Discover SPECIAL ISSUE

20 GREATEST BREAKTHROUGHS

MEDICAL MYSTERIES

Summer 2018

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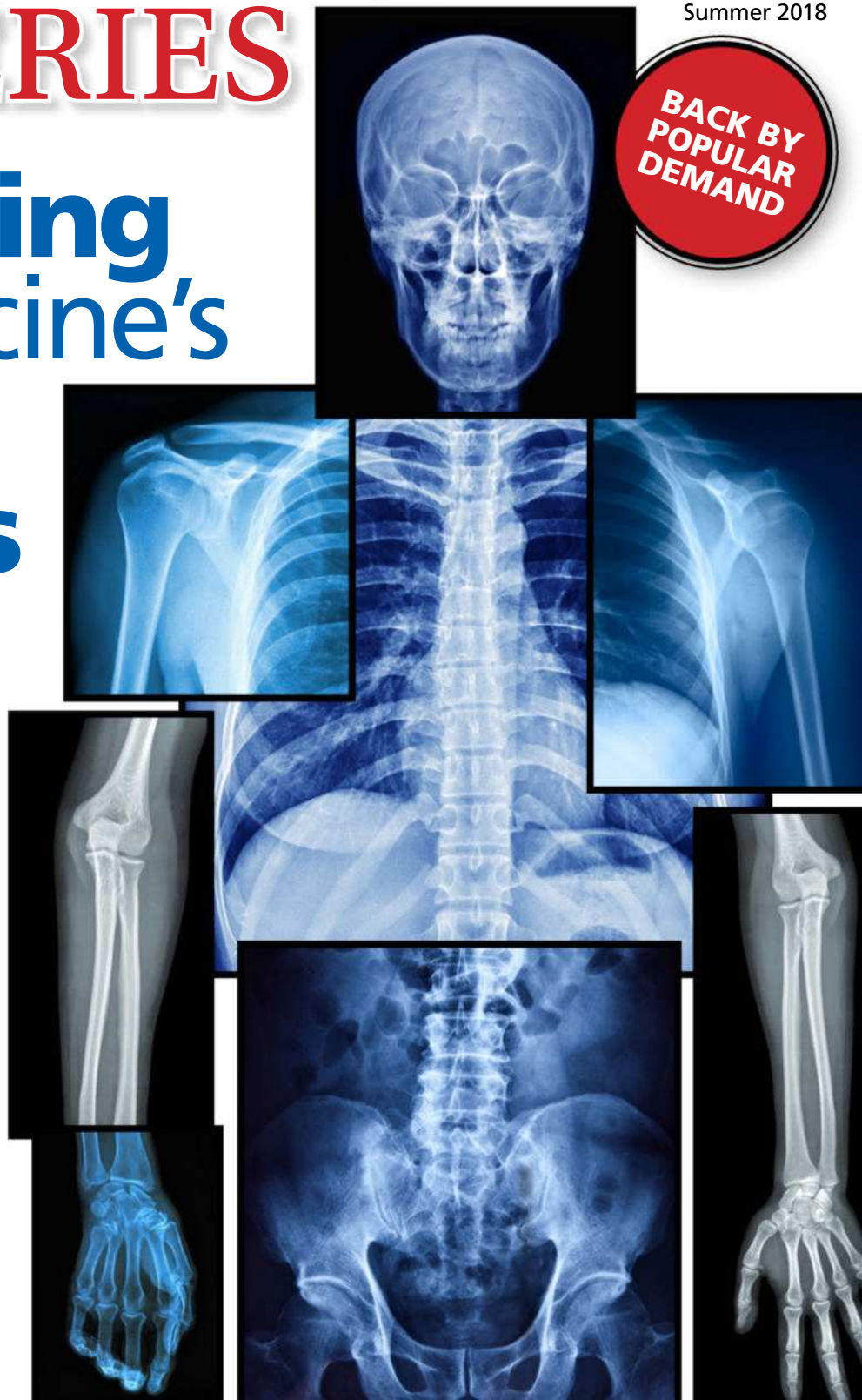
Unraveling Medicine's Biggest Riddles



Bizarre Stories From the ER

What Your Doctor Needs to Know

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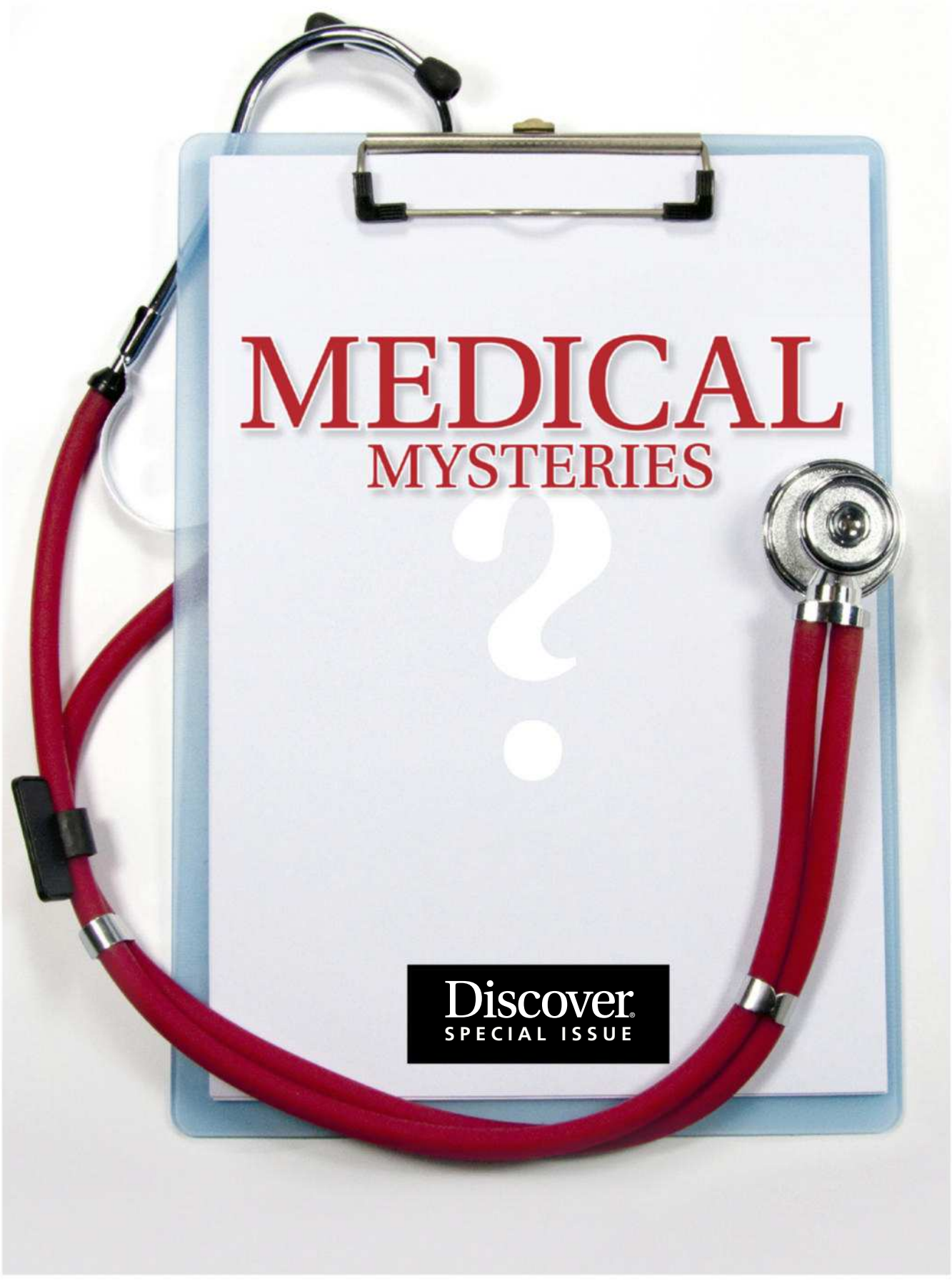

FLYTOSKY11/THINKSTOCK

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The cases in VITAL SIGNS are real, but names and certain details have been changed.

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LUCHSCHEN/SHUTTERSTOCK

I collapsed at the breakfast table one hot morning in the summer of 1977. I had a fever — 104 and climbing — with nausea, vomiting and terrible aches and pains soon to follow. I was 9 years old and occasionally got high fevers like this. The fever didn't alarm my mother. What alarmed her was how suddenly it had come on. And she'd never known me to get sick like this in the heart of summer.

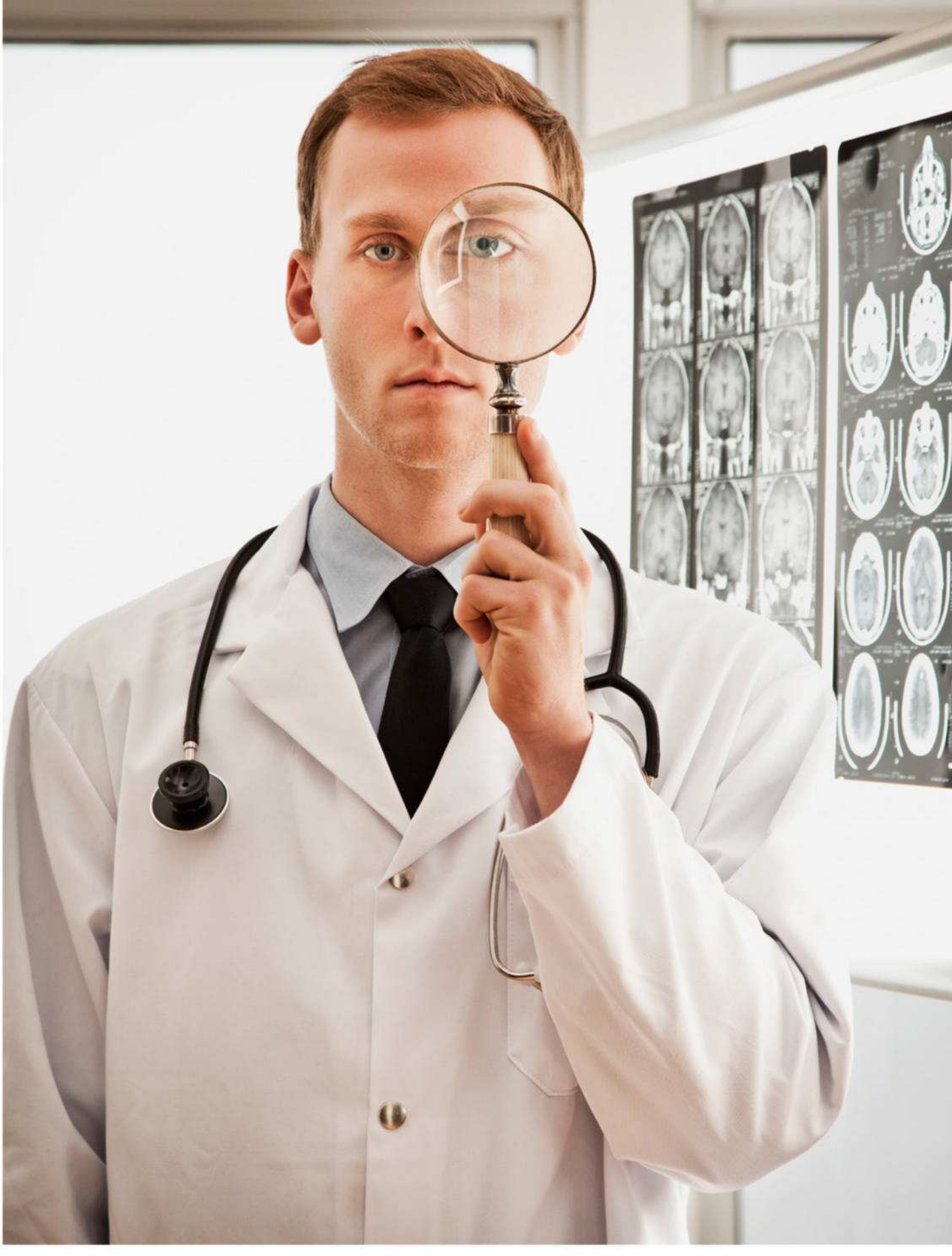
We had just moved to a small town in the Midwest and didn't yet have a regular doctor, but Mom took me to three of them in the next 24 hours in an effort to find one who was willing to take more than five minutes before making a snap diagnosis. The first one dismissed me as suffering from heat exhaustion. The second said it was probably the flu. Both advised her to take me home, keep me cool, give me plenty of fluids. But the third doctor was different. He asked *lots* of questions: where we lived, what kind of house we lived in, where I'd been playing in the past day or so, if I had any unusual welts or insect bites. Bingo. He found the bite in my armpit — probably from a brown recluse spider.

There's a big gap in my memory after that, although I'm told I was lavishly sick all the way to the hospital, and there was a moment of high drama involving kidney failure. (Good times!) But I emerged from that illness with my health restored and a profound respect for that doctor, the one who asked all the questions and solved my medical mystery with the grace of Sherlock Holmes.

It's a sense of respect that's renewed every time we're preparing an issue of *Discover*, when I get to edit the new Vital Signs column, spotlighting the diagnostic detective work of doctors like the one who helped me. You'll find several such columns in this special issue, along with many other stories that illuminate the investigatory efforts of hundreds of doctors throughout history. Hopefully, these stories show how their tireless work and endless inquisitiveness have changed the face of medicine as we understand it. Have changed our lives, in fact.

And in my case (maybe yours too), saved it.

STEPHEN C. GEORGE, EDITOR IN CHIEF



Doctor/ Detective

Every new patient is a mystery waiting to be solved. To arrive at a correct diagnosis, a good doctor must bring not only medical knowledge to bear, but also review a patient's symptoms with the inquisitiveness of an investigative reporter and the deductive powers of a master sleuth. Match your wits against these cases, and learn about the tools that help doctors solve medical mysteries every day.

Simple Sickness Gone Awry

WHY IS HER HEART SUDDENLY FAILING?

BY **ANNA REISMAN**

When 43-year-old Barbara Harris found herself panting as she climbed the steps to her front door, she knew something was wrong. She was overweight and had high blood pressure, but she'd never been sick like this. In the hospital, she was shocked when her doctors told her she was suffering from mild congestive heart failure. Because her high blood pressure had gone untreated for years, her heart muscle had been damaged and was now unable to pump enough blood for her body's needs. Blood returning to the heart was backing up, resulting in fluid buildup in her lungs and making her short of breath.

She also had a mild heart murmur, probably a remnant of a childhood bout with rheumatic fever. An echocardiogram (an ultrasound of the heart) confirmed that her mitral valve was slightly leaky, allowing blood back into the atrium and forcing her heart to work harder to pump it out. Harris was treated for two days and went home with medication to lower her blood pressure and decrease the buildup of fluid.

Two weeks later, on a cold February evening, she was back in the hospital.

"It was OK at first when I went home," she told us from her hospital bed. I was working that month on the inpatient wards as an attending physician, along with a resident and a medical student. Harris adjusted the prongs of the oxygen tubing in her nostrils. "But it started again pretty quickly. I didn't even want to walk anymore; it got too hard. I'm out of breath. And my ankles are killing me." I pressed one of her ankles, leaving a little dent in the warm flesh, and asked her to rotate her feet. Wincing, she moved them a tiny bit. Ankle swelling could be a sign of heart failure, but mild cases do not usually cause pain. It was probably a red herring.

Once a patient has congestive heart failure, treatment is a delicate balancing act that includes nuanced adjustment of medication, a low-salt diet and frequent weight checks. In some people this is easy; in others, missed medications or too much salt can cause the symptoms of uncontrolled congestive heart failure to return. But Harris had been avoiding salty food, and she hadn't missed any pills. She was so compliant, in fact, that her blood pressure and leaky heart valve probably could not explain the relapse at hand.

It was time to rethink. We sat in the doctors' station and talked about what might have triggered her symptoms. A heart attack was a possibility; we would get better information from a stress test. Alcohol could do it, although Harris told us she didn't drink. So could a condition affecting the heart valves (she did have the heart murmur, but it was mild) or bacterial endocarditis, a potentially life-threatening infection of a valve.

Over the next two days, we kept her busy. We cultured her blood for bacteria, which, if present, would increase the likelihood of bacterial endocarditis. We also sent her for various heart tests. But none of this told us anything new. Her blood was clear of infection, and her heart was pumping well enough to rule out a heart attack. What had knocked it out of control?

"Look at this," Harris panted, pulling her sheet aside so we could see her legs. "My ankles are fine now, but I'm hurting in my wrists — I can barely move my hands. And my knees, look how puffy!"

HER HEART WAS PUMPING WELL ENOUGH TO RULE OUT A HEART ATTACK. WHAT HAD KNOCKED IT OUT OF CONTROL?

Dan, the resident, listened to her heart, his brow furrowed in concentration. "Her heart sounds different," he said. "It's weird. She has a bunch of new murmurs." Before, the lub-dub of her heart had been clear; now, all I could hear were loud whooshing sounds.

I was stunned. Dan and I were thinking the same thing: It had to be bacterial endocarditis. In endocarditis, small masses of bacteria form on the surface of a heart valve, and these little infected clumps — septic emboli — can slip off into the bloodstream. Depending on where they settle, they can cause major problems: abscesses, strokes, kidney disease, blood clots and, by interfering with a heart valve's normal function, congestive heart failure.

I asked the student to draw some more blood to culture

again for bacteria and to order another echocardiogram, which would show whether bacteria had built up on a valve.

We were flabbergasted when the echocardiogram results came in that afternoon.

It looked like another patient's heart, and a really bad heart at that. The mitral valve no longer leaked a small amount; now a jet of blood regurgitated backward into the left atrium with each beat. And it wasn't only the mitral valve. The aortic valve also spewed blood in the wrong direction. The valves were damaged, but the echocardiogram showed no bacterial clumps. This didn't seem to be bacterial endocarditis. So why were her heart valves worsening before our very eyes?

Dan wondered if we were missing a clue in her medical history. "New murmurs, the ankle pain that went to her wrists and knees, congestive heart failure. … Could she be having another bout of rheumatic fever?" he asked.

Because it had happened so many years earlier, we hadn't given much thought to her history of rheumatic fever, an inflammatory disease that can affect the heart, joints and central nervous system.

"Interesting thought," I said to Dan. "But something would have triggered it. And she said she'd been fine except for the congestive heart failure two weeks ago."

"That's true," Dan said. "But what if she had something minor, like a sore throat, and didn't get treated for it?"

Rheumatic fever is a complication of something astonishingly basic: an untreated strep throat infection. When a particular type of strep bacterium — the group A beta-hemolytic *Streptococcus* — infects the throat and isn't treated promptly, it can trigger an autoimmune response, causing the body to turn on itself.

One of the proteins on the strep bacterium's surface, the M protein, structurally resembles certain heart proteins. The body's natural response to a bacterial infection is to create antibodies to fight it; in the case of this particular *Streptococcus,* the antibody to the M protein also works against the body's own heart proteins. The result: autoimmune destruction of some heart tissue and the heart valves. Damage to those valves can lead to permanent and often serious rheumatic heart disease.

The prevalence of rheumatic fever and rheumatic heart disease has plummeted in the past century in the United States and other industrialized countries, thanks to antibiotics and improved living conditions. In 1994, the last year the Centers for Disease Control and Prevention tracked the incidence of acute rheumatic fever, there were just 112 cases in the country.

Only a small number of sore throats in adults are caused by the strep bacterium that can, if untreated, trigger rheumatic fever. And most of us don't think about getting a culture every time we have a sore throat, since most are caused by viruses. But in people with a history of acute rheumatic fever, it's a different story. They are prone to significant risk from strep throat, especially if their original bout of rheumatic fever affected their heart.

WE WERE FLABBERGASTED WHEN THE RESULTS CAME IN THAT AFTERNOON. IT LOOKED LIKE ANOTHER PATIENT'S HEART, AND A REALLY BAD HEART AT THAT. THIS DIDN'T SEEM TO BE BACTERIAL ENDOCARDITIS. SO WHY WERE HER VALVES WORSENING BEFORE OUR VERY EYES? DAN WONDERED IF WE WERE MISSING A CLUE IN HER MEDICAL HISTORY.

Dan and I had to go back to our patient for that missing piece of the puzzle.

She stared out the window and thought back over the previous few months. At first she couldn't recall being sick, but then she remembered. Back in January, she said, she'd had a sore throat and fever.

"I thought I had the flu," she said. "It lasted a couple of days, and then I started to feel better."

That was the clue we were looking for. We sent off one more test that might give us the answer, a blood test for an antibody signifying recent exposure to strep.

The next day the puzzle was solved. Harris had recurrent rheumatic fever.

The original damage her mitral valve sustained as a result of her childhood rheumatic fever wasn't too serious. But the immune response to her strep throat in January had been dramatic, with a new wave of antibodies eventually wreaking havoc on her heart valves. It's a condition I had only read about and have never seen since.

The response to treatment, at least for the joint pains, can be magical. Penicillin and high-dose aspirin erased Harris' discomfort in less than 24 hours. The damage to her valves, unfortunately, was permanent. Although we could control her symptoms with diuretics and other medications, and although antibiotics stopped the strep bacteria's destructive barrage, we could not repair the heart itself.

Because rheumatic fever is such an uncommon disease in the United States, nobody had educated Harris about the importance of promptly evaluating a sore throat. It simply wasn't something that most doctors, including me, thought about anymore.

Our patient was better for now. We were finally treating the infection that was weakening her heart valves. If she hadn't been treated, she probably would have suffered additional valve damage and ended up with more advanced congestive heart failure. She might have needed more medication and, perhaps, surgery to replace the damaged valves.

None of us would ever forget how dangerous an untreated strep throat infection could be, nor how a missing clue could so easily hide in plain sight. **MM**

Anna Reisman *is an internist in West Haven, Conn.*

MIX3R/SHUTTERSTOCK

The Man With the Mustache

CHANNELING SHERLOCK HOLMES, AN ATTENDING PHYSICIAN UNRAVELS A HAIRY SITUATION.

BY **LOUIS JANEIRA**

It was my first day as an attending physician. Nervousness and excitement competed for the most prominent emotion inside me.

I was assigned a medical ward full of patients, each an enigma, each a challenge. I introduced myself to the students, interns and residents as I entered the conference room where we would begin hospital rounds.

Jane, the senior medical resident, began her report on the toughest case on our service.

"Mr. Peterson is a previously healthy 61-year-old man who presented two weeks ago to his primary care physician complaining of protracted vomiting and diarrhea. All outpatient testing was normal." Jane paused to retrieve the patient's chart. "Every test known to man was normal."

"There are always more tests," I said, smiling. "So why is he in the hospital?"

"Dehydration," said Jane. "Every few hours, he begins to throw up, then has massive diarrhea. And all for no apparent reason." Jane bit her lower lip. "We really hope you can help us shed some light on this case."

"Does this poor guy have these symptoms all day and all night?" I asked.

"No. It all quits when he's asleep."

Intrigued, I held out my hand to receive the patient's chart. Slowly, I leafed through his test results. Jane's right, I thought, as I studied the results of the tests already obtained. Everything was normal! Blood work, liver and kidney function, radiologic tests, ultrasound, CT scans — normal. Cultures from blood, urine, stool — unremarkable. There are no signs of infection.

"What do the GI consultants say?" I asked Jane as I began to read the lengthy report from the gastrointestinal doctors who reviewed the case.

"GI is as perplexed as we are," said Jane. "Scoping of the stomach and lower intestines shows non-specific signs of inflammation with mild redness and swelling, but nothing diagnostic or even remotely helpful."

"OK," I began, unsure of what to say but desperately searching for something important to add. "We've ruled out the usual. Now we need to think of the weird things." I smiled, remembering the words of the famous detective Sherlock Holmes. I declared, with a deliberate professorial English tone in my paraphrasing, "Once you've eliminated the usual causes, whatever's left, however improbable, must indeed be the correct diagnosis."

"Like what?" asked Lauren, one of the medical students, obviously unimpressed by my words of wisdom.

"Let's go see the patient first. Then let's research for unusual causes of his symptoms," I said. "Jane, please lead the way to Mr. Peterson's room."

As we proceeded down the hall, I silently reviewed the causes of diarrhea, not wanting to miss something by overlooking the obvious. Food poisoning occurs when one ingests foods that have toxins produced by infectious agents such as *Staphylococcus aureus* and *Escherichia coli*. But staph and *E. coli* were ruled out. My patient had not been traveling in an area where he might have contracted traveler's diarrhea, which can be due to infectious organisms such as Shigella, Salmonella, Giardia or Campylobacter, among others. Tests for all these were negative. Pseudomembranous colitis? This is a condition caused by an overgrowth of a normal colonic bacteria, *Clostridium difficile*, typically after taking a course of antibiotics. I looked in the chart. Yep, it was ruled out already! What else? Viral gastroenteritis, an infection of the walls of the stomach and intestine, was ruled out. So was lactose intolerance.

I probed deeper into my memory, trying to recollect the extremely unusual causes of our patient's symptoms. There are some exceptionally rare instances when vomiting and diarrhea can be caused by histamine- or serotonin-producing tumors, the so-called carcinoid syndrome and mastocytomas. Produced in normal amounts, histamine and serotonin are crucial in the regulation of gut movement. But when the body produces too much, massive diarrhea can ensue. Syndromes like these are incredibly unusual. What are the chances that my first patient ever as a medical attending would have one of these? I took a deep breath as I re-entered

my contemplative state. I see a few hours in the medical library in my near future relearning these conditions, I thought.

We reached the patient's room. The first thing I noticed — you couldn't miss it — was the man's mustache, impressive and handsomely full. Even more striking than its bulk was how jet-black his mustache was. The same went for his hair color. I sat down at his bedside and tried to ignore my mustache envy.

I began explaining what I'm sure Mr. Peterson already knew and probably was tired of hearing over and over again. "All the tests we've done so far have been negative. We still don't know why you continue to have vomiting and diarrhea."

I was happy when Jane decided to chime in, "We'll continue to study your case until we have something to go by."

I noticed that as we spoke, the patient would occasionally run his tongue along his mustachio. Left to right, then right to left. Up and down. Then he would bite the hair. I tried to imagine what that must feel like.

And then it occurred to me.

"Don't you worry, Mr. Peterson," Jane was saying, "we'll figure you out yet and — "

"How long have you had that mustache?" I interrupted. Jane and the others looked at me like I had just lost my mind.

"Almost a month," he said proudly, temporarily halting his mustache sucking and sweeping.

"And how is it that you keep it so black?" I said. "I'm amazed a man your age doesn't have some grays."

"Oh, I do. I use hair color."

WE REACHED THE PATIENT'S ROOM. THE FIRST THING I NOTICED — YOU COULDN'T MISS IT — WAS THE MAN'S MUSTACHE, IMPRESSIVE AND HANDSOMELY FULL. EVEN MORE STRIKING THAN ITS BULK WAS HOW JET-BLACK HIS MUSTACHE WAS. THE SAME WENT FOR HIS HAIR COLOR. I SAT DOWN AT HIS BEDSIDE AND TRIED TO IGNORE MY MUSTACHE ENVY.

It looked like I wasn't going to spend overtime in the medical library after all. "We need to see your hair-color product," I said. "I believe your vomiting and diarrhea are caused by your ingestion of the chemicals as you … " I pointed at his tongue, which, as I spoke, was making a pass through his thick upper lip hair. "I believe if you shave your mustache, your vomiting and diarrhea will go away."

As I explained, hair coloring involves the use of oxidation dyes, typically benzene or toluene-type chemicals. Over the years, concerns about the cancer-causing potential of these agents have been brought forth, but studies remain inconclusive. What is known is that these chemicals can be toxic. At the very least, they can cause skin irritation — a standard warning you'll find in the instructions of most hair-coloring products.

Certainly, they should never be ingested. Chronic intake of these chemicals may lead to serious health consequences such as liver and kidney toxicity and failure, and even death. In that light, my magnificently mustachioed patient was lucky that gastrointestinal symptoms were the worst of his problems.

Thankfully, even those became a thing of the past for the patient. My hunch turned out to be correct: He shaved off the offending facial hair and remained free from his disabling symptoms evermore. **MM**

***Louis Janeira**, a regular contributor to* Discover's *Vital Signs column, also writes medical mystery novels under the pen name L. Jan Eira. His books are available through Amazon and janeirabooks.com.*

QUIZ

MIND THE SIGNS

HOW MUCH OF A SYMPTOM SLEUTH ARE YOU? TAKE OUR MEDICAL MINI-QUIZ TO FIND OUT.

BY **CHRISTIAN MILLMAN**

A patient walks into a doctor's office. "What brings you here?" asks the doc.

"Well, I'm not sure," says the man, "but it hurts when I touch my shoulder, it hurts when I touch my knee, it hurts when I touch my ankle and it hurts when I touch my nose."

The doctor checks the man over closely before pronouncing his diagnosis: "You have a broken finger."

If you saw that one coming a mile away, then take a crack at the following quiz questions and really test your medical mettle.

ALL PHOTOS: ATIC12/THINKSTOCK

SYMPTOMS QUIZ

1. YOU HAVE THE FOLLOWING SYMPTOMS:

- Explosive vomiting and diarrhea, often at the same time.
- Severe nausea and stomach cramping.
- Low-grade fever.
- Shivers, chills and muscle ache.

Which of these is the most likely explanation?

A. An impending visit from your mother-in-law.
C. The flu.
B. A norovirus.
D. The stomach flu.

2. YOU HAVE THE FOLLOWING SYMPTOMS:

- Part of the white of one eye has turned blood red.
- Your vision is unaffected.
- There's no pain.
- There's no discharge.

Which of these is the most likely explanation?

A. A subconjunctival hemorrhage.
C. Pink eye.
B. A bar fight.
D. Allergies.

3. YOU HAVE THE FOLLOWING SYMPTOMS:

- A flattened, scaly area appears on your skin.
- It develops into a circular rash, with a red border and clearer skin in the middle.
- Sometimes red bumps appear within the border.
- Your dog sleeps in your bed.

Which of these is the most likely explanation?

A. Leprosy.
C. Eczema.
B. A paintball strike.
D. Ringworm.

For answers, turn to page 21.

4. YOU HAVE THE FOLLOWING SYMPTOMS:

- Fever, sore throat, headache and fatigue.
- Back and neck pain or stiffness.
- Within a week, a noticeable slowdown in your reflexes.
- Loose and floppy limbs, often more so on one side of the body.

Which of these is the most likely explanation?

A. A stroke.
C. A hangover.
B. Polio.
D. Multiple sclerosis.

5. YOU HAVE THE FOLLOWING SYMPTOMS:

- A pulsating feeling near your belly button; it may have been there for a while.
- A deep and constant abdominal pain.
- Back pain.
- You're male, and either a smoker or former smoker.

Which of these is the most likely explanation?

A. An umbilical hernia.
C. An abdominal aortic aneurysm.
B. Appendicitis.
D. An alien is about to hatch from your stomach.

6. YOU HAVE THE FOLLOWING SYMPTOMS:

- A big toe that burns like fire in the middle of the night.
- Intensifying pain in that toe, or sometimes other joints, usually most severe in the first 12 to 24 hours after it starts.
- Redness and swelling in the affected joint.
- Discomfort and aching that linger for days or weeks after the real pain stops.

Which of these is the most likely explanation?

A. Lucy pulled the football away and you stubbed your toe.
C. Your shoes are too tight.
B. Rheumatoid arthritis.
D. Gout.

7. YOU HAVE THE FOLLOWING SYMPTOMS:

- You crave and crunch ice cubes.
- You're exhausted all the time.
- Your hands and feet are constantly cold.
- You get tingling or crawling feelings in your legs.

Which of these is the most likely explanation?

A. Iron deficiency anemia.
C. MDMA (Ecstasy) withdrawal.
B. Sickle cell anemia.
D. Ants in your pants and you need to dance.

8. YOU HAVE THE FOLLOWING SYMPTOMS:

- Sudden fever, and a severe headache that feels different than any you've had before.
- Pain in your neck when you try to touch your chin to your chest.
- Confusion and overwhelming sleepiness.
- Sensitivity to light, to the point where it hurts.

Which of these is the most likely explanation?

A. Flu.
C. The undead bite of a vampire.
B. Meningitis.
D. Rabies.

9. YOU HAVE THE FOLLOWING SYMPTOMS:

- A rash shaped like a bull's-eye that expands over several days then goes away.
- Flu-like symptoms that clear up in a few days.
- Nothing for a while, perhaps days or weeks.
- Facial tics or twitches begin, joints swell and ache like arthritis, shooting pains that wake you up; all of which may come and go for months or years.

Which of these is the most likely explanation?

A Chronic fatigue symptom.

C Fibromyalgia.

B Lyme disease.

D The Sunday night blues.

10. YOU HAVE THE FOLLOWING SYMPTOMS:

- A superhuman sense of smell, especially for repulsive scents.
- Extreme mood swings, even if you're as laid back as a Barcalounger.
- Frequent urination and constipation.
- You feel funny ... just funny. And not funny ha-ha.

Which of these is the most likely explanation?

A Another impending visit from your mother-in-law.

C PMS.

B Ovarian cysts.

D Pregnancy.

ANSWER KEY

1. CORRECT ANSWER: B
People often confuse a **norovirus** with the flu or so-called stomach flu. True flu, or influenza, is a respiratory infection. And there's no medical diagnosis called stomach flu; that's a folk term. A norovirus is highly contagious, comes on suddenly and causes 1-3 days of moaning in a fetal position on the bathroom floor. It spreads best in such crowded places as cruise ships, schools, hospitals and nursing homes.

2. CORRECT ANSWER: A
The outside of your eyeball is covered with a thin, clear membrane called the **conjunctiva**. Occasionally, a tiny blood vessel bursts underneath it, flooding the surrounding area with blood. It looks creepy — or, depending on your perspective, zombie-cool — but it's almost always harmless and heals in about a week. Most of the time, a cause is never determined, but can be from violent coughing, sneezing, vomiting or even a set of overzealous squats.

3. CORRECT ANSWER: D
Despite the vermicular vernacular, **ringworm** isn't a worm, but a fungus, closely related to the fungi behind athlete's foot and jock itch. It's also one of the more widespread zoonotic diseases — those which can be passed from animal to human — and dogs are common carriers. In most cases, it's easy to treat: You simply apply antifungal cream to the affected area until it's gone. Get it from your pharmacist and vet.

4. CORRECT ANSWER: B
More specifically, paralytic **polio**, the version that put many children of previous generations in iron lungs and wheelchairs. Although the last naturally occurring case of polio in the U.S. was in 1979, the disease remains either endemic or present in other parts of the world; such places as Afghanistan, Pakistan and Nigeria. Also, since late 2012, at least 20 cases of a mysterious polio-like illness have been seen in children in California. The disease, which shares many features with polio, including permanent loss of muscle function, still hasn't been identified.

5. CORRECT ANSWER: C
You may remember an **abdominal aortic aneurysm** as the killer of actor John Ritter. Men, especially those with a smoking history, have a much-increased risk for this ballooning of the aorta as it runs through the abdomen. An ultrasound exam for those older than 60 screens for its presence. Caught early, it's eminently treatable; if it ruptures, it's almost impossible to survive.

6. CORRECT ANSWER: D
Gout used to be known as the rich man's disease because it generally affected men who could afford overindulgent lifestyles full of booze and fatty foods. But these days, it doesn't check the contents of your wallet before it decides to hobble your stride. It's a complex and separate type of arthritis that usually strikes men. It's caused by an overabundance of uric acid in the blood, which forms sharp, pain-causing crystals that build up in joints. Treatment can come from a host of drugs, as well as such lifestyle changes as avoiding alcohol and decreasing meat intake.

7. CORRECT ANSWER: A
Iron deficiency anemia causes big and widespread problems. Your body needs iron to produce hemoglobin, and your body needs hemoglobin to transport oxygen throughout it. With anemia, it's basically as if every function in your body is slowly suffocating. It can be caused by a bleed somewhere in your body, say from an ulcer, a uterine fibroid or a colon polyp. Or it can be caused by a lack of iron in your diet or an inability to absorb iron. Treatment typically involves taking iron supplements, identifying the cause and other remedies based on the particular cause.

8. CORRECT ANSWER: B
The early signs of **meningitis** are often confused with the flu, delaying the immediate treatment that's needed to avoid shock, seizures, brain damage, even death. The key differences to look for are the unusual headache, neck pain, extreme drowsiness making it difficult to even wake up and the sensitivity to light. Seek medical help right away.

9. CORRECT ANSWER: B
Lyme disease often goes undiagnosed and untreated for long periods of time, even years. By then it has had a chance to do some real damage, including arthritis, cognitive problems or Lyme carditis, a potentially fatal infection of the heart. The problem with the tick-borne disease is that its temporary telltale rash around the bite is often missed if it's on the scalp or someplace else difficult to see. And the rest of the symptoms are vague enough to be confused with other conditions. If you have any of the related symptoms, get to your doctor as soon as possible and ask for the blood tests to rule Lyme in or out. A round of antibiotics, especially when taken in the early stages of infection, can cure many cases, although some people may need a longer course of treatment.

10. CORRECT ANSWER: D
Before the toe-tapping wait for lines to show up on a test stick, there are numerous unusual early signs of **pregnancy**. These are only a few of the lesser-known ones — well, lesser known to men, anyway. Women also report, "just knowing," even though they can't explain how or why.

SCORING

Give yourself one point for every correct answer.

A perfect 10: You're an avid reader of *Discover*'s Vital Signs column, or you've had medical training. Either way, well done.

8-9: Smart, really smart. Can we be your friend?

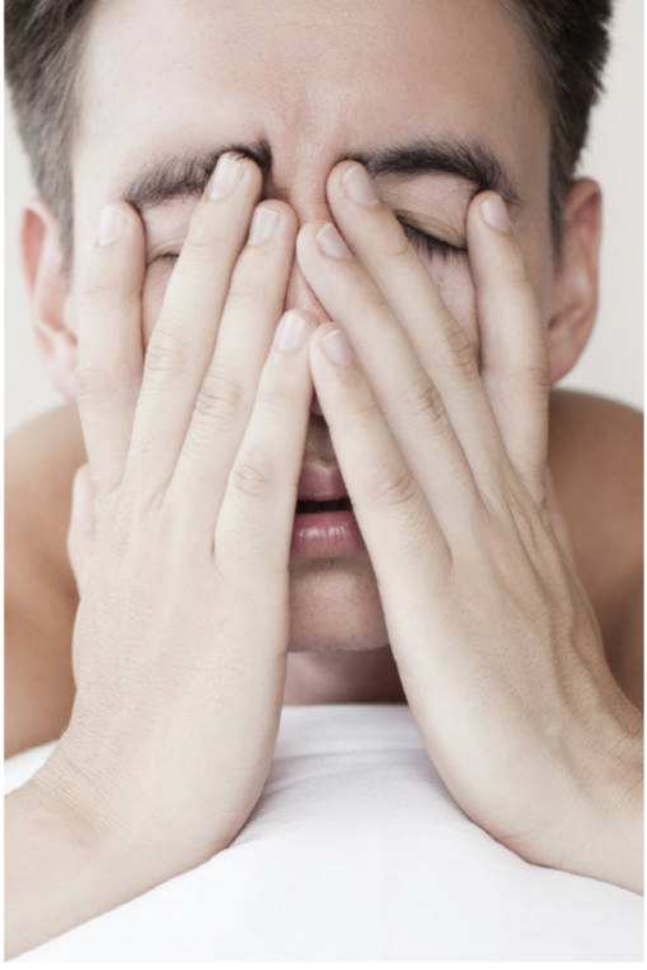
6-7: Above your average bear, which would be better if this were a veterinary medicine quiz.

4-5: You know a bit. Just enough to be dangerous.

3 or below: Don't touch us; not even in an emergency.

Normal Fatigue? Hardly

A YOUNG DOCTOR'S COMPLAINT SEEMED STRAIGHTFORWARD, BUT FINDING THE CAUSE WAS ANYTHING BUT.



BY **H. LEE KAGAN**

It was the end of August when Thad returned from his Caribbean honeymoon, sporting a rich tan and a look of contentment. But as he sat in my exam room, he complained to me that he felt tired. "Tired after a honeymoon?" I said. "Sounds about right."

"No, it's not that," he said with a smile. "This is not like any kind of tired I've felt before." Healthy and fit his entire life, Thad was a young physician about to begin his orthopedic specialty training. I trusted him to be an accurate observer, and so I inquired about other possible symptoms he might have had. Then I examined him for evidence of conditions that can cause fatigue, like anemia. All was in order, I reassured him, but just to be certain, I drew some blood for screening tests.

Two days later, the lab reported that all the results were normal save one: Thad's level of thyroid hormone was low. Now his symptoms made sense. The thyroid gland, sitting low along the front of the throat, manufactures the hormone and releases it into the bloodstream, which carries it throughout the body to play a critical regulatory — mostly stimulatory — role in almost all body functions. When there isn't enough of the hormone, things generally slow down, including metabolism. Weight may go up, mental activity may get sluggish, and fatigue may develop. Though not common in 20-somethings, hypothyroidism can occur at almost any age.

In the United States, the most common reason for a drop in thyroid hormone production is autoimmune thyroiditis, an attack on the thyroid gland by the body's own defense mechanisms. Normally our finely tuned immune system fends off only foreign material, like microbes, and leaves the body's own tissues alone. But for reasons that are not well understood, the immune cells will sometimes attack a normal organ, gradually destroying it and turning it into useless scar tissue. The treatment for chronic thyroiditis is to replace the missing hormone with pills taken daily.

Thad was relieved that we had found an explanation for his persistent fatigue. He began taking the replacement thyroid hormone, confident that he would soon see his energy restored. He knew that thousands of people take thyroid hormone every day and live perfectly normal lives. But when I next heard from Thad, he told me that he was still tired. It had been four months since we last spoke.

He said he had been too busy since then to return for a check of his hormone levels. Could it be that the dose I had prescribed for him was too low? I arranged for Thad to have a repeat blood test, which soon confirmed that his thyroid hormone blood levels were perfectly normal. The replacement dose was just right — but Thad wasn't. Something other than hypothyroidism was causing him to feel unwell.

Fatigue is a singularly nonspecific symptom; the list of possible causes is one of the longest in all of medicine, ranging from malignancies, infected heart valves and anemia to just plain lack of sleep. Consequently, when a patient's sole

KIEFERPIX/ISTOCK

complaint is tiredness, the underlying cause can be elusive. In dealing with such a case, I often repeat to myself what I have told my medical students countless times over the years: When the history points nowhere, you have to look everywhere. Thad's history and physical exam would need to be revisited with a fresh eye. I called and asked him to return to the office for another evaluation.

At the follow-up visit, it was immediately apparent that Thad had lost weight. Not even his tan could hide the fact that something was amiss. A glance at the vital signs in the chart confirmed that this previously healthy young man had dropped nearly 10 pounds in four months. My level of concern rose. I began working my way through a long list of questions. Though it is tedious and time-consuming, the systematic review of symptoms is a staple of the diagnostician's armamentarium that more often than not yields important clues. Yet this time nothing new emerged, apart from the fact that Thad had lost not only his energy and some weight, but also his appetite. I sat back and looked at my patient, mentally searching myriad diagnoses for ones that fit this clinical picture.

It was then that I finally saw it — saw what I had been staring at all along. Sitting across from me was a man who, four months after returning from the Caribbean, was as bronzed as the day he'd come home. And no, I quickly ascertained, he had not been visiting a tanning salon. Appetite, weight, energy — all were diminished. The one thing my patient had not lost was his tan. Why?

Apart from his pigmentation, Thad's only other noteworthy physical finding was a low-normal blood pressure. When I asked him to rise from a lying to a standing position, his blood pressure fell to a seriously low level, low enough to cause light-headedness and even fainting in most people. But Thad said he felt none of this. "He's young and fit," I told myself, "and the problem has come on gradually. His system's been able to adapt." But what was the problem?

By now I was reasonably sure that I had enough pieces to put the puzzle together. Fatigue, hypotension (low blood pressure) with postural changes, loss of appetite with accompanying weight loss, and hyperpigmentation all fit with a diagnosis of Addison's disease, a disorder of the adrenal glands that results in lack of cortisol, a vital hormone produced by the gland's outer layer. It is one of the body's steroid hormones, essential to mounting the fight-or-flight response to serious stress or trauma as well as the day-to-day regulation of numerous physiological functions.

When the body senses that the paired adrenal glands — one lying atop each kidney — are failing to produce sufficient cortisol, the brain sends a chemical signal to prompt the glands to make more. Oddly enough, that same signal also triggers special cells in the skin to generate more melanin, or skin pigment, causing hyperpigmentation. The coloration can look just like a tan — albeit one that darkens the skin bodywide, even the palms and armpits. My patient's honeymoon tan had transformed into the classic pigmentation of Addison's disease.

New blood tests confirmed that Thad's cortisol levels were quite low. They also revealed disturbances of his body's electrolyte (mineral) concentrations and water regulation. These, too, are part of the Addisonian picture, a result of low levels of another adrenal hormone called aldosterone. I immediately prescribed replacement steroids for Thad to take. Confirmatory tests would have to be done, but it was imperative that replacement steroids be started right away. Left untreated, adrenal insufficiency can lead to an "Addisonian crisis," a serious and sometimes fatal condition brought on by emotional or physical stress. It is not for nothing that cortisol is often called the stress hormone.

FATIGUE IS A SINGULARLY NONSPECIFIC SYMPTOM; THE LIST OF POSSIBLE CAUSES IS ONE OF THE LONGEST IN ALL OF MEDICINE, FROM MALIGNANCIES TO ANEMIA TO JUST PLAIN LACK OF SLEEP.

In the developing world, infections like tuberculosis are the leading cause of adrenal insufficiency. But in the United States, Addison's most commonly results from an autoimmune disorder.

Autoimmunity: There it was again. Looking at the bigger picture, I saw that Thad had now sustained two separate glandular failures due to immune malfunction: his thyroid and his adrenals. In fact, he was manifesting the features of a rare disorder known as Schmidt's syndrome, a type of malfunction of the immune system called autoimmune polyglandular syndrome, or APS. It is not only the thyroid and adrenal glands that are at risk in APS; the syndrome can affect the pancreas, which produces insulin (the lack of which is found in diabetes), and the testes and ovaries, which produce the hormones necessary for normal sexual development and function. No one knows the underlying cause of this disorder or why it has a predilection for endocrine tissue. And no one knows how to shut off the process once it starts.

Like John F. Kennedy, that most famous of people with Addison's, Thad would need to be on replacement hormones for the rest of his life. He would also have to remain vigilant for additional glandular insufficiency. But I was happy to be able to remind my young colleague that so long as he remained on the hormone substitutes I had prescribed, there was no reason why he should not be able to live a full, essentially normal life. Though he would regain his energy, his appetite and his weight, there was one thing he would lose. His tan, I assured him, would fade once his adrenal stimulatory signal was properly regulated. It was a small price to pay. **MM**

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14 TOOLS THAT CHANGED MEDICINE

WE SHAPED THE INSTRUMENTS. THEN THEY SHAPED US.

BY **CHRISTIAN MILLMAN**

In the earliest days of medicine, people needed a trip to the doctor like a hole in the head. Because that's exactly what they got: Healers and witch doctors were downright wanton in their use of trepanning — the practice of sharpening a stone to cut away a section of skull in fully conscious patients. Trepanning was done to relieve headaches, remove fractured skull fragments, provide spirits with an easy entrance or escape, sometimes just to provide rondelles — the leftover bony disks valued as charms or talismans.

At 7,000 years old, the stone trephine is considered the earliest surgical tool, but it's not its antiquity that makes it important; it's how the concept has remained relevant from the Neolithic to the now. Modern neurosurgeons don't dangle rondelles around their necks, but they do still remove sections of skull.

The procedure, now called a craniotomy, is used to relieve pressure on a swelling brain, or grant access to a stroke victim's hemorrhaging blood vessel, among others.

Although the trephine was the first tool to transform medicine, it was far from the last. Here, in no particular order, are 14 others carrying on in that heady tradition.

SKRYL SERGEY/SHUTTERSTOCK

Hypodermic Needle

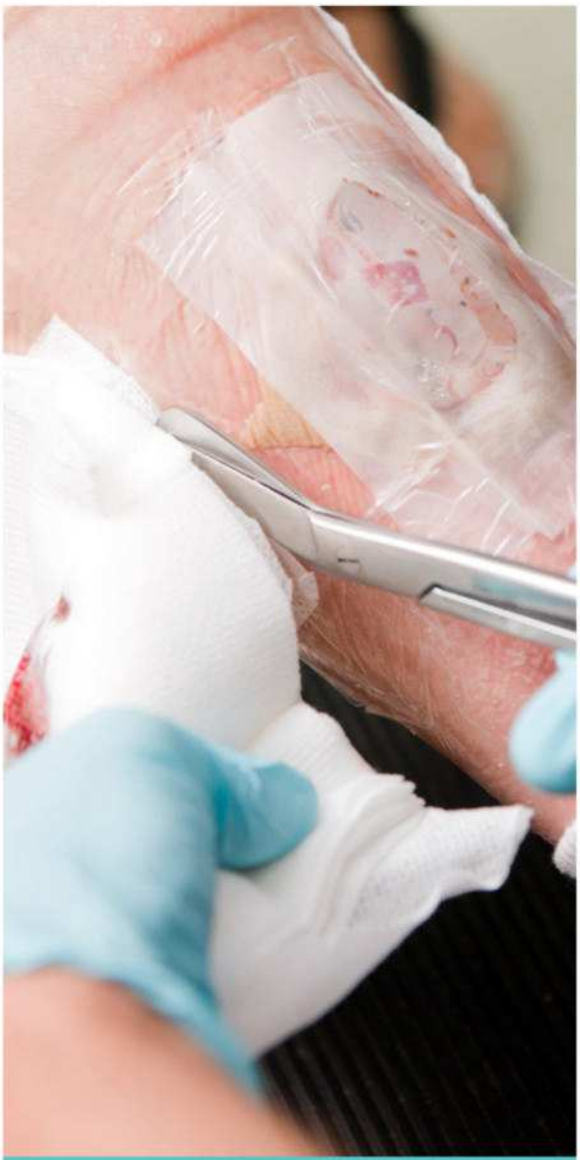
Physicians have wanted direct access to the bloodstream for a very long time. In 1492, as Columbus sailed the ocean blue, Pope Innocent VIII was on very a different path: He had an apoplectic stroke that year that left him in a coma. In an attempt to resuscitate him with an infusion of fresh blood, his physician cut open the veins of three healthy boys, then those of the pontiff, and stitched them all together. All four died from his macramé transfusion method.

Over the following centuries, various other attempts at intravenous infusion — including one involving a quill and pig's bladder — met with similar results. It wasn't until 1844 that an Irish physician named Francis Rynd developed a hollow needle fine enough to both pierce skin and administer or extract fluids. By 1853, other doctors had added glass, a steel tube and a plunger to Rynd's needle to create essentially the same hypodermic syringe we know today.

Absolutely everything in medicine changed. In a flash, needles outpaced all bartenders ever born for providing therapeutic shots. Today, they're used for about 20 billion injections each year of such essential compounds as antibiotics, morphine, vaccines, anesthetics, anti-coagulants and insulin. And that's just the legal stuff.

REMEDY FOR A WRONG: SHOT PAIN

For most people, being needled stinks. Here's something nifty that might make it stink less: the cough trick. You simply cough once as the injection site is being prepped, then cough once again during the puncture. Studies show it reduces discomfort significantly, although no one knows exactly why.



Maggots

There's nothing in the tool rule book that says medical instruments can't be alive. The Maya and Australian Aboriginals were among the first to realize this. They tightly tamped wounds with maggots, knowing the off-white wigglers would feast on infected and necrotized tissue. In more recent history, doctors in the Civil War, World War I and World War II all used maggots to treat infected wounds.

But the larval marvels haven't been consigned to the history books: Today, more than 800 U.S. health care centers have used medical maggots on patients. The immature flies are creating buzz as an important option for treating open wounds that won't heal, caused by methicillin-resistant *Staphylococcus aureus* (the MRSA superbug), diabetic foot ulcers, flesh-eating disease and others.

Stethoscope

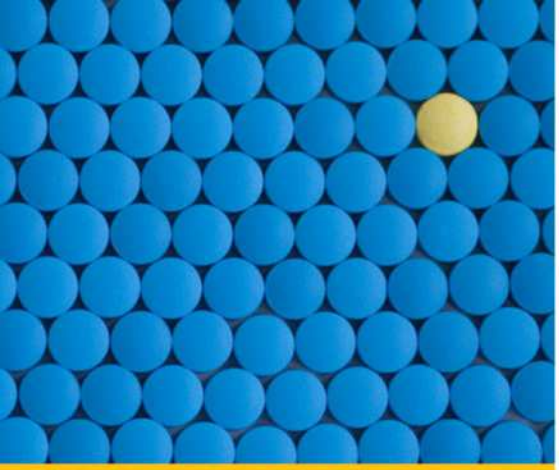
Rene Laennec, a French physician, learned to tap on a patient's chest to diagnose pulmonary and cardiac conditions from none other than Napoleon Bonaparte's personal physician. But, like talking through a tin can telephone, it had auditory limitations. So Laennec took a more direct route: putting his ear directly on a patient's chest to learn the difference between normal and abnormal heart and lung sounds.

This, too, had its drawbacks. It was difficult to hear clearly through the chests of his chubbier patients. Also, the social mores of the early 1800s made his head's presence on the chest of a female patient awkward at best, highly objectionable at worst. To better deal with the plump and the priggish, he fashioned the first crude stethoscope in 1816. It was so quickly embraced and improved upon that, by the 1850s, its ubiquitous presence around doctors' necks made it the emblem of medical authority.

There's good reason they're kept so immediately at hand: Stethoscopes are used constantly to pick up such things as irregular heartbeats, abnormal blood pressure, problems with lung function, diminished flow in veins and arteries, and worrisome silence in the bowels. They can even quickly diagnose an enlarged liver.

Medical historian Jacalyn Duffin at Queen's University in Ontario argues the stethoscope's invention redefined medicine itself, changing much of it from vague shrugs and symptoms to specific pathologies. What was previously just a cough, for example, suddenly became tuberculosis due to the diagnostic power of the stethoscope, accompanied by new and increasingly effective treatments.

FROM LEFT: KAREN MOWER/GETTY IMAGES; FRANNYANNE/SHUTTERSTOCK; CONNECTION ONE/ALAMY; UK ALAN KING/ALAMY



Randomized Controlled Trial

In 2013, the London-based Medical Research Council, one the world's leading organizations for funding medical research, polled a group of physicians and leading thinkers as a way to mark its 100th anniversary. The question: What medical advance from the past century has made the greatest impact?

One particular answer came up multiple times — and it was surprising in that it was a tool, not a treatment: the randomized controlled trial. An RCT randomly assigns medical study participants into an experimental group or a control group.

Sir Simon Wessely, chair of Psychological Medicine at the Institute of Psychiatry at King's College London, explained it this way: "It allows us to evaluate properly all the other discoveries and advances." In other words, RCTs show us what works — and, just as importantly, what *doesn't* work.

Amputation Kit

As weaponry has advanced over the long course of human warfare, so too has the magnitude of injuries they cause on the battlefield. Often called the first modern war because of its devastating new weapons, the American Civil War from 1861 to 1865 set a new standard for its sobering ability to inflict complex wounds in unparalleled numbers.

New rifles extended the range of a volley from the 50 to 100 yards of musket fire to more than 500 yards, with much-increased accuracy. Those rifles also fired newly invented minié balls, soft lead bullets that could shatter 2 to 3 inches of bone and embed such debris as filthy clothing into the wound, creating an extremely high infection rate. And with the discovery of penicillin more than 60 years away, soldiers died from infected wounds far more than from anything else.

The amputation saw had been around in one form or another since at least Roman times, when Aulus Cornelius Celsus, a Roman medical writer, described an amputation technique using a scalpel and bone saw. But it was the Civil War that turned amputation kits from little-used medical curiosities into indispensable life-saving tools.

Amputations, even in the unsanitary and rudimentary conditions of the time, turned complex injuries into simple ones by changing untreatable tattered wounds into manageable stumps. And there were more than 60,000 of them done — making up about three-quarters of all surgeries performed — saving more lives than any other wartime medical procedure.

All it took was a few minutes, a restraint team and a surgeon with an amputation kit containing scalpels, tenaculums to pull out and tie off arteries, and bone saws. Limbs were generally thrown into piles off to the side. One exception was that of the amputated right leg of Maj. Gen. Daniel Sickles, a Union commander struck by a 12-pound cannonball. He packaged it up in a small box and sent it to the Army Medical Museum with a card reading, "With the compliments of Major General D.E.S." For years afterward, he visited his leg on the anniversary of its amputation.

MEDICAL LORE: A LEG TO STAND ON

The innovations in ordnance that led to such frequent Civil War amputations also led to innovation in another field: prosthetic limbs. Several new kinds of braces, articulated artificial legs and prosthetic arms with various grasping devices all were developed for Civil War amputees. Much of this work was done at South Street Hospital in Philadelphia, earning it the nickname "Stump Hospital."

Dialysis Machine

The ability to artificially maintain the function of a failing organ didn't begin with the first kidney dialysis machine. Tools such as the iron lung saved thousands of polio victims' lives when the disease caused respiratory failure.

But it was the invention of the first practical dialysis machine in the 1940s that showed doctors could replace the function of even the most complex organs almost indefinitely. Compared to the relatively simple lung, a kidney's function is remarkably complex. And the iron lung, as well as its predecessor, the ventilator, are downright elementary in design compared with the large number of technologies that converge in a modern dialysis machine.

Most importantly, though, is the impact of dialysis. Over 430,000 Americans currently receive lifesaving dialysis, an increase of 57 percent since 2000, making it the most common organ replacement therapy device in use.

Condom

The earliest evidence of condoms is found in a 12,000-year-old cave painting in Europe. Rubbers bounced around for the next few thousand years as a form of birth control, but it was only in 1494 that they truly became a medical device of extraordinary importance.

A massive outbreak of syphilis began in Europe, and soon spread to Asia, decimating the infected: "Its pustules often covered the body from the head to the knees, caused flesh to fall off people's faces, and led to death within a few months," according to one description.

Condom usage to prevent disease had begun in earnest. The first versions used such materials as oiled linen and silk, sheep intestines, goat bladders and thin sheaths of leather. It took until 1855 for the first rubber prophylactics to come on the market, using Charles Goodyear's recently invented vulcanization process. Modern latex versions arrived in the 1920s.

As a transformative medical device, few can claim a role of such enormity as the condom in giving doctors a tool for preventing the scourges of STDs. For example, a report by the National Institutes of Health showed that correct and consistent use of condoms cuts the risk of contracting an HIV infection by 85 percent. Equally impressive numbers apply to chlamydia, syphilis, herpes, gonorrhea and others.

NON-MEDICINAL USE: BRING PROTECTION

Latex condoms are a very useful addition to any wilderness survival kit. They can carry up to a gallon of fresh water. (Transport carefully; the slightest nick pops them.) Latex condoms also make great fire starters: They're highly flammable, light easily and burn for over a minute. Or use them to sheath matches, cell phones, or other moisture-sensitive items.

Transorbital Lobotomy Orbitoclast

Two things warrant the inclusion of the transorbital lobotomy orbitoclast on any list of tools that most changed medicine: what it did and what it spawned.

Invented in 1946 by Walter Freeman, an American physicist, as a faster, easier way to perform a lobotomy, the orbitoclast was controversial from the start. Lobotomies surgically destroy connections and tissues in the brain's prefrontal cortex to treat depression, panic disorders, schizophrenia and other manias.

Many in medicine already viewed lobotomies as barbaric. And Freeman's orbitoclast made the procedure quick and easy. He would simply lift the upper eyelid away from the eyeball, insert the sharp point of the orbitoclast (essentially a modified ice pick), hammer it through the back of the socket, and pull it back and forth. The patients, sedated but still conscious, were usually sent home with sunglasses to hide any bruising.

The medical advance of the orbitoclast was unquestionable. It turned what had been major brain surgery into an outpatient procedure. Freeman, a fervent evangelizer of his invention, personally performed over 4,000 of the 60,000 lobotomies done in the U.S. and Europe between 1936 and 1956. One study showed that 63 percent of lobotomized patients saw improved symptoms, 23 percent had no improvement, and another 14 percent got worse or died. But the horror of the procedure was too much to allow that many neutral or negative results.

By the 1950s, the medical community and the general public wanted options. This is how the orbitoclast changed medicine again: It led to a search for options, spurring the psychiatric community to develop psychoactive drugs and new talk therapies.

Chlorpromazine to treat schizophrenia became available in the U.S. in 1955. The antipsychotic Haloperidol followed in the 1960s, marking the first wave in drug therapy.

Freeman used his cherished orbitoclast for the last time in 1967 on a longtime patient — a woman he had already twice lobotomized. She died of a cerebral hemorrhage, and he was banned from further operations.

FROM LEFT: SCIENCE PHOTO LIBRARY/ALAMY; STOCKBYTE/GETTY IMAGES; BRIAN KUBASCO/MUSEUM ODDITIES

Permanent Marker

Wrong-site surgeries happen a lot — researchers estimate about 20 times a week in the United States alone. That can lead to such disasters as a healthy breast being removed instead of a diseased one, or the wrong knee getting turned into titanium.

Fortunately, the Sharpie is mightier than the scalpel. "Wrong-site surgery is preventable by having the surgeon … place his or her initials on the operative site using a permanent marking pen prior to the patient being moved to the location of the procedure and then operating through or adjacent to his or her initials," says the American Academy of Orthopaedic Surgeons. One study estimated this simple scrawl could eliminate about 62 percent of wrong-site surgeries.

Toothbrush

More than 7,000 years ago, Sumerians laid the blame for dental decay at the feet of tooth worms (or, if you want to be anatomically accurate, the paired setae of tooth worms). Ever since, a series of teeth-cleaning methods came into sporadically popular use, including twigs with frayed ends, toothpicks, handles with boar bristles and the intoxicating practice of cleaning teeth with a sponge soaked in brandy.

Despite all this creativity, the main function of dentists and their surrogates over the centuries was to pull out the rotten teeth and, occasionally, replace them with false ones.

Then, in 1938, the company now called DuPont introduced Dr. West's Miracle-Tuft toothbrush, the type of nylon-bristled brush you hold in your hand every day. And the toothbrush as a device that changed the course of medicine was born.

Soldiers in World War II used the newly cheap and effective brushes with regimented fervor and became aseptic ambassadors of oral hygiene upon their return to home shores. As a result, we now live in an age where people are keeping their teeth longer than ever before.

And that matters much more than for looking spiffy in a selfie. A burgeoning body of research shows a healthy mouth means a longer and better life. One recent study, which followed 5,611 older adults in California for nine years, found that never brushing at night increased the risk of death by 20 to 35 percent. Not flossing meant a 30 percent higher chance of dying during the study period. Losing all teeth, even if replaced with dentures, also gave a 30 percent higher risk. And the best way to avoid these brushes with death is through regular visits to Dr. West or his many descendants.

FROM LEFT: ALTRENDO IMAGES/GETTY IMAGES; QVIST/SHUTTERSTOCK; SCOTT KOCHSIEK/GETTY IMAGES

Ambulance

The first ambulances, created by Anglo-Saxons in A.D. 900, were simple in both purpose and design. The purpose was patient transport. The design was a hammock combined with a cart. The ambulance as a vehicle of change didn't begin to get real traction until 1952, and it took the horrific Harrow and Wealdstone rail crash, England's most catastrophic rail accident, to make it happen.

Public outrage was intense when people learned many of the 112 dead could have survived with faster treatment. In response, ambulances began shifting into a new role of mobile hospital.

Governments around the world began experimenting with the new heals-on-wheels model. In 1968, when the city of Jacksonville, Fla., implemented its first ambulance service capable of both on-site and in-transit emergency care, the effect was dramatic. Within three years, those who initially survived a car crash but then died from those injuries dropped by 24 percent.

Now called emergency medical services, or EMS, the training, methods and machines have continued to evolve. For example, one study showed that when helicopters staffed with a doctor and nurse transported trauma victims to a hospital, mortality was cut in half.

Defibrillator

The idea of restarting stopped hearts with electricity had been kicking around in medical circles since the 18th century, and even showed up as a way to animate the monster in Mary Shelley's 1818 publication of *Frankenstein*. But it took until 1899 for two University of Geneva physiologists to demonstrate it on some unlucky Swiss dogs, whose exposed hearts were both stopped and restarted with shocks.

A 14-year-old patient of Claude Beck, a pioneering heart surgeon at Case Western Reserve University in Cleveland, fared a whole lot better. In 1947, the boy was the first human to be successfully revived with a defibrillator, one Beck designed.

Much has improved since those early days of the spread-sternum jump-and-jolt. By the 1950s, paddle electrodes provided shocks through the chest wall. In the 1960s, the units became portable enough to begin showing up in ambulances. By the early 1990s, ever-smaller automated external defibrillators (AEDs) were in police cars.

Today, millions of no-experience-necessary AEDs are publicly available, with 200,000 more being added each year in such locations as workplaces, airports, schools, shopping malls and churches. There are even $1,500 models for home use. The sophisticated devices actually talk people through the process of using them. And what a difference they're making.

Studies show that if a bystander promptly uses an AED on someone in cardiac arrest, the chances of surviving doubles or triples. Now that's a shock.

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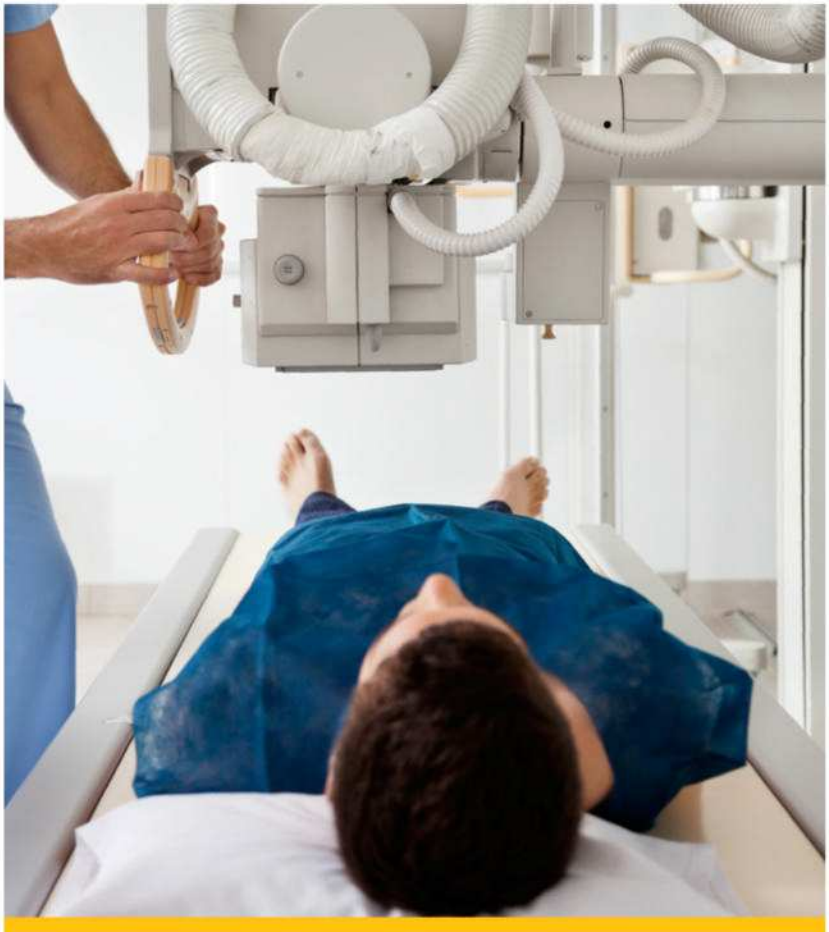


Medical Imaging

If stethoscopes transformed doctors' ability to make diagnoses by the mere fact of listening to your innards, imagine the exponential advantage medical imaging provides by letting them see *inside* you.

Begat by Wilhelm Röntgen's accidental yet Nobel Prize-winning discovery of the X-ray in 1895, medical imaging progressed to the first diagnostic ultrasounds of the 1940s, and then on to today's sophisticated 3-D imaging from computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).

It's hard to overstate the impact these machines have had on patients: earlier diagnoses, faster and better treatment and a vastly reduced need for exploratory surgery. For example, exploratory surgeries to try to diagnose abdominal problems declined from 85,000 operations in 1993 to around 35,000 by 2006. That 60 percent reduction was echoed in exploratory lung surgeries over the same period.

MEDICAL LORE: MRI MISSILES

MRI machines contain massively powerful magnets, and rare accidents happen, including one in which a nearby oxygen canister turned into a missile and killed a child. But problems most often arise because of incomplete info given by the patient. The most common injury is a burn, caused by the supermagnets heating metals in such things as drug delivery patches containing foil, safety pins, hair clips, tattoos with iron oxide pigment and wires built into insulin pumps and some pacemakers. Be absolutely honest with MRI technicians about any additions to your body, whether or not you think it's metallic.

Band-Aids

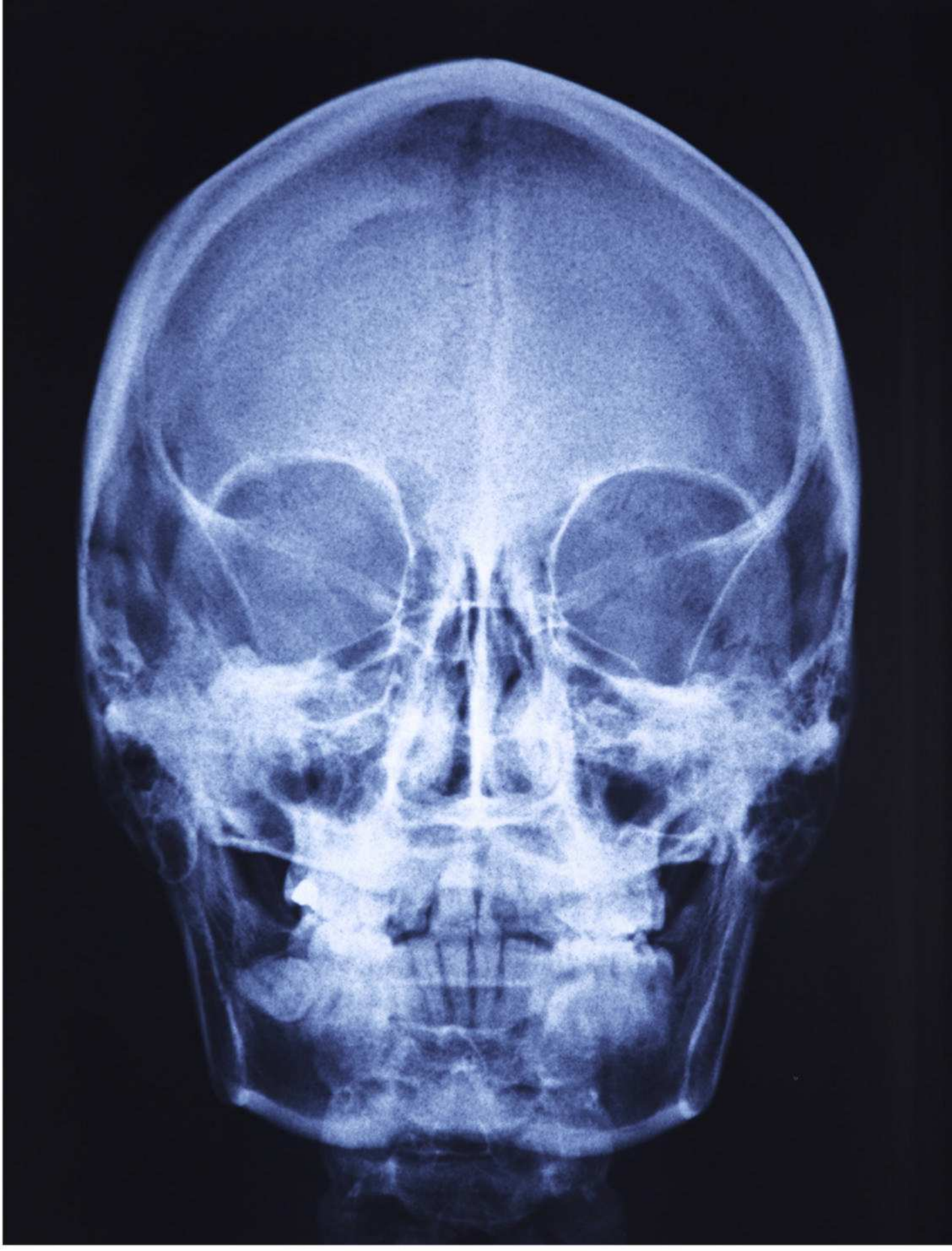
It may seem odd to consider anything adorned with Rugrats or Spider-Man as a medicine-changing tool, but don't make the mistake of dismissing Band-Aids simply because they can be cute. Huge numbers of people see the world's first self-adhesive bandages not just as temporary fixes but, rather, a device helping put the care into health care.

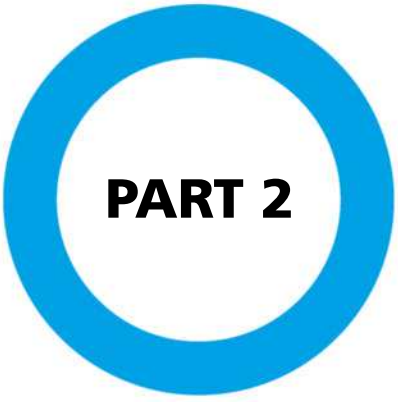
A caring cotton buyer for Johnson & Johnson (Band-Aids' maker) invented them in 1920 so he could tend to the many cuts and minor burns his beloved and accident-prone wife got while cooking and keeping house.

By 1942, millions of Johnson & Johnson's adhesive bandages accompanied World War II soldiers overseas. In 1963, Mercury astronauts took them into space. Back here on Earth, Band-Aids became the go-to therapy for parents wanting to make boo-boos better.

They act as medals for bravery in the face of inoculations, they hide the tear-inducing sight of a skinned knee, and they actually do help minor wounds heal better with fewer scars and infections. Turns out, we really are stuck on Band-Aids. By 2001, the number manufactured had rocketed past 100 billion.

FROM LEFT: STÍGUR KARLSSON/GETTY IMAGES; TYLER OLSON/SHUTTERSTOCK; SPWIDOFF/SHUTTERSTOCK





The Strange Case of...

Take a walk on medicine's weird and wild side as we explore some of the most unusual medical cases of these doctors' careers and review some startling medical experiments that yielded positive and lasting results. Then get acquainted with your own medical history to see what mysteries may lurk there.

GUALTIERO BOFFI/SHUTTERSTOCK

Confusion Reigns

AN OLD *DISCOVER* ARTICLE HELPS SOLVE THE MYSTERY OF HIS STRANGE ALTERED STATES.

BY **TONY DAJER**

I sensed a commotion rippling across the emergency room. Near the entrance, a man sporting a surgical mask and pajamas was pacing like a tethered ferret. It was 2 a.m., but as a rule most patients don't wear their PJ's to the ER. Something was strange about this one. Heading over, I watched as Claudia, the intake nurse, tried to coax him into the triage chair. He sat for a moment, stood up, then plopped back down.

"I need to see your expert," he spat out. "I have to do this quickly."

"Do what, sir?" Claudia asked.

The patient sprang up. "I can't feel my legs. I can't breathe. Where's your expert?"

His wife walked calmly over from the registration desk.

"John was hospitalized uptown four days ago," she told me. "It started then just like it did tonight, with a headache and confusion."

The spinal tap done uptown had shown a high white blood cell count, indicative of infection, but all the cultures were negative. John had stayed in the ICU and gotten better overnight — a surprise for the uptown staff, who then diagnosed viral meningitis. (Meningitis is an inflammation of the meninges, or lining of the brain and spinal cord, usually caused by bacteria or a virus. Bacterial meningitis can be life threatening, but viral meningitis usually acts more like a passing flu.) In line with that diagnosis, they'd sent John home.

"Yet just before bed tonight he had a headache, then woke up babbling again," his wife explained.

Now I turned to the patient himself. John looked about 40. He stared at me with a vacant, intense glare that reminded me of someone high on angel dust. The disturbing gaze cinched my first impression: This patient was suffering from altered mental states, the catchall term for "malfunctioning brain." That meant his brain could indeed be under siege by a virus resulting in meningitis; the inflammation and any associated virus causing his confusion could have gone away without treatment. But there was no explanation for why it had returned. What had they missed uptown?

I glanced at John's vital signs. Blood pressure, pulse, breathing rate and temperature were all normal. That was interesting. Viral meningitis usually causes a fever and accelerated heart rate.

I turned to the patient again. "What happened tonight, sir?"

"It's all right, darling," the wife said soothingly. "This is no worse than last time."

"No fever, vomiting or new medications?" I asked. She shook her head.

"I can't stay," John said in a rush. "We have to go."

"First, can I make sure you're OK?" I pleaded. "It really would be better if you stayed," I said in my softest please-don't-make-me-tie-you-down voice.

"See? The doctor is very nice," the wife implored.

"How about we get you in a comfortable room?" I offered. "It has a TV."

My first-year student, Stacy, materialized; she was there voluntarily, her idea of fun being an overnight in the ER.

Together we shepherded John into a room. We had to move quickly; altered mental status in an otherwise healthy patient mandates a head CT scan to rule out bleeds and tumors and a spinal tap to check for meningitis and encephalitis (inflammation of the brain).

John, surgical mask still in place, kept popping out of the room. "What are you going to do?" he demanded. "I need the expert. A neurologist!"

His wife laid her hand on his arm. He stopped talking and calmed down. I told him we would be running tests, but in light of the mega workup he'd gotten uptown, I questioned whether they would show much at all. The safest approach lay straight up the middle: First rule out immediate life-threatening things, then rethink.

"OK," I told Stacy. "Go in there and get more detail. Fever? Headache? Nightmares? Travel? Hearing voices? The weirdest part is how he got better, then bang, bad again. I'm counting on ya, kid."

For a few minutes, all was calm. Then Stacy came trotting out of the room.

"Dr. Dajer, can he have water and an Advil? He has a headache."

"Sure," I started saying. Then I stopped.

Advil?

In a Vital Signs column in *Discover* magazine published 20 years ago, an infectious-disease physician had described the conundrum of a young woman with recurrent meningitis. Hospitalized four times in a matter of months, the patient

exhibited high fevers, delirium and a stiff neck — all signs of life-threatening bacterial, septic meningitis. CT scans were normal. Spinal taps revealed high white cell counts in the cerebrospinal fluid — usually a harbinger of severe infection — but bacterial and viral cultures grew nothing. The patient was becoming ill and then abruptly getting better. The fourth time, to general eye-rolling, a medical student was tasked with asking the woman for the umpteenth time whether she had taken anything, *anything*, prior to getting sick. He hit pay dirt: Advil.

The patient hadn't considered over-the-counter, everyday Advil a medication. It is also sold as Rufen or Motrin, and the chemical moniker is ibuprofen. Ubiquitous as this drug is, until reading the article I hadn't known that in rare cases it can cause meningitis.

Case reports are the lifeblood of diagnosis. The dry, reductionist, what-percent-have-cough and what-percent-have-fever lists in medical texts will put you to sleep. But good stories stick. Doctors trade odd diagnoses like baseball cards; we glean them from journals, TV and friends, stockpiling them against the next tough diagnosis.

Remembering that story — even two decades later — primed me to jump on one small clue.

"Advil!" I cried to Stacy. "Did he take any tonight before he came in?"

"Yes, when he went to bed. Three hours ago."

"How about four days ago?"

"I didn't ask."

"Well," I smiled, "let's."

John was up again, still too bright-eyed and staring, but more there.

"What are the results?" he demanded. "I require transportation home." His wife stood by warily.

"Do you remember taking any medications last time?" I asked him.

"He had a headache that night." The wife tapped her lips. "Maybe some Advil?"

I showed my cards.

"Look," I began, "I can't prove this, but I think all your symptoms are due to the Advil. The best evidence is whether you took some before each episode."

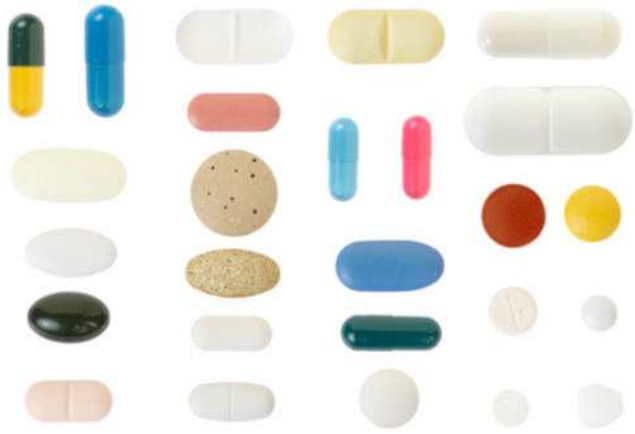
The wife's face lit up. "Yes. He definitely took some the first time. Could that really be it?"

"It's poorly understood," I said. "It's probably a hypersensitivity immune reaction. The ibuprofen may bind to specific tissues, like the meninges that line the brain, and set off an antibody attack. Most reported cases are in patients with immune disorders like lupus. But some have been in healthy people. It can happen with other anti-inflammatory drugs, like Aleve. The hallmark, besides the confusion and meningeal irritation, is that you get better quickly off the Advil."

I turned to Stacy and smiled, "Nice work, Sherlock."

She blushed. "Thanks."

To John I said, "I'm not going to scan or tap you." I crossed my arms. "I think you're OK."



ANDERSPHOTO/SHUTTERSTOCK

"You sure?" he asked.

I had an improving patient, a solid story, a negative recent workup and a very intelligent and attentive spouse. I felt it was safe to release him.

"Go home," I ventured. "Get some sleep, and I'll call you later this morning. Have your neurologists recheck everything this afternoon. What's non-negotiable is this: You come back lickety-split if anything feels worse."

Still dubious, John asked, "Can I take off the mask?"

"Yes, dear, please," his wife sighed.

Eight hours later we spoke.

"I'm better," John ventured, still hesitant. "The legs are a bit tingly, but I can walk, and the headache's gone."

A week later, his wife phoned to tell me a neurologist had decided John had a form of temporal lobe seizure. These can cause bizarre behavior but none of the muscle clenching or loss of consciousness seen in "regular" grand mal seizures.

"He started John on Keppra," she recounted, referring to a potent anti-convulsant. "But it's making him very drowsy."

John's course after discharge was as I had predicted, give or take a few vague symptoms. And diagnosis of a seizure relies heavily on patient history. There is no test that proves it. While the neurologist was trying his best to make a diagnosis based on vague, nonspecific symptoms, I was sure I had it right.

"Look," I told the wife, "every specialty has its default diagnosis. Seizures can do just about anything, but they don't cause white cells in spinal taps. I truly think John is OK. It boils down to so little data, so many competing hypotheses."

She fell silent, then said, "I'm taking him off the Keppra."

A month later, he was doing fine.

No more than 100 cases of ibuprofen-induced meningitis have been reported in the literature. But you have to wonder, given that ibuprofen is practically in the drinking water, how many more mistaken cases of "viral meningitis" are out there. **MM**

Tony Dajer *is site director of the emergency department at New York-Presbyterian/Lower Manhattan Hospital.*

Brain Got Your Tongue?

A 6-YEAR-OLD GIRL CANNOT SPEAK OUTSIDE HER HOME. IS SHE JUST SHY, OR IS SOME BIGGER PROBLEM KEEPING HER SILENT?

BY **MARK COHEN**

My medical assistant put the chart on my desk. "Your next patient is in room 5, Dr. Cohen. Her name is Taylor, and she's a cutie!"

"Thanks, Mary," I said, pulling up Taylor's medical record on my desktop computer. I glanced at the consultation request: a 6-year-old girl with a speech problem. As a developmental pediatrician, I am often called on to evaluate children's speech and language. Those are among the most complex tasks the young brain has to master, so it's no wonder many childhood disorders express themselves in those areas.

Kids with developmental delay or autism commonly show up in the pediatrician's office with a parent who simply says, "My child isn't talking."

When I opened the door to the examining room, I saw a petite girl with long, blond hair sitting very still on the exam table. She wore a purple jumper over a short-sleeved white blouse, and her hair was tied at the back with a ribbon that matched her dress. She was deeply engrossed in reading a Dr. Seuss book. She looked up at me and smiled.

"Hi," I said. "I'm Dr. Cohen. What's your name?"

The girl continued to smile, but she didn't say anything and quickly went back to her reading. Hmmm. Could just be a shy one, I thought.

I turned to her mother. "I understand your daughter is having some problems with her speech. Can you tell me what your concerns are?"

The mother was also petite and neatly dressed. She looked directly at me and said, "Well, she seems to have trouble talking."

OK, maybe I was wrong. This was probably a child with some articulation problems. "What kind of trouble?" I asked.

The young woman grimaced slightly before answering. "Well, she, uh … she doesn't talk."

Maybe I wasn't so wrong after all. Not talking is a complaint I hear from parents of children who turn out to have severe speech and language disorders. But those conditions generally declare themselves before age 6. Something was different here.

"Doesn't talk?"

"No, not at all. At least that's what her teacher says."

"Her teacher? So she doesn't talk at school?"

"Not a bit."

"What about at home?"

The girl's mother shook her head with a rueful grin. "At home I can't shut her up! She talks a mile a minute." She paused, and the grin faded. "I just don't understand it." Apparently, Taylor's pediatrician had not understood it either, but her mother had just given me the key. I was pretty sure I knew what was keeping this child quiet. Now I just needed a little more information to confirm the diagnosis.

"How about when she's somewhere else, like the mall — does she talk then?"

"No, not a peep. When she was younger, she talked all the time, and everywhere. Then when she was about 3, she started getting quiet. We would go out to eat, and she wouldn't say a word the entire time we were at the restaurant. At first we just thought she was shy and we encouraged her to talk, but she would just sit there. So we just gave up."

I turned back to the girl. "Hi, Taylor! That's a pretty dress

you have on." She looked at me with a faint smile. "I bet you like purple." Her smile broadened. "Hey, your mom is wearing a purple skirt. Is it her favorite color, too?" She nodded slightly, and then her smile faded, and a wary look came into her eyes. Realizing I had made her uncomfortable by asking a question, I quickly shifted gears. "*Green Eggs and Ham* — I read that when I was a kid. I bet you like to read." She smiled again and nodded vigorously.

"You see?" her mother asked with a worried expression. "This isn't normal, is it?"

"No, it isn't," I said. "But I think I know what's going on here and what we can do to help." Strictly speaking, Taylor didn't have a speech problem at all.

The telltale symptom was that Taylor talked perfectly well when she was at home but went silent when she was away from her familiar environment. She had a classic case of a condition called selective mutism.

I've had a handful of patients with selective mutism in my 30 years of practice, and I've seen our understanding of this condition increase dramatically over that time.

When I was in training, it was called *elective* mutism. The thought back then was that these children had been traumatized in some way, and then decided ("elected") not to talk in certain settings. In the late 1980s, speech pathologists and psychologists began to recognize that these children often demonstrated other symptoms of social anxiety and that this was the root cause of their not speaking. In 1994 the name of the disorder was changed from *elective* to *selective* mutism, emphasizing that the child was not making a conscious decision to remain silent but was actually unable to speak in certain situations.

Selective mutism is relatively rare: One study found it in less than 1 percent of children referred to mental health professionals. It is different from simple shyness. A shy child may find it uncomfortable to talk with someone she doesn't know, but she will usually manage to warm up, given time and support. A child with selective mutism truly cannot talk in some settings and will not improve over time without treatment.

Selective mutism is not a language disorder, either, since children communicate perfectly well when they are in their comfort zone. And it is completely different from autism. Although autistic children may interact more with familiar people than with strangers, they have severe problems with communication and social interaction no matter where they are. (Some children with selective mutism are mistakenly believed to be autistic by friends and family who don't see them interacting and conversing perfectly well at home.)

Selective mutism is now considered by many clinicians to be a manifestation of a type of social anxiety or social phobia. A certain amount of anxiety is useful to keep us out of dangerous situations, but in anxiety disorders, the perception of what is dangerous may be distorted.

Some researchers suggest that these disorders may be triggered by an imbalance of neurotransmitters in an area of the brain called the amygdala. The amygdala helps determine the emotional significance of things we perceive: "Uh-oh, is that somebody brandishing a knife — or just a bush moving in the wind?" Directors of horror movies are experts at manipulating this part of the brain.

Activity in the amygdala is regulated by at least three systems of brain chemicals called neurotransmitters — serotonin, norepinephrine and GABA (gamma-amino butyric acid). An excess or deficiency in any of these neurotransmitters can affect the activity level of the amygdala and thereby influence how likely we are to perceive a given situation as threatening. For a child with selective mutism, being in a situation where she has to talk to someone she doesn't know induces a feeling of terror, exactly as if she were facing genuine danger.

In addition to an imbalance in neurotransmitters, genetics, temperament, family dynamics and environmental factors may also play a role in selective mutism, according to recent research. The relative contribution of each of these factors varies from child to child.

I referred Taylor to our practice's child psychiatry department, where her treatment would include behavioral therapy aimed at decreasing social anxiety. This therapy takes advantage of the fact that the amygdala doesn't respond just to the emotional neurotransmitter systems; it also receives messages from the cortical centers of cognition and judgment, which we can influence through rational thought.

One treatment method, called cognitive behavioral therapy, helps a person to rethink a frightening situation and see it as something benign. When you can tell yourself, "Oh, that shape is just a bush, not a dangerous assailant," that message is transmitted back to the amygdala, and your level of panic drops significantly. Done repeatedly, this type of exercise can eventually help a patient overcome his or her fear of a particular situation.

Some children affected by selective mutism have such severe anxiety that in order to benefit from cognitive therapy, they may first require treatment with a medication such as fluoxetine (Prozac), which adjusts the levels of serotonin in the brain. Since there are so many factors involved in the condition, there is no one-size-fits-all treatment, but some combination of behavioral therapy and medical treatment seems to work for most children.

There are no good long-term studies of selective mutism, but I was optimistic about Taylor's prospects. Published reports indicate that most children respond well to treatment and are able to speak in public within a few months, although some of them continue to experience significant symptoms of anxiety.

Taylor had been diagnosed and referred for treatment relatively quickly. I was hopeful that within a year she would be able to stand in front of her class and read out loud from *Green Eggs and Ham*. **MM**

Mark Cohen *is a developmental pediatrician with Kaiser Permanente in Santa Clara, Calif.*

Q&A

BARRY MARSHALL

THE PHYSICIAN WHO DRANK INFECTIOUS BROTH, GAVE HIMSELF AN ULCER AND SOLVED A MEDICAL MYSTERY.

BY **PAMELA WEINTRAUB**

For years an obscure doctor hailing from Australia's hardscrabble west coast watched in horror as ulcer patients fell so ill that many had their stomach removed or bled until they died. That physician, an internist named Barry Marshall, was tormented because he knew there was a simple treatment for ulcers, which at that time afflicted 10 percent of all adults. In 1981 Marshall began working with Robin Warren, the Royal Perth Hospital pathologist who, two years earlier, discovered the gut could be overrun by hardy, corkscrew-shaped bacteria called *Helicobacter pylori*. Biopsying ulcer patients and culturing the organisms in the lab, Marshall traced not just ulcers but also stomach cancer to this gut infection. The cure, he realized, was readily available: antibiotics. But mainstream gastroenterologists were dismissive, holding on to the old idea that ulcers were caused by stress.

Unable to make his case in studies with lab mice (because *H. pylori*

Barry Marshall (right) and Robin Warren shared a Nobel for their ulcer research.

TONY ASHBY/AFP/GETTY IMAGES

affects only primates) and prohibited from experimenting on people, Marshall grew desperate. Finally he ran an experiment on the only human patient he could ethically recruit: himself. He took some *H. pylori* from the gut of an ailing patient, stirred it into a broth, and drank it. As the days passed, he developed gastritis, the precursor to an ulcer: He started vomiting, his breath began to stink, and he felt sick and exhausted. Back in the lab, he biopsied his own gut, culturing *H. pylori* and proving unequivocally that bacteria were the underlying cause of ulcers.

The man called "the guinea-pig doctor" can now talk about his work with the humor and passion of an outsider who has been vindicated. For their work on *H. pylori*, Marshall and Warren shared a 2005 Nobel Prize. Today the standard of care for an ulcer is treatment with an antibiotic. And stomach cancer — once one of the most common forms of malignancy — is almost gone from the Western world.

Having rid much of the globe of two dreaded diseases, Marshall is now turning his old enemy into an ally. As a clinical professor of microbiology at the University of Western Australia, he is working on flu vaccines delivered by brews of weakened *Helicobacter*. And in an age when many doctors dismiss unexplained conditions as "all in the head," Marshall's story serves as both an inspiration and an antidote to hubris in the face of the unknown.

You grew up far from big-city life. What was it like?

I was born in Kalgoorlie, a gold mining town about 400 miles east of Perth. My father was a fitter and turner, fixing steam engines and trains. My mother was a nurse. All the miners owed a lot of money and drank a lot of beer, so Mom said, "We've got to get out of here before we go the way of everybody else." In 1951 we headed for Rum Jungle, where a uranium boom was on, but halfway there we stopped in Kaniva, another boomtown, with a whaling station and high-paying jobs. Then my father started managing chicken factories in Perth. We never wanted for anything. It was like the TV show *Happy Days*.

What sparked your interest in science?

My mother had nursing books around. I had three brothers, and we always had electronics and gunpowder and explosions and welding. All I can say is that some things you get from your parents through osmosis. In high school I had B's and C's, not

too many A's, but I must have done well on that medical school test, and I must have had some charisma in the interview, so I ended up in medicine. Being a general practitioner was all I aspired to. I was good with patients and very interested in why things happened. Eventually I developed a more mature approach: I realized that at least 50 percent of patients were undiagnosable.

You found yourself confronting unexplainable diseases?

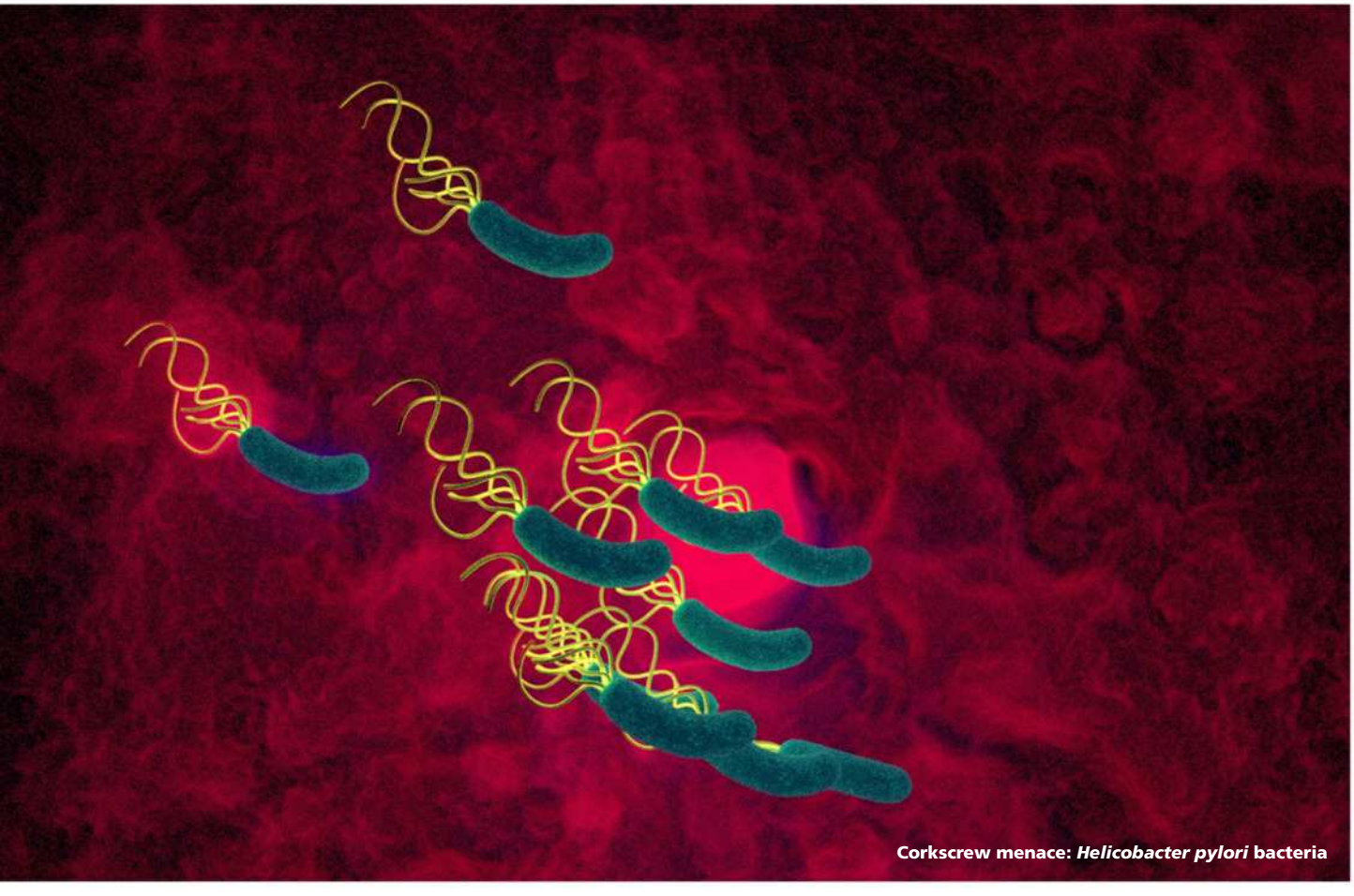
In medical school it's quite possible to get taught that you can diagnose everybody and treat everything. But then you get out in the real world and find that for most patients walking through your door, you have no idea what's causing their symptoms. You could slice up that person into a trillion molecules and study every one, and they'd all be completely normal. I was never satisfied with saying that by ruling out all these diseases, a person must have a fake disease, so I accepted the fact that lots of times I couldn't reach a fundamental diagnosis, and I kept an open mind.

Is that how you came to rethink the cause of ulcers?

Before the 20th century, the ulcer was not a respectable disease. Doctors would say, "You're under a lot of stress." Nineteenth-century Europe and America had all these crazy health spas and quack treatments. By the 1880s doctors had developed surgery for ulcers, in which they cut off the bottom of the stomach and reconnected the intestine. We're pretty certain now that by the start of the 20th century, 100 percent of mankind was infected with *H. pylori*, but you can go through your whole life and never have any symptoms.

What was the worst-case scenario for ulcer patients?

An ulcer with a hole in it, called a duodenal ulcer, is acutely painful due to stomach acid. When you eat a meal, the food washes the acid away temporarily. When the meal is digested, the acid comes back and covers the raw base of the ulcer, causing pain to start up again. These problems were so common that the Mayo Clinic was built on gastric surgery.



Corkscrew menace: *Helicobacter pylori* bacteria

After that surgery, half the people would feel better. But about 25 percent of these cured patients became so-called gastric cripples, lacking appetite and never regaining complete health.

With so much physical evidence of a real condition, why were ulcers routinely classified as psychosomatic?

Eventually doctors realized they could see the ulcers with X-ray machines, but, of course, those machines were in big cites like New York and London — so doctors in those cities started identifying ulcers in urban businessmen who probably smoked a lot of cigarettes and had a high-pressure lifestyle. Later, scientists induced ulcers in rats by putting them in straitjackets and dropping them in ice water. Then they found they could protect the rats from these stress-based ulcers by giving them antacids. They made the connection between ulcers, stress and acid without any proper double-blind studies, but it fit in with what everybody thought.

How did you come to challenge this prevailing theory?

I was in the third year of my internal medicine training, in 1981, and I had to take on a project. Robin Warren, the hospital pathologist, said he had been seeing these bacteria on biopsies of ulcer and stomach cancer patients for two years, and they were all identical.

What was distinctive about these infections?

The microorganisms all had an S-shaped or helical form, and the infections coated the stomach. Warren had found them in about 20 patients who had been sent to him because doctors thought they might have cancer. Instead of cancer, he had found these bacteria. So he gave me the list and said, "Why don't you look at their case records and see if they've got anything wrong with them." It turned out that one of them, a woman in her 40s, had been my patient. She had come in feeling nauseated, with chronic stomach pain. We put her through the usual tests, but nothing showed up. So of course she got sent to a psychiatrist, who put her on an antidepressant. When I saw her on the list, I thought, "This is pretty interesting."

Then another patient turned up, an old Russian guy who had severe pains. Doctors gave him a diagnosis of angina, pain that occurs when blood to the heart can't pass through a narrowed artery. It's rare, but you can theoretically get that in your gut, too. There was no treatment for an 80-year-old man in those days, so we put him on tetracycline and sent him home. He goes off, and two weeks later he comes back. He's got a spring in his step, he's practically doing somersaults into the consulting room. He's healed. Clearing out the infection had cured him. I had one more year to go, so I did the paperwork to set up a proper clinical trial with 100 patients to look for the bacteria causing the gut infection; that started in April of 1982.

Before the 20th century, the ulcer was not a respectable disease. … Nineteenth-century Europe and America had all these crazy health spas and quack treatments. By the 1880s doctors had developed surgery for ulcers, in which they cut off the bottom of the stomach and reconnected the intestine. We're pretty certain now that by the start of the 20th century, 100 percent of mankind was infected with H. pylori.

But at first nothing was turning up, right?

Yes — not until patients 34 and 35, on Easter Tuesday, when I got this excited call from the microbiologist. So I go down there and he shows me two cultures, the grand slam, under the microscope. The lab techs had been throwing the cultures out after two days because with strep, on the first day we may see something, but by the second day it's covered with contamination, and you might as well throw it in the bin. That was the mentality of the lab: Anything that didn't grow in two days didn't exist. But *Helicobacter* is slow-growing, we discovered. After that we let the cultures grow longer and found we had 13 patients with duodenal ulcer, and all of them had the bacteria.

When did you realize *H. pylori* caused stomach cancer, too?

We observed that everybody who got stomach cancer developed it on a background of gastritis, an irritation or inflammation of the stomach lining. Whenever we found a person without *Helicobacter*, we couldn't find gastritis, either. So as far as we knew, the only important cause of gastritis was *Helicobacter*. Therefore, it had to be the most important cause of stomach cancer as well.

How did you get the word out about your discovery?

I presented that work at the annual meeting of the Royal Australasian College of Physicians in Perth. That was my first experience of people being totally skeptical. To gastroenterologists, the concept of a germ causing ulcers was like saying that the Earth is flat. After that I realized my paper was going to have difficulty being accepted. You think, "It's science; it's got to be accepted." But it's not an absolute given. The idea was too weird.

Then you and Robin Warren wrote letters to *The Lancet*.

Robin's letter described the bacteria and the fact that they were quite common in people. My letter described the history of these bacteria over the past 100 years. We both knew that we were standing at the edge of a fantastic discovery. At the bottom of my letter, I said the bacteria were candidates for the cause of ulcers and stomach cancer.

That letter must have provoked an uproar.

It didn't. In fact, our letters were so weird that they almost didn't get published. By then I was working at a hospital in Fremantle, biopsying every patient who came through the door. I was getting all these patients and couldn't keep tabs on them, so I tapped all the drug companies to request research funding for a computer. They all wrote back saying how difficult times were and they didn't have any research money. But they were making a billion dollars a year for the antacid drug Zantac and another billion for Tagamet. You could make a patient feel better by removing the acid. Treated, most patients didn't die from their ulcer and didn't need surgery, so it was worth $100 a month per patient, a hell of a lot of money in those days. In America in the 1980s, 2 to 4 percent of the population had Tagamet tablets in their pocket. There was no incentive to find a cure.

But one drug company did provide useful information, right?

I got an interesting letter from a company that made an ulcer product called Denel, which contained bismuth — much like Pepto-Bismol in the United States. The company had shown that it healed ulcers just as quickly as Tagamet, even though the acid remained. The weird thing was that if they treated 100 patients with this drug, 30 of them never got their ulcer back, whereas if you stopped Tagamet, 100 percent would get their ulcer back in the next 12 months.

So the company said: "This must heal ulcers better than just removing the acid. It must do something to the underlying problem, whatever that is." They sent me their brochure with "before" and "after" photographs. On the "before" photograph they had *Helicobacter* in the picture, and in the "after" picture there was none. So I put their drug on *Helicobacter,* and it killed them like you wouldn't believe. They helped me present at an international microbiology conference in Brussels.

The microbiologists in Brussels loved it, and by March of 1983 I was incredibly confident. During that year Robin and I wrote the full paper. But everything was rejected. Whenever we presented our stuff to gastroenterologists, we got the same campaign of negativism. I had this discovery that could undermine a $3 billion industry, not just the drugs, but the entire field of endoscopy. Every gastroenterologist was doing 20 or 30 patients a week who might have ulcers, and 25 percent of them would. Because it was a recurring disease that you could never cure, the patients kept coming back. And here I was handing it on a platter to the infectious-disease guys.

Didn't infectious-disease researchers support you, at least?

They said: "This is important. This is great. We are going to be the new ulcer doctors." There were lots of people doing the microbiology part. But those papers were diluted by the hundreds of papers on ulcers and acid. It used to drive me crazy.

To move forward, you needed solid experimental proof. What obstacles did you encounter?

We had been trying to infect animals to see if they would develop ulcers. It all failed; we could not infect pigs or mice or rats. Until we could do these experiments, we would be open to criticism. So I had a plan to do the experiments in

I swizzled the organisms around in a cloudy broth and drank it the next morning. My stomach gurgled, and after five days I started waking up in the morning saying, "Oh, I don't feel so good," and I'd run in the bathroom. … I would be good enough to go to work, although I was feeling tired and not sleeping so well. After 10 days, I had an endoscopy that showed the bacteria were everywhere. There was all this inflammation, and gastritis had developed.

humans. It was desperate: I saw people who were almost dying from bleeding ulcers, and I knew all they needed was some antibiotics, but they weren't my patients. So a patient would sit there bleeding away, taking the acid blockers, and the next morning the bed would be empty. I would ask, "Where did he go?" He's in the surgical ward; he's had his stomach removed.

What led up to your most famous and most dangerous experiment, testing your theory on yourself?

I had a patient with gastritis. I got the bacteria and cultured them, then worked out which antibiotics could kill his infection in the lab — in this case, bismuth plus metronidazole. I treated the patient and did an endoscopy to make sure his infection was gone. After that, I swizzled the organisms around in a cloudy broth and drank it the next morning. My stomach gurgled, and after five days I started waking up in the morning saying, "Oh, I don't feel good," and I'd run in the bathroom and vomit. Once I got it off my stomach, I would be good enough to go to work, although I was feeling tired and not sleeping so well. After 10 days, I had an endoscopy that showed the bacteria were everywhere. There was all this inflammation, and gastritis had developed. That's when I told my wife.

How did she react?

I should have recorded it, but the meaning was that I had to stop the experiment and take some antibiotics. She was paranoid that she would catch it and the kids would catch it and chaos — we'd all have ulcers and cancer. So I said, "Just give me until the weekend," and she said, "Fair enough."

Your personal experience convinced you that *Helicobacter* infection starts in childhood. Can you explain?

At first I thought it must have been a silent infection, but after I had it, I said, "No, it's actually an infection that causes vomiting." And when do you catch such infections? When you're toddling around, eating dirty things and playing with your dirty little brothers and sisters. The reason you didn't remember catching *Helicobacter* is that you caught it before you could talk.

You published a synthesis of this work in *The Medical Journal of Australia* in 1985. Then did people change their thinking?

No, it sat there as a hypothesis for another 10 years. Some patients heard about it, but gastroenterologists still would not treat them with antibiotics. Instead, they would focus on the possible complications of antibiotics. By 1985 I could cure just about everybody, and patients were coming to me in secret — for instance, airline pilots who didn't want to let anyone know that they had an ulcer.

So how did you finally convince the medical community?

I didn't understand it at the time, but Procter & Gamble [the maker of Pepto-Bismol] was the largest client of Hill & Knowlton, the public relations company. After I came to work in the States, publicity would come out. Stories had titles like "Guinea-Pig Doctor Experiments on Self and Cures Ulcer," and *Reader's Digest* and the *National Enquirer*

covered it. Our credibility might have dropped a bit, but interest in our work built. Whenever someone said, "Oh, Dr. Marshall, it's not proven," I'd say: "Well, there's a lot at stake here. People are dying from peptic ulcers. We need to accelerate the process." And ultimately, the NIH and FDA did that. They fast-tracked a lot of this knowledge into the United States and said to the journals: "We can't wait for you guys to conduct these wonderful, perfect studies. We're going to move forward and get the news out." That happened quite quickly in the end. Between 1993 and 1996, the whole country changed color.

You have since devised tests for *H. pylori*. How do they work?

The first diagnostic test, done after a biopsy, detected *Helicobacter* that broke down urea to form ammonia. More recently I developed a breath test for *Helicobacter* based on the same principle. That test was bought by Kimberly-Clark, and they sell it all over the world. That one little discovery set me up for the rest of my career.

Is it possible to create a vaccine against *Helicobacter*?

After 20 years and a lot of hard work by companies spending millions, we have still been unable to make a vaccine. The reason is that once it's in you, *Helicobacter* has control of your immune system. Once I realized this, I said, well, if it's too difficult to make a vaccine against *H. pylori*, what about loading a vaccine against something else onto the *Helicobacter* and using it as a delivery system?

So that is my vaccine project, and it is my life at the moment. I'm making a vaccine against influenza. We'll find a strain of *Helicobacter* that doesn't cause any symptoms. Then we'll take the influenza surface protein and clone that into Helicobacter and figure out how to put it in a little yogurt-type product. You just take one sip and three days later the whole surface of your stomach is covered with the modified *Helicobacter*. Over a few weeks, your immune system starts reacting against it and also sees the influenza proteins stuck on the surface, so it starts creating antibodies against influenza as well.

How would this be better than current flu vaccines?

Right now it takes a year to make 50 million doses of flu vaccine, so you only get vaccinated against last year's flu. Whereas we are building swine flu vaccine as we speak. We know the sequence of the swine flu virus. You can make the DNA. You can put it in *Helicobacter* — with a home brew kit, I can make 100,000 doses in my bathtub. Using the same method, a *Helicobacter* vaccine against malaria would be dirt cheap. You could make 100 million doses in the middle of Africa without a refrigerator. You could distribute it at the airport through something like a Coke machine.

Based on this experience, should we be taking a fresh look at other diseases that do not have well-understood causes?

Helicobacter made us realize that we can't confidently rule out infectious causes for most diseases that are still unexplained. By the 1980s, infectious disease was considered a has-been specialty, and experts were saying everyone with an infectious disease could be cured by antibiotics. But what about when your kids were 2 years old? Every week they'd come home with a different virus. You didn't know what the infections were. The kids had a fever for two days, they didn't sleep, they were irritable, and then it was over. Well, you think it is over. It might be gone, but it has put a scar on their immune system. And when they grow up, they've developed colitis or Crohn's disease or maybe eczema. There are hundreds of diseases like this, and no one knows the cause. It might be a germ, just one you can't find.

How can we track down these mystery pathogens?

What we would like to do, hopefully with funding from NIH, is launch big, long-term programs. You would enter your baby into a trial the day he is born. We would have his genome decoded. We'd survey your microbiome [all the microorganisms in the body and their DNA] and maybe your husband's microbiome, and all that would go in a database. Then we would come along and take a feces culture from your baby each month. And if ever he got a fever, we would swab his cheek and save that.

We would do 10,000 kids like this. Then, in 20 years' time, we would find that 30 of them developed colitis, and we would go back. If we could get all of that material out of the deep freeze and run it through the sequencing machine, we would find the answer. In the last 20 years, people have been so focused on linking disease with environmental factors like chemicals and pollution. But the environmental factor could be an infectious agent that you had in your body at some time in your life. Just because somebody ruled out an infectious cause in the 1980s or '90s doesn't mean this was correct.

Even now, though, isn't it hard for new ideas to be heard when medical journals are gatekeepers of the status quo?

It's true, but they have their ears pricked up now because every time a paper comes to them, they say: "Hang on a minute, I had better make sure that this is not a Barry Marshall paper. I don't want to have my name on that rejection letter he shows in his lectures." Now they might say, "It's so off-the-wall. … Is it true?" MM

Pamela Weintraub *is a contributing editor for* Discover.

10 WEIRD, WACKY AND WORTHWHILE EXPERIMENTS

UNEXPECTED AND OFFBEAT DISCOVERIES SOMETIMES YIELD THE MOST STARTLING ADVANCES IN MEDICAL SCIENCE.

BY **CHRISTIAN MILLMAN**

The medical record is surprisingly rich with bumbles and quirks, bold moves and devil-may-care experimentation. But important and interesting discoveries have come from these often outrageous acts: by sheer accident, through daring self-sacrifice, from people eccentric enough to look at medical issues through an equally unconventional perspective.

Here's a look at 10 successes from the annals of the avant-garde that actually worked, along with a brief analysis of their continuing impact on areas as diverse as heart disease, pain management, gastroenterology and seat belts.

ALFRED EISENSTAED/PIX INC./TIME LIFE PICTURES/GETTY IMAGES

This Is Spinal Tap

THE BIZARRE ORIGINS OF EPIDURALS.

German surgeon August Bier remains best known for two things: First, the quote "A professor is a gentleman with a different point of view." Second, the way he embodied that different point of view while pioneering spinal anesthesia as a surgical procedure.

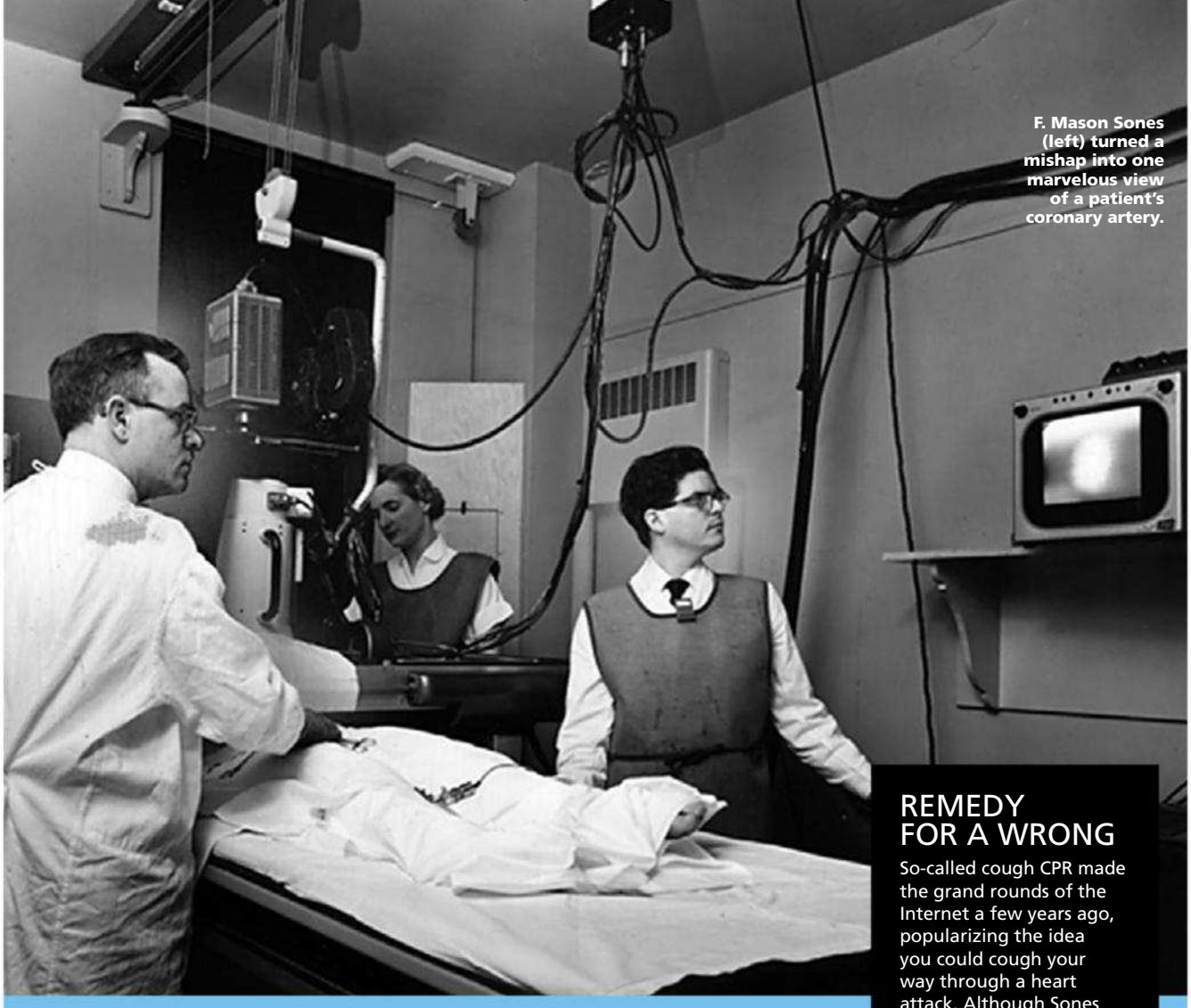
Inspired by the work of New York neurologist James Corning, who experimented with injections of cocaine as a local anesthetic, Bier took that research to an entirely new level in 1898. He surmised that injecting a cocaine solution into the cerebrospinal fluid would block pain during surgery without the dangers of general anesthesia.

With the help of his assistant, August Hildebrandt, Bier inserted a needle between vertebrae in his own neck. Unfortunately, a loose-fitting syringe caused the cocaine solution, and a good bit of Bier's cerebrospinal fluid, to leak out. This would eventually leave Bier flat on his back for nine days with a severe headache and dizziness.

But rather than abort the mission, the two switched places. Bier successfully injected the cocaine mix into Hildebrandt's spine — so successfully, in fact, that Bier was able to stub out a cigar on his assistant, jam a needle through his thigh muscle down to the femur and smash him in the shin and testicles. All without pain — at the time.

Not surprisingly, a bitter Hildebrandt soon parted company with Bier, but their legacy lives on in the epidurals administered millions of times each year to block the pain from childbirth, back problems and other types of surgery.

Epidural injections ease pain during many procedures, especially for childbirth. Six out of 10 U.S. moms-to-be opt for spinal anesthesia, according to the National Center for Health Statistics.



F. Mason Sones (left) turned a mishap into one marvelous view of a patient's coronary artery.

REMEDY FOR A WRONG

So-called cough CPR made the grand rounds of the Internet a few years ago, popularizing the idea you could cough your way through a heart attack. Although Sones did use a version of cough CPR — and doctors still use it in certain clinical situations — it isn't useful during a heart attack, which is different from the cardiac arrest Sones accidentally induced in his patient. The American Heart Association doesn't include it in CPR training because it just delays more effective treatment.

Cast the Dye

A FLUKE GIVES US CORONARY ANGIOGRAPHY.

By the late 1950s, doctors were regularly using high-contrast dyes to give them a view of the larger structures of the heart and aorta, but the much-smaller arteries feeding blood to the heart itself remained off limits.

That's because the dye, inserted directly into these arteries, would cause a deadly heart attack. And in 1958, F. Mason Sones, a cardiologist at the Cleveland Clinic, found that out the hard way, as did the 26-year-old man on his exam table.

Sones and his assistant had injected a large cloud of dye into the area where the young man's arteries branched out from his aorta, in the hope that some of the contrast agent would seep into the smaller vessels and give the doctor a view inside them.

When Sones flicked on an X-ray machine to view the results, he was astonished to see a brilliantly clear image of the man's right coronary artery — something never shown on an angiogram before.

There was a flicker of recognition and a moment's horror before he shouted to his assistant, "Pull it out!" The tip of the needle had accidentally pierced the coronary artery and filled it with dye. Sones' beautiful view came with an immediate cost: The man's heart flatlined.

As his patient rapidly began to lose consciousness, Sones shouted at him to cough. The young man managed to crank out three or four sharp barks. The resulting pressure cleared the patient's coronary artery of the dye, allowing the heart, thankfully, to beat normally again.

After what was assuredly a period of brow-wiping and breath-catching, Sones went on to refine the right amounts and types of contrast dyes to produce the kind of clear images of coronary arteries we see today — images crucial in diagnosing the blocked arteries that can lead to most heart attacks.

The Marshall Plan

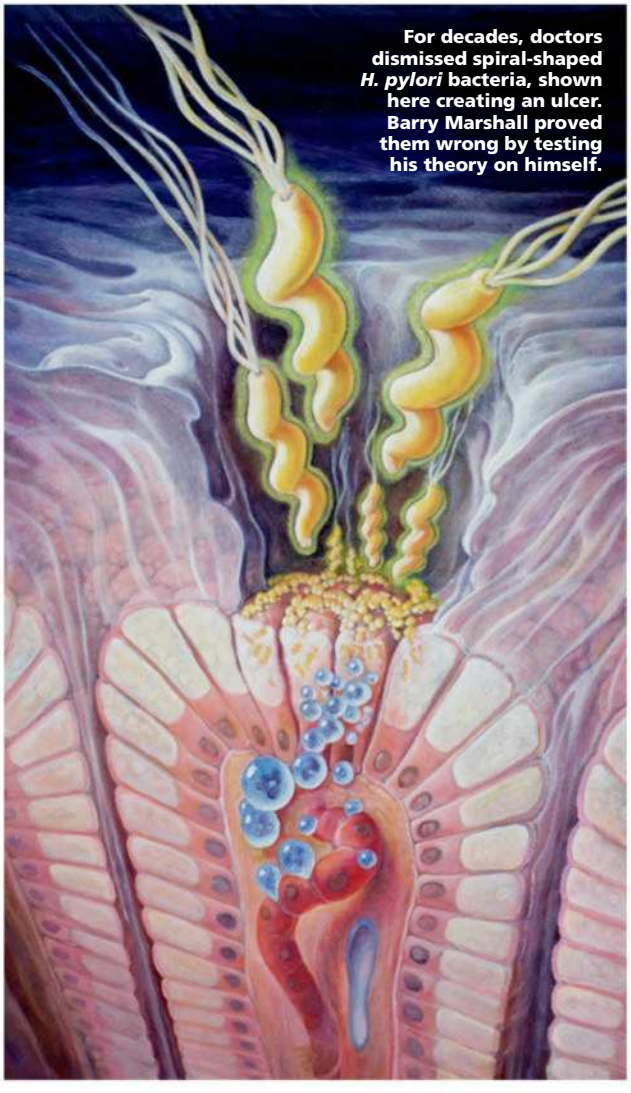
AN ULCER COCKTAIL WINS HIM A NOBEL.

Australian physician and internist Barry Marshall needed a willing human subject to test his then-radical hypothesis that ulcers were caused by a bacterium, not stress or spicy foods. But medical ethics prevented him from deliberately infecting a person with a potentially dangerous bug.

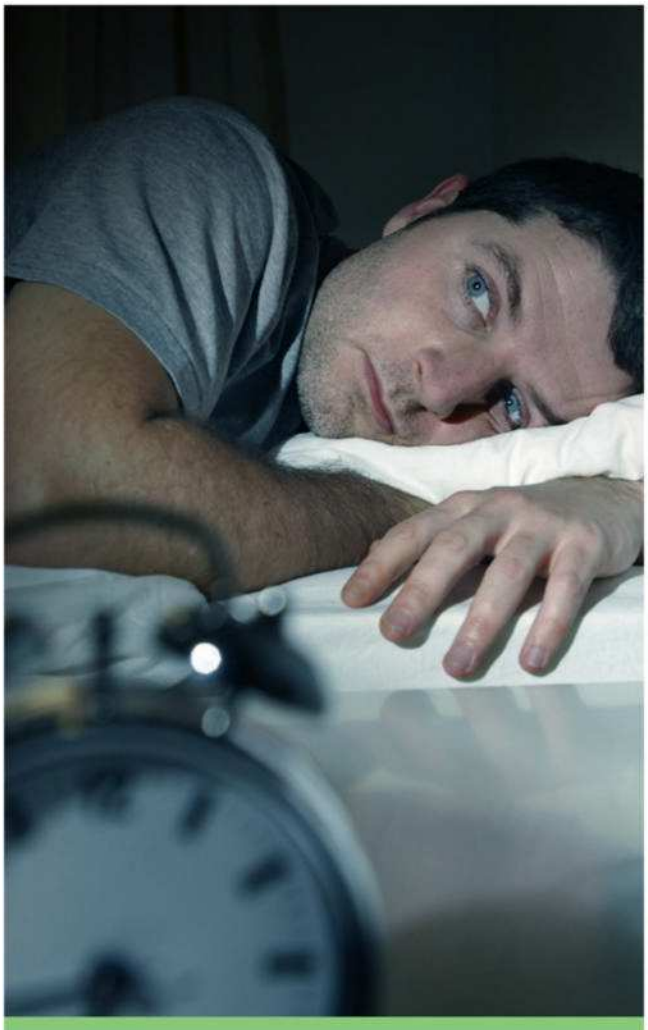
So in 1984, he cultured some *Helicobacter pylori*, stirred it into an infectious cocktail and drank it. A few uneventful days passed. Then, success — if you consider success to be vomiting, grotesquely fetid breath and utter exhaustion, all from a wicked case of gastritis, a known precursor to ulcers.

From there, a cure was as simple as giving himself a round of antibiotics. Today, stomach cancer, which is almost exclusively caused by untreated ulcers, has been virtually eradicated from those whose ulcers and *H. pylori* infections are treated.

The impact of Marshall's self-experimentation was recognized with a 2005 Nobel Prize, which he shared with pathologist and co-conspirator Robin Warren. For more on Marshall's plan, see *Discover*'s interview with him on page 40.



For decades, doctors dismissed spiral-shaped *H. pylori* bacteria, shown here creating an ulcer. Barry Marshall proved them wrong by testing his theory on himself.



The Strangest Side Effect of Sleeping Medicine

WAKING UP COMATOSE PATIENTS.

Since at least 1999, news outlets have reported on a bizarre effect of zolpidem (brand name Ambien). No, not the many reports of sleepwalking; in fact, quite the opposite.

These stories talked of comatose people gaining a temporary return to consciousness after being given the sleeping medication. The level of consciousness has varied, from minor improvements to the ability to fully converse with family.

Intrigued, medical researchers began to look closely at zolpidem. One of the largest and most recent studies, released in February 2014, tried the therapy in 84 vegetative and minimally conscious people. Researchers found the drug worked at least to some degree in about 5 percent of patients, and the effects typically lasted one to two hours. Not at all a cure, but perhaps a wake-up call for researchers to pursue further study.

Dive Down, Stand Up

HOW SCUBA DIVING LET A MAN WALK AGAIN.

Mark Chenoweth has spina bifida, a birth defect that leaves the spinal cord exposed or otherwise unprotected by vertebrae. He lived a relatively normal life until 1996, when at age 34 he lost the ability to walk and began using a wheelchair.

Two years later, with an upcoming vacation, he decided he wanted to try scuba diving. So he asked his doctor to sign off on a medical clearance. The doc's answer was unequivocal: Don't do it. Chenoweth sought clearance from five others — the answer was always the same.

Undeterred, Chenoweth went to a Mediterranean resort and fudged a medical clearance, then took a brief training course. On his first open-water dive, he descended 55 feet. He enjoyed it so much, he dove twice more.

After the third dive, he noticed something different about his legs. Then he did something astonishing. On the dive boat, in front of everyone, he stood up for the first time in years.

The ability to walk returned for longer and longer periods the deeper he dived. These days, after hundreds of dives, he has to use a wheelchair only about twice a year.

A few years ago, his wife reports, a research center in Hull, England, wanted to study scuba's effect on Chenoweth and others with spina bifida, but funding wasn't available. So his near-cure remains a genuine medical mystery — for now.

Come Hungry, Leave Angry

CAFETERIAS CAN MAKE US NASTY.

You already know trans fatty acids, or trans fats, are exceedingly unhealthy in frequent doses. But you might not know they're also linked to increased aggression and irritability.

In a large study of almost 1,000 people, researchers at the University of California, San Diego, found that people who ate more trans fats were significantly angrier — at everything — across all the measures the researchers used.

Trans fats seem to interfere with the body's ability to regulate DHA, another fatty acid that helps stabilize moods and acts as a natural antidepressant.

Now guess which organizations tend to serve menu items high in trans fats. Did you guess prisons and schools? Don't get all bent out of shape if you didn't — it's probably just the french fries talking.

Hand Over Fistula

GASTROENTEROLOGY'S ORIGINS MAY BE HARD TO STOMACH.

Three unlikely elements came together in 1822 to create what we now know as the medical specialty of gastroenterology: an unlucky frontiersman, a misaimed musket and a less-than-scrupulous doctor.

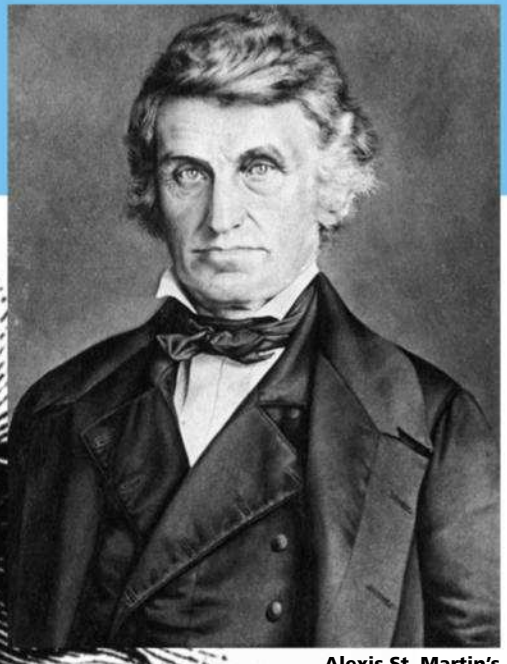
Alexis St. Martin, a 20-year-old trapper and fur trader, took an accidental close-range musket blast, tearing a ragged hole in his ribs and stomach. St. Martin promptly presented himself and his grim wound to William Beaumont, a U.S. Army surgeon on Mackinac Island, in what is now the state of Michigan.

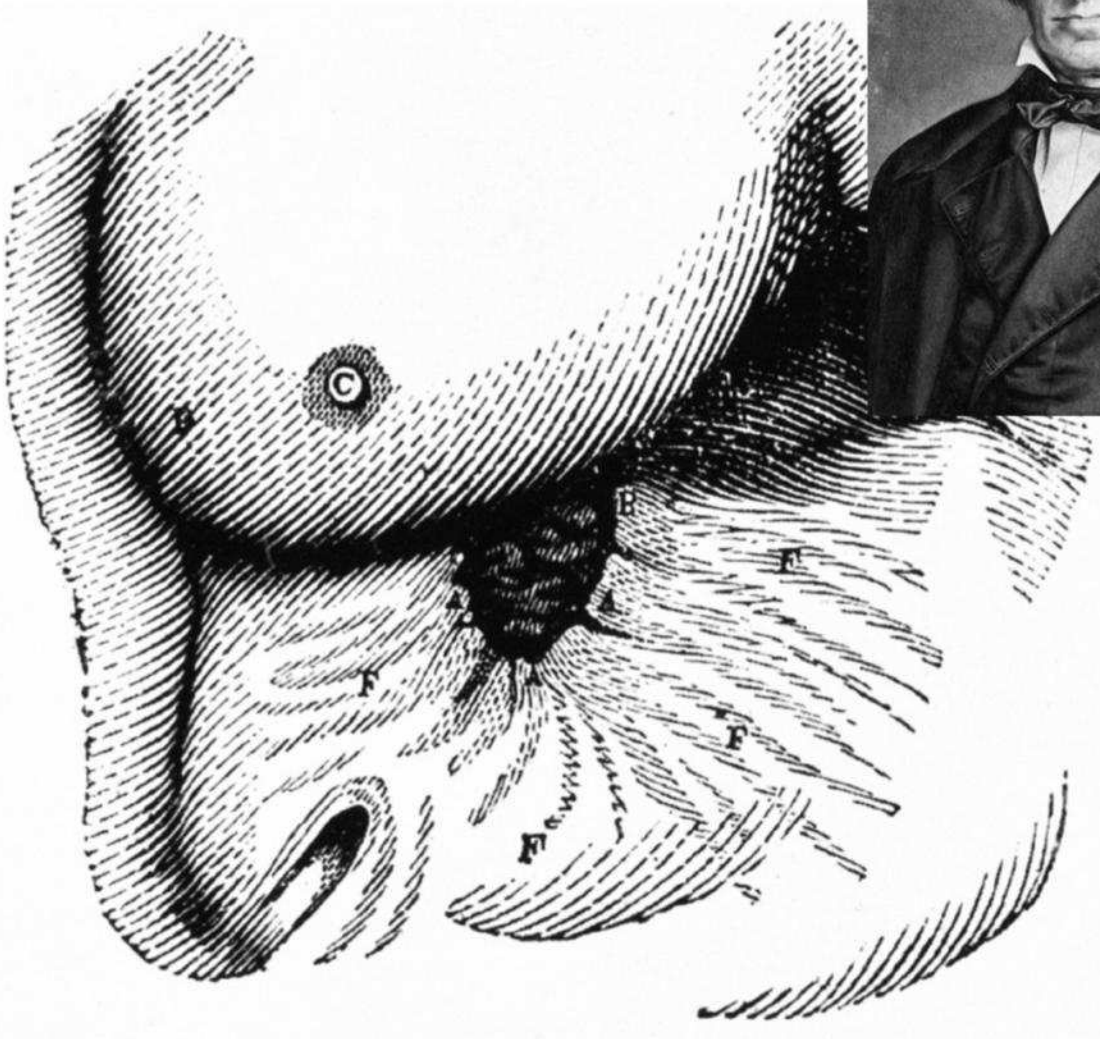
At first, Beaumont didn't see much hope for St. Martin. For 17 days, everything the patient ate came right back out of the wound. But by day 18, the injury had healed enough to keep food inside, although a hole — the medical term is *fistula* — remained, giving Beaumont the rarest of permanent windows directly into St. Martin's stomach.

Beaumont seized the opportunity to study the little-understood digestive process and took advantage of St. Martin's illiteracy by having him sign a contract that essentially turned the trapper into a servant and medical guinea pig.

Beaumont experimented with St. Martin's digestive tract by attaching chicken, beef, oysters and many other food items to a string and shoving them through the fistula for various periods of time. After he pulled them out, Beaumont recorded the rate of digestion and collected a sample of gastric juices.

This went on for 11 years before St. Martin was finally able to return to his home in Quebec, where he lived until his death in 1880 at age 78. Although few would remember St. Martin's name today, Beaumont is still known as the father of gastric physiology.





Alexis St. Martin's horrific musket injury (left) gave William Beaumont (above) unprecedented insight, quite literally, into the human digestive system.

Help From a Horror Drug

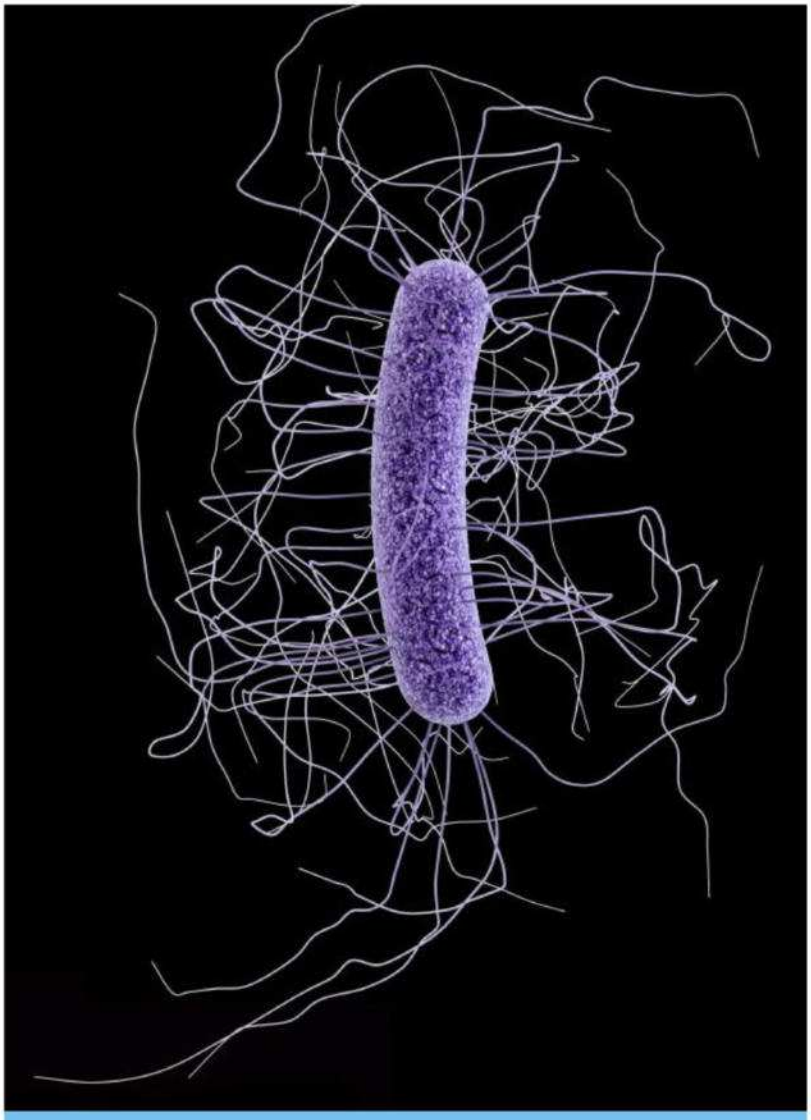
NEW HOPE FOR LEPROSY.

From 1957 until 1962, the now-infamous drug thalidomide led to a generation of horrifying birth defects after mothers-to-be took it to relieve morning sickness. About 10,000 babies were born with missing or malformed limbs, deformed eyes and hearts, and other tragically critical issues. Only half of those children survived.

The drug was yanked from the market, and it seemed unlikely to survive its vilification or ever find a place back in the pharmacopeia. That changed in 1964 when a Jerusalem dermatologist, Jacob Sheskin, used thalidomide on a patient with leprosy. How he got his hands on the then-illegal drug, and why he decided to experiment with it, remains a mystery.

What's not a mystery is the effect it had on one of leprosy's main symptoms — painful lesions called erythema nodosum leprosum. After only four doses over three days, Sheskin's patient saw his lesions almost completely heal, all the more miraculous since the primary treatment for leprosy back then was simply to shunt sufferers into lives of isolation in leper colonies.

Sheskin treated another six patients and recorded similar results as long as treatment continued, suggesting thalidomide acted as a suppressor, not a total cure. Thalidomide, under tight controls, is still used to treat leprosy, along with several other newer drugs.



The No. 2 Cure

FECAL TRANSPLANT WARDS OFF A BAD BUG.

One problem with extended courses of antibiotics is the drugs can kill off good bacteria in your gut. But one bug that survives particularly well is of the bad sort: *Clostridium difficile* (above). When it becomes overrepresented in your intestinal tract, you can end up with such unpleasantries as pseudomembranous colitis, toxic megacolon, perforations of the colon and sepsis. The Centers for Disease Control and Prevention says roughly 350,000 Americans have a *C. difficile* infection, which also causes debilitating diarrhea and up to 50,000 deaths each year.

Enter the fecal transplant, a practice borrowed from veterinarians who inserted feces from healthy horses into the rectum of other equines with intractable diarrhea. In 1958, doctors asked a human donor with healthy levels of gut bacteria to provide a fresh specimen. Then they whipped it into a slurry and squirted it into the colon of a *C. difficile*-stricken patient. Nowadays, it's done over a five-day period with a series of enemas.

Result: complete cure. Since then, only a few hundred other such transplants have been performed worldwide, a mystifyingly low number since the cure rate is well over 90 percent.

LEFT: BETTMANN/CORBIS/AP IMAGES. RIGHT: JENNIFER HULSEY/CDC

Pushing the G-Force Envelope

SEAT BELTS AND SUPERSONIC SUNDAY DRIVES.

Among its many legacies, World War II also gave us unprecedented G-forces. With the advent of jet aircraft, humans were subject to more deliberate acceleration and deceleration than ever before. Although jets played a limited role in the war, the post-conflict period saw their rapid development as a fighting machine. This posed a particular problem for pilots who had to escape a damaged or malfunctioning airplane traveling at supersonic speeds. Punching out of a supersonic jet exposes pilots to 40 to 50 Gs, or the sudden increase of his body weight by 40 to 50 times.

At the time, G-force was considered fatal above 18 G. But no one was certain. Who would be crazy enough to willingly subject himself to that much force? A guy named John Paul Stapp, that's who. The U.S. Air Force flight surgeon was the first to strap in for a series of self-inflicted experiments designed to test the limits of human G-force tolerance.

Beginning in 1946, he designed rocket-powered sleds that could reach speeds of 750 mph and slam to the kind of sudden stop similar to ejecting at speed. The first runs didn't look good: A test dummy slipped out of its harness and was flung over 700 feet. So Stapp designed better restraints.

Then he went for a ride himself. First at 90 mph. Then at 150. Then 200, increasing speed for a total of 29 runs over seven years, during which time he suffered blackouts, headaches, concussions, broken and dislocated bones, and watched six fillings go flying out of his mouth. The sequence of photos (shown below) feature Stapp on a typical ride, with pictures 1 through 3 showing his appearance in the first five seconds of acceleration as his sled shot up to a speed of 421 mph. The last photo shows the start of deceleration, as Stapp's body was subjected to 22 Gs.

His last ride, in 1954, was also his fastest. He blasted to 632 mph, withstood a windblast equivalent to an ejection at 1,000 mph at 35,000 feet of altitude, was subjected to over 46 Gs, and proved that humans could survive the extreme forces of their newest machines.

Stapp's heroic work has saved many more lives than those of pilots. In a time of cars with no seat belts, his research showed that people could survive high-force impacts if properly restrained. Stapp himself became a vocal advocate for seat belts and auto safety and was at Lyndon Johnson's side in 1966 when the then-president signed a law requiring carmakers to install seat belts. **MM**

Stapp's wild ride: The intrepid flight surgeon endures a 1954 rocket sled ride that took him from zero to over 400 mph in just five seconds.

KEYSTONE/HULTON ARCHIVE/GETTY IMAGES

A Rock and a Hard Place

CONFRONTED WITH THE UNUSUAL CAUSE OF HIS SYMPTOMS, A SECRETIVE PATIENT STONEWALLS THE DOCTOR.

BY **DOUGLAS G. ADLER**

THOMAS JACKSON/STONE/GETTY IMAGES

Most gastroenterologists don't choose their subspecialty based on its inherent glamour. The nitty-gritty of GI doctors' work may not make for good party talk, but gastroenterology does afford its practitioners the opportunity to take care of a wide range of patients — young and old, male and female, and with a diverse set of problems ranging from heartburn to colon cancer. A big part of gastroenterology involves performing screening colonoscopies to look for and remove colon polyps that could develop into cancer. Sometimes when we look into the colon, however, we find the unexpected.

The patient in question, let's call him Jasper, was a 55-year-old man who had developed some intermittent abdominal discomfort and a feeling of heaviness in the right lower quadrant of his belly. The symptoms had been present for some time and were mentioned only to his primary care doctor in response to some standard questions about his overall health. As Jasper had never had a screening colonoscopy (and was well overdue to have one — most patients need their first screening colonoscopy at age 50 and every few years thereafter), he was referred to me for an evaluation. Given these facts, and because a colonoscopy is also part of the standard workup of lower abdominal pain, I scheduled him for the procedure.

When Jasper arrived in the endoscopy unit, he looked quite robust and healthy. On questioning him, he reported no other troubles beyond those that he mentioned to his primary care physician. After obtaining his informed consent for the procedure, he was sedated, and we began his colonoscopy.

A complete colonoscopy involves inserting the colonoscope to a depth of about 5 feet, all the way into the cecum, a chamberlike region in the right lower quadrant of the abdomen. The cecum marks the beginning of the colon, and it sits just below the very end of the small intestine.

When I advanced the colonoscope into the patient's cecum, I encountered a profoundly unusual sight — a large collection of what were undoubtedly stones. I don't mean gallstones or kidney stones, or some other unusual calcification created by the human body itself, but actual geologic rocks from the earth.

There were at least a dozen stones the size of marbles, and well over 100 pebbles amid a heap of what can only be described as sand and mud. The entire collection would have filled a small cup and would probably have weighed a couple of ounces. It was immediately obvious that there were too many stones to remove with the colonoscope. Using the camera built into the colonoscope, I quickly captured several color pictures of my findings and then completed the rest of the examination, which was otherwise unremarkable. I printed the images and incorporated them into the procedure note itself.

After the effects of the sedatives had some time to wear off, I met with Jasper and his wife. I reviewed the findings of the examination and showed him the photos of the rocks, pebbles, sand and mud in his bowel. I asked him if he could tell me anything about this. The patient met most of my questions with a look that could only be described as astonishment. His wife likewise stared at me with a mix of puzzlement and shock on her face. Jasper told me that he had no idea how the stones and pebbles had gotten there. Then it was my turn to be astonished, as he went so far as to ask if I had put them there during the procedure!

It certainly seemed to me that we had identified the cause of the heavy sensation he was experiencing in his right lower quadrant, where his rock-filled cecum was located. I told him that I could envision a time when there would be so many rocks and stones that he could develop a blockage or tear in his bowels — which would likely require emergency surgery — or that he could get some sort of infection from such objects that clearly did not belong in his digestive system.

Frankly, Jasper was lucky that his symptoms were so minor, given how much material was in his colon. I offered to prescribe him a laxative regimen that could help him purge the existing stones and debris over time. I told him that if he did not have good success with laxatives, I might have to

repeat his colonoscopy and, using some special tools, try to dig out all the rocks, pebbles and mud with the colonoscope. Failing that, he might need surgery.

After all this, Jasper still insisted that there must be some mistake — and some other cause for his symptoms. He curtly assured me that he would follow up with his primary care doctor to look for other causes of his troubles. Standing up, he thanked me for my time, asked his wife to go get the car and pull it up to the front of the building, and began to change from his hospital gown into his street clothes. Jasper's tone and body language were clear: I had been dismissed. I mentally raised a single eyebrow in his direction and went back to my desk to look up the next patient on the roster for the day.

A few minutes after his wife left the endoscopy unit, Jasper made a point of catching my eye and gingerly motioned for me to return to his bedside. When I came over to him, his manner was entirely different from the abruptness I had seen just a few minutes ago. Glancing around to make sure nobody else in the recovery room was listening, he looked at me and said, "It's true, I ate those stones, all of them. You are the first person to ever know about it."

Jasper acknowledged a long-standing history of eating pebbles and rocks of all manner on a daily basis. When I asked why he did it, he could give no explanation for this behavior and stated that he was, despite his secretiveness, untroubled by this odd habit. He told me that while he walked about over the course of any given day, he frequently would scan the ground for pebbles or small stones or even small patches of sand that looked appealing and scoop them up. When nobody was looking, he would put them in his mouth, roll them around for a while, and eventually swallow them. Jasper told me that he didn't mind it if the stones were dirty or muddy, either — he would just clean them off in his mouth and swallow everything.

WHEN I ASKED WHY HE DID IT, HE COULD GIVE NO EXPLANATION FOR HIS BEHAVIOR AND STATED THAT HE WAS, DESPITE HIS SECRETIVENESS, UNTROUBLED BY THIS ODD HABIT.

He had been doing this since childhood — as far back as he could remember — and enjoyed it. He recognized it was an unusual urge, enough that he didn't want his wife or anyone else to know about it, but he said he felt great satisfaction in finding just the right kind of pebble or stone to eat.

Jasper insisted he never had any abdominal symptoms that he could relate to this habit, and even now he resisted the idea that his current symptoms were at all related to the stones I found in his colon. When I delved deeper into his medical and personal history, I learned that he had no history of mental illness, had a stable employment history and, in addition to being married, was also the father of several children. To the best of his knowledge, no other family members had similar behavior.

He asked me if I thought there was any risk to what he was doing. I immediately reiterated my concerns about a blockage or tear. After thinking about this for a few moments, he shrugged. "If I was going to get sick from this," he told me, "it would've happened a long time ago." When I asked if he was going to stop doing it, he said, "I'm not sure I could stop if I wanted to, and I am not even sure I want to stop." At this point, a nurse came and told us that Jasper's wife was waiting for him. Jasper stood up, shook my hand, thanked me for looking out for him, and left.

My patient had what is known as a pica: the intentional ingestion of a variety of nonfood objects. Some picas can seem incredibly strange. For example, hyalophagia refers to the consumption of glass, whereas trichophagia refers to eating hair or even wool. A common perception holds that picas represent an attempt for the body to satisfy some unmet need, such as a deficiency of calcium in a child who eats chalk, but in reality the causes of most picas are less than clear. We don't commonly see picas among adults, although many of us remember the kid from elementary school who ate paper or paste and then over time outgrew the habit.

Jasper undoubtedly had a lifelong pica called lithophagia — sometimes referred to as geophagia — the ingestion of sand, mud or rocks. As in Jasper's case, this pica can be asymptomatic or can lead to the GI problems I outlined to my patient. It is impossible to know how common this pica is as most people, like my patient, would be reluctant to acknowledge behaviors that others might find strange or off-putting. Jasper took pains to hide his habit from those around him, even his family members, making sure he was unobserved when he did it.

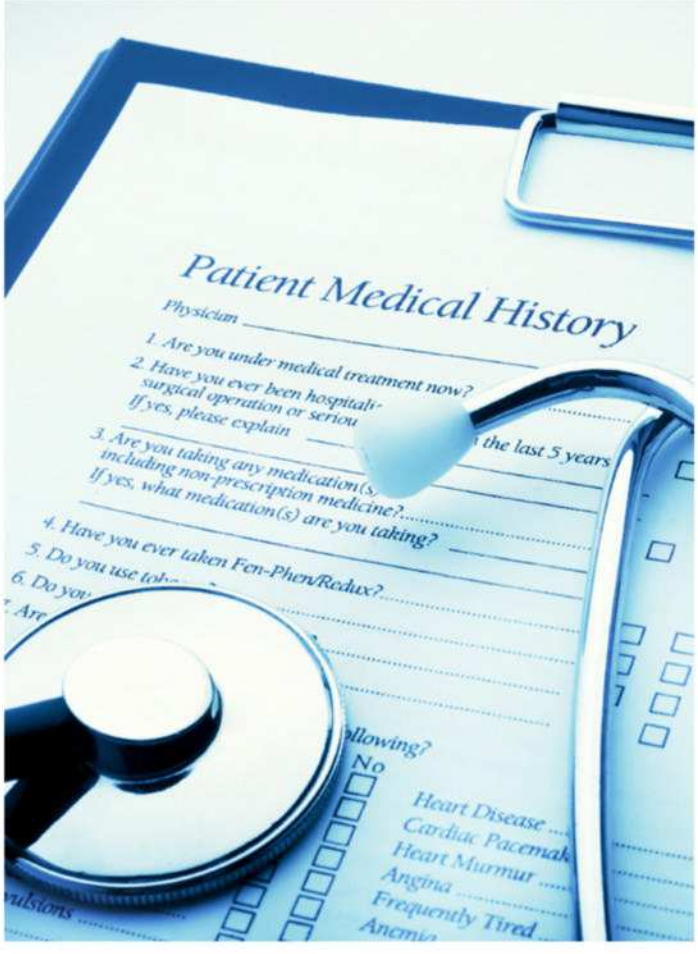
Although I obviously felt Jasper should stop this potentially harmful habit, it was difficult to know how hard to push him to get treatment. I let his referring physician know about the day's events — he assured me that he would discuss it with Jasper at his next visit and see if he wanted to see a psychologist about the whole situation. In mental health, a good rule of thumb is that if the illness does not trouble the patient or those around him, it may not require any treatment (and my patient certainly did not seem to be bothered by his pica).

As Jasper left, I couldn't help but wonder how a follow-up conversation with his regular doctor would go over with my patient (and his wife).

But what I really wanted to know was whether he would choose a stone from our front walk on the way to his car. MM

Douglas G. Adler *is a gastroenterologist at the University of Utah School of Medicine in Salt Lake City. He has published over 250 scientific articles and four textbooks on gastroenterology.*

TRUE OR FALSE



If you're seeing a doctor or specialist, you don't really need to bring a medical history or list of meds. It's the computer age! They can pull up all the information they need.

FALSE

In the era of electronic records, your doctor may have *too much* info and won't have time to wade through screens of data from every clinic or doctor you've ever visited. A good bit of the data they *need* comes from talking to you.

That's why it's important to review and write down your medical history, including the most recent symptoms or reasons that are bringing you to the doctor. As part of your history, make notes about physical or mental changes since your last visit (get a friend or family member to review the list with you, and note changes you've overlooked). In addition to your history, do bring a list of all medication names and dosages (including supplements and over-the-counter meds). On the opposite page, we've composed a checklist of this and other information to discuss. Fill it out and bring it with you, along with a notebook and pen for writing down the answers you get.

ALEXANDER RATHS/SHUTTERSTOCK

Good Health … Check

With a typical office visit lasting only about 15 minutes, it's essential to go prepared. Use this checklist (and extra paper if you need it) to make sure you cover all your bases. Some of it takes some preparation, so look it over now and start gathering info.

Your history should include:

- Symptoms you're currently experiencing.
- Any condition (chronic or otherwise) for which you're currently getting treatment.
- Health milestones: Surgeries, major tests and screenings, and medical problems for which you've received treatment. Include dates if you can.
- Any allergies or sensitivities.
- Medical history of immediate family (including your parents and siblings), noting diseases and, for deceased family members, causes of death.

Medications and other consumables:

List all of them and include both frequency and dosage. Include vitamins, supplements, over-the-counter medicines, herbals, homeopathic remedies, alcohol, tobacco, caffeine and even illicit drugs (don't worry; your doctor is forbidden from sharing your health info).

Blood pressure:

Check your blood pressure every time you pass one of those automated cuffs at a pharmacy or supermarket. Aim for at least 10 readings, each on a different day, and record all of them. Also note the time of day you took the reading.

Blood tests to discuss:

Over the course of your life, doctors will order lots of blood tests. But these tests might get overlooked, so ask about them.

- ❑ A1C: Also known as hemoglobin A1C, this measurement reflects average blood sugar level over the past two to three months, unlike the spot check of a regular blood glucose test. It's a better indicator if you have diabetes or pre-diabetes.
- ❑ CRP: This is also called a C-reactive protein or sensitive-CRP test. It checks for systemic inflammation in the body and can help diagnose early heart disease and other issues.
- ❑ Thyroid function: Doctors may not check if you have no family history, but get this done every five years. Wobbly thyroid output can go unnoticed for years and cause exhaustion, mood swings and other vague symptoms.
- ❑ DHEA: Dehydroepiandrosterone, sometimes called a male hormone, plays a role in both genders. Low levels can affect immune function, bone density, erectile ability and others.
- ❑ Aspirin resistance: If you're on an aspirin regimen, some researchers recommend getting checked for aspirin resistance — about 15 to 25 percent of people are not getting the benefit they should from it.

Anything Different?

Log any changes you have noticed in your health. Examples:

- Moles that look different.
- Changes in energy levels or libido.
- Mental or emotional changes or mood swings.
- Changes in urination or stools.
- Sleep alterations or increased snoring.
- Tingling or numbness anywhere.
- Sensory problems (ringing in the ears, strange smells).
- Anything you can think of that's not the same; your doctor can tell if it's significant or not. Let the doctor make the call.

Diagnosis for the Future

The history of medicine — and its future — is one of ordinary scientists making stunning breakthroughs. Doctors face new challenges every day, and meeting them means staying on the cutting edge of medical research. It also means forging stronger partnerships with patients who today are more knowledgeable and engaged than ever before.

SYDA PRODUCTIONS/SHUTTERSTOCK

'We Can Take His Heart Out...'

A CARDIAC TUMOR IS ALL BUT INACCESSIBLE. THE ONLY WAY TO DEAL WITH IT: OPERATE ON THE HEART OUTSIDE THE BODY.

BY **W. ROY SMYTHE**

NEIL MASSEY/GALLERY STOCK

I was in the middle of a normal clinic day, seeing candidates for surgery, when a nurse told me that one of them had arrived with a diagnostic video. When I had a free moment, I walked over to a computer and put the CD into the drive. As the program booted up, I noticed that the video was a cardiac MRI (magnetic resonance imaging) study. I clicked through the images, and what I saw was frightening. A large mass was growing in the patient's heart, in the back wall of the left atrial chamber, perhaps the worst possible place to have a problem like this. The right atrium and both ventricles are somewhat accessible to the surgeon's knife. But the left atrium at the back of the heart next to the spine is a difficult, if not impossible, area to reach.

As I watched the video, more details emerged. As the left atrium attempted to pump blood, the wall opposite the growth ballooned out awkwardly instead of contracting with the rest of the chamber, its movement altered by the growth. The mass also took up a lot of space and was impeding blood flow. If it got just 5 percent larger, the chamber would be almost completely obstructed, resulting in a high risk of sudden death.

I called one of my cardiac surgery colleagues, Mike Reardon, and asked him to take a look.

"Oh, man," Mike said, "that's a tumor, all right — and in a bad place."

My own heart sank. Primary tumors, which originate in tissues rather than spreading there from some other place in the body, are uncommon in the heart. They occur in less than 0.05 percent of autopsies. Seventy-five percent of them are benign, but this one did not look harmless. Benign tumors typically grow out from the surface of the cardiac wall like a mushroom on a stalk; malignant tumors look more like a bulge of varying thickness in the wall. Most cardiac surgeons will encounter only a few benign primary tumors in a career, and many will never deal with a malignant one.

"If we were to think about removing it," I asked, "how would we approach it?"

"How old is the patient?"

"Thirty-seven," I answered.

"Any history of coronary disease?"

"The transfer notes don't mention anything."

"Good," said Mike. "There might be one way to remove this, but it is drastic. We can take his heart out of his body, remove the tumor, reconstruct the heart and put it back in."

"OK … wow," was all I could say.

He was describing an extremely rare procedure: a cardiac auto-transplant. We would operate on the patient's heart outside the chest cavity and use cardiopulmonary bypass to support his body while we worked. The first successful auto-transplant to remove a cardiac tumor was performed in the 1990s. Since then, the procedure has been undertaken fewer than 50 times worldwide.

Mike and I went into the exam room to discuss the options with the patient, Mr. Johnson, and his wife. We told him the mass was probably a cardiac sarcoma, a malignant tumor originating in either the heart muscle or the blood vessels located there. We also told him that he faced significant risk of sudden death if the chamber became completely blocked, and that chemotherapy was usually ineffective for larger tumors of this type. Surgery was the only reasonable option, and we needed to move fast.

"However," I said, "there will be a fair amount of risk."

"How much risk?" Mr. Johnson asked quickly.

"There are three things to worry about," I replied. "One is whether or not we can remove the entire tumor. The second is whether we can put the heart back together again so it will function normally. And the last thing is the overall risk of having to stop your heart, remove it, fix it, put it back in and restart it."

"We normally quote a 1 to 5 percent risk of dying for heart surgery," I continued, "but your risk will be higher. The best-case scenario, if all goes well, is perhaps a 10 percent risk, and the worst case would be maybe five times that."

There was no hesitation. "Let's do this," Mr. Johnson said.

Two days later we were in the operating room, where I would assist Mike. As the anesthetizing medications were administered, Mr. Johnson's blood pressure dropped dangerously. The anesthesia team quickly gave him epinephrine to bring it back up. "Not much blood getting into that left side," the anesthesiologist said as he looked at the monitor. "That's why his pressure dropped. Good thing you didn't wait too much longer."

We divided Johnson's sternum and placed retractors to open up the chest. We then cut into the pericardium, the outer sac protecting the heart, and inserted tubing into the large vessels entering and leaving the heart to allow blood to bypass the organ.

"Go on bypass," Mike said, loudly enough for the technicians managing the pump behind us to hear. The heart began to empty of blood.

We put a cold saline slush around the organ to help put it into a kind of suspended animation. Then Mike and I went to work, using surgical scissors and scalpels to sever the vessels entering and leaving the heart. Once the large vessels and other attachments were cut, Mike lifted the organ out of the body.

I looked into Mr. Johnson's open chest as Mike placed this cold, now flaccid heart on an operating table a few feet away. Where his heart should have been was a void with tubes leaving it from the margins.

The only other time a doctor has this view is during a heart transplant, after the removal of the diseased organ and immediately before placing a donor heart into the recipient's chest. The difference in this situation, however, was critical. During a transplant, we never take out the diseased heart until we have the new one in the room. In this case, there was no new heart and a chance we wouldn't be able to fix the one we had taken out.

Mike and I worked quickly at the table, using our scalpels to remove the tumor.

"It's bigger than it looked in the images," Mike said, "but I think we got all of it."

We placed the tumor and the portion of the fleshy heart wall that we removed in a small plastic bucket to transfer to a pathologist. He would check the tissue to make sure that we had removed the entire mass.

WE WOULD OPERATE ON THE PATIENT'S HEART OUTSIDE THE CHEST CAVITY AND USE CARDIO-PULMONARY BYPASS TO SUPPORT HIS BODY WHILE WE WORKED.

A few moments later, the pathologist called into the room. "There is some microscopic tumor at the margin," he said.

Mike stared down at the opening in the back of the heart where the tumor had been.

"If we take any more," he said, "we may not be able to reconstruct it."

"We can try chemotherapy," I replied. "It has a better chance of working with microscopic disease. Better to have a chance than not to leave the OR."

"I agree," he said. "We don't have much time. We need to get this organ back in there."

He sewed a piece of bovine pericardium — the heart sac from a cow — into the opening left by the removed tumor. We then carried the heart back over to the patient and placed it in the void.

We sewed the large vessels back together and allowed the heart to gradually warm. We knew that a healthy organ will often start to beat once it is warmed, even without a blood supply re-established.

But nothing happened.

We continued to work, completing the suture lines. Blood began to flow back into the coronary vessels.

"No action here," the anesthesiologist said, watching the electrocardiogram.

Mike inserted a small needle into the muscle to measure the temperature. "Should be working; the temp is good," he said.

Several more seconds passed. Still nothing.

Then we noticed a quiver near the apex of the heart, followed by another, and then the heart sprang back to life, beating vigorously. We removed the tubes and closed Mr. Johnson's sternum.

Our patient made a good recovery and was discharged from the hospital several days later. After a regimen of chemotherapy to treat the microscopic tumor left on the heart, he had a good chance of complete remission and possibly even a cure. **MM**

W. Roy Smythe *is chairman of surgery for the Texas A&M Health Sciences Center College of Medicine.*

Of a Wife and a Whiff

WHEN THE FAINTEST CLUE IS OVERLOOKED, A WATCHFUL SPOUSE IS A PATIENT'S BEST ADVOCATE.

BY **H. LEE KAGAN**

Jerry was in fine form as he stood at center stage, his hand resting on the microphone stand, waiting for the laughter to subside. He had invited me to watch him perform stand-up at this West Los Angeles comedy club, and he didn't disappoint. But his wife, Sandy, wasn't laughing. She leaned across the small cabaret table we were sharing and said, "I need to talk to you about Jerry."

They had been patients of mine for many years. Both were late middle-aged, and neither had ever had a serious medical problem. I looked at her quizzically and she said, "His breath."

I leaned closer and asked, "What about his breath?"

"It's different. Not bad, but it's changed. Something's not right."

"How long?"

"Maybe three months."

I asked if anyone else had mentioned anything, and she shook her head.

"How does he feel?"

"He says he feels fine. But something is wrong. I'm his wife, and I can tell. Something has changed."

I looked up at Jerry. He was pulling faces now, mimicking his elderly father as part of his routine. The audience was loving it.

"Have him come see me in the office," I told Sandy.

"Honest to God, doc, I'm fine," Jerry insisted a week later. "If you ask me, I think it's my wife's sniffer that needs a checkup." Jerry did indeed look well, and when I put my face close to his and asked him to exhale through an open mouth, I could detect no unusual or unpleasant odor. Likewise, when I had him breathe out through his nose, nothing struck me as especially noxious.

He told me there had been no recent dental problems, sores in his mouth or other symptoms. He didn't wear dentures and hadn't begun using any new medications or supplements. The examination of his nose, mouth, tongue, throat and gums was unremarkable to my internist's eye. I took one more sniff. Nothing. Frankly, I wasn't sure that anything was wrong, but I told him to go see his dentist.

"I was just there three months ago," he protested. "Everything was OK."

I nodded and said, "See him again anyway." Halitosis, defined as a foul or fetid odor carried on the breath, originates in the oral cavity or sinuses 80 to 90 percent of the time. The literature reports that it occurs in about 15 to 30 percent of the population. Since it is often difficult to notice one's own odor, millions of people walk around with bad breath and don't know it.

The malodor of halitosis usually results from the bacterial breakdown of amino acids in food debris, saliva, blood and postnasal drip in the oral cavity. The residue of everything from caviar to cannoli provides the raw material for the volatile sulfur compounds primarily responsible for the offensive smell. Concentrations of the culpable microbes are particularly heavy in the spaces between the teeth and gums

OBSERVER/ALAMY

and on the back of the tongue.

The nasal passages and sinuses are the second-most common source of bad breath. Less common causes in the mouth are diseases such as gingivitis. Although an assortment of illnesses — such as advanced kidney disease and liver failure — can cause unpleasant odors on the breath, it is rare for any of them to produce halitosis without any other signs or symptoms.

Two weeks later I got a call from Sandy. "So, what did the dentist find in your husband's mouth?" I asked.

"Nothing," she told me. "The dentist didn't even think his breath was bad. He just told him to floss regularly and gave him a toothbrush. But I know something's wrong. Can't you just give him some antibiotics?" She was obviously frustrated.

I told her I didn't think that was a good idea. Although interdental and gingival sources of malodor may be transiently improved with antibiotics that suppress bacterial counts, in Jerry's case I didn't know what, if anything, I would be treating. "Let me see him in the office again," I suggested.

The following afternoon, Jerry and Sandy sat in my exam room. When I asked him how he was feeling, Jerry said he was still doing just fine. "But my wife smells ghosts," he quipped. He and I smiled and looked over at Sandy.

"I am not crazy," she insisted.

"Of course not," I said. I asked her if she had noticed changes in the odor of any other things that she smelled — foods, other people's breath. She shook her head vigorously before I was even done asking the question. "No. It's not me. I checked." She went on to tell me that she had Jerry take an over-the-counter ulcer medication for a week in case a stomach problem was the cause, but it hadn't made any difference.

"Not surprising," I told her. "Halitosis almost never arises from the esophagus, stomach or intestine." Undaunted, she repeated, "Something's wrong."

I thought for a moment and then said: "Fair enough. You know, sometimes conditions in the lungs can cause the breath to be bad. Let's do a chest X-ray." Even though I was certain that the yield on the X-ray would be small, I wanted to be able to tell her we had turned over every stone in search of the cause of Jerry's non-problem.

So even though Sandy was the only one who thought her husband's breath was bad; even though Jerry had no symptoms, findings or risk factors whatsoever; and even though his lungs sounded clear when I listened to them at his first visit, I had my medical assistant walk him down the hall for the chest film.

Several minutes later my assistant put the X-ray up on the view box in my office. I took one look and had to suppress an expletive. Sitting in Jerry's right midlung was a rounded density with a central cavity containing air and fluid. It was the radiographic signature of an abscess.

Amazingly, Jerry had been harboring a chronic infection in his right lung, but it had not been accompanied by any of the typical symptoms of an abscess — fever, cough, sputum production, sweats and weight loss. He had none of them. None, that is, except for an odor on his breath. The smell of purulent sputum incubating deep within a lung may waft its way up the bronchial tree, resulting in serious halitosis. But in Jerry's case, the odor was so subtle that it took the exquisitely sensitive olfactory memory of his wife to pick up the change. The "ghosts" she smelled were real, and antibiotics were exactly what it was going to take to get rid of them.

Adding to my surprise was the fact that Jerry had none of the risk factors associated with a lung abscess. Among patients with intact immune systems (not compromised by HIV or chemotherapy, for example), lung abscesses occur most frequently in those with conditions that impair the swallowing mechanism and allow for the aspiration of food or saliva into the lungs. Disorders such as strokes or neurodegenerative disease and conditions that depress consciousness like alcoholism, seizures and drug abuse can all predispose to oral contents "going down the wrong pipe." When coupled with poor dental hygiene, which can lead to the buildup of bacteria, these disorders set people up for aspiration pneumonias, infections that can smolder and destroy normal lung tissue, literally rotting out a "dead zone" in the lung.

But in a small number of cases, lung abscesses may arise in the absence of any identifiable risk factor. It is possible that Jerry had a congenital anomaly in his bronchial tree that led to the pooling of mucus, and eventually to infection, but it is impossible to know for certain.

In the pre-antibiotic era, lung abscesses were fatal one-third of the time and left another third with lifelong debilitating lung disease. The introduction of lobectomy, the surgical removal of part of the lung, improved these numbers, but an extended course of antibiotics long ago replaced surgery as the mainstay of treatment for these infections.

In consultation with an infectious-disease expert, I started Jerry on clindamycin, a potent antibiotic effective against the anaerobic (non-oxygen-consuming) bacteria that most frequently populate this type of infected cavity. After six weeks, an X-ray showed the abscess had shrunk down to a stable and probably permanent scar on Jerry's lung. There was no reason to expect any recurrence. But had Jerry's abscess gone undiagnosed, it might well have continued to grow and could have eventually necessitated the surgical removal of part of his lung.

At a visit shortly after finishing the antibiotic course, Jerry told me he had gained new respect for both his wife's dogged persistence and her uniquely talented nose. Then he said he was considering adding a bit to his stand-up routine about hiring his wife out to the bomb squad at the Los Angeles International Airport.

"Or," I suggested, "maybe you could just get her a bouquet of sweet-smelling flowers and take her out to a nice dinner." **MM**

***H. Lee Kagan**, is an associate clinical professor of medicine at the Keck School of Medicine of USC in Los Angeles.*

Q&A

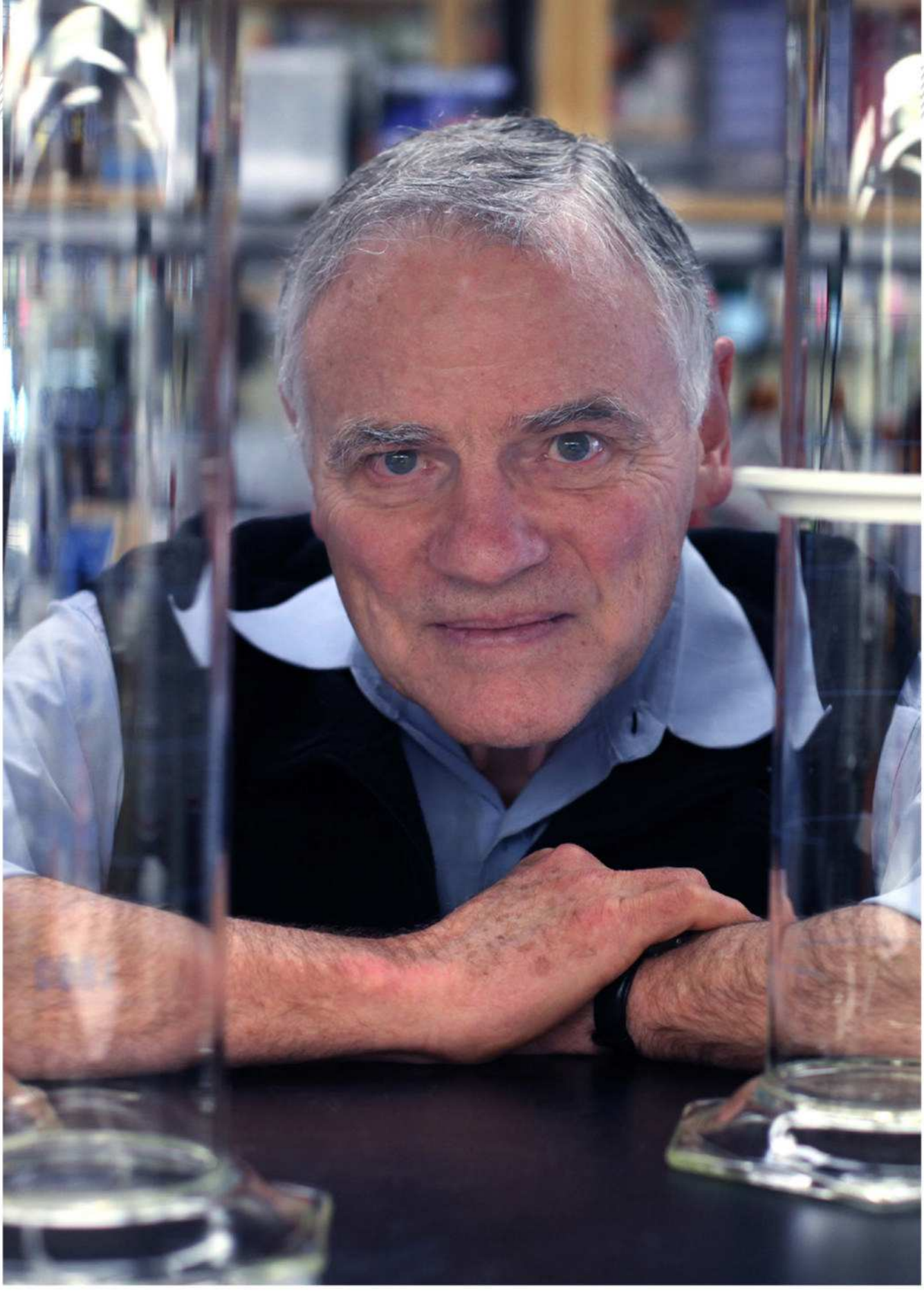
LEROY HOOD

FIRST HE MADE A MACHINE THAT CAN READ DNA AT LIGHTNING SPEED. NOW HE WANTS TO REACH INTO THE GENOME TO REVOLUTIONIZE MEDICINE.

BY **PAMELA WEINTRAUB**

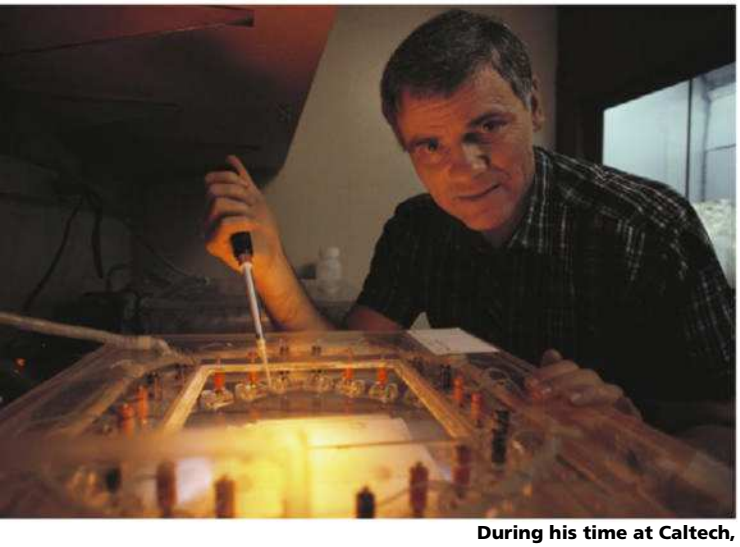
In 1985 Leroy Hood was one of the high-profile molecular biologists called to a power summit in Santa Cruz, Calif. The goal of the meeting was to determine whether an institute should be established there to sequence the entire human genome — a costly and complex undertaking. The idea had its skeptics, but Hood viewed the effort as crucial to creating information-based medicine and, ultimately, treating disease at the genetic level. His view prevailed, and the project famously completed its full map of the human genome in 2003.

With this vast wealth of information in hand, Hood is pushing a new approach to medicine that he calls P4 — predictive, personalized, preventive and participatory. "The foundation of P4 medicine is the idea that in the near future we will have the tools to reduce enormously complex data from 300 million Americans to simple hypotheses about



STEVE RINGMAN/SEATTLE TIMES

health and disease for each individual," he says. So far the payoff for treating genetic disease has been scant. But a flurry of breakthroughs has made Hood, now president of the Institute for Systems Biology in Seattle and a recent recipient of the National Medal of Science, hopeful that his elegant, new techniques for mining the genome and studying its interplay with the environment will soon transform medicine.



During his time at Caltech, where he worked until 1992, Leroy Hood helped develop an automated sequencer to color-code the different bases that make up a strand of DNA.

You have said that medicine is at the edge of an "information revolution." Can you explain?

In less than a decade, each of us will be surrounded by a virtual cloud of billions of points of medical data. Genome sequencing will cost only a few hundred dollars, so that will become a part of the medical record of each individual. A fraction of a drop of blood will be used to measure 2,500 blood proteins that assess the possibility of disease in each of your 50 major organs. Medicine will be personalized and preventive: Your genome might predict that you have an 80 percent chance of breast cancer by the time you are 50, but if you take a preventive drug starting when you are 40, the chance will drop to 2 percent. We will have the computational tools to connect all this information so we can gain enormous insights into health and disease and fashion an unbelievably predictive medicine of the future.

What prompted you to push for the Human Genome Project more than 25 years ago?

I realized we couldn't understand complexity one gene or one protein at a time; we needed a parts list of every human gene and the protein it coded for. My group at Caltech [where Hood worked at the time] had developed the enabling technology to analyze the genome, an automated DNA sequencer that uses fluorescent dyes to color-code the four different bases — the A's, C's, T's, and G's — that make up a strand of DNA. It's like having a pearl necklace with four different-colored beads on it. If you could snip them off one at a time and determine their colors, you could order the beads on the necklace. By ordering the beads, we determine the DNA sequence for a given gene.

How else have you helped advance the genomics revolution?

Two of our faculty members at the University of Washington [another of Hood's previous homes] invented the first key methods for proteomics, the study of proteins found in a cell, an organ or an individual organism. We developed a high-speed cell sorter to separate different types of cells. We also helped develop DNA arrays — chips containing short sequences of DNA that match up with parts of genes. For any given cell or tissue sample, these arrays can probe for the genes essential for understanding the underlying state of wellness or disease.

In 2000 you left academia to found the not-for-profit Institute for Systems Biology. Why?

The Human Genome Project gave us a parts list of genes and their proteins, but we still needed to understand them in the context of the entire biological system. This includes the networks that connect the genes and proteins, organizing them into cells, tissues, organs, individuals and populations. At each of these levels, the environment impinges on the signal coming from the DNA and changes it. The grand fallacy back then was that genomics could give us the answer to everything. It can give some insights, but unless you put them together with other levels of information, you can't understand what's going on. That integration is "systems biology."

In 2010, your team and another at Baylor College of Medicine published landmark studies linking a specific gene with a specific disease by sequencing the genomes of an entire family. What did you do?

Past studies looked at large populations of unrelated individuals and came up with long lists of genes that could be categorized as behaving in unusual ways in a particular disease. But there were so many DNA sequencing errors imposed by the equipment, it was difficult to determine which gene caused the disease. So we started thinking, why don't we select a single family with an interesting disease and see whether studying a smaller group of related individuals makes it possible to identify the genes involved in that disease. In the family we chose, the mother and father were healthy, but the two children each had two single-gene diseases: ciliary dyskinesia, in which the defective gene was known, and Miller's syndrome, a craniofacial defect for which the causative gene was unknown. Our analysis located the gene causing Miller's syndrome. This is important because it shows that we can find the genetic cause of diseases — even common diseases involving many mutations — if we sequence family genomes.

Why did looking at a single family yield information that you could not get from earlier studies of large groups?

With a single family, we can use the principles of Mendelian genetics to correct more than 70 percent of the DNA sequencing errors caused by the equipment and the chemistry. How? If you know the mother's genome and the father's genome and you see that the children have some genes that neither parent has, then you know that difference is either a mutation or a processing error. When we did this correction, we were finally able to study models of genetic disease. It's that simple.

Will you now use family genome sequencing to study other diseases?

We plan to study Alzheimer's, which is really a whole series of diseases. Before we can find the genes involved, we have to stratify Alzheimer's patients into distinct types. So far we've identified about 100 blood proteins specific to the brain. Each of those proteins represents the operation of the brain network that synthesized it. If a brain is normal, each of those proteins will have one level of expression. But if the brain is diseased, a subset of those proteins will have their concentration changed. Each form of Alzheimer's should perturb different brain networks and so influence the concentration of different proteins measured in the blood.

In less than a decade, we'll be surrounded by a virtual cloud of medical data. Genome sequencing will cost only a few hundred dollars and will become part of your medical record. A fraction of a drop of blood could assess the risk of disease in each of your major organs.

How will your P4 concept change the overall shape of health care?

It will take medicine from a focus on disease to a predictive, personalized, preventive and participatory mode that focuses on wellness. It will reverse ever-escalating medical costs to the point where I think we can export P4 medicine to the undeveloped world and make possible a democratization of health care that was absolutely inconceivable even five years ago. **MM**

Pamela Weintraub *is a contributing editor for* Discover.

10 BREAKTHROUGH MOMENTS

IDEAS AND INNOVATIONS THAT SOLVED SOME OF MEDICINE'S MOST CONFOUNDING MYSTERIES.

BY **CHRISTIAN MILLMAN**

Here's a simple question to ponder, although not an easy one to answer: Which medical advances from the past 100 years have made the greatest impact? And if you then posed that question to some of the world's leading physicians and top intellectuals, how would they respond? What would they say to something that holds untold millions of lives in its answer?

Luckily, this is not a rhetorical exercise. Just last year, the Medical Research Council in London, a research-funding initiative with global reach, posed this very question to these very types of people. Many of the survey results are in the following pages, alongside other breakthroughs of such profound importance throughout the centuries that they changed the very core of medical practice.

SSPL VIA GETTY IMAGES

Penicillin was initially hard to make. This 1943 photo shows culture flasks, each containing only one dose of the antibiotic, which took three weeks to extract.

Antibiotics and Their Incalculable Impact

When the Medical Research Council conducted its survey of medical advances of greatest import, the largest number of responses was for the discovery of antibiotics by Alexander Fleming. "Without antibiotics, modern medicine as we know it would be unrecognizable," wrote Stephen Whitehead, chief executive of the Association of the British Pharmaceutical Industry.

A dramatic statement for a dramatic discovery — and one that owes its existence to the decidedly nondramatic fact that Fleming was a slob. In 1928, Fleming was researching the properties of the well-known *Staphylococcus* bacterium, which continues to haunt us today in the form of MRSA, the antibiotic-resistant superbug.

One September morning, he entered his messy lab to begin work and noticed that one of his staph cultures had been overgrown by a fungus. Ordinarily, such a thing would have necessitated nothing more than throwing out the petri dish.

But this fungus was different. It was from the *Penicillium* genus, and all the staph colonies near it had died while those farther away were normal. At first, he called the bacteria-killing substance it was secreting "mould juice" before finally settling on the more formal name of penicillin.

After determining penicillin's ability to kill many kinds of gram-positive bacteria — such as those that caused scarlet fever, meningitis, diphtheria and bacterial pneumonia — Fleming abandoned most of his work with the new drug because of the difficulties in producing large amounts of it. The job of mass-producing penicillin fell to two Oxford researchers roughly 10 years later: Howard Florey and Ernst Chain.

So while Fleming continues to receive the lion's share of recognition for penicillin, all three researchers actually won the 1945 Nobel Prize in Medicine. Florey and Chain receded into historical anonymity while Fleming's reputation lives on. So does his original laboratory, which has been turned into a museum in London.

It's still pretty messy.

A replica of Joseph Lister's "donkey engine," a hand pump used to spray disinfectant and create an antiseptic environment before surgery.

The World-Changing Application of Germ Theory

It's a peculiarity that most people today know the name Lister only from the label of a tear-inducing mouthwash. That's a loss of historical significance on par with Einstein becoming nothing but the name of a bagel franchise in the future.

Although germ theory — the understanding that microorganisms cause many diseases — was first proposed in the 16th century and honed by the work of Louis Pasteur 300 years later, it wasn't until Sir Joseph Lister actually began applying that knowledge in the 1860s that medicine changed for the better because of it.

Lister was a surgeon in Scotland during a time when most of his peers considered it a status symbol to sport unwashed hands and bloodstained gowns as they moved from operation to operation. Lister, who was familiar with the work of Pasteur and others, made the connection between the lack of sanitation and "ward fever," the high rate of patient infections and deaths unrelated to the preceding surgeries.

In an attempt to control infections, he was the first to implement the kind of sterile procedures that are the norm today. He changed gowns and gloves, and he washed his hands thoroughly between patients. He also sterilized surgical instruments and operating rooms by using a "donkey engine" (like the one shown) to spray everything with a fine mist of carbolic acid, a known disinfectant.

Many other surgeons scoffed at Lister — until the rate of infections and ward fevers fell dramatically after his surgeries.

These days, the dangers of hospital-acquired infections are well known, and hospitals and other health providers that do not follow sanitary procedures are held accountable through regulatory actions and lawsuits. All because of a renegade Scottish surgeon whose contributions to medicine have saved many millions of lives.

MEDICAL LORE

Even though he had retired and suffered a stroke, Joseph Lister could not place his reputation on a similar pension. When King Edward VII contracted appendicitis in 1902 and needed his appendix removed, the risk of post-operative infection and death was still very high. So his surgeons sought Lister's advice before operating — successfully. The king later told Lister, "If it had not been for you and your work, I would not be sitting here today."

A somewhat romantic vision of the first smallpox vaccination.

Prevention, Not Treatment

Since the time of Galen and Hippocrates, medicine's purpose has been to heal the sick. While that remains the noblest of undertakings, a British doctor named Edward Jenner thought medicine could be something more. What if, he surmised, you could prevent people from getting sick in the first place?

That idea took root in 1796, when he noticed something unusual about milkmaids. Those who worked closely with cows and contracted an illness called cowpox didn't contract the horror that was smallpox. Exceptionally contagious, smallpox killed hundreds of millions, or even billions, of people since prehistory, sometimes causing the collapse of entire civilizations.

Cowpox, by contrast, caused many of the same symptoms as smallpox, yet they were less severe in nature, and the disease was not fatal. So Jennings tried something that would change history: He drained some pus from a milkmaid's active cowpox blisters and persuaded a farmer to let him inject the pus into the arm of the farmer's son.

Then, in a move that would get him barred for life from any modern medical association, Jenner injected the boy with *smallpox* pus. The boy became mildly ill but did not develop smallpox, and he fully recovered in a few days.

Thus was born the smallpox vaccine, and a vaccination campaign that lasted until the World Health Organization declared the disease — one of humanity's greatest scourges — eradicated by 1980.

Born alongside the smallpox vaccine on that day in 1796 was its fraternal twin, vaccine therapy, otherwise known as immunology. Since Jenner's discovery, vaccines have been developed for many other diseases. To name a few: measles, rubella, diphtheria, mumps, polio, meningitis, hepatitis A and B, influenza, rabies, yellow fever and tetanus.

The impact of immunology on the human race is incalculable — almost. Early in 2014, the Centers for Disease Control and Prevention quantified it just a little bit. It estimated that the vaccines given to American infants and children over the past 20 years will prevent 322 million illnesses, 21 million hospitalizations and 732,000 deaths over the course of those lifetimes.

A Big Dig Through Data Uncovers Epidemiology — and a Cesspool

Medicine can be so intense: the frenzy of the ER while saving a trauma victim. The claustrophobia-inducing hum and clank of an MRI. The triumphant high-five between surgeons after a delicate operation.

Some aspects of medicine are much softer in their walk and talk, yet no less important. Such is epidemiology — the use of observation and statistics to find patterns, causes, sources and effects of illnesses in populations. It's a field akin to accounting and actuarial science — more Ernst & Young than *Young Dr. Kildare*.

Yet that's the point: Epidemiology finds strength in numbers. The medical specialty's origin dates to an 1854 cholera outbreak that swept the city of London. John Snow, a doctor and early advocate of the then-controversial germ theory, suspected the cholera bug was being spread by polluted water.

Snow investigated the source of the outbreak, interviewing locals to determine the circumstances of the cholera victims. Then he did something pivotal. He marked up a map with the location of all the deaths and found a shared water pump in the middle of a cluster of victims. Others who lived outside the cluster had drunk from the same pump while passing through the area.

When city officials removed the handle from the pump, which had been dug next to an old cesspool, the outbreak stopped.

Although unrecognized in his time, Snow is considered the father of epidemiology to today's disease detectives, and his work greatly influenced public sanitation and other public health measures put in place worldwide.

Looking for water in a time of cholera had deadly consequences.

OPPOSITE PAGE: SCIENCE MUSEUM, LONDON/WELLCOME IMAGES. THIS PAGE, FROM LEFT: GASTON MELINGUE/THE BRIDGEMAN ART LIBRARY; PHOTOS.COM/THINKSTOCK

The Ugly Face of War Leads to Modern Plastic Surgery

Plastic surgery may conjure images of Hollywood starlets and their enlarged and enhanced bodies, but it was developed and advanced for far less cosmetic reasons. During World War II, aircraft and their crew were deployed in unprecedented numbers. Also unprecedented were the ghastly burns many of the crew suffered when their planes were shot down, igniting the fuel in the process.

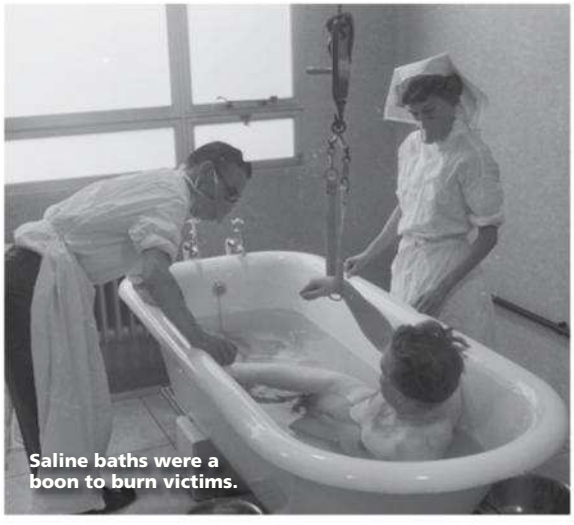
Archibald McIndoe, a New Zealand doctor, was among those charged with the daunting task of treating those men. In 1938, he was appointed consulting plastic surgeon to the Royal Air Force, one of four in the nascent field in Britain.

Medical convention at the time was to treat a burn with a burn. Acid was applied to remove the damaged skin, followed by a two-month waiting period to allow the area to heal enough to tolerate surgery. Not surprisingly, that was eight weeks of agony for those patients. It also left those burn victims with scars so severe that they often avoided going out in public for the rest of their lives.


Sir Archibald McIndoe

For McIndoe, such radical wounds called for a radical departure from convention. The first new method he developed was a saline bath for crew who had extensive burns. The idea for this came from pilots who ditched at sea and, therefore, ended up in saltwater. Their burns healed noticeably better than those who bailed out over land.

Next up for McIndoe was to operate immediately, incising the damaged tissue and developing a new skin-grafting technique to replace it, also immediately. Not only did this give patients much less scarring, it allowed them to begin using the burned area far sooner in the healing process.


Saline baths were a boon to burn victims.

Aside from his surgical prowess, McIndoe also became much loved for his recognition of the psychological impact of burns. He stopped the practice of dressing patients in convalescent gowns, and instead he insisted they be allowed to continue wearing their usual military uniforms. He also recruited local families and had them invite patients over for meals and other gatherings, which helped his patients reintegrate into society, rather than hide from it.

His patients quickly dubbed themselves The Guinea Pig Club, as an affectionate and tongue-in-cheek acknowledgement of how McIndoe's pioneering methods had helped them. In 1947, he received a knighthood for his work healing the bodies and psyches of his wartime patients. And his methods, including the skin graft he invented, are still in use today in reconstructive surgeries.

Making Blood Transfusions Work, Finally

You only need to read a book set in the 1800s or earlier to know that, through history, women often died in childbirth. One of the most common reasons for that was uncontrolled bleeding after delivery.

James Blundell, a British obstetrician, knew that transfusing blood into these women could save them. He also knew that others had been experimenting with transfusions for almost 200 years, often with fatal results, mostly because of the practice of using animal blood.

After successful experiments transfusing blood from one animal of the same species to another, Blundell made his first human attempt in 1818 on a woman who was hemorrhaging after childbirth. With her husband as a donor, he transfused 4 ounces of blood into the woman.

She survived, but not all of Blundell's subsequent patients were so fortunate. Although Blundell was the first to understand that human blood needed to be used on other humans, no one yet knew that blood came in different types — and that a transfusion with the wrong type would lead to immune rejection and, often, death.

Transfusions remained a dicey affair until 1901 when an Austrian doctor, Karl Landsteiner, discovered the different blood groups and which ones could be safely mixed with others.

Continuing research by others gave doctors the ability to bank blood, separate it into such components as plasma and screen for blood-borne pathogens. Today, about 15 million transfusions take place in the United States each year.

FROM TOP: UNIVERSAL HISTORY ARCHIVE/GETTY IMAGES; POPPERFOTO/GETTY IMAGES; CHRIS WARE/KEYSTONE FEATURES/GETTY IMAGES

The End of Hysteria and the Advent of Women's Health

"You're hysterical!" Funny stuff, huh? Well, not during the Victorian era.

Female hysteria was a widely used medical diagnosis, particularly during the 1800s and early 1900s, although the term is attributed to Hippocrates, who based it on the ancient Greek word for "uterus" (*hysteron*) in the fifth century B.C.

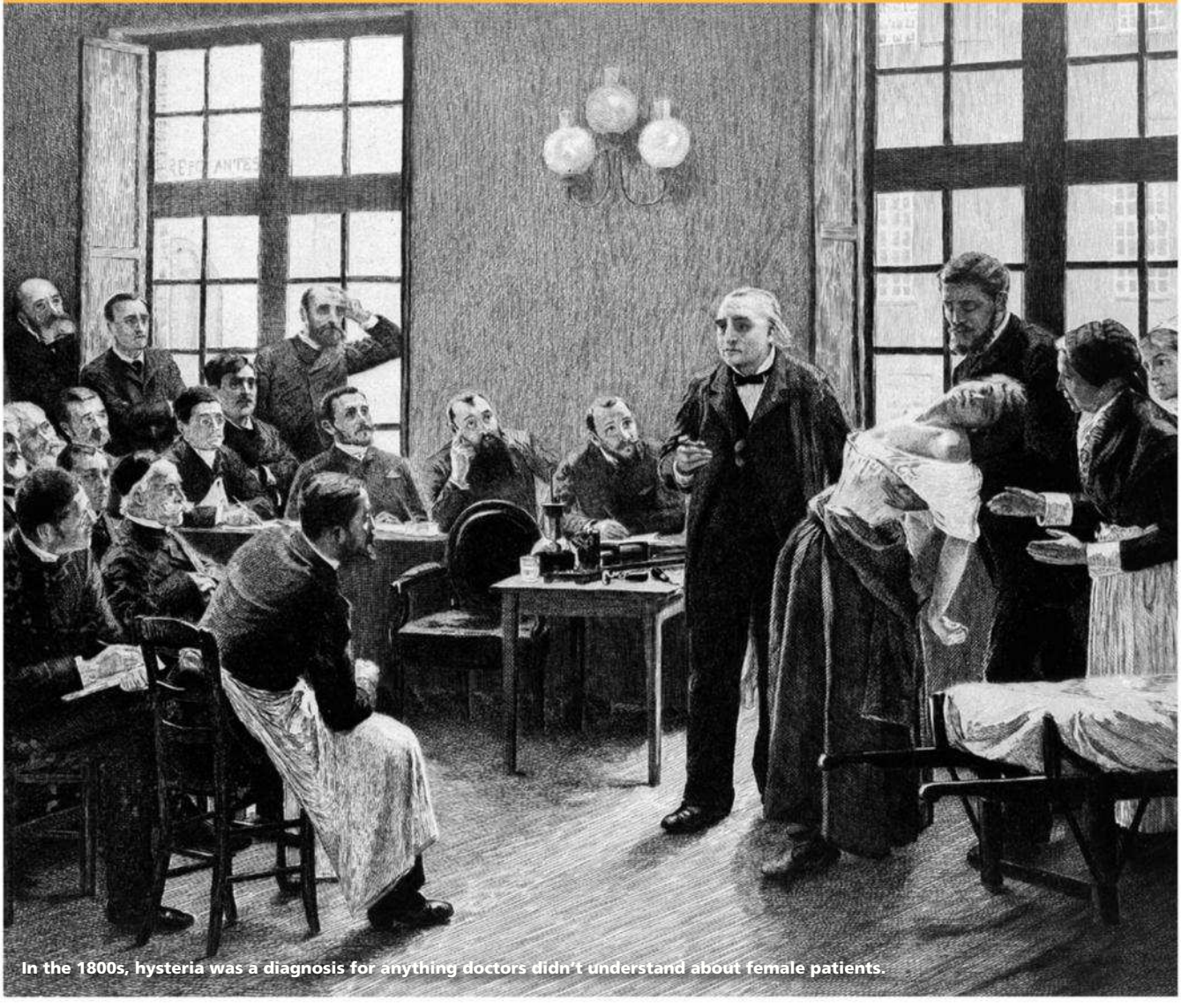
Hysteria took on many meanings over the centuries, and by the time of its demise as a medical diagnosis, it had served as a catchall for anything male doctors (and they were almost all male doctors) didn't understand about their female patients.

The symptoms of hysteria were, well, anything. Some examples: fainting, nagging, irritability, sexual dissatisfaction, loss of appetite, insomnia, laziness and a loss of speech but, weirdly, not of singing.

In the 20th century, the diagnosis began to be more heavily scrutinized. Unsurprisingly, it did not withstand that scrutiny. It was finally abandoned as a diagnosis through its removal from the 1980 DSM-III, the third edition of *The Diagnostic and Statistical Manual of Mental Disorders*, the medical world's widely agreed-upon way to classify mental disorders.

The demise of hysteria incidentally overlapped a rise in women's health as a separate field in medicine. Throughout the 1960s and 1970s, more and more women entered the field of medicine, to the point where newly minted physicians are now almost equally split by gender. Between the early 1900s and the early 2000s, the proportion of female graduates from obstetrics and gynecology residency programs grew from zero to about 80 percent. And in 1991, the U.S. Department of Health and Human Services established the Office on Women's Health.

Not a bad list of accomplishments for a gender once thought to be overwhelmingly incapacitated by hysteria.



In the 1800s, hysteria was a diagnosis for anything doctors didn't understand about female patients.

WELLCOME LIBRARY, LONDON/WELLCOME IMAGES

Where There's Smoke...

Most histories of the link between smoking tobacco and lung cancer attribute the discovery to a British doctor, Richard Doll, who made the claim in 1950 amid an epidemic of lung cancer in the postwar United Kingdom.

Although he proved the connection unequivocally by starting a 50-year longitudinal study in 1951 that showed half of smokers died from their addiction and that quitting was remarkably effective at reducing or eliminating that risk, he wasn't actually the first to notice the link.

German physician Fritz Lickint published a 1929 paper that showed lung cancer patients were also overwhelmingly smokers. But because that research appeared during the time of unrest in Germany that preceded World War II, it remained an overlooked, if not ignored, contribution to medicine for many years.

Not that it mattered. In the face of a powerful tobacco industry and associated lobby, it would take until 1964 for the U.S. surgeon general to issue his first report educating Americans on the incredibly toxic effects of smoking, including being the primary cause of lung cancer.

In the interim, the tobacco industry had been busy promoting the health benefits of their product. "More doctors smoke Camels," boasted one 1946 advertisement. "Smoke a Lucky to Feel Your Level Best!" said another one, from a 1949 Lucky Strike advertisement with a 17-year-old girl as a model.

Cigarettes were credited with better digestion, keeping a slender figure and creating an all-around sophisticated image. For a time, even the TV show *The Flintstones* was sponsored by Winston. Every episode ended with Fred and Wilma firing up a smoke together to show a Winston "tastes good like a cigarette should," even in the Stone Age.

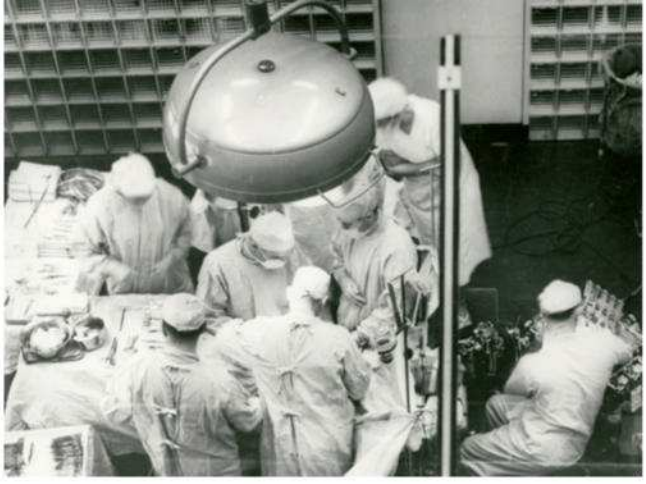
Educating America on the truth about smoking.

It was in this environment that the 1964 surgeon general's report was released. It was sent to media outlets on a Saturday, in order to minimize the effect on the stock markets and maximize coverage in Sunday newspapers.

The surgeon general at the time, Luther Terry, later said the report "hit the country like a bombshell." But it worked. A 1958 Gallup poll showed only 44 percent of Americans thought smoking might cause cancer; by 1968, another Gallup poll pegged that number at 78 percent.

In January 2014, the *Journal of the American Medical Association* commemorated the 50th anniversary of that report by issuing a sober statistic: Over 8 million American lives have been saved by anti-smoking efforts since the release of the 1964 report.

We've come a long way, baby.



From Grinding Organs to Transplanting Them

Nowhere is the interconnected nature of medical advances more on display than in the field of organ transplantation. When doctors began to understand how blood came in different types, they also began to understand the nature of immune rejection and what made donors incompatible with their recipients.

A doctor who benefitted greatly from this knowledge was Joseph Murray, an American physician who, like Archibald McIndoe (see "The Ugly Face of War Leads to Modern Plastic Surgery," page 76), served as a plastic surgeon in World War II. Murray gained additional experience with tissue rejection while trying to graft the skin of deceased donors to the badly burned areas of his patients.

After the war, Murray's focus turned to suppressing or avoiding the immune response that caused tissue rejection. If Murray could solve this problem, doctors could begin to figure out the long-sought-after ability to transplant organs.

A Ukrainian surgeon had attempted to transplant a cadaver kidney into a patient with renal failure in the 1930s, ending up with two dead bodies after the surgery. When Murray made medicine's next attempt to transplant a kidney in 1954, he did so by taking a healthy one from his patient's identical — and living — twin brother. Because there was no immune system rejection of the genetically identical kidney, both brothers survived the operation (shown above) and made full recoveries.

Murray then refocused his time on helping to find drugs that would suppress the immune response enough to allow transplants between less-compatible donors and recipients. With his guidance, others in the field of immunosuppressive drugs soon came up with such agents as Imuran, azathioprine and prednisone, allowing Murray to perform the first kidney transplant from an unrelated donor in 1959.

Murray won a Nobel Prize in Medicine in 1990 for his work in organ and cell transplantation. In 2012, he suffered a stroke at home at the age of 93. Murray died in Brigham and Women's Hospital, the same place where he performed his first organ transplant operation.

Since that first successful operation, the field of organ transplantation has advanced exponentially. About 30,000 transplants are performed in the U.S. each year, including lung, heart, liver, pancreas, bowel and bone transplants, among others.

TOP: BRIGHAM AND WOMEN'S HOSPITAL ARCHIVES. BOTTOM: AL FENN//TIME LIFE PICTURES/GETTY IMAGES

WELLCOME LIBRARY, LONDON/WELLCOME IMAGES

Bedlam Is Now Just an Expression

Chances are you've said this: "Man, it's bedlam in here." It's just a saying, right? Yes, and that's exactly the point.

Although the hospital that was once called Bedlam — the Bethlem Royal Hospital in London — still exists, the period of its history when it earned that nickname is long gone.

Uproar, confusion, screeching, wailing, chains worn indefinitely, madness unchecked — all were attributes of the place where the worst practices in treating the mentally ill were used over hundreds of years.

While it's easy to chalk that up to a simple lack of any kind of compassion for the mentally disturbed, there's a larger point at play: There weren't any good options for treating mental illness.

That only began to change in the 1950s with the development of the first antipsychotic drugs, foremost of which was chlorpromazine, also known as Thorazine. Although nowhere close to a perfect drug, Thorazine at least gave struggling doctors an effective option for treating such mental illnesses as schizophrenia and the manic phase of bipolar disorder.

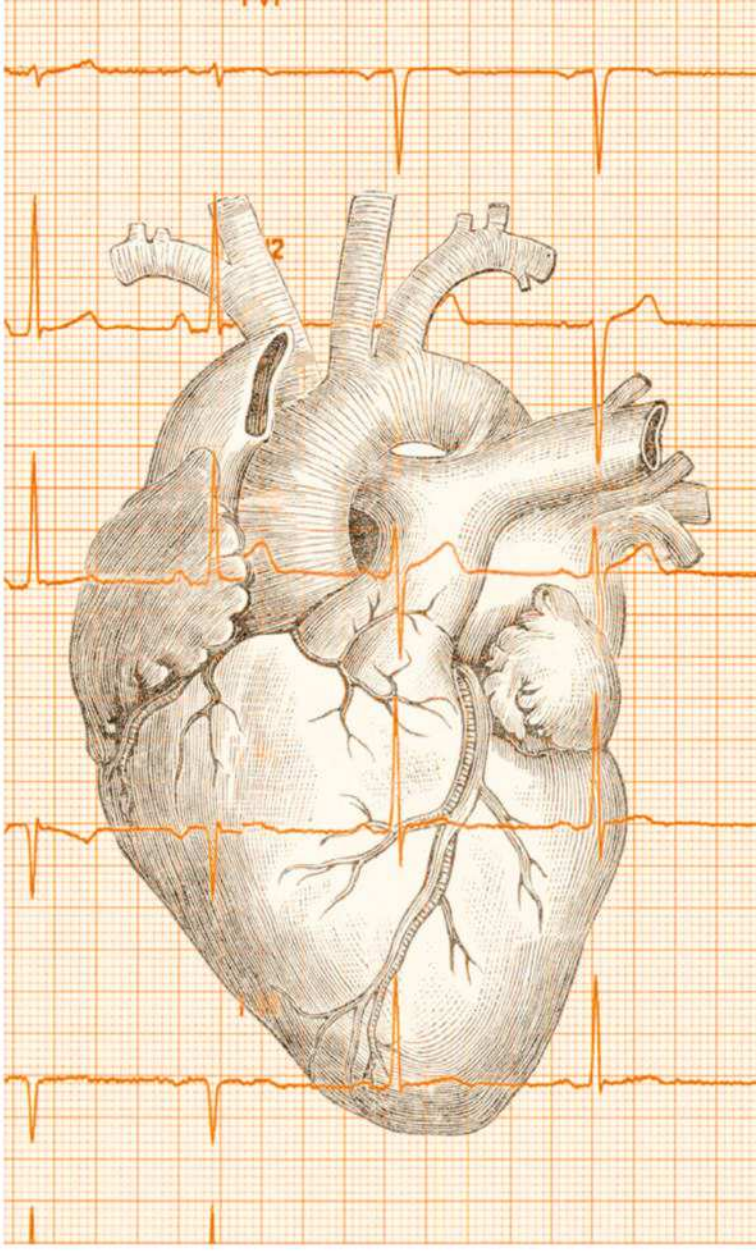
Thorazine's success in mitigating the worst behaviors of such diseases led to rapid and ongoing development of many other drugs for mental ailments, including antipsychotics and antidepressants. Many critics believe the mentally ill are overmedicated and demonize psychoactive drugs, but few would want to return to the days before these drugs were available.

"Without the discovery of chlorpromazine, we might still have the miserable confinements witnessed [in the time] of desperate remedies," wrote Trevor Turner, a psychiatrist at the Homerton Hospital in London, in his nomination of the drug as one of the most significant medical advances of recent history. "It is hard not to see chlorpromazine as a kind of 'psychic penicillin.'" **MM**

A Family Secret

WHEN HIS MOTHER'S HEALTH IS ON THE LINE, A PHYSICIAN'S OBJECTIVITY MIGHT VANISH — BUT NOT HIS POWERS OF OBSERVATION.

BY **TONY DAJER**



I know the moment it started. Seven years ago, my mother and I were strolling — not briskly — by my hospital. As we chatted, it hit me that something was amiss.

"Mom, are you OK?" I asked.

"I'm fine, why?" she replied, her chest heaving.

"Are you out of breath?"

"Oh, I'm just out of shape." She smiled and batted her right hand to wave me off. At 71, my mother is an expert denier, but she has had her share of serious medical issues, including lupus — an autoimmune disease that can target almost every organ — and a stroke that rendered her left arm nearly useless. An accomplished piano teacher, she still managed to resume teaching. She never met a symptom she wouldn't rather ignore.

"You're out of breath." I wasn't asking anymore.

My three children will attest that their father is a champion minimizer himself, whose benchmark for declaring perfect health in family members is having a pulse. If mom's shortness of breath was getting my attention, then it was serious.

My first thought was an impending heart attack.

Any doctor who thinks chest pain is the only unfailing symptom of heart disease is going to kill patients. Only half of heart attacks in women are heralded by chest pain. In men and women older than 65, the percentage is even smaller. So-called "atypical" symptoms range from shortness of breath to left *and* right arm pain, dizziness, upper abdominal pain and back pain.

Of that list, shortness of breath is the most common. Why would clogged coronary arteries leave you short of breath? The classic symptom, angina, is the pain that comes when heart muscle is starved for oxygen. But lack of oxygen can also make heart muscle stiffen, causing fluid to back into the lungs. Why one person might suffer pain and another might experience breathlessness isn't known, but it is the subtlest of those atypical symptoms, and sometimes easy to overlook.

Not going to fool me, though, I thought.

Still, having learned the hard way that objectivity vanishes when it comes to family and friends, I called my favorite cardiologist, hoping he could take a look at Mom.

"I'm booked," he explained. "Do you need me to see her now?"

"Now," I answered. "I think this is new."

"Bring her up."

Forty-five minutes after delivering my mother to the exam room, they called me in.

"She's OK," came the objective verdict.

My colleague had done an electrocardiogram (EKG), a noninvasive test to measure the heart's electrical activity and look for underlying problems, including damage to the heart muscle and signs of blockage or impeded blood flow.

ENVISION/GETTY IMAGES

In addition, the cardiologist questioned her closely and performed a detailed exam. The result and her symptoms, he concluded, didn't suggest that Mom was on the verge of a heart attack.

While I initially breathed a sigh of relief, over the months that followed, Mom's breathing steadily worsened. I wrote it off to some smoking in her 20s, and to the past episodes of fluid buildup around her lungs due to the lupus. Both can cause chronic, progressive scarring to the lungs. Repeatedly, Dad took her to the best lung specialists in town. They determined the problem was emphysema and treated it accordingly: with inhaled bronchodilators and powerful steroids when needed. And she did seem to need them. One time, just walking to the kitchen, Mom panicked, threw her head back and gulped air while her right hand clutched at her throat. Dad rushed over with her inhaler, and after a few puffs she seemed to settle down.

But something nagged at me.

Mom hadn't smoked *that* much. Plus, during the kitchen episode, she had not wheezed. For that matter, I had *never* heard her wheeze. In emphysema, wheezing is caused by the collapse of small airways during exhalation — the result of surrounding supportive tissues being destroyed by years of cigarette smoke. Absence of wheezing doesn't *always* mean absence of emphysema, but close enough that it made me wonder. Mom, however, claimed sometimes she did wheeze and that the inhalers helped.

Whenever my father summarized her doctor visits, I'd ask: How do they know she has emphysema? The less-than-satisfying answer was that, since her symptoms were so obvious, they apparently saw no need to perform standard pulmonary function tests — an automated measure of lung function. So we sought yet another opinion at Boston's Brigham and Women's Hospital, a world leader in pulmonary medicine. But even they came back with the same treatment plan: Keep doing what you're doing.

Over the next few years, I watched Mom slowly lose function. We're big on Christmas vacations; my three sisters and I, spouses, and 10 cousins all get together. During those gatherings, it was hard to overlook Mom's decline. Last year, when we toured a lakeside boardwalk, Mom got so out of breath that her now-strapping grandsons had to hoist her in an arm-carry to the car. Laughing the whole way, she announced, "Look! I'm the queen mother!"

While I admired her pluck, I was dismayed by her confounding symptoms. The stroke had damaged coordination in her left foot, which led to chronic pain. The less she walked, the more deconditioned — and short of breath — she got.

Six months ago, she endured a bout of "emphysema" so severe that her pulmonologist put her on high-dose steroids and aggressive inhalers — a classic double-down strategy. Horrified at such high doses of steroids, Mom stopped taking them and, surprisingly, did OK.

A few weeks later, while we were all staying at my sister's in Boston, Mom padded out of her room in the morning and remarked, "You know, I had a little pain last night. Here."

She rubbed the middle of her chest.

MY THREE CHILDREN WILL ATTEST THAT THEIR FATHER IS A CHAMPION MINIMIZER WHOSE BENCHMARK FOR DECLARING PERFECT HEALTH IS HAVING A PULSE. IF MOM'S SHORTNESS OF BREATH WAS GETTING MY ATTENTION, THEN IT WAS SERIOUS. AND MY FIRST THOUGHT WAS AN IMPENDING HEART ATTACK.

Which is when the past seven years suddenly made blinding, forehead-smacking sense: Yes, this had to be heart disease, and yes, despite the occasional brain-freeze, sometimes you are the best doctor for your family.

We saw a nearby cardiologist the next day. I relayed my suspicions. Two days later, he placed her on a treadmill and did a simultaneous EKG. This time, the EKG showed the telltale changes of decreased blood flow through the coronary arteries. The next step was a coronary angiogram, where a catheter is threaded up the femoral artery, and dye is injected into the three coronary arteries to see any blockages.

The procedure showed severe, long-standing blockage: One of the three arteries — completely clogged — was being fed by a small collateral artery coming off a branch of its neighbor. A second artery was severely narrowed. Her heart had been starved of oxygen for so long that it had essentially jury-rigged new plumbing to bypass the worst blockages. It's not clear why some people's bodies can form these collaterals and some can't. This imperfect solution had kept her alive, but it had also made her symptoms that much harder to pin down, and confounded earlier attempts at diagnosis. But it was clear now that her worsening symptoms indicated the collaterals were losing the battle.

After much hand-wringing, we proceeded with open-heart surgery. The idea is simple, though the technique takes years to master: Harvest a vein from the leg, attach one end to a small new opening in the aorta, the other to the coronary artery beyond the blockage, and presto! A new aqueduct brings fresh flow to a parched watershed. Short version: After seven years of misdirection and uncertainty, Mom got two new pipes.

She gained much more than that, of course. Six months later, I am happy to report, though she certainly deserves one, Mom has no more need of a queen mother's carriage. MM

Tony Dajer *is site director of the emergency department at New York-Presbyterian/Lower Manhattan Hospital.*

WHAT PERCENTAGE OF DIAGNOSES ARE WRONG?

5% or less
10% to 30%
30% to 50%
50% or more

LUIS LOURO/SHUTTERSTOCK

According to a review of several studies, anywhere from 10 to 30 percent of errors are errors of diagnosis. But don't rush to blame the doctor. Many conditions elude conclusive diagnosis. You can narrow the odds by giving your doctor as many specifics about your symptoms as you can, and better understand the ramifications of a diagnosis by asking these questions:

- Please explain my diagnosis. What symptoms or facts about my case led you to that diagnosis?
- What does this condition mean for my overall health? How will it affect my daily routine?
- Is there anything I can do to control or manage the condition or its symptoms?
- What are my treatment options? What are the benefits or side effects of these options?
- Will I need surgery? Please explain the procedure. Who will perform it? How often has that person performed it?
- Does my condition have to be treated? What are the consequences if I don't get it treated?
- Do you recommend further tests to confirm the diagnosis? What are these tests for? What will they tell us?
- What are the benefits of seeking a second opinion?
- How can I find out more information about this condition or disease?
- Are there any clinical trials underway for this condition or disease?

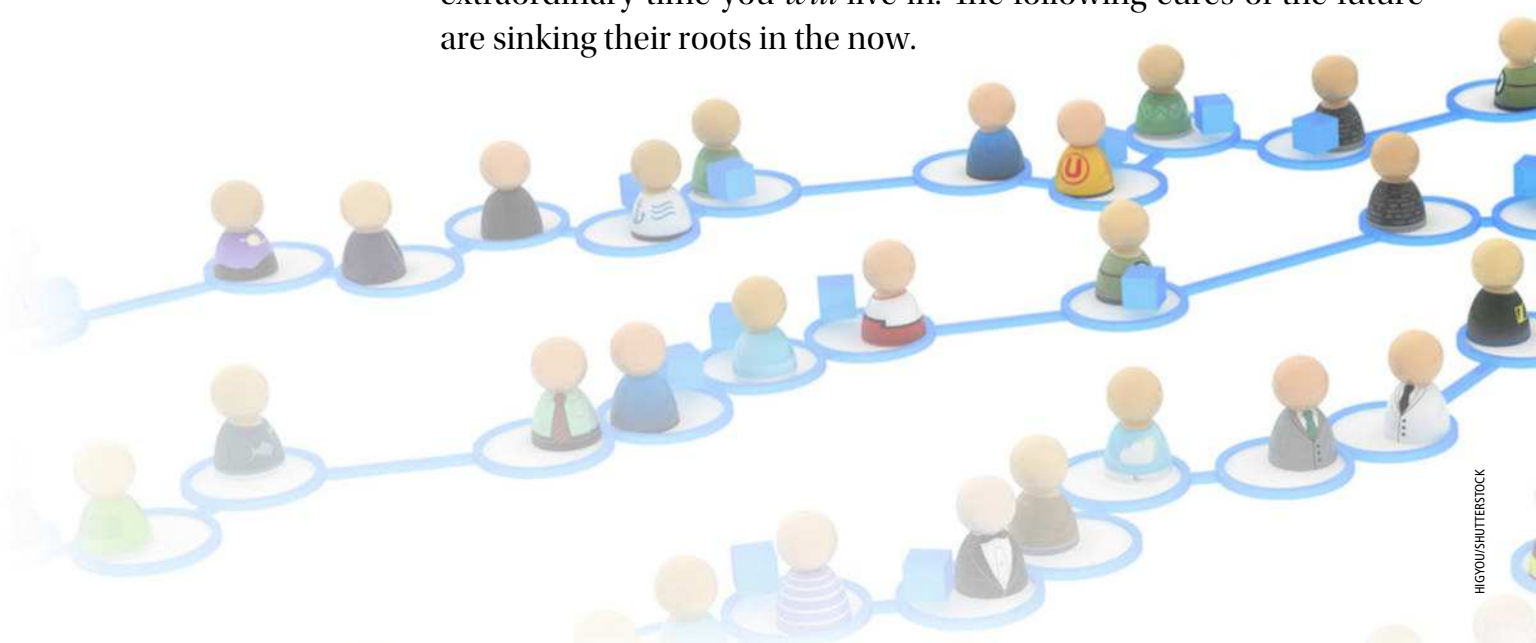
FUTURE CURES

10 MEDICAL METHODS AND MACHINES THAT WILL IMPROVE HEALTH AND HEALTH CARE AT EXPONENTIAL RATES.

BY **CHRISTIAN MILLMAN**

Yogi Berra was right when he said, "The future *ain't* what it used to be." Only he wasn't right in the way he meant it, which was usually the case. The future really isn't what it used to be — it's much, much brighter.

Consider the extraordinary time you live in: There has never been a period in history of such rapid advances in medical knowledge and technology. Now consider the even more extraordinary time you *will* live in: The following cures of the future are sinking their roots in the now.



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A Crowd and a Source

Crowdsourcing's basic premise, that individual knowledge can never match collective wisdom, applies to diagnostic medicine as well. Well-trained physicians and other health professionals typically diagnose health conditions. But some things confound even the experts, and even the experts confound some things.

Imagine a future where diagnoses are made or confirmed by a cast of thousands. It's starting right now: If you have an unsolved medical case, you can submit your symptoms to the crowd-sourced CrowdMed website.

Scores of "Medical Detectives" track incoming cases and, if they feel they can offer insight, they'll jump in to try and make or confirm the diagnoses. If a detective makes the right call, he or she may get a cash reward. The successful detective gets to keep the reward or donate it to a charity that funds treatment for patients in need. The patient uses the diagnosis to seek treatment.

Submitting a case is free and confidential. Becoming a Medical Detective is also free, and you don't need to be a physician to make diagnoses or earn rewards — just have good medical instincts. Detectives with verified health credentials can also join an expert review board, for which patients pay a fee to use. For more information, visit crowdmed.com.

The Power in Empower

Similar to CrowdMed in function but different in purpose, PatientsLikeMe website users already have an accurate diagnosis. This online community of fellow patients encompassing numerous diseases and disorders joins others in the same situation to share advice, new treatments, novel trials, recent research and plain old empathy.

The community was founded in 2004 by three MIT engineers, two of whom are brothers who have a third brother with Lou Gehrig's disease. That difficult-to-treat condition led to the inspiration for the community, which now provides support to patients with more than 2,000 different conditions.

The site tracks every approach used by community members, assigns each a result — including positive or negative aspects — and shares those results with medical organizations and health providers to help them improve their delivery of care.

To learn more, visit patientslikeme.com.

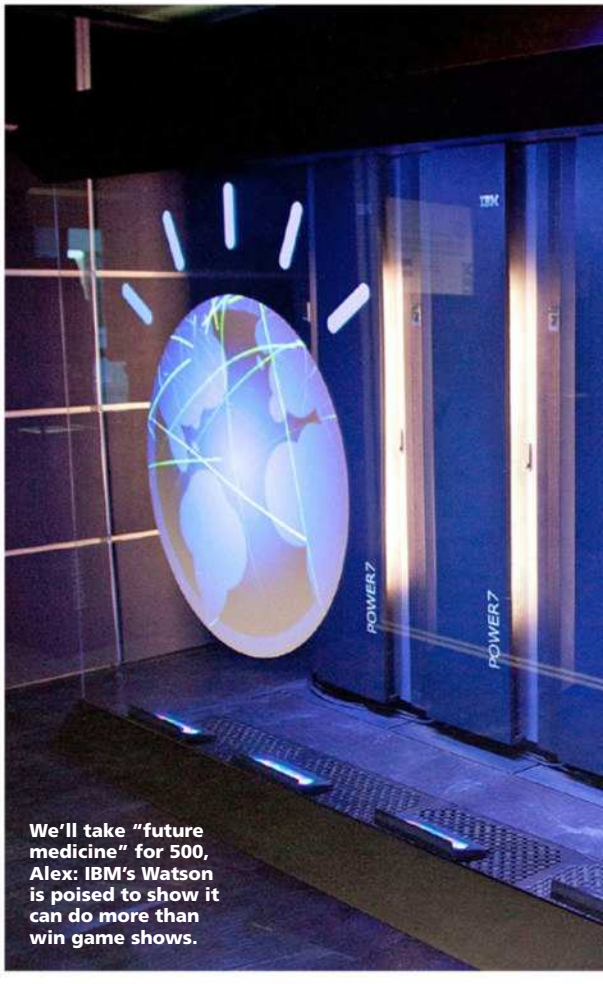
Face of the future: A 3-D-printed prosthetic nose and ear, on display at a 3-D expo in London.

Forget Sherlock; It's All About Watson

Watson is the real stickler for data, data, data — but not the Arthur Conan Doyle character. Instead, it's the IBM supercomputer getting buzz for such flashy feats as winning rounds on *Jeopardy!*

But it also has a far more serious purpose than impressing Alex Trebek. Watson is what's called a cognitive system. When used in a health care setting, that means doctors can speak in a natural voice to it about a patient's symptoms, then watch as the supercomputer goes to work mining all available patient data, and related medical research and clinical findings from around the world.

After it sifts its terabytes, the computer suggests diagnoses and treatments. IBM says the goal for Watson is to exceed the diagnostic success rate of mere mortals — where, in the U.S., approximately 1 in 5 diagnoses are wrong or incomplete, and about 1.5 million people are injured by medication errors each year.



We'll take "future medicine" for 500, Alex: IBM's Watson is poised to show it can do more than win game shows.

Bones by Design, Organs on Demand

The rapidly evolving field of 3-D printing is just out of its infancy, but it's already having a huge impact on medicine. These printers have CAD-like abilities and can spray almost any material, including biomaterials, through specialized nozzles to build incredibly complex three-dimensional objects.

Imagine diseased, damaged or missing body parts becoming a thing of the past — it's already happening. Metal jawbones and hips are among the first replacement bones to be made on a 3-D printer. Further, Massachusetts General Hospital researchers have grown an artificial ear from animal tissue and are working on doing the same with human tissue.

Livers. Kidneys. Bladders. These and more are in various stages of 3-D development, which is huge news to the 18 or so people who die every day — that's 6,500 annually — in the U.S. alone while waiting for a traditional organ transplant.

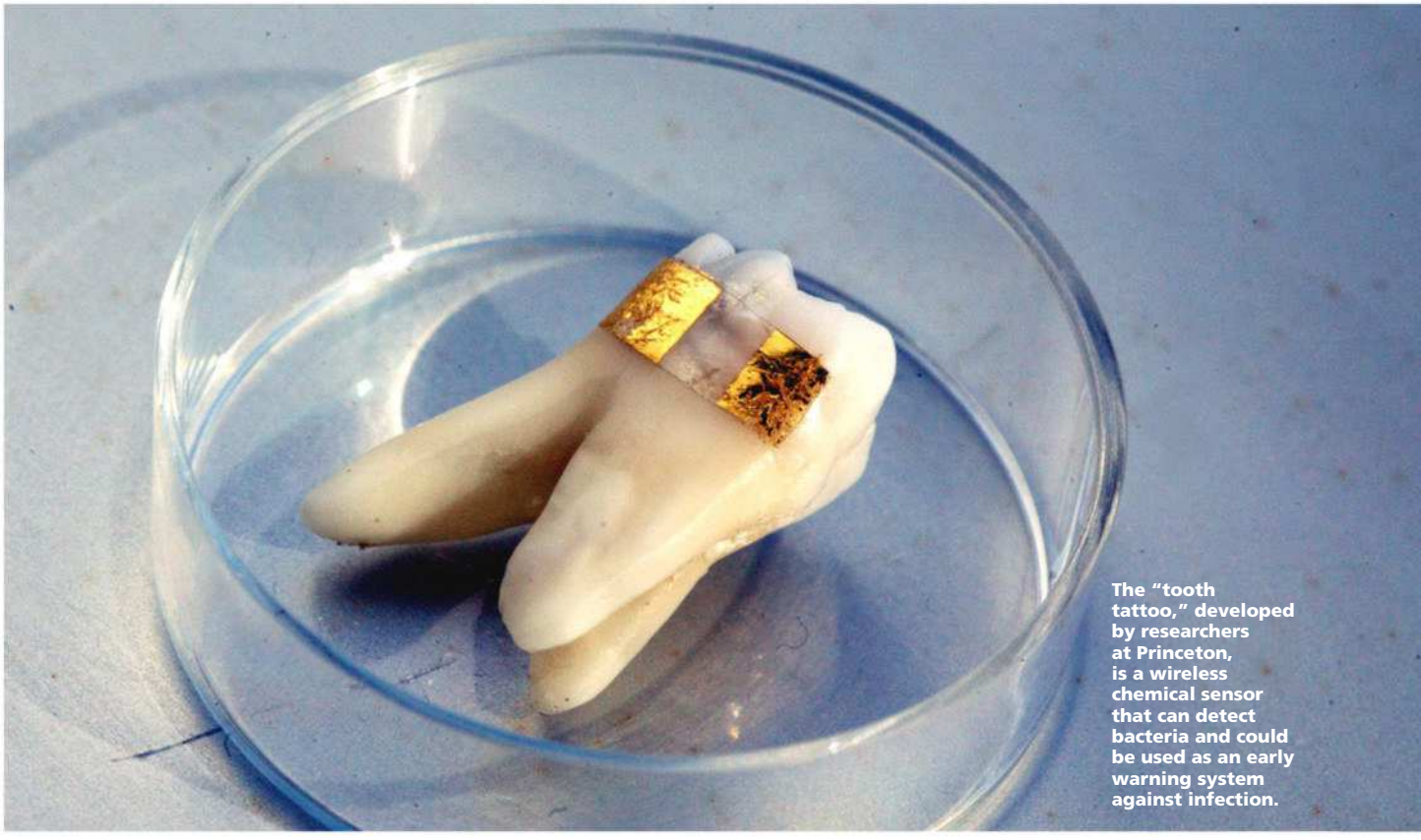
CLOCKWISE FROM BOTTOM LEFT: OLESKY MARK/ISTOCK/THINKSTOCK; BLOOMBERG VIA GETTY IMAGES; IMAGE POINT FR/SHUTTERSTOCK; BEN HIDER/GETTY IMAGES

That's Dr. Siri to You

If your idea of a righteous smartphone app is Candy Crush Saga, Instagram or Pandora Radio, you're missing out on one of the most impressive areas of health care innovation.

Apps either available now or in advanced development are remaking the ability of smartphones to ally with you and your doctor to keep you in the pink. In 2012, to pick a recent example, the FDA cleared an iPhone app that lets your doctor take a remote EKG just about anywhere there's a suitable connection.

Others currently on the market help radiologists decipher medical images and let people track suspicious moles for signs of unwanted change. One app, called CellScope, takes a picture of your child's inner ear, shoots it over to your family doctor, and lets her decide whether your child is screaming about an ear infection or an annoying sibling. If there's no infection, you and your child avoid an unnecessary trip to the doctor's office and pharmacy.



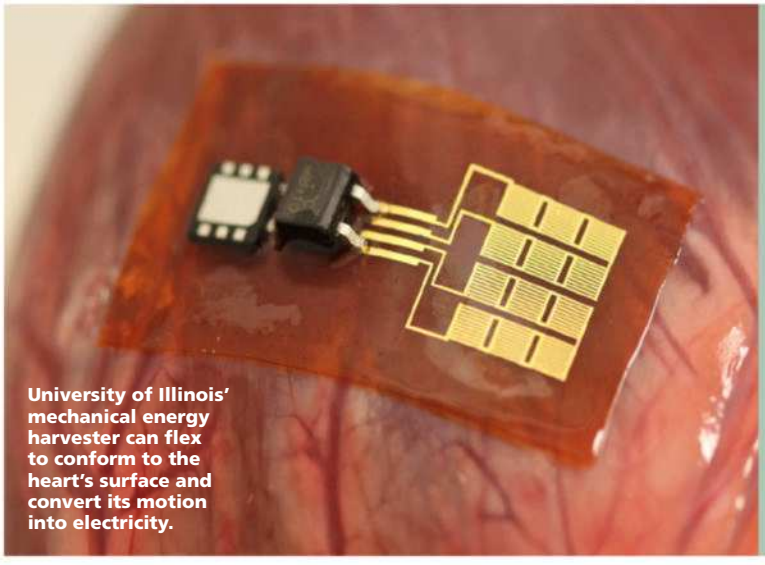
The "tooth tattoo," developed by researchers at Princeton, is a wireless chemical sensor that can detect bacteria and could be used as an early warning system against infection.

Straight From the Horse's Mouth

Your doctor isn't sure what your particular symptoms mean. Soon, she'll be able to reach for a slew of sensors to give her an insider's view of what's going on. Called biohackers, these sensors will be either sewn into your clothing or implanted in your body.

One in advanced development is a sensor embedded in a tooth that measures irregular jaw movements, toxic inhalants, how often you're coughing, and what harmful junk you're eating and drinking. Others are still in the tinkering stage: internal GPS units that can lead hikers to safety and medical treatment; bandages that change color or squeak if they're too tight or loose; and socks that record temperature and heart rate during exercise.

Others will report on your sleep patterns, hydration levels, urine composition, stress hormones and almost anything else that can be measured. The goal, say most researchers working in this field, is to help you take steps before a problem arises, or quickly diagnosis it when one does.



University of Illinois' mechanical energy harvester can flex to conform to the heart's surface and convert its motion into electricity.

The Beating Battery

Millions of pacemakers in millions of chests run out of juice every seven years and need to be replaced. Technology being developed at the University of Arizona and the University of Illinois will enable them, and other implanted devices, to harness electricity from the beating heart itself. Think of it as your own thoracic turbine.

Researchers are creating nanogenerators that convert the mechanical energy of a heartbeat into electrical energy. Not only will these internal power plants provide electricity, they'll also eventually become sophisticated enough to troubleshoot any problems in the device they're powering and, in some cases, even fix them.

TOP: FRANK WOJCIECHOWSKI/REX FEATURES/ASSOCIATED PRESS. BOTTOM: UNIVERSITY OF ILLINOIS, UNIVERSITY OF ARIZONA

From the Mean Streets to the Cancer Clinic

Breathalyzers are world champions when it comes to testing the breath of boozy drivers, but now they're almost ready for a new role in the medical community: diagnosing cancer.

In ongoing trials at Georgia Tech, a $100 Breathalyzer-style device has been detecting lung and breast cancer in patients with up to 80 percent accuracy. The new device samples as many as 75 different volatile compounds characteristic of these cancers to reach or confirm a diagnosis.

The first benefit of this approach is in its cost-savings: A biopsy procedure costs up to $5,000. A PET scan can rack up $4,000 in bills. The second, more important benefit, is the potential for an earlier diagnosis for lung cancer. The Georgia Tech researchers note that when lung cancer is caught in Stage 1, which is the earliest stage, it has a 70 percent cure rate. Most lung cancers, however, aren't caught until Stage 3, when symptoms become more obvious. The cure rate at that point, however, plummets to less than 25 percent.

If this device holds up in larger human trials as well as it did in its early testing phase, expect to see it as an option right in your own doctor's office within a few years.

Instead of detecting alcohol levels, new Breathalyzer-type devices will trap compounds that can be tested for cancer.

GARY MEEK/GEORGIA TECH

A Return to the Glory Days of Antibiotics

Few people alive today can fully appreciate the earthshaking importance of Alexander Fleming's 1928 discovery of penicillin. Countless lives have been saved from that antibiotic and the numerous others that followed.

Fast-forward over 80 years and we find ourselves in the highly dangerous position of many bacteria becoming resistant to the current slate of antibiotics, with at least 2 million Americans getting an antibiotic-resistant infection each year, some 23,000 of them fatal. This has been made worse by a decades-long dry spell in the development of uniquely new antibiotic drugs.

That's about to change: With no fewer than a dozen novel antibiotics in clinical trials, this new generation of drugs works in fascinating ways. Some are simply better versions of the older flame-throwing antibiotics, which kill almost every kind of bacterium in their path. Most do this by adding silver to existing antibiotics, a move that gives them enhanced strength.

But others, colloquially called antibiotic smart bombs, are much more elegant. They're designed to target and destroy specific strains of bad bacteria that actually cause disease in humans. This approach has the added benefit of leaving unharmed most of the other benign or beneficial bugs that normally reside in your body.

Antibiotic smart bombs may help redefine the world of antibiotics.

Chinese Container Hospital Could Reinvent Access to Health Care

What good are advances in medical treatment if you don't have access to the medical facilities that provide them? That's the idea behind a Chinese initiative to use shipping containers to create a kind of hospital in a box.

Each hospital is made up of 10 shipping containers, with rooms for clinics, pharmacies, operating theaters, diagnostic equipment and public health services.

The containers can be configured and equipped for each individual location and local need at a fraction of the $17 million it takes to build a small three-story hospital in the U.S.

Although the first container hospitals are designated for several countries in Africa, the idea is applicable worldwide — in any rural community where the closest health care facility is too distant to be convenient, even accessible. **MM**

A container hospital ready for deployment.

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