the ASO therapy into human patients. First, most of the studies in mouse models were conducted by injecting ASOs during embryonic development. It is unclear at what time point in human fetal development ASO injection would have to be performed or whether ASO treatment could work postnatally or even in older children and adults. Additionally, it appears that continuous administration of ASOs is required for treatment of SMA, which raises the questions of cost and feasibility. [13]

SMA type	*Age of onset*	*Ability to sit?*	*Ability to stand?*	*Ability to walk?*
1	< 6 mo.	No	No	No
2	6-18 mo.	Yes	No	No
3	>18 mo.	Yes	Yes	Yes
4	Adult	Yes	Yes	Yes

The third, and to date the most effective potential approach to treating SMA, is gene therapy, which, unlike ASOs, would require only one successful injection of a viral vector. A 2009 breakthrough showed that when a specific adeno-associated virus (AAV) vector was injected systemically, it was able to successfully cross the blood-brain barrier into the CNS, including motor neurons. [14] A year later, this technology was employed in a mouse model of severe SMA. Remarkably, when the vector carrying SMN1 was injected systemically into the facial vein of postnatal mice, roughly 40% of motor neurons were transduced, leading to complete phenotypic rescue of the SMA mice. [15] Even more encouraging is the news that the vector can be successfully delivered to motor neurons in postnatal primates. [16]

However, there are multiple challenges facing the translation of this AAV-based therapy from animal models to humans. These include the problem of scaling up the production of the viral vector, since it is estimated that roughly 10^{14} viral particles are required to treat one infant. Secondly, virally mediated therapy is prone to rejection by the immune system, making long-term treatment difficult. Finally, for AAV vector therapy to be effective, it must be administered shortly after birth. The only way to detect SMA in infants is by DNA-based screens. Therefore, neonatal screening, currently based on the detection of proteins and other organic molecules by mass spectrometry, requires a long-awaited upgrade that integrates DNA technology. [17]

In light of recent developments in finding the cure for SMA, it is clear that the sharing of ideas is of prime importance. It is crucial that the research and clinical fields be on the same page in anticipation of new clinical trials that could emerge from ASO and AAV vector therapies. At Columbia University, the MNC researchers work in strong collaboration with the Department of Neurology and the Spinal Muscular Atrophy Clinical Research Center. This center operates a pediatric SMA clinic that not only provides patients with expert clinical care, but also gives families the opportunity to participate in

clinical trials and studies geared towards better understanding the natural history of SMA.

For the past five years, Drs. Petra Kaufmann and Darryl DeVivo have been collecting observational data on SMA patients, which will be used in the design of future clinical trials. In light of the recent discoveries on the biology of SMA and the emergence of multiple candidate therapeutic drugs, there is a need for a validated and reliable clinical trial design in order to test drug candidates. This is especially important in diseases such as SMA, where muscular strength and functional skills—major descriptive measures—vary widely from patient to patient. The observational studies run by the SMA Clinical Research Center have led to further validation and improved efficiency in the assessment of motor function of non-ambulatory patients with SMA types II and III, which will allow the enrollment of a wider phenotypic range of the disease population and ultimately facilitate recruitment for future studies. [18]

Columbia's strategy of establishing centers that bring experts together highlights the importance of collaboration between clinicians and bench researchers. With the combined efforts of the SMA Clinical Research Center and the Motor Neuron Center, as well as the wider community of SMA researchers, the promise of finding a cure for SMA has never been greater.

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FoxO1: The most important metabolic player you're not hearing about?

By **Joshua R. Cook**
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Over one third of Americans currently meet the American Heart Association's criteria for the metabolic syndrome [1]—a constellation of dysregulated metabolic parameters including abdominal obesity, dyslipidemia, hypertension, and insulin resistance. The metabolic syndrome, in turn, is associated with a significantly increased risk of developing cardiovascular disease. In response to this public health crisis, basic and clinical researchers have come to implicate as many as a thousand genes in the pathophysiologic mechanisms linking obesity and metabolic disease, particularly type 2 diabetes.

Among the proteins to have emerged from consistently robust findings in the laboratory is forkhead box-containing transcription factor O1 (FoxO1). FoxO1 (FKHR1), a member of the forkhead box-containing transcription factor family, modulates energy homeostasis at both the cellular and whole-body levels. The regulation of FoxO1 activity is quite complex, involving a number of reversible posttranslational modifications that affect the intracellular localization and transactivation potential of the protein. Insulin signaling stimulates an Akt-mediated serine/threonine phosphorylation of FoxO1 at three sites, which results in its nuclear exclusion and cytoplasmic sequestration. [2] However, even within the nucleus, FoxO1 activity is modulated through the acetylation or deacetylation of seven lysine residues, changes that profoundly affect the

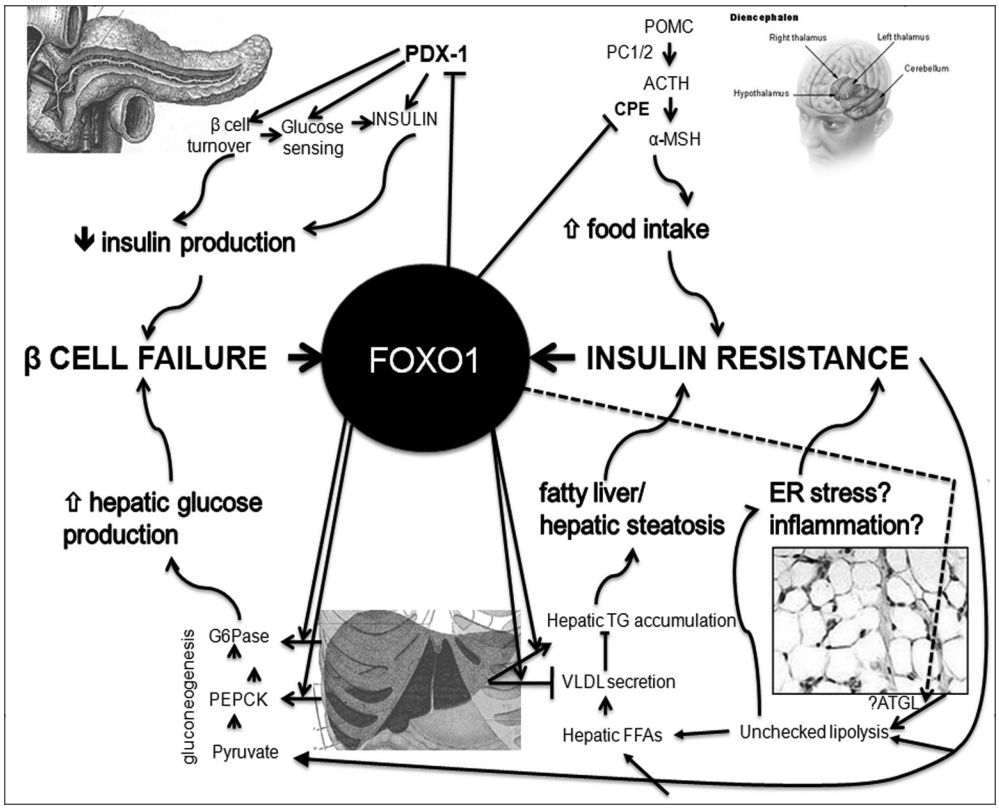
ability of the protein to promote the transcription of its target genes. [3]

In spite of a tremendous amount of biochemical and murine physiologic data, the definitive function of FoxO1 in the body is not yet known. FoxO1 is expressed widely, and much experimental work has shown FoxO1 to have differential—and sometimes opposing—effects in different tissues. Much of that work has been performed in the lab of Dr. Domenico Accili of the Naomi Berrie Diabetes Center. This review will emphasize evidence collected at the Columbia University Medical Center (CUMC) as to the particular physiology of FoxO1 in the brain, the adipose tissue-liver-endothelial axis, and endocrine pancreas in the context of the pathogenesis of diabetes. According to Dr. Accili, there remains "a lot of unmet need in type 2 diabetes mellitus. We treat insulin resistance with metformin, a very old drug. Then, we treat β-cell dysfunction with sulfonylureas, which seem to make it worse, or DPP-IV inhibitors that aren't very effective. So, we need to improve on existing therapies. Step one is to understand the disease process better than we do." The biology of FoxO1 offers just that possibility.

Brain

FoxO1 has previously been implicated in the hypothalamic control of food intake and energy expenditure, sparking speculation as to a role for FoxO1 in the pathogenesis of obesity. [4] Representing a major step in that direction, the Accili lab, in concert with Dr. Sharon Wardlaw, also of the Berrie Center and the director of the CUMC Neuroendocrine Unit, has recently uncovered a novel functionality of FoxO1 in the arcuate nucleus, the portion of the hypothalamus thought to be most crucial in the central regulation of energy homeostasis. [5] Mice null for FoxO1 specifically in pro-opiomelanocortin (Pomc) neurons—the population of cells most important for reducing food intake and increasing energy expenditure—were found to have lower body mass indices, due specifically to a 27% decrease in fat mass. The weight-adjusted food intake of the mutant mice was lower than controls, whereas their energy expenditure was indistinguishable from that of the normal mice. In other words, the Pomc neuron-specific FoxO1-null mice ate significantly less, but still burned as much energy as their wild-type littermates. On investigation, it was found that in adult FoxO1 mutants, there was surprisingly no significant difference in the expression of the Pomc gene versus controls. However, there were significantly greater quantities of the Pomc cleavage product α-melanocyte stimulating hormone (α-Msh) in the Pomc neurons of mutants relative to controls. Therefore, it was suspected that the inactivation of FoxO1 promoted the activity of some neuronal factor responsible for processing full-length Pomc to the active anorexigenic fragment, α-Msh.

The enzyme responsible for this regulated cleavage is carboxypeptidase-E (Cpe). It has been previously demonstrated that humans with rare inactivating mutations in CPE are obese, infertile, and diabetic, but the mechanisms whereby its loss resulted in metabolic disease were not previously understood. It was found that the inactivation of FoxO1 significantly increased neuronal Cpe production and activity. Moreover, in normal mice placed on a high-fat diet, Pomc neuronal Cpe production fell by half as diet-induced obesity (DIO) took hold, and presumably obesity-associated insulin resistance resulted in increased FoxO1 activity in Pomc neurons. Conversely, the Pomc-specific FoxO1-null mice were protected from weight gain, and infecting the wild-type DIO mice with an adenovirus encoding Cpe resulted in decreased food



Schematic of FoxO1 involvement in the two main "hits" of the pathogenesis of type 2 diabetes: insulin resistance and beta cell failure, at the level of various organs. This figure highlights only some of the pathogenic pathways thus far elucidated; it is not comprehensive. Figures all in the public domain. [19]

intake. Interestingly, however, the exact mechanism whereby FoxO1 inhibits Cpe production remains a mystery because even a mutant recombinant FoxO1 lacking its DNA binding domain was able to co-repress the transcription of the Cpe gene *in vitro*. According to Dr. Wardlaw, "The importance of this research relates to the role that the brain plays in regulating metabolism" because "when you become obese (and therefore insulin resistant, including in neurons), you get a vicious cycle of worsening obesity. So, insulin signaling centrally is a drug target."

Furthermore, the same neurons that control body weight independently affect glucose tolerance. So, perhaps the most intriguing element of these findings, in Dr. Wardlaw's opinion, is that it reflects the idea that insulin signaling can exert paradoxical effects in different tissues in driving toward its net effect on whole-body energy homeostasis. "When you give people insulin they gain weight because of peripheral effects," Dr. Wardlaw says. "But insulin signaling in the brain (such as in the case of intracerebroventricular insulin administration in animal models) is more consistent with a lean phenotype. So, there's a disconnect. And here, through FoxO1, we have a pathway that helps us understand how the system works."

Adipose tissue-liver-endothelial axis

The inability of insulin to blunt hepatic glucose production and the resulting hyperglycemia are thought to be central to the etiology of diabetes and the pathology of its complications. [6] Largely due to studies performed at Columbia, FoxO1 has been known for several years to directly promote the expression of the key enzymes of gluconeogenesis: phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. [7] Through FoxO1, as Dr. Accili remarks, "We now know how insulin regulates this process. It's a mind-bogglingly simple and elegant method to provide for short- and long-term hepatic glucose production. Now it can be a target for therapy."

FoxO1 can also play a major role in the regulation of hepatic lipid metabolism, including lipolysis and the secretion of atherogenic lipoproteins. [8] A transgenic mouse with a liver-specific deletion of FoxO1 (the so-called L-FoxO1 model) exhibits indices of improved insulin sensitivity. However, these mice were not found to demonstrate any dramatic changes in the expression of genes related to hepatic lipid metabolism. Interestingly, however, oxidative stress induced by high concentrations of glucose results in the constitutive nuclear localization of FoxO1. [9] Consequently, in the context of diabetes—that is, chronic hyperglycemia—FoxO1 might indeed affect the hepatic lipid program and thereby promote downstream dyslipidemic clinical sequelae.

To test this hypothesis, L-FoxO1 mice were treated with the diabetogenic β-cell toxin streptozotocin (STZ). Fasted, STZ-treated L-FoxO1 mice exhibited a twofold increase in serum triglycerides, apparently due to increased very low-density lipoprotein (VLDL) secretion relative to STZ-treated wild-type mice; there was no observed effect on hepatic lipoprotein clearance. In searching for the source of substrate for the observed increase in VLDL secretion, it was noted that L-FoxO1 hepatocytes secrete greater quantities of fibroblast growth factor-21 (Fgf-21) than do wild-type hepatocytes. Fgf-21, in turn, stimulates adipocytes to increase the expression of hormone sensitive lipase (Hsl), a key regulator of glucagon- and catecholamine-responsive lipolysis. Upon further examination, it was concluded that white adipose tissue lipolysis proceeds at such an accelerated rate in diabetic L-FoxO1 mice—even relative to diabetic wild-type mice—that the excess free fatty acids reaching the liver are funneled into esterification pathways. This, then, results in the observed increased triglyceride synthesis and, ultimately, pro-atherosclerotic VLDL secretion.

While intact hepatic FoxO1 appears to prevent excess secretion of VLDL, vascular endothelial FoxO1 appears to promote atherogenesis. [10] That is, the hyperglycemia chronically activating FoxO1 in the liver has a similar effect in vascular endothelial cells. There, FoxO1 transactivates the expression of inducible nitric oxide synthase (iNOS), resulting in increased production of NO-peroxynitrite, a reactive oxygen species that oxidizes low-density lipoproteins (LDL) to the atherogenic species oxLDL. On the contrary, an endothelium-specific knockout of FoxO1 prevents this effect of hyperglycemia on atherosclerotic plaque progression.

The reason for the disparity in the tissue-specific atherogenicity of FoxO1, per Dr. Accili, is that FoxO1 should be viewed as a "primordial stress sensor." As he explains, "You can subsume all the actions of FoxO1 under the common denominator that their action is intended to defuse cellular or metabolic stress," whether that be by decreasing secretion of lipoproteins, as in the liver, or by producing nitric oxide, as in the vascular endothelium. Nevertheless, with regard to integrative physiology, Dr. Accili sees these processes as promoting a fine physiological balance to minimize cellular and metabolic stress globally.

Endocrine pancreas

The functions of FoxO1 described thus far posit a role in the insulin resistance arm of the pathogenesis

of type 2 diabetes mellitus. However, the onset of diabetes also requires the failure of β-cells to provide adequate insulin to overcome systemic insulin resistance. Indeed, as Dr. Accili reminds, "No individual, no matter how insulin resistant, will ever go on to develop hyperglycemia without faulty β-cells." Even though the precise lesions that occur on the route to diabetes remain incompletely elucidated, Dr. Accili notes that "it is clear that [the β-cell] doesn't make enough insulin at the right time, and that even if you force the cells to make insulin at the wrong time" [such as by giving sulfonylureas], "you make it worse." Once again, FoxO1 appears to lend biochemical insight; in addition to its actions in the brain and in peripheral insulin-responsive tissues, FoxO1 has been shown to affect β-cell function directly.

A constitutively nuclear form of FoxO1 (FoxO1-ADA), effectively mimicking the insulin resistance characteristic of type 2 diabetes, prevents compensatory hyperplasia of β-cells under conditions of impaired glucose tolerance. [11] Conversely, haploinsufficiency for the FoxO1 gene ameliorates insulin resistance and diabetes in mice heterozygous for a null mutation in the insulin receptor, a genetic model of diabetes. This implies a mechanism whereby insulin resistance negatively affecting insulin target tissues also impinges upon the β-cell's ability to hypersecrete compensatory insulin, hastening the progression to diabetes. Moreover, it suggests a physiologic conflict in which the hyperinsulinemia associated with insulin resistance is the major stimulus for islet compensation even as the decreasing sensitivity of β-cells to insulin prevents such hyperplasia and increased secretion of insulin.

Pancreas/duodenum homeobox gene-1 (Pdx-1) is considered the key transcription factor underlying the differentiation and maintenance of β-cells, responsible for the transactivating expression of genes involved in all steps of insulin production, such as glucose sensing and -cell proliferation, as well as of insulin itself. [12] Deleterious mutations in the human Pdx-1 gene cause the type 1 diabetes-like syndrome, maturity-onset diabetes of the young type 4 (MODY4) [13]—recapitulating the effect of constitutively active FoxO1, as in insulin resistance. Importantly, the subcellular localization of β-cell FoxO1 and Pdx-1 displays a mutual exclusivity. [14] That is, after dephosphorylation of cytoplasmic FoxO1 and subsequent trafficking to and activation in the nucleus, there is a reciprocal nuclear export and deactivation of Pdx-1. In addition, nuclear FoxO1 potently transrepresses expression of Pdx-1.

As aforementioned, insulin stimulates the Akt-mediated phosphorylation and deactivation of FoxO1; in conditions of insulin resistance, this key inhibitory mechanism ceases to function. Consequently, FoxO1 tonically inhibits the expression and nuclear localization of Pdx-1, hence the incremental derangement in compensatory insulin production during the descent from impaired glucose tolerance into frank diabetes. This serves to explain why partial loss of FoxO1 function permits insulin-resistant β-cells to proliferate and produce insulin, preventing fasting hyperglycemia (i.e., diabetes). This also suggests that the insulin deficiency of type 1 diabetes may prevent the regeneration of β-cells in a FoxO1-dependent manner. However, despite the foregoing, it is important to note that self-limited, compensatory proliferation of β-cells within a prediabetic milieu represents a temporizing measure that appears deleterious in the longer term. [15] Therefore, although FoxO1's short-term actions seem to promote progression to diabetes, over time FoxO1 seems to conserve a degree of residual β-cell function by mitigating the burdensome drive to hypersecrete insulin and replicate; this is consistent with the idea of FoxO1 as a stress sensor.

The above findings led to the hypothesis that FoxO1 could point the way toward a longstanding goal of diabetes research: the regeneration of the insulin-producing cells of the endocrine pancreas *in vivo*. Prior research has suggested that FoxO1 expression is limited to the insulin-producing β-cells of the adult endocrine pancreas. [14] However, the Accili group revealed that there is a small but definite population of $FoxO1^{+}$/$insulin^{-}$ cells lining pancreatic ducts hypothesized to represent a population of endocrine progenitor cells that could be responsible for the small degree of β-cell turnover that occurs in adult life. [16] As of murine embryonic day 14.5 (E14.5), FoxO1 is expressed nearly globally throughout the developing pancreas, but by E17.5 is confined to a small subset of cells, and after birth could be found virtually exclusively in β-cells. These $insulin^{+}$ cells, which were also found to be $glucagon^{-}$, are derived from juxtaductal $FoxO1^{+}$/ $Insunlin^{-}$ precursors, as opposed to simply representing β-cells that happen to reside near ducts. According to Dr. Accili, these findings show that "we're going in an incredibly exciting direction because we've discovered that FoxO1 is a negative regulator of β-cell development. So, by inhibiting FoxO1, you can expand the population of endocrine progenitor cells," a monumental step toward curing diabetes.

An equally exciting and significant leap in that direction is a not yet published study [17] demonstrating that inhibiting FoxO1 in the enteroendocrine cells of the gut has, in Dr. Accili's words,

"beneficial metabolic effects in a totally unpredictable way." That is, the very reprogramming of enteroendocrine cells into insulin-producing cells *in vivo*—in other words, a FoxO1-based cure for diabetes.

This review has attempted to emphasize recent strides in the understanding of FoxO1 at CUMC. The Accili lab's data have shown that a single protein plays a crucial role in both of the "hits" that govern the complex etiology of type 2 diabetes: insulin resistance and β-cell failure, substantially different processes. Indeed, this represents a conclusion that was not considered inevitable a priori. The actions of FoxO1 in the hypothalamus further substantiate the importance of central control of whole-body energy homeostasis by providing a direct link between insulin action and food intake that can help explain the vicious, forward-feeding nature of obesity and associated insulin resistance. FoxO1's action to promote lipolysis in adipose tissue—especially maladaptive in the case of obesity in light of the copious substrate—then aggravates peripheral insulin resistance by several mechanisms, including the harmful ectopic deposition of fatty acids in skeletal muscle and the liver. [18] Concurrently, FoxO1 hyperactivity in an increasingly insulin-resistant liver allows for unchecked hepatic glucose production, placing yet further demands on already strained β-cells. The capacity of β-cells, in turn, to produce and secrete insulin as well as to undergo compensatory proliferation is further dampened by the direct actions of FoxO1 in insulin-resistant states, eventually precipitating frank diabetes. Additional roles for FoxO1 in macrophages, skeletal muscle, and brown adipose tissue, all believed to be important contributors to insulin resistance, are also currently under investigation.

Looking forward, Dr. Accili plans to take on the number one killer of patients with diabetes, namely, heart disease, and to ascertain why it is that diabetics represent such a disproportionate fraction of patients who die from the complications of atherosclerosis. Per Dr. Accili, "We now have evidence that the underlying pathophysiology again involves FoxO1, especially in liver, through its ability to act as a regulator of glucose versus lipid and lipoprotein metabolism." Furthermore, in peripheral tissues, particularly in macrophages, FoxO1 may have anti-inflammatory properties. Considering his lab's success to this point, there is little doubt that this is also a problem that they will tackle. Indeed, as Dr. Accili muses regarding his tremendous contributions to the understanding of one of our society's greatest scourges, "Through a lot of hard work and a little bit of luck, we figure it out."

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Non-invasive modalities of central nervous system vasculitis detection: A retrospective cohort

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Introduction: Cerebral angiography is considered the best imaging modality for confirming vasculitis affecting the brain. However, a pro-inflammatory state of the affected and neighboring vessels, hypercoagulable milieu, and alteration in vasomotor tone and lumen patency may increase the risk of procedural complications. Therefore, non-invasive radiographic methods are being continually improved to help establish the diagnosis of cerebral vasculitis. We sought to evaluate the utility of MRI and MRA in predicting angiographic vasculitis.

Methods: Between 2004 and 2009, 38 patients underwent MRI, MRA, and cerebral angiography in our institution because of suspected cerebral vasculitis. Medical records were reviewed for demographic and clinical information. Magnetic imaging studies were reviewed by two experienced neuroradiologists for evidence of ischemia, hemorrhage, or significant narrowing of vessels indicative of vasculitis.

Results: In our cohort, 30 (79%) patients were women and the mean age was 47 ± 19 years (range 1–77 years). Twenty (52%) had a history of autoimmune or systemic inflammatory condition. Twenty-four (63%) and 10 (26%) had ischemic or hemorrhagic stroke on admission MR, respectively. When either was associated with vessel narrowing on MRA (52%), there was an 80% chance of angiographic confirmation of vasculitis. No signs of vasculitis were seen on angiography (n = 5) when all MR was normal. The association between MR findings and final angiography results was significant ($p < 0.001$).

Conclusions: MR findings of either hemorrhagic or ischemic stroke, in conjunction with vessel narrowing, are strongly associated with the angiographic confirmation of cerebral vasculitis. Moreover, when MRI and MRA are both normal, the possibility of angiographic vasculitis may be very low.

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Introduction

Vasculitis of the central nervous system (CNS) is a disease entity that encompasses a wide range of underlying pathologies and clinical presentations [1]. Vasculitis, defined as the inflammation of blood vessels, is a progressive disease that can ultimately result in the degeneration, rupture, stenosis, or occlusion of the affected vasculature [Figure 1]. Vasculitis can affect vessels as small as capillaries (Wegener's granulomatosis [Box 1]) and as large as the aorta (Takayasu's arteritis [Box 2]) [1–3].

The large number of conditions that can lead to vascular inflammation has proven to be diagnostically and therapeutically challenging because of the wide overlap of signs, symptoms, and test results. Although there is no widely accepted classification system, vasculitic disease processes are generally grouped based on the size, location, and type of vessel most often affected [1, 4–6]. Despite the abundance of causes, most etiologies of vasculitis are relatively uncommon (< 40 cases/million), with the exception of giant cell temporal arteritis (1 case/5,000 patients over 50 years of age) [2, 7].

The pathogenesis of vasculitis can be broken down into four major chronic reactions to acute events: 1. Cytokine-mediated alteration of epithelial adhesion and the concurrent activation of leukocyte invasion into the vascular walls; 2. Bystander injury of vascular epithelial cells by antibodies and complement activation; 3. Abnormal anti-neutrophil cytoplasmic antibody (ANCA) production and vascular

Box 1: Wegener's granulomatosis:
An ANCA positive inflammatory disease commonly associated with lung and kidney damage requiring long term immunosuppression. It is known to affect both small and medium blood vessels and often presents with rhinitis, epistaxis, rapidly progressive glomerulonephritis, arthritic pain and swelling, pulmonary lesions, etc. Mortality is relatively low with treatment

Box 2: Takayasu's disease:
A granulomatous giant cell arteritis that generally affects the aorta and major vascular branches to the limbs and head. It is often characterized by absence of peripheral pulses in both arms as well as claudication, wide differences in the brachial blood pressure found right and left arms, major vessel stenosis or occlusion, and systemic symptoms of inflammation. Prognosis is typically good in most cases.

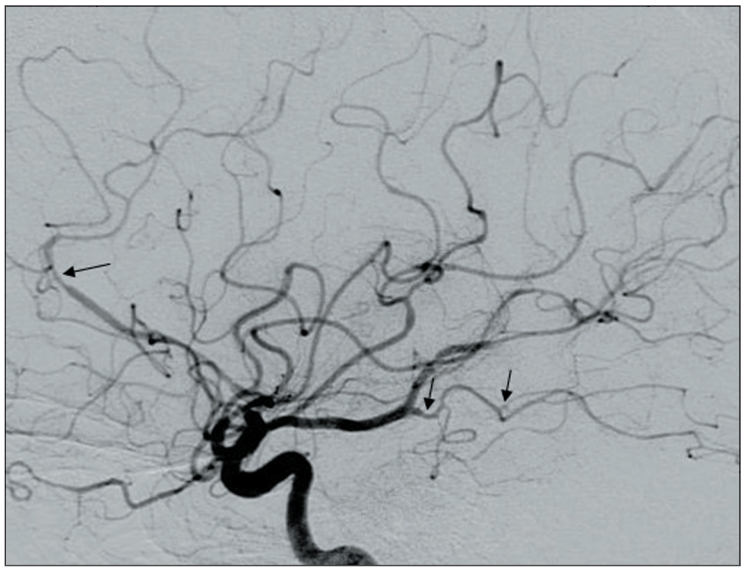

Figure 1: Angiography demonstrating anterior cerebral artery vasculitis stenosis with concurrent mild vasculitic stenosis and flow delay at the posterior cerebral artery.

adhesion followed by subsequent neutrophil-mediated injury; 4. Granulomatous inflammation initiated by T cell immune responses to a detected antigen. Given the inflammatory nature of the disease processes, steroids, intravenous immunoglobulin, and cytotoxic agents are used with varying success [1, 2, 8–11].

Given the nature of the CNS and its high level of vascularization, it is susceptible to many of the etiologies of vasculitis [Table 1] [1, 2]. Sustained inflammation can potentially lead to serious neurological consequences. In one large study of primary CNS vasculitis, morbidities on presentation included persistent neurological deficits (40%), visual loss or impairment (42%), hemiparesis (44%), and hemorrhage (8%) [12].

Vasculitis etiologies reported in CNS vasculature
Giant Cell arteritis
Primary anginitis/vasculitis of the CNS
Takayus's disease
Polyarteritis nodosa
Kawasaki disease
Churg-Strauss syndrome
Wegener's granulomatosis
Behcet's disease
Systemic lupus erythematosus
Spirochetal infection
Viral infection

Table 1: Common examples of pathologies capable of instigating vascular inflammation

Combined with the significant overlap of presenting characteristics with other neurological diseases [Table 2] [13], the diversity of vasculitis progression, treatment, and prognosis make early clinical suspicion of a vascular inflammatory process crucial to the preservation of neurologic function. To this end, a number of diagnostic tools have been developed to address this need. The gold standard of confirmation has long been histological evidence of vasculitis. However, the invasiveness of this process in the CNS, combined with findings pointing to a lower sensitivity (75%) than previously believed, have shifted favor away from biopsy and towards cerebral digital subtraction angiography [1, 4, 12, 14].

Cerebral angiography itself, however, is also an invasive technique with well-established risks of mortality (< 1%), disabling stroke, transient ischemic attacks, infection, and allergic reaction [15]. Recent studies have also shown that angiography fails to detect pathologic changes in some subgroups of CNS vasculitis. Current estimates of the specificity and sensitivity of angiographic detection of vasculitis are 30% and 60–80%, respectively [4, 12, 14, 16–20].

Much interest has thus been directed towards the improvement of non-invasive radiologic testing as a potential replacement of first-line angiography. Magnetic Resonance Angiography (MRA), which visualizes vasculature based on flow detection, and Magnetic Resonance Imaging (MRI) have both had success in detecting systemic vascular inflammation, but have until recently been less successful in distinguishing CNS vascular inflammation from other causes of radiographic abnormalities of the CNS parenchyma [4, 14].

The utilization of newer imaging techniques and equipment (e.g. vessel wall contrast detection, FLAIR MRI, T3 MRI scanners), combined with increasing knowledge of the radiographic manifestation of vasculitis, has begun to close the gaps in comparison to detection with angiography [14, 17]. In this study, we seek to share our experience at the Columbia University Medical Center Department of Neurological Surgery and to assess the current strengths of MRI/MRA

relative to angiography and to identify useful predictors of cerebral vasculitis.

Methods and Materials

Records of patients who underwent MRI, MRA, and cerebral angiography between 2004 and 2009 at Columbia University Medical Center were reviewed and those with confirmed or suspected systemic and cerebral vasculitis were included in the study. Patient demographics and admission clinical characteristics were recorded.

All MR studies were performed with a 1.5-Tesla MRI using standard techniques and protocols. T1, T2, FLAIR, and DWI/ADC sequences were obtained. MR imaging and angiography were reviewed by a team of neuroradiologists and neurosurgeons/interventional neuroradiologists, respectively, for evidence of infarct (acute, subacute, or chronic), intracerebral hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, and abnormal vessel morphology, including beading and stenosis.

For MR studies, a positive radiologic sign was defined as the presence of infarct, presence of hemorrhage, or presence of stenotic vessels [Figures 2 and 3]. Positive angiographic studies were based on the presence of vasculitic changes, with vessel stenosis defined as the primary result suggestive of a vascular inflammation [Figure 4]. For statistical purposes, angiography was considered the final determinant, or gold standard, of the presence of vasculitis. MRA and MRI studies were designated as being correlated with angiography when lesions in both imaging studies were ipsilateral and localized to the territories of the affected vasculature. Additional lesions in the brain did not exclude the two studies from correlating. Comparisons of MR and angiography were based on the assumption that ipsilateral lesions within the proper area of blood supply correlated with the same underlying pathology. Additional lesions located on the contralateral side of the brain did not exclude this correlation if they were concurrently present with ipsilateral lesions. Ipsilateral radiologic lesions with abnormal positioning relative to the vasculature in question were also not exclusion criteria when appropriate lesions were also present. A Fisher's exact test was used for analysis using SPSS software.

Mimics of CNS Vasculitis
Moyamoya
Arterial dissection
Sickle Cell disease
Vasospasm
Metabolic vasculopathies
Atherosclerosis
Illicit drugs

Table 2: Examples of diseases capable of mimicking test results and examination findings of vasculitis

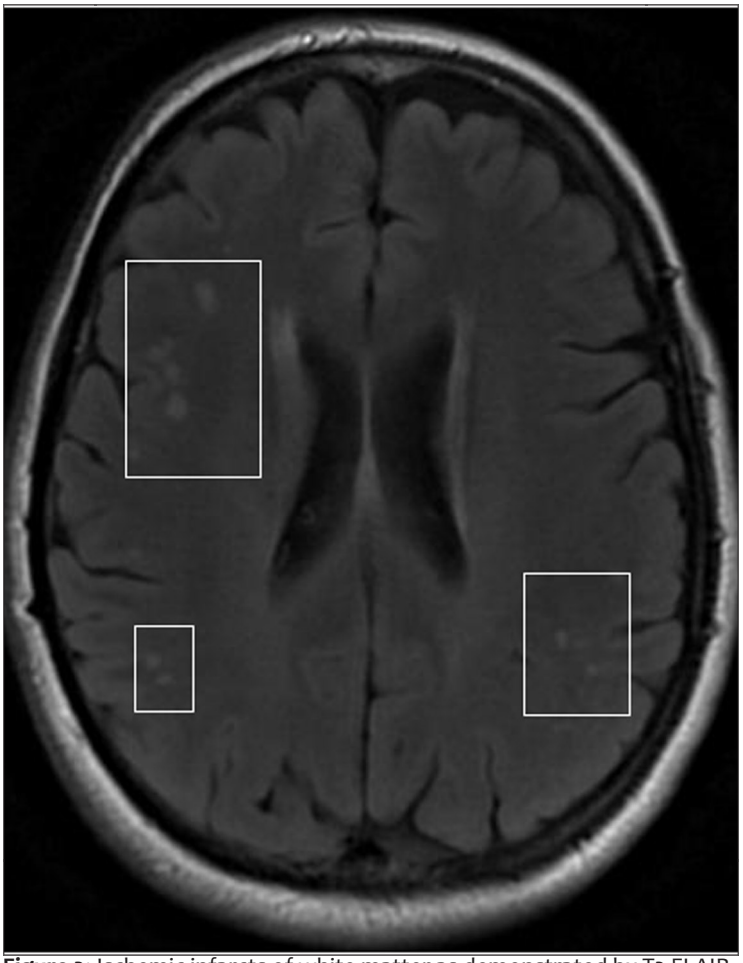

Figure 2: Ischemic infarcts of white matter as demonstrated by T2 FLAIR MRI

Results

A total of 38 patients met the study criteria and were included in the analysis. In our cohort, the demographic data collection revealed that 30 (79%) were female and that the mean age was 47 ± 29 years (range 1–77 years). 5 (13%) of the patients were aged 18 or younger. 20 (52%) had a history of autoimmune or systemic inflammatory conditions. 19 (50%) presented with severe headache, 5 (13%) with acute mental status changes, 7 (18%) with visual symptoms, and 13 (34%) with motor deficits [Table 3]. Angiography showed positive signs of potential vasculitis in 25 (66%) patients. MRI review identified 24 (63%) cases of ischemic stroke and 10 (26%) cases of hemorrhagic stroke on admission. 4 (11%) patients did not show signs of stroke. Only in one of these cases was hemorrhagic stroke associated with an area of independent ischemic stroke. Of the 33 (87%) stroke positive cases, 20 (61% of stroke patients; 52% of total patients) showed signs of vessel narrowing on MRA.

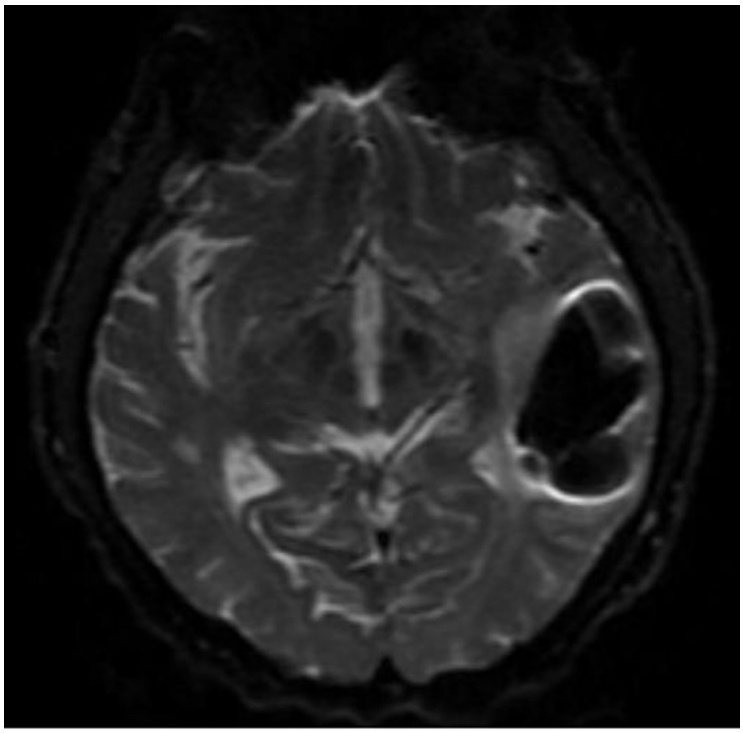

Figure 3: Left temporal hemorrhagic stroke as seen by T2 gradient echo

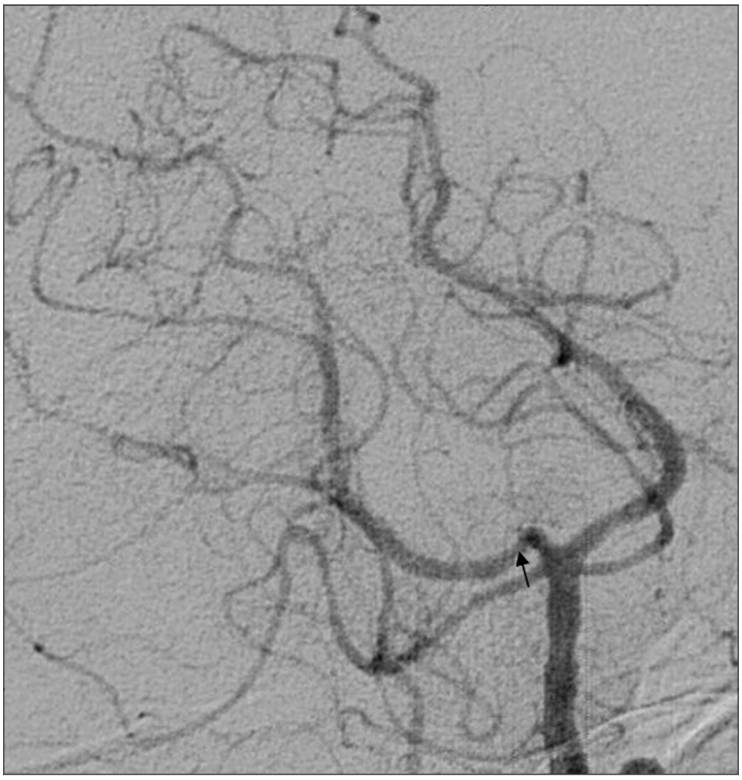

Figure 4: Mild stenosis of the proximal right posterior cerebral artery as detected by angiogram

There were no cases of angiographic narrowing without signs of stroke on MRI. When MRA narrowing and MRI stroke were present, there was an 80% chance of positive signs of potential vasculitis on angiography. In 9 (36%) cases of the 25 positive angiograms, there was a negative MRA. There were no cases of negative MRI with positive angiograms. In 8 cases (21%), a positive MRI had a negative angiogram for vasculitis. In 5 (13%) cases, neither MRI nor MRA showed signs of vasculitis or ischemia. In each case, angiography was also negative for vasculitis [Table 4]. The associations between positive combined MRA/MRI and positive angiogram test results were statistically significant ($p < 0.001$). The association between negative combined MRA/MRI and negative angiography was also significant ($p < 0.001$). Due to brain biopsy being used in only seven cases, these data could not be compared to other findings.

Demographics	
Mean Age (range)	47 ± 19 years (1-77)
Female (%)	30 (79%)
Symptoms on Admission (%)	
Severe Headache	19 (50%)
Acute Mental Status Change	5 (13%)
Visual Symptoms	7 (18%)
Motor Deficits	13 (34%)
Other	4 (11%)
Other (%)	
History of autoimmune or systemic inflammation	20 (52%)

Table 3: Summary of presenting characteristics of the case study population

Discussion

Since the early 1990s, MR imaging has gained considerable ground as a major diagnostic modality in vasculitis and clinical deliberation. At one time, negative MRI excluded a vasculitis diagnosis, although this is no longer accepted [19]. Our results suggest that a combination of MRI and MRA is comparably sensitive to that of angiography in the case of preliminary vasculitis diagnosis. As mentioned above, all completely negative MRI/MRA batteries were correlated with a negative angiographic test for the stenotic findings of the relevant cerebrovascular lumen. It should be emphasized, however, that angiography itself is not a perfectly sensitive test for vasculitis. Thus, the benefit in this case is one of potential non-inferiority in terms of sensitivity combined with the advantages of non-invasive testing, lower cost, and a lower risk of complications during preliminary differential diagnosis. In addition, angiography has no treatment function in vasculitis, unlike some vascular diseases, and thereby the risks weigh more heavily against the benefits. However, given the low number of cases involved in this judgment, caution should be administered until more, larger cohorts are available.

It should be noted that in 36% of positive angiogram readings for vasculitis, MRA was negative. This was not unexpected, as MRA has been reported to be less able to detect vascular lesions in smaller vessels compared with angiography [4, 12, 20]. The location of lesions, beyond comparisons across radiographic tests, was not part of this study, and it cannot

Radiological Finding	Positive Results (%)
Angio +	25/38 (66%)
MRI+	33/38 (87%)
MRA+	20/38 (52%)
MRI-, MRA-, and Angio-	0/38 (0%)
(MRI+, MRA+, and Angio+) divided by (MRI+ and MRA+)	16/20 (80%)
(MRI-, MRA-, and Angio-) divided by (MRI- and MRA-)	5/5 (100%)
([MRI+ or MRA+] and Angio+) divided by (Angio+)	25/25 (100%)

Table 4: Summary of the radiologic results of vasculitis assessment among individual radiologic tools as well as relevant combinations of MRI, MRA, and angiography.

be said with assurance that undetected lesions were only in the smaller cerebral vessels. This further examination of the vascular regions of successful MRA visualization will be pursued in future studies. In all cases, MRI still showed ischemic or hemorrhagic abnormalities when angiography was positive for a potential stenotic lesion. This is very important on a population level, because the relative rarity of vasculitis and the non-specific symptoms most commonly seen (headache, mental status changes, motor deficits, visual symptoms) do not always justify the use of an invasive radiologic assay.

Given the strong correlation between normal MR and angiography studies, we are inclined to endorse a modified methodology of what Küker outlined in 2007 [4]. It was proposed that MRI and optional MRA be the first line of diagnostic protocol, with angiography being used in inconclusive cases to search for smaller vessel inflammation. Based on our results, we would argue for a combined MRI/MRA study with follow-up angiography only in the case of abnormal MR signals suggestive of vasculitis. In the case of a doubly positive MRI and MRA finding, angiography would be reserved for cases in which there is enough doubt to require more support for a vasculitis diagnosis (such as in a situation where other tests have been inconclusive). Angiography would also maintain its useful application in the differentiation between vasculitic pathologies when such differentiation would significantly affect the clinical care of the patient. In this case of positive MRA/MRI with the additional need for angiography, treatment should nonetheless be prepared and administered if deemed prudent in the intervening period.

The demographic and presentation data presented here have some differences from past studies. Although mean age correlated well with other studies, there was a stronger presence of female cases in this study (79% in our series versus 57%, 48%, and 39% in others) [12, 21–23]. The greater relative risk of women for systemic inflammation or autoimmune reactions may have caused an increase in the fraction of women in our study. Further, while headache, visual symptoms, and motor dysfunction were comparable, mental status deficits appeared to be somewhat decreased (13% in our series versus 50%, ~50%, and 30%). [12, 21–23] While interesting, this may be a result of the random selection of a group of patients that does not correlate well with the more specific diagnosis of primary CNS vasculitis in these studies. A further review of current data and the ultimate etiology of each case is required.

There were a number of limitations to this study. Among the foremost was the assumption that positive or negative angiography dictated the presence or absence of vasculitis. As discussed, this has not been shown to be the case in past studies, and this issue can only be resolved with further long-term evaluation of follow-up for each patient with a final diagnosis relying on a combination of physical exam findings, brain biopsy, cerebrospinal fluid and serum findings, and additional radiologic studies. In particular, the absence of brain biopsy in the majority of studies prevents the stronger identification of true positive cases of vasculitis. Nonetheless, we feel that the data presented are still potentially able to provide strong justification for using MRI/MRA evaluation as the first line of imaging for suspected vasculitis if the testing results are sufficiently similar. The presence of potential false positives would not affect current data because the goal of this study was not to evaluate the quality of angiographic detection, and results have already demonstrated inferiority in MRI/MRA specificity relative to angiography.

A second major limitation to the study was the lack of differentiation between the various etiologies of vasculitic disease, which often was not attempted or not possible at the time of the radiology visits. Because vasculitis encompasses a very diverse set of diseases, drawing generalizations about a potentially significant number of subgroups within the data could result in poor treatment strategies or the oversight of specific findings to a given subgroup, as recent literature has demonstrated [14, 16]. It is much more likely that, upon future examination of the specific pathologies of the cases presented here, there will be a primary bias toward large-vessel identification. It is also likely that some patients with small-vessel vasculitis were diagnosed without the use of all three radiologic tools or even despite negative results due to the poor resolution of small-vessel vasculitis. The data here may be further skewed by the fact that other, more easily identified cases may not have required all three radiologic tests to confirm the identity of the vasculitic pathology, or that treatment was successful before a need for exact identification using three tests.

Conclusions

Our study supports the idea that there is a significant correlation between positive results suggestive of vasculitis in

doubly positive MRI/MRA studies and angiography, and also that doubly negative results are suggestive of the angiographic absence of vasculitis. Current evidence does not yet call for a shift from angiography as the gold standard of CNS vasculitis detection, but it is possible that, with further studies indicating non-inferior sensitivity, combined MRA/MRI studies may be used as a safe, non-invasive screening test for potential cases of vasculitis in place of angiography. When clinical suspicion or positive test results indicate, angiography or brain biopsy should be utilized to assist in a definitive diagnosis. Nevertheless, with current advances in MRI technology and technique, it is expected that in the near future non-invasive diagnosis will replace our current methods as the gold standard of CNS vasculitis detection.

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