

PhysicianUpdate

FOR HOPKINS CLINICAL FACULTY AND REFERRING PHYSICIANS

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Marfan Syndrome's Grand Theme

Often obscured among the accolades that have accrued to **Victor McKusick** since he launched the nation's first medical genetics division at Johns Hopkins 50 years ago is the fact that he began his career specializing in heart disease.

"Some people thought I was committing professional suicide switching from cardiology to focus on rare and supposedly unimportant disorders," says the 1997 Lasker Award winner, "but my interest in medical genetics grew out of treating patients with Marfan syndrome."

Of all that has come from McKusick's prescience—Google medical genetics and you'll get more than 73 million hits—what excites him most is the discovery of a breakthrough treatment for the very disorder that started it all.

In 1956, when McKusick coined the phrase *heritable disorders of connective tissue* to describe Marfan and four related syndromes, he postulated that Marfan's distortions of the skeleton, eye, lungs and aorta were due to a mutation in an unknown but single, fibrous element. The "aha" moment seemed to

come in 1991 when McKusick's colleague **Hal Dietz** showed that mutations in the gene that encodes fibrillin-1—a protein needed for formation of elastic fibers in connective tissue—cause Marfan.

Celebration, however, turned quickly to near despair when Dietz realized that the finding opened no practical avenues for treatment. If Marfan patients were born with a structural predisposition to tissue failure, then they were "like a house with a rotten frame that could only be fixed by tearing it down and starting over," says the pediatric cardiologist. "Things looked so bleak then that if I had been only a researcher and not a clinician, I would have turned my attention to something else."

Still, Dietz couldn't shelve the conundrum of how a structural deficiency alone could explain Marfan's bone overgrowth and thickened mitral valves. Heading back to the lab, he and his colleagues created a mouse model of Marfan and ended up finding what McKusick himself admits he would never have predicted: that fibrillin-1 also regulates a key developmental signaling molecule called transforming growth factor beta, and it is an excess of TGF-beta activity that in fact triggers the skeletal, pul-



Pediatric cardiologist Hal Dietz is testing a well-known medication that shows unprecedented promise.

monary and cardiac features of Marfan.

Armed with this new understanding, Dietz instantly saw a therapeutic target and, enlisting the help of cardiologist **Dan Judge**, began scouting for a drug that would block TGF-beta. Their search turned up losartan, a hypertension medication in use for two decades. Now, thanks to their rigorous studies showing that Marfan mice treated with losartan are essentially indistinguishable from normal mice, the National Institutes of Health has begun a multicenter clinical trial to determine whether losartan can

prevent aortic aneurysm in people with Marfan (see sidebar).

For both McKusick and Dietz, the odyssey has been an eye-opener. "We always thought that the Human Genome Project would revolutionize medicine," Dietz says. "Now we have an excellent example of how a systematic effort to find the genes responsible for a disease can uncover unanticipated mechanisms and lead to rational therapy."

"It's not at all what you would have expected," agrees McKusick. "But you do get there." ■

The Losartan Trial

This spring, a much-anticipated clinical study began enrolling people with Marfan syndrome to determine whether a well-known angiotensin receptor blocker can stop—and perhaps even reverse—aortic root enlargement. Funded through the National Heart, Lung and Blood Institute and conducted by the Pediatric Heart Network, the losartan trial is taking place at 16 U.S. sites, plus two in Canada and one in Belgium. At Johns Hopkins, principal investigator Hal Dietz hopes to enroll up to 100 patients. And to that end, he says, "We will partner with referring physicians and centers everywhere."

For details, go to www.marfan.org

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Miniscule Scope, Maximum View

For the most part, the patient in his mid-70s had had few medical problems and had enjoyed generally good health. When he began to deteriorate rapidly, however, his physicians suspected a gastrointestinal cancer. Trouble was, they couldn't prove it. Every imaging test showed only ascites, and an abdominal puncture to extract a sample of the fluid produced an amount too small for analysis. Given the patient's age and weakened condition, an exploratory laparotomy or traditional laparoscopy under general anesthesia was deemed far too risky. Was diagnosis now also out of the question?

In 1983, when **Sergey Kantsevoy** finished medical school, the nascent field of laparoscopy had yet to prove its value for cholecystectomy and other operations. Even so, the young Russian surgeon was quick to recognize its potential. The work he began in 1985 to develop a minimally invasive appendectomy was pioneering, but he was already no stranger to the laparoscope's unprecedented views of the peritoneal cavity. "Back then," he says, "laparoscopy was really only for diagnosis, and I was doing 300 to 600 cases a year."

Kantsevoy, who signed on at Hopkins a decade ago, has never abandoned those roots. Although today he's best known for his prowess scoping throughout the GI tract, it was his skill with an emerging laparoscopic technique that made him the obvious consultation choice for the patient with ascites.

Unlike traditional laparoscopy, which requires making 5- to 10- millimeter holes in the abdomen that must be

closed with sutures, the method Kantsevoy used is called minilaparoscopy because the miniaturized scope is inserted through a 2-millimeter opening that can be covered with a Band-Aid. He performs the entire procedure in an outpatient setting with local anesthesia. "It takes 30 minutes if you have to investigate around," Kantsevoy says, "and less if you know where you're going."

For this patient, Kantsevoy's tiny scope quickly confirmed that he indeed had disseminated cancer. "I saw multiple, 2- to 3-millimeter metastases on the peritoneum," he says. "They hadn't been visible on ultrasound and CT scan because they were too small."

Even though the tumors were unresectable and the patient was transferred to hospice, Kantsevoy is convinced that making the diagnosis so quickly eliminated many less informative tests and alleviated the patient's suffering.

Minilaparoscopy, which debuted about four ago, has yet to gain a foothold in the United States but has been studied and used extensively in Europe, especially for patients who need a liver biopsy.



Sergey Kantsevoy takes minimally invasive to a whole new level.

Rendering a clear view of the peritoneum, the tiny apparatus lets the endoscopist explore more than two-thirds of the liver surface as well as the small bowel and omentum.

"When you're not sure if the patient is a surgical candidate—for example, the tumor appears big but there's no evidence of metastasis on ultrasound—minilaparoscopy can avoid an exploratory laparotomy," Kantsevoy says. "It's very promising for cancer staging

because you can do any biopsy inside the peritoneal cavity. Instead of doing a cell aspiration as you would with ultrasound, you can actually take a large sample of tissue. It could be used for ovarian, bowel, stomach, and pancreatic cancer staging or for diagnosis of benign conditions in clinically difficult situations such as extrauterine pregnancy or acute appendicitis. I see it becoming a routine procedure." ■

☎ 410-955-4166 to learn more.

Homing In on ARVD

In their quarter-century campaign to accurately diagnose one of the most mysterious causes of sudden cardiac death, scientists are closing in on their quarry with the aid of improved genetic screening. "In many cases," says cardiologist **Hugh Calkins**, "we can now pin it down."

One of every 5,000 people has arrhythmogenic right ventricular dysplasia. But ARVD's presence too often becomes clear only after an autopsy reveals such telltale signs as a severely dilated right ventricle whose walls are thinned and replaced with fibro-fatty tissue. While getting an accurate early diagnosis can avert deaths, the condition's genetic links also give it a

ripple effect: A third of an afflicted person's children will likely get it.

That link further magnifies the value of accurate early diagnosis. Confirmed cases can trigger prudent family-wide screening, but cases that are merely suspected can bring unnecessary worry and, worse, unnecessary treatment that often includes an implanted device.

The concern is no minor detail. Calkins describes one recent study that scrutinized cases of reported ARVD in which patients were treated. After an elaborate battery of tests using the full gamut of established criteria, most of the suspected diagnoses proved incorrect.

The process of diagnosing ARVD has

always been taxing, says Calkins, who serves on a task force charged with revising the condition's diagnostic criteria. Current criteria include various combinations of six different factors, ranging from major dilation of the right ventricle (reducing ejection fraction) to EKG readings that show arrhythmias characterized by inverted T waves in the right precordial leads.

While a family history of ARVD is obviously a strong indicator, research conducted at Johns Hopkins has recently brought mutations in one gene—plakophilin-2—to the fore. *PKP2* errors are associated with up to 45 percent of ARVD patients, and those with a *PKP2*

mutation are also more likely to develop ARVD at an early age, which hints at the condition's especially tragic distinction—its disproportionate toll on young athletes. Today, Hopkins is the only U.S. medical center offering clinical genetic *PKP2* testing for ARVD.

If ARVD is caught in advance, arrhythmias can be temporarily relieved with ablation therapy. But, Calkins says, the more optimal long-term solution currently resides with the implantation of a defibrillator. He hopes the revised criteria for ARVD will be published in early 2008. ■

☎ 410-502-0550 to learn more.

Making Michael Fletcher's New Nose

When the Humvee started to roll over during a high-speed turn near Iraq's border with Kuwait, a piece of Michael Fletcher's top-mounted turret gun caught him in the face, impaling him beneath the heavy machine moments later. He remembers intense heat. He remembers standing up and taking a few steps and throwing his helmet off before passing out. Then he remembers waking up in Walter Reed Army Medical Hospital to see televised images of his beloved New Orleans in the wake of Hurricane Katrina. It looked like a twisted wasteland. He remembers thinking: "Am I in hell, or what?"

If he'd seen his face in a mirror then, Fletcher wouldn't have felt assured. The center of his face was crushed, his nose a formless scramble of flesh. His other injuries seemed almost incidental, including the way his left eye, now blind, was spaced farther from his nasal region than normal, or that his left arm was amputated at the shoulder. That he was alive at all was a testament to modern combat medicine.

By the time Fletcher came under the care of Hopkins' **Patrick Byrne** in January 2006, the four metal plates installed beneath the flesh of his mid-face had begun to settle. Byrne, an expert in facial plastic reconstruction, counseled Fletcher about the torturous



With the help of a meticulously crafted plastic guide, **Patrick Byrne** rebuilds the most prominent facial feature.

changes ahead, and told him there might be an easier way. They could fashion a real-looking artificial nose. "A prosthesis is a fine option if you want to bail out," said Byrne.

Though Fletcher welcomed anything that would reduce the awkward staring of strangers, he told Byrne he'd suffer any pain required to have a real nose again. The challenge was on.

Byrne has long-established unique skills for rebuilding noses in patients who've suffered disfiguring nasal cancers, but the Fletcher case was something else altogether. Much of the relevant skin was missing; the nasal cartilage was completely absent. Byrne

and his colleagues would have to build it from scratch—and match the contours of Fletcher's original nose.

Byrne had noticed the work of anaplastologist **Juan Garcia**, trained in both medical illustration and the development of facial prosthetics, and the pair linked up with a 3-D image engineering firm. In a process that graduated from silicone to stone to wax, Garcia fashioned a replica of the original nose, which was transferred to a 3-D image that would aid in the production of a clear plastic guide. The guide would serve as the governing mold that Byrne would fill with carefully sculpted flesh—from parts of Fletcher's own body.

The six elaborate medical procedures unfolded over the course of a year. One demanded that Byrne carve out a vaguely T-shaped pattern from the flesh of Fletcher's forehead—a nearly perfect match for exterior human nose flesh—and then attach it to the nasal area. This would help the new flap become more independently vascularized for eventual transfer. In the longest procedure, Byrne headed a team of surgeons who harvested portions of Fletcher's ribs from which Byrne could carve portions of cartilage. Using a sketch of the "sub-units" of the nasal structure mapped out in concert with Garcia, Byrne sculpted bits of cartilage into eight specific components. He then stitched them together to craft a scaffold on which the new portions of flesh would attach. Further aided by tissues transferred from Fletcher's inner forearm and neck and bits of cartilage from his ears, Byrne eventually crafted a new nose that conformed with the plastic guide.

Though there were setbacks over the months that included a lingering process of infection, the final bandage came off in May. Michael Fletcher's new nose looks strikingly normal. He can breathe, sneeze and even sense human touch to the nose in a normal fashion. "Unbelievable!" Fletcher exclaimed, regarding his reflection in a hand mirror moments after the bandage was removed. "I really like it." ■

☎ 410-955-4985 to learn more.

UROLOGY AND NEPHROLOGY

When Breaking Up (Stones) Is Hard to Do

About 80 percent of kidney stones in this country turn out to be run-of-the-mill calcium stones, and most of these will respond well to extracorporeal shock wave lithotripsy. But once in a while, this conventional treatment fails to break up the stones. "And that," says urologist **Brian Matlaga**, "is when you might say, Aha—this could be cystinuria."

Only 1 percent of stones are caused by this metabolic defect that results in excessive urinary excretion of cystine, explains Matlaga, and cystine stones are harder than their calcium counterparts, making them less responsive to shock wave lithotripsy. Additionally, calcium stones typically present in middle age, whereas cystinuria tends to present early in life. This used to be another tip-off that a patient might have cystinuria, but "that's starting to change," says Matlaga. "Now we're seeing more kids and more elderly people with calcium stones."

But cystinuria isn't just increasingly challenging to diagnose; it's also a challenge to treat. Stones tend to recur, so

invasive surgery or surgery that harms the kidneys will become problematic with cumulative procedures. Medications, which can elevate a patient's urinary pH or bind to the cystine and prevent crystals from forming, all have harsh side effects.

To provide better care for cystine stone formers and other patients who present with complex medical situations, Matlaga has joined forces with Hopkins nephrologist **Michael Choi**. "We both have an interest in stone disease," explains Matlaga, "so it made sense to establish a clinic where I could evaluate patients from a surgical standpoint and say, This is going to be the best way to get rid of the stones, and then he could evaluate them from a medical perspective, and say, This is the best way to prevent these stones from coming back."



Michael Choi and Brian Matlaga

The clinic fills a longstanding gap. "Shock wave lithotripsy is by far the most commonly used treatment for stones," says Matlaga, "and it does work well for most stones." But for cystinuria, the clinical picture is complicated. For stones lodged in the tubes leading to the bladder, Matlaga uses ureteroscopy with laser lithotripsy to capture and remove or break up the stones. When stones are large, he relies on percutaneous nephrolithotomy, which requires making a half-inch incision in the

back and using X-ray guidance to reach, break up and extract the stones.

Another bonus of the clinic is that dietitians will also be on hand. "It's seamless for the patient" says Matlaga, "because we're all here together. It's also better care." ■

☎ 410-550-3506 to learn more.

For Pituitary Tumors, a Full Court Press

Monica Cisternelli had no inkling of the mass stealthily enlarging in her brain until her right peripheral vision plummeted, seemingly overnight. Referred by her local physician to the Wilmer Eye Institute, the 38-year-old marine biologist was stunned at how quickly neuro-ophthalmologist **Paul Hoffman** nailed the problem. “Within 30 seconds,” recalls Cisternelli, “he said, ‘I know exactly what you have.’”

An MRI confirmed what Hoffman had deduced—the presence of a large pituitary tumor stretching her optic nerve—and Cisternelli suddenly found herself transformed from a woman who “was never sick, never went to a doctor, never took medication” to a patient needing the expertise of a cadre of subspecialists.

Estimated to occur in one of every 10 people, pituitary growths are almost invariably benign and often clinically insignificant, says endocrinologist **Roberto Salvatori**. Still, some wreak havoc. They can suppress hormone secretion or launch excess hormone production, producing symptoms that range from the common (fatigue, headaches, sleep loss) to the odd (hirsutism, temper outbursts, changes in facial features). And since not all pituitary tumors are visible on imaging, their diagnosis demands not only adeptness at interpreting their heterogeneous signs but a battery of detailed blood and urine hormone tests. Treatment, which must be tailored to tumor type and size as well as the patient’s age and overall health, spans medical management, radiotherapy and surgery.

In more than two-thirds of cases, Sal-



Roberto Salvatori and Henry Brem.

vatori and fellow endocrinologist **Gary Wand** can monitor patients for signs of progression or keep their tumors in check with medication. It was for patients like Cisternelli, however, that Salvatori co-founded Hopkins’ Pituitary Tumor Center to ensure that what can be highly complex care is well coordinated.

Cisternelli’s evaluations by Hoffman and Salvatori showed a 4-centimeter growth-hormone-secreting adenoma that had to be removed, meaning her next consultation would be with **Henry Brem**.

The director of neurosurgery, Brem heads a surgical team fully versed in the intricacies of operating on the pea-size gland that hangs just below the optic nerves. Among their options for resecting microadenomas (tumors smaller than 1 centimeter) are a new endoscopic technique that allows the surgeon to view and remove the mass via an incision in the lining of the nose, and the transsphenoidal hypophysectomy, in which the surgeon makes an incision behind the

upper lip and drills a hole through the sphenoid bone. Today, Brem and his group use intraoperative MRI and intraoperative computer navigation to monitor their progress.

For macroadenomas such as Cisternelli’s, removal is trickier. Brem, who believes in starting with the least aggressive mode whenever possible, first debulked her tumor in a transsphenoidal operation. Several months later, because the stiff capsule that had surrounded the growth was still compressing her optic nerve, he performed a craniotomy to remove the remaining husk.

Now, Cisternelli sees Salvatori every six months for follow-up, has a semiannual MRI, and adheres to her regimen of hormone replacement therapy and monthly injections aimed at preventing tumor regrowth and controlling its hormone over-production. “There was some residual tumor after the second surgery,” she says, “but so far, it’s stable. I’m trying everything to avoid radiation therapy.”

To determine if that next step is ever needed, Salvatori and Brem confer with their colleagues in radiation oncology, who can choose such modalities as the gamma knife or linear accelerator/ focused beam radiation to stall recurrent tumor growth.

The good news for patients, Brem says, is that no matter what their Hopkins entry point is, the Pituitary Tumor Center will “plug them into a network of physicians and nurses who work closely together. It doesn’t matter what they think they’re coming here for, we’re all advocates for what each individual patient really needs.” ■

☎ 410-955-4526 or go to www.hopkinsneuro.org/pituitary to learn more.

Your Vital Links

Johns Hopkins Medicine offers the following links to physicians in the surrounding community. It also urges M.D.s to use its Physician Liaison Service to offer suggestions and comments. Good communication, we believe, is vital.

RESOURCES FOR REFERRING PHYSICIANS

Hopkins Access Line (HAL): Physician-Only Line for Consultations, Referrals and Patient Transfers

1-800-765-5447 (Continental United States)

410-955-9444 (Baltimore area and international calls)

Online Referral Directory

www.hopkinsmedicine.org

Physician Liaison Service:

Concerns or Suggestions for Hopkins Medicine

1-800-759-7734 (Continental United States)

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