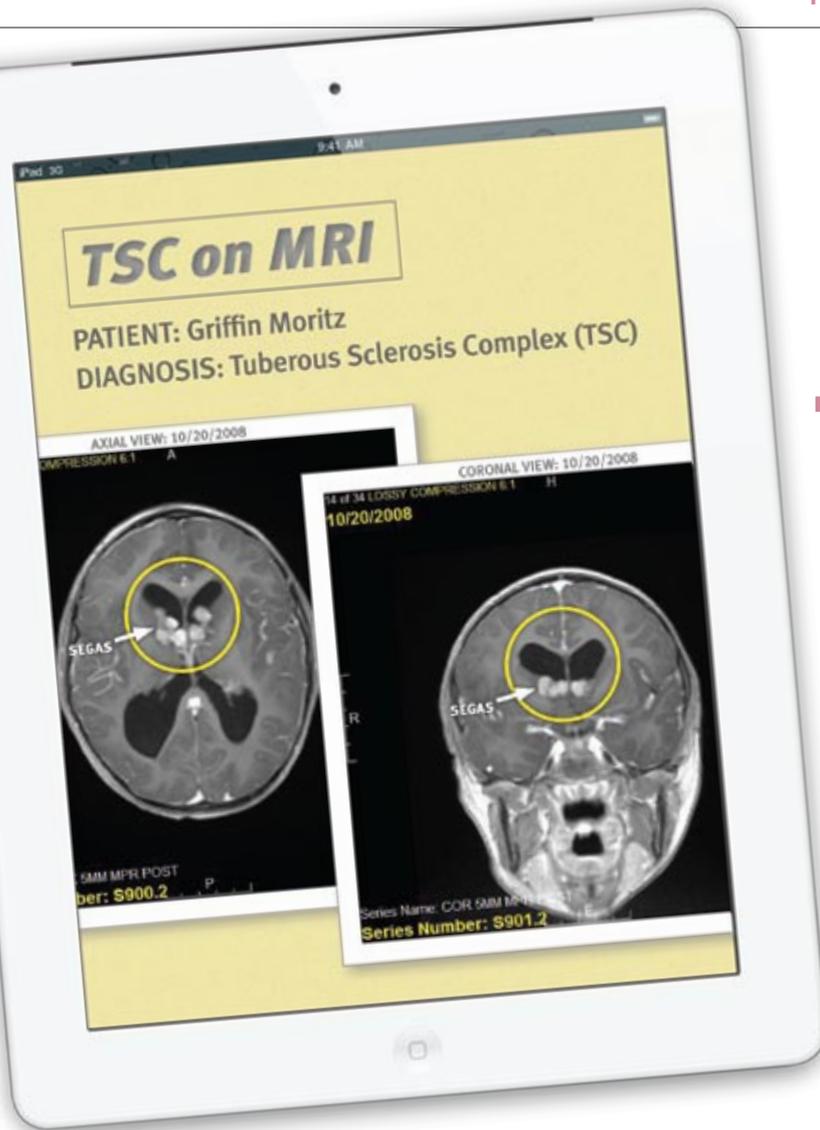


Tuberous Sclerosis Complex

New therapies show promise in treating this neurologic condition, but their long-term side effects are unknown.

BY AMY PATUREL, M.S., M.P.H.



When Griffin Moritz of Scottsdale, AZ, was born with a white patch of hair, the maternity ward nurses said it was nothing to worry about. Five months later, Griffin began pulling his hands and feet up and collapsing into a fit of tears—repeatedly. At the time, his mother, Debora Moritz, had no idea the two symptoms were related. Three days later, she was sitting in a pediatric neurologist's office with a diagnosis for her son: tuberous sclerosis complex (TSC), a genetic disease affecting one in 6,000 births.

White patches of hair, reddish skin, and infantile spasms—a specific type of seizure that begins in infancy and is linked to later cognitive problems—are common among people with TSC. But the hallmarks of the disease are non-cancerous brain tumors called cortical tubers because of their shape. Some people may have just one or two, while others have tubers covering nearly every portion of their brain. Many individuals also have subependymal giant cell astrocytomas (SEGAs), another type of benign brain tumor that puts people at risk for increased pressure on the brain and other potentially fatal problems.

Almost all people with TSC have treatment-resistant epilepsy, and many are cognitively impaired or autistic. What's more, the disease causes benign tumors to grow outside the brain as well

as inside. Heart tumors, called cardiac rhabdomyomas, may result in arrhythmia (irregular heart beat), obstruction, or murmurs (usually prenatally or within the first year of life). Kidney tumors, called angiomyolipomas, can grow very large; some may bleed. Lung tumors can develop into a potentially fatal disease, called lymphangioleiomyomatosis, that causes holes in the lungs.

“Having TSC is like walking in a minefield,” says Elizabeth Thiele, M.D., Ph.D., director of the Pediatric Epilepsy Program and the Herscot Center for Tuberous Sclerosis Complex at Massachusetts General Hospital in Boston. “You get over one thing, and you walk right into another. That's what sets this disorder apart from epilepsy. It's not just the seizures. It's not just the brain involvement. It's everything.”

Yet some people with TSC have few symptoms or may not even know they have the disorder. As a result, neurologists tend to prescribe treatments for each symptom as it strikes.

During the past decade, however, researchers have made tremendous strides in treating TSC after stumbling upon the two proteins that cause the uncontrolled growth of tumors. That discovery enabled researchers to move from simply managing TSC symptoms to developing new approaches for treating the underlying disease.

SEIZING CONTROL

Seizures, such as infantile spasms, are often the first sign that a person has TSC. In fact, nine out of 10 patients with TSC have them. Like Griffin, many of these patients have their first seizures during infancy, when they're easily mistaken for colic because the baby doubles up during the spasm and cries afterward. At first, spasms may be as subtle as a slight bob of the head or a thrust of the chin. But over time, they usually become more pronounced.

Unfortunately, once a child begins having these spasms, he or she will often fail to meet new developmental milestones and may even lose mental or physical skills learned before the spasms began. Social interaction may also diminish, and the child may seem irritable and stop smiling.

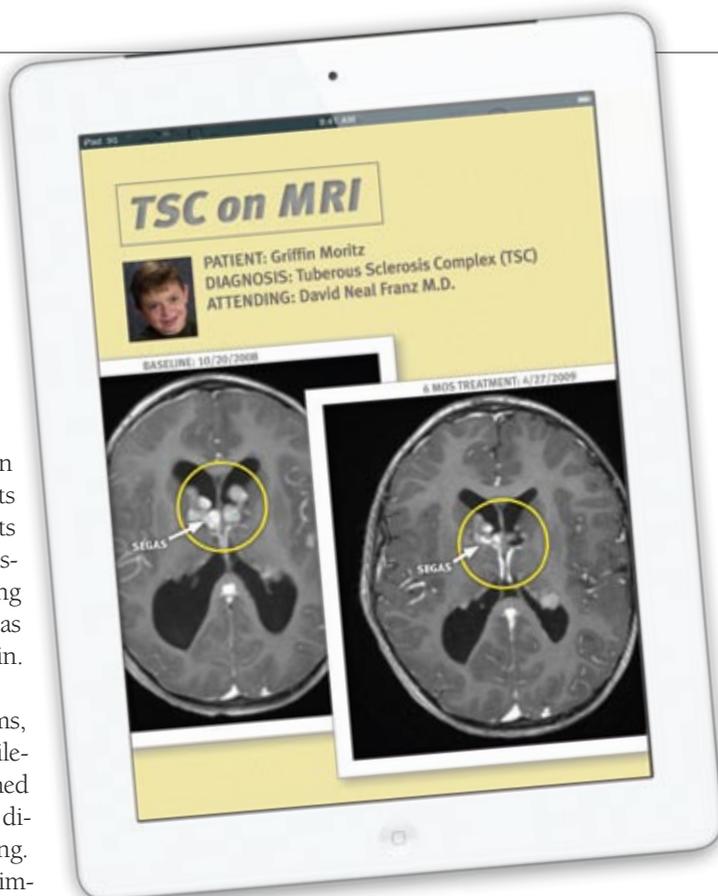
"Infantile spasms are huge risk factors for cognitive impairment and autism," says Dr. Thiele, "so being vigilant about spasms and aggressive in treating them is really important." A study published in the medical journal *Psychological Medicine* in 2003 found that approximately 45 percent of TSC patients have learning difficulties—and for all of these patients, a history of seizures, particularly infantile spasms, predicted the degree of intellectual impairment.

During the last two years, the U.S. Food and Drug Administration (FDA) approved two medications to treat infantile spasms: adrenocorticotropic hormone (ACTH) and vigabatrin (Sabril). Both medications have serious side effects. Vigabatrin can cause irreversible damage to the retina of the eye, impairing a patient's periph-

Missing the Diagnosis

Many clinicians still don't recognize tuberous sclerosis complex (TSC) in patients. A study published in the medical journal *Pediatrics* earlier this year found that 39 percent of TSC patients reported missed symptoms or signs of TSC that should have led to an earlier diagnosis. Seizures were the most commonly missed symptom and were noted in 19 percent of patients. Other missed symptoms included infantile spasms, family history of TSC, cardiac rhabdomyomas, and skin disorders.

"TSC is not uncommon, and there needs to be a heightened awareness of the disease among all types of clinicians," says Dr. Thiele. "New treatments are emerging, but even with the treatments we have now, if we know a person has TSC, there's a lot we can do to keep him or her healthy."



eral vision. Adrenocorticotropic hormone is associated with high blood pressure (hypertension), irritability, gastrointestinal problems and bleeding—even death.

Several studies show that infantile spasms are better controlled with vigabatrin than ACTH. "Sometimes even just a few doses of vigabatrin controls the spasms," says Mustafa Sahin, M.D., assistant professor and clinic director at Children's Hospital at Harvard Medical School in Boston, MA, and member of the American Academy of Neurology (AAN). In 2000, researchers at the National Institutes of Health Tuberous Sclerosis Complex Consensus Conference stated that vigabatrin should be the first treatment doctors prescribe for infantile spasms in children with TSC—even though the medication wasn't yet FDA approved for any use and wasn't even available in the United States.

"We learned Griffin had TSC on Monday, and we drove to Mexico for vigabatrin on Wednesday," Moritz recalls. "The neurologist said the faster you can get it under control, the better the outcome." (Please note: medications should only be purchased outside of the United States with caution and under the direction of a medical doctor.) Unfortunately, vigabatrin didn't work for Griffin. He had one good day without any spasms, but then no matter how his neurologist adjusted the dose, the spasms kept coming.

So the Moritzes turned to ACTH. The steroid caused Griffin to lose all muscle tone and become ravenously hungry. "He looked like this big, red, cranky blob," says Moritz of her son, who weighed 30 pounds by the time he was nine months old.

After six weeks on ACTH, Griffin's infantile spasms gradually stopped. But, as with many children who have TSC, Griffin began experiencing another kind of seizure as he grew older—in his case, simple partial seizure, during which a person remains alert. The Moritzes never got complete control over these seizures. "We were constantly trying different medications in

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various combinations and dosages. Yet we were told by neurologists that when several medications fail, the chances of other medications working begins to diminish,” says Moritz.

NON-DRUG TREATMENTS

When drug cocktails fall short, many families investigate other options, including the ketogenic diet, which is a strict, medically supervised nutritional regimen that contains a large amount of fat, adequate protein, and very small amounts of carbohydrates. Typically, the diet requires eating four times as much fat as protein and carbohydrates. (The typical American diet is 34 percent fat, 50 percent carbohydrate, and 16 percent protein.) Under normal circumstances, the body uses carbohydrates for energy, but on a ketogenic diet, fat becomes the primary fuel. The goal is to force the body to produce ketones, which may improve seizure control and can be detected in the blood and urine. (Ketones are also made if your body cannot use blood sugar properly, which is why people with diabetes are tested for them.)

“Kids who go on the ketogenic diet, regardless of the type of

seizures they’re having, often become seizure-free—and those are kids that have been on at least four medications before trying the diet,” claims Dr. Thiele. “It’s the most successful treatment we have for seizures caused by TSC.” (For more from *Neurology Now* on the ketogenic diet, go to <http://bit.ly/e3EehH>.)

Unfortunately, the ketogenic diet is extremely difficult to maintain, especially if there are other children in the household. Staples include butter, heavy whipping cream, mayonnaise, and oils. Because carbohydrates and protein have to be severely restricted, everything the child puts in his mouth has to be monitored. Even toothpaste has sugar in it!

In a small study of 12 children with TSC published in the medical journal *Epilepsia* in 2005, 11 children had a greater than 50-percent reduction in their seizures at six months on the ketogenic diet, and eight had a greater than 90-percent response. Five children were seizure-free for five months. Diet duration ranged from two months to five years, with an average of two years.

In terms of side effects, Dr. Thiele says patients may experience constipation, increased acidity in the blood (acidosis), and kidney stones due to the dietary restrictions. She’s not aware of any health-related risks as a result of the excess fat from this diet—lipid profiles of kids on the ketogenic diet are usually not significantly elevated, she says.

Another option is vagal nerve stimulation (VNS), which sends regular, mild pulses of electrical energy to the brain. Think of it as a little pacemaker for the brain that’s implanted under the skin on the chest. A wire extends from the device to the vagus nerve in the neck, which relays messages between the brain and the organs. The neurologist programs the strength and timing of the impulses and can adjust the settings with a programming wand connected to a laptop computer.

For all patients, the device runs continuously, usually with 30 seconds of stimulation followed by five minutes of no stimulation. For patients who experience warnings or auras before a seizure, holding a special magnet near the implanted device can abort a seizure before it happens. Researchers aren’t clear why VNS works, but for up to 40-60 percent of patients with epilepsy, it does reduce seizure frequency.

Some patients aren’t good candidates for VNS because of where their seizures originate in the brain, which is why a thorough examination is required first. Side effects of VNS include a worsening of obstructive sleep apnea and, in rare cases, behavioral problems or an increase in seizure activity. For TSC patients, the most significant “side effect” is the inability to perform MRIs (with an implanted device, MRIs aren’t possible). This is a problem for people with TSC, because physicians follow the health of their kidneys and other organs with imaging tests such as MRIs.

Signs and Symptoms of Tuberous Sclerosis Complex

- Difficult-to-control seizures
- Brain tubers
- Kidney tumors
- Heart tumors
- Skin abnormalities
- Cognitive delay
- Behavioral disorders

However, symptoms of tuberous sclerosis complex (TSC) vary widely from one person to the next, with some experiencing only minor skin abnormalities, and others experiencing severe seizures, cognitive disabilities, and behavioral disorders. Symptoms of TSC also typically change over time within the same individual. This variability and unpredictability is a hallmark of TSC and can make accurate diagnosis difficult. It also presents challenges to those who have been diagnosed, their family, and their doctors.

Source: livingwithTSC.com/about/diagnosis.htm

(Cyberonics, a VNS manufacturer, claims that although full-body scans should not be done with the implant, brain MRIs can be done with proper equipment.)

SURGERY

Until recently, undergoing surgery to remove TSC tubers was considered only after all other methods, including the ketogenic diet and VNS, had failed. Now, many patients undergo surgery early in the disease process—even months after birth. “If you target the network [the area responsible for the seizure activity] early, not only will the surgery results potentially be more durable, but also the developmental outcomes may be better,” says Howard Weiner, M.D., professor of neurological surgery and pediatrics at New York University School of Medicine.

Kids with multiple hotspots in the brain generating seizures were once deemed poor candidates for epilepsy surgery. The reason is that the surgeon has to cut out multiple areas in the brain, so the risk of removing areas required for cognition and movement is increased. But now, these children are increasingly being considered for surgery.

“One of the big pushes over the last 10 years is the recognition that TSC patients who do not meet the classic selection criteria for epilepsy surgery may still benefit from surgery,” says Dr. Weiner.

Seven-year-old Evan Moss is a good example. He had severe seizures and, upon first evaluation, he wasn't a clear candidate for surgery. But using extensive pre-surgical testing, Dr. Weiner and his colleagues identified the area in the brain causing Evan's seizures and realized they could operate without impacting important functions such as cognition and movement. They uncovered a group of tubers in a specific part of Evan's brain as well as seizure-causing tissue in the area around the tubers.

“We removed the areas generating seizures and the surrounding area that could lead to seizures down the line,” says Dr. Weiner, who performs these procedures in three separate operations during a single hospital stay. Step one involves implanting electrodes into the brain to find the main area that's causing the seizures (the seizure focus). During step two, the surgeons remove the seizure focus and introduce new electrodes to identify other areas of the brain that might generate seizures. Then, after additional days of monitoring, the patient undergoes a third operation to remove any additional tissue that could give rise to seizures (as well as the electrodes). The three-step process allows Dr. Weiner to preserve as much healthy brain tissue as possible.

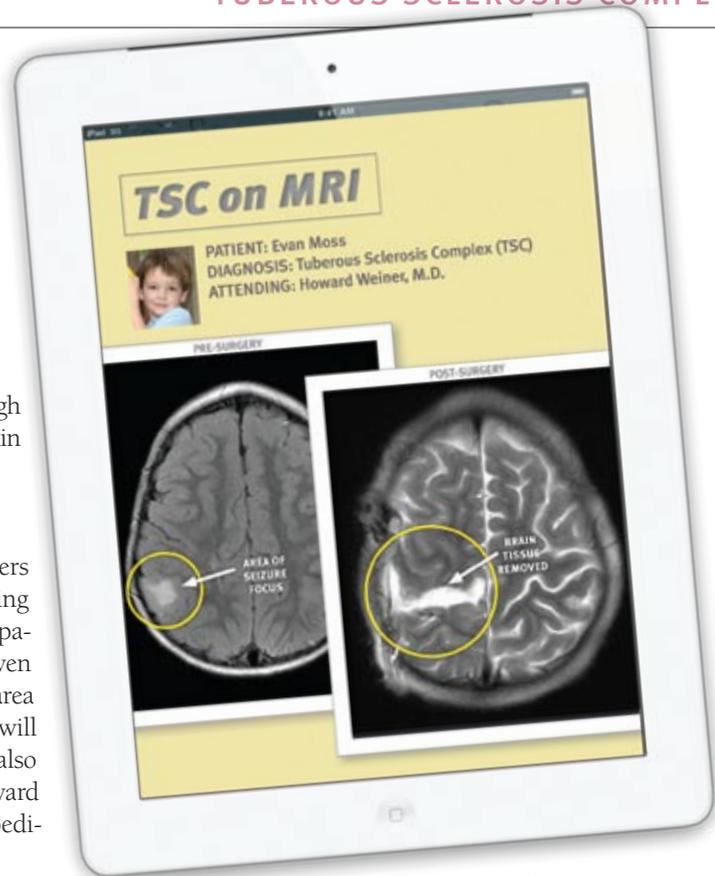
In one study that included 15 patients who did not meet traditional surgical criteria because several areas in their brains

generated seizure activity but underwent surgery after careful evaluation, eight remained completely seizure-free during the 10-year follow-up period.

Evan wasn't as fortunate. Initially, his seizures stopped completely, but they returned—though on a much lesser scale—within a few years. “Since Evan's seizure focus was in close proximity to the part of the brain that controls his motor function, we were limited by how much tissue we could remove without creating problems for him,” says Dr. Weiner. “While we had a good strategic attack of the network causing Evan's seizures, it somehow found a way to reactivate itself. Sometimes that happens spontaneously, or sometimes it happens from a patient experiencing a head trauma, or missing medication, or experiencing some other stressor that reactivates the system.” No one knows for sure. What they do know is that even with a return of seizures, most parents claim the surgery is worthwhile.

According to a study published earlier this year in the medical journal *Epilepsy and Behavior*, most parents of children with TSC who had surgery to treat seizures were happy with the results. Of the 39 families interviewed, 77 percent had greater than 90 percent reduction in disabling seizures, and 46 to 85 percent had at least a moderate improvement in quality of life—including families whose seizures didn't resolve.

Brain surgery is not a risk-free endeavor, to be sure. Every surgery comes with risks, including unexpected reactions to anesthesia or medications, which may cause major injury or death. Brain surgery carries added risks of damage to nerves or blood vessels, which can cause stroke or neurologic impairments that may be either temporary or permanent. The risk of such complications, while very small, varies according to the type of procedure and is different for each individual. On the other hand, uncontrolled seizure activity poses its own serious risk.



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A NEW FRONTIER

All of the problems caused by TSC—from epilepsy and autism to kidney and lung problems—seem to stem from mutations in two genes, TSC1 and TSC2. Scientists discovered the genes during the 1990s. Until recently, researchers hadn't unraveled the process through which the proteins synthesized by TSC1 and TSC2 (hamartin and tuberin) cause the runaway growth fueling TSC tumors. It involves something called the mTOR pathway, which exists in every cell of the body and serves as a master switch to regulate normal cell growth. In the brain, for example, mTOR controls the synthesis of proteins needed to form synapses, which allow cells to communicate with one another and are important in learning and memory. But when defects in TSC1 or TSC2 prevent hamartin and tuberin from doing their job—acting as a brake to control cell growth—mTOR is left in the “on” position. As a result, cells divide uncontrollably, leading to the development of TSC tumors.

When Griffin was 10 years old, a routine MRI revealed an explosion of tumors on both sides of the brain that were increasing pressure in his head at an alarming rate. Treatment for tumors of this size is usually surgery, but Griffin wasn't a candidate because his were so widespread.

Moritz knew researchers were investigating mTOR inhibitors in clinical trials. She found a trial at Cincinnati Children's Hospital that had been open for two years and submitted Griffin's medical records. The next day she received a call, and within a week, Griffin was enrolled in the trial. Within the first week of starting the medication, everolimus (Afinitor), Moritz began noticing changes in Griffin.

“His skin looked less red, he was sleeping better, and his behavior began to change,” says Moritz. “He fidgeted a little less, he walked a little more calmly, and he responded a little more quickly.” The first follow-up MRI 90 days later revealed remarkable results: The increased pressure on Griffin's brain was resolving, and he already had a 30-percent reduction in tumors.

Results like Griffin's prompted the FDA to approve everolimus in 2010, after a study revealed that one-third of the 28 patients studied experienced a reduction of 50 percent or greater in the size of their largest tumor within six months of starting everolimus treatment (and none of the patients developed a new tumor while taking the drug).

“The most dramatic reduction in tumor volume occurs within the first three months of everolimus therapy,” says Dr. Sahin. “It continues to improve out to six months, and the response is sustained—or even improved—for up to two years.”

Originally approved only for tumors, mTOR inhibitors are showing promise in other aspects of TSC, including seizure activity, cognition, and autism. When infant mice engineered to have

brain disorders resembling TSC are given the mTOR inhibitor rapamycin, they usually do not develop seizures. “Researchers have also treated adult mice with TSC with rapamycin just for five days, and the mice perform better in tests of learning and memory,” says Dr. Sahin, who is currently screening patients to participate in the first controlled trial on everolimus and cognition.

Rapamycin has been used in children requiring kidney transplants for the past two decades, so there's well-documented evidence about safety and side effects, which include mouth ulcers, immune suppression, and increases in blood lipids (fats). “They're not benign medications,” says Dr. Thiele. And this area of research is so new that scientists aren't sure what the long-term effects of the medications are.

Griffin has been on everolimus for two-and-a-half years and, according to Moritz, every month he's on the drug, his seizures become less severe. “It didn't happen overnight, but each month he had fewer and fewer seizures, and they were less intense,” she says. During the sixteenth month, Griffin didn't have a single seizure, and 2010 was practically clear. He had a few little blips—mild seizures, lasting no longer than 15 seconds—but Moritz has not used any “rescue” seizure medication on him in more than a year.

“Right now, treatment for TSC continues to be symptomatic, but the preliminary evidence we're seeing with the rapamycin-like drugs is very encouraging,” says Dr. Thiele. “However, none of us thinks these are the silver bullets.” When people go on these drugs, they might see the tumors shrink, but once they stop the drug, there's rapid re-growth, she says, so decades of treatment can be expected.

The good news: The peak onset of TSC tumors is during the first two decades of life. “That's one of the positive things about the natural course of this disease,” says Dr. Sahin. “But the question becomes, if you treat these tumors with everolimus, can you take patients off the drug after age 20?” At this point no one knows.

For Griffin, mTOR inhibitors have dramatically improved his physical, mental, and emotional health with negligible side effects. He's even communicating with a device that allows him to deliver common phrases with the touch of a button. “When we were sitting in the waiting room for Griffin's speech therapy, the therapist he used to see came out to do some paperwork,” says Moritz. “He reached to his device and said, ‘Hi, how are you?’ Two years ago, he would have thrown that device across the room when he saw her.”

Moritz now views Griffin's explosion of tumors as a blessing because it gave him access to medication that would not have been offered to him otherwise—medication that has dramatically altered the course of his life. NN



For more information on tuberous sclerosis complex, see **RESOURCE CENTRAL** on page 44.