

## RETT SYNDROME

■ A MEDICAL ODYSSEY

## Clue to disorder buried for 17 years

Rett says bias prevented his research from reaching others

There are several reasons why Andreas Rett's paper describing the syndrome that would bear his name went unread for 17 years. Some lie with the man, some with his method.

By 1966 English had become the language of science and American medical journals the showcase for international research.

Rett knew this but published his paper in German in an obscure Viennese medical newsletter that he said even his Austrian colleagues held in low esteem.

In an interview in October, Rett explained he did not know how to write or speak English in 1966, and he was busy running the clinic that had become a publicly supported hospital for handicapped children.

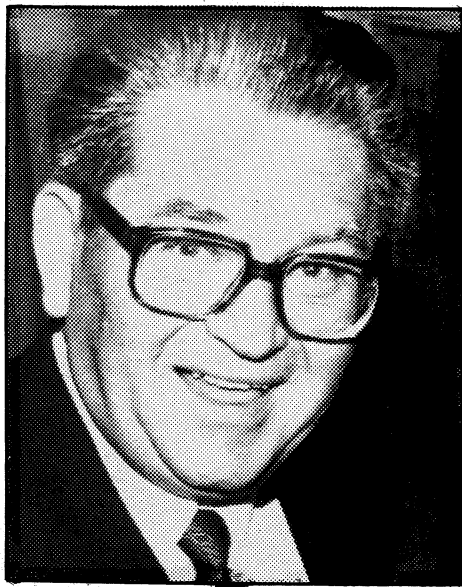
He said he received little support for his work from other Viennese doctors or from the influential University of Vienna. And he spoke with some bitterness of the isolation of his professional life, an ostracism he attributes to his decision to care for children no one else wanted.

Rett said he was fired in 1950 by his first employer, the head of a large pediatric clinic in Vienna, because he was seeing handicapped youngsters in his practice.

"He told me, 'Go out with these children,'" Rett recalled. "He said, 'They are dirty. They are ugly to see. My other patients won't come to see me.'"

Rett said the anecdote illustrates the upward battle he has always fought — and fought alone.

He also spoke of an emotional legacy left by World War II that even today convinces him the Allies have not forgiven the Axis powers. He did not have his paper translated into English for



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submission to American journals because, he said, it would have been futile.

"I did not try because I knew the American journals don't publish papers from Germany and Austria," he said.

It was a bias he never tested. Other European researchers interviewed, even those who believe they have to work harder than their American counterparts to get published in American medical journals, expressed incredulity at Rett's assertions.

Dr. Arnold Pollack, an associate professor at the University of Vienna who studied neonatology for a year at Women & Infants Hospital of Rhode Island and who has published in American journals, attributes the bias to differences in research style.

The Europeans rely heavily on patient observation as the basis of diagnosis, while American researchers emphasize laboratory tests to show something is amiss. The inaccuracy of Rett's testing of urine samples would have damned him according to the American criteria for publication, Pollack speculated.

Dr. Arnold Relman, editor of the New England Journal of Medicine — perhaps the most widely read medical journal in the world — concedes a bias against publishing work that lacks laboratory evidence to back up observations. But he said it is a necessary precaution.

"For every Rett who makes a 10-strike by identifying a new disease simply by using his eyes and his ears, there are literally thousands who make equally important-sounding observations that prove to be erroneous," Relman said. "So science has tried to rely on measurements — a blood pressure, an X-ray — to try to weed out the bias, the mood, the motive of the observer."

"It's not the case that the Europeans are all wet," he said. "They are right, to a certain extent, that we don't emphasize sufficiently the physical diagnosis. But in Europe they tend to believe that you can do everything by history and physical diagnosis."

Still, three years of sophisticated biochemical studies in half a dozen nations have yet to reveal the gene, chemical or combination of chemicals gone awry in Rett girls. Rett syndrome can be diagnosed only by the hand-wringing characteristic and other distinctive physical symptoms and by a history of seemingly normal development until 1 or 2 years of age.

—I.W.

## SYMPTOMS OF RETT SYNDROME

■ Period of seemingly normal development followed by regression and loss of skills, usually between one and two years of age

■ Period of autistic behavior

■ Hand-wringing, compulsive clapping or hand-to-mouth gestures

■ Stiff-legged, broad-based stance and walk

■ Facial grimaces and teeth-grinding

■ Seizures

■ Normal head size at birth but unusually slow growth, leading to abnormally small head size in later years

■ More spastic, less mobile with age

■ Gradually decreasing autistic symptoms as child grows older

■ Poor circulation in legs

■ Severe to profound retardation

■ Curvature of spine in later years

## UNANSWERED QUESTIONS

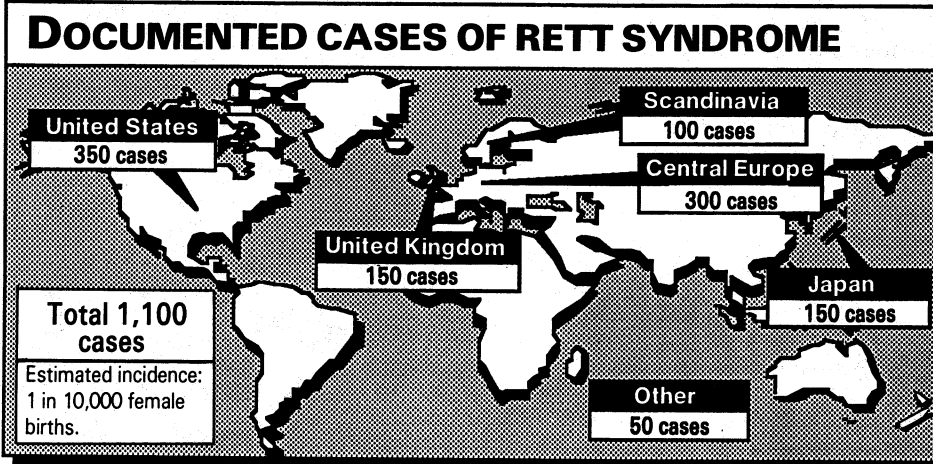
■ Why does it strike only girls?

■ How is it transmitted?

■ If it is a genetic disorder, which gene is malfunctioning?

■ If the genetic disorder causes a brain-destroying biochemical imbalance, which proteins, fats or carbohydrates are affected?

Source: International Rett Syndrome Association, Fort Washington, Md.



—Journal-Bulletin Graphic

## Tammy

Continued from preceding page

A Xerox copy of the page in the Rhode Island Society for Autistic Children newsletter that brought Diane Fleetham's letter into Carol's life.

"I read that letter, and every word was screaming at me — Tammy. Tammy. TAMMY! It was all there: the teeth grinding, the curvature of the spine, the way it came on, the way the doctors said it was autism.

"I had to sit there for a few minutes just to absorb it," Carol said, her voice drained. "Then I got on the phone."

She called Eddie at work, so agitated he could barely make out what she was saying. She called her mother. Then she wrote a letter to Kathy Hunter of Fort Washington, Md., whose address was listed at the bottom of Diane Fleetham's letter.

## A similar story

Kathy Hunter is president of the International Rett Syndrome Association (IRSA), which she founded in January 1985.

Her story is similar to Carol's — years of mystery followed, finally, by a diagnosis for her daughter. Mrs. Hunter started IRSA to end the pain of not knowing for other families and to bring families and researchers together in a common effort.

Mrs. Hunter lives outside Baltimore, an easy drive from Johns Hopkins and the Kennedy Institute and Hugo Moser's team of Rett syndrome specialists. When Moser offered to host the 3rd International Conference on Rett Syndrome in November 1985, Mrs. Hunter became a key member of the planning committee.

They were putting the finishing touches on the program when Carol Araujo's letter arrived at IRSA's headquarters — Kathy Hunter's laundry room.

The letter was a detailed account of Tammy Galuszka's 21 years. Mrs. Hunter replied immediately:

"From what you describe of her, it does indeed sound like she has Rett's Syndrome," she wrote. She mentioned a doctor at Children's Hospital in Boston who was familiar with the syndrome, and she invited Carol to bring Tammy to the conference, to be examined by Rett. Carol wasted no time. She made plane reservations for herself, her mother and Tammy. She wanted to hear the diagnosis from someone who knew. If Tammy had Rett syndrome, and the man who had discovered it was going to be in Baltimore, Tammy would be there, too.

"Before I knew it, we were on the plane," Carol said. "I'll never forget walking into the lobby of that hotel. We were all assigned at the same place, and everybody was checking in when we got there.

"We walked in the door and there they were: fifty girls looking and acting just like Tammy."

## Rescued from isolation

Carol's memory of the conference is a series of snapshots — meeting Andreas Rett, Tammy being hugged by Rett, trading experiences with other mothers of Rett girls.

The sense of rescue from years of isolation was indescribable. So was Carol's feeling of vindication.

She stuffed her handbag with brochures and other literature on Rett



—Journal-Bulletin Photo by RACHEL RITCHIE

HAND-WRINGING: Tammy twists her hands in the motion characteristic of Rett girls. The distinctive gesture was among those that initially brought "the hand-washing girls" to the attention of doctors such as Andreas Rett and Bengt Hagberg.

syndrome to take back to Tammy's doctors and teachers in Rhode Island.

Indeed, Carol and her mother would sit down weeks later with a stack of envelopes, copying from the Yellow Pages the names and addresses of every pediatrician in Rhode Island and southeastern Massachusetts, sending them the information they had collected at the conference.

Partly as a result of their efforts, three more girls with Rett syndrome would be diagnosed in Rhode Island.

But the most precious thing Carol carried home from Baltimore was a single sheet of writing paper:

"To Whom It May Concern:" wrote Dr. Alison M. Kerr of Glasgow, Scotland, a specialist in Rett syndrome. "This is to state that I have seen and examined Tammy Galuszka today and consider that she has Rett's Syndrome."

In the upper right corner Kerr had recorded the date: November 23, 1985.

## The end of the search

November 23, 1985. Nearly 20 years of searching ended for Carol Araujo on that day.

But for the researchers struggling to understand the whys and hows of Rett syndrome, the quest has just begun. And it is one that holds the tantalizing prospect of success equal to science's triumph over phenylketonuria (PKU).

"I am not pessimistic," said Bengt Hagberg, who believes a screening test for baby girls will be available within 10 years — a blink in time by science's standards. Perhaps, he said, treatment to prevent the brain destruction also will be known by that time.

"Particularly if the United States puts

in resources, we have a good chance," Hagberg said. "You have the laboratories, the trained researchers and good clinicians. All this is very important."

And the United States has committed those resources.

Last spring, thanks to the testimony of Kathy Hunter and other IRSA representatives, Congress appropriated \$500,000 for Rett syndrome research to the National Institute of Child Health and Human Development.

Another division of the National Institutes of Health (NIH), the National Institute of Neurological and Communicative Disorders and Stroke, sent Dr. Joseph S. Drage to the 4th International Conference on Rett Syndrome in Vienna two months ago.

As chief of the institute's developmental neurology branch, Drage helps decide which research projects get NIH funding. Since Rett syndrome has reached a trigger point on the interest scale, Drage said, he went to Vienna to prepare for the applications that are sure to come.

And the diversity of scientists now involved with Rett syndrome also is promising. The October conference in Vienna attracted scientists, doctors and researchers from the United States, Austria, Sweden, Japan, West Germany, Ireland, England, France, Portugal, Israel, Switzerland, Scotland, Italy, Belgium and Australia.

No longer was it a gathering of pediatric neurologists.

There were biochemists, geneticists and people like Dr. Vincent M. Riccardi of Baylor College of Medicine. A world authority on neurofibromatosis (Elephant Man's disease), he is drawn to Rett

syndrome by the challenge of yet another genetic puzzle.

Riccardi sees the Rett syndrome story as more typical than not. It is not uncommon, he said, for important scientific work to languish in obscurity only to be rediscovered at a more propitious time.

"Something happens, and there's a collision of social forces and medical forces and economic forces and human forces that pushes it to the surface," Riccardi observed.

## 'Twenty years lost'

Andreas Rett has trouble appraising his life and his contribution through the distant filter of history.

He feels old. He is 63, with a solid build and thick gray hair combed straight back. But his health is poor, he says, eroded by years of 16-hour days caring for the patients he calls "my children."

He presided over the October conference in Vienna — three days of supreme vindication, one might think — but his manner was that of a weary soldier, hollow-eyed, detached from the camaraderie. In a month he was scheduled for open-heart surgery.

"The sickness, the Rett syndrome, is so severe," he mused one night in a corner booth of a beer garden where scientists and parents mingled in exuberant respite from the scientific sessions. Rett had opened those sessions in a booming voice of welcome, arms spread wide to the scientists and parents joining his quest.

But now his voice was almost a sigh. The words came haltingly. Yes, he said, he is happy to see so many finally committed to the study of Rett syndrome.

But his is a pleasure underlaid with sadness.

"Twenty years lost — it is too much," he said. "Here we are still, with nothing to offer these parents and nothing for the babies born today and tomorrow and next week."

Rett fell silent and studied the table for a long moment. When he looked up, his eyes were brimming. "It is very difficult for me," he said finally, "to have such a severe sickness with my name and no possibility of help. I wish that I could live to see a cure."

## Letting go of the dream

For Carol Araujo, the tears came on the last day of the October conference. She had gone to Vienna hoping for a breakthrough comparable to Tammy's diagnosis a year before in Baltimore.

The day before the trip, Carol and Eddie, frustrated by a series of disagreements with the group home's managers, had brought Tammy home.

Carol was excited and a little nervous about having Tammy home again. She spent the 7-hour trans-Atlantic flight talking almost nonstop about the need for babysitters, since Tammy cannot be left unattended, and about the day program for mentally handicapped adults that Tammy would attend at the James L. Maher Regional Center in Bristol.

There was a giddy edge to Carol the week of the conference — her first time in Europe, a strange language to master on shopping expeditions and all that was new and different and a little unreal.

It was early autumn in Vienna but unmistakably, the dying season. Leaves crunched underfoot, and the main flowers in the city's gardens were chrysanthemums — heralds of winter in Austria no less than in Rhode Island.

Only the weather that week was out of sync. Sunny, 65, even 70 degrees. Everywhere people talked about the respite from October's chill. You could sit on a park bench and close your eyes and pretend it was spring, embroidering the daydream with buds and pale green shoots and other signs of new life, second chances, rebirth.

Carol let her dreams float for a while. She listened selectively to the scientists' reports, scribbling notes when someone mentioned a drug or vitamin or therapy the girls seemed to respond to.

Carol's enduring and most cherished dream was that her Tammy, the Tammy that used to be — the laughing little baby she bounced and caressed each morning before the rest of the household awoke — that Tammy could be unlocked.

Carol knew her child was brain-damaged, but she pictured it as a problem of getting the messages out. She believed the old Tammy was still in there. She thought she caught a glimpse of her, every now and then, in Tammy's eyes.

But on the third day of the conference, when the scientists relentlessly unloaded evidence of devastating and irreparable brain destruction — not just to the pathways of communication but in the areas governing emotions and intelligence — Carol felt the dream slip away.

Tears ran silently down her face. A sodden pile of tissues grew in her lap, and still the tears came. She apologized to the people on either side of her and stretched her mouth wide, as if the facsimile of a smile could fool her eyes into behaving. But the tears fell anyway.

"I guess," she said, "I never stopped hoping."