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Unusual dog leads veterinarian on unusual path

How a sick shar-pei puppy steered clinician to research

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By: Edie Lau

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Photo courtesy of Wurtsboro Veterinary Clinic

In her first year as a veterinarian, Dr. Linda Tintle fell in love with shar-pei dogs due to their plush, velvety coat, intelligence and distinctive personality. Shar-pei happen to be uniquely susceptible to a variety of medical problems that were little understood at the time. Today, Tintle is a leading authority on shar-pei health.

The first time Dr. Linda Tintle placed her hands on the soft, wrinkled skin of a Chinese shar-pei, it was the middle of the night and she was a brand-new veterinarian just six weeks out of school.

Tintle was on call when a client of the clinic where she worked in New York's Hudson Valley phoned at 1 a.m. with an emergency. A breeder with a boarding business, the client was taking care of a litter of 4-week-old puppies and their mother while the dogs' owners were out of town. One of the pups had spiked a fever exceeding 104 degrees.

The puppy was a shar-pei, a breed originating in China that in those days was rare in the United States. Tintle had never seen, let alone treated, a shar-pei, and she had no idea why the pup was so sick.

As it turns out, Tintle was no more ignorant as an inexperienced doctor than she would have been as a veteran practitioner. That's because in 1981, few in veterinary medicine knew that shar-pei are prone to bouts of fever, and no one knew why.

Today, the particular medical vulnerabilities of the breed are far better understood, thanks to research plumbing the genetic underpinnings of shar-pei health. The knowledge that shar-pei are prone to a host of autoinflammatory diseases, and why, can be traced in large part to the feverish puppy in New York. It

was that puppy's doctor, Tintle, who spurred researchers to take a close look at shar-pei and who participated and continues to participate in the research herself.

"She's really been a driving force," said Dr. Jeff Vidt, a Chicago-area veterinarian and vice president of the Chinese Shar-Pei Club of America. "She saw the problem in the breed, knew it was unique and mustered the necessary scientists and other experts to figure out the answer." Moreover, she reached beyond veterinary circles to researchers in human medicine, Vidt said. "She certainly represents my ideal of a veterinary scientist."

In academia, veterinarians routinely combine clinical practice with scientific research, but as a full-time private clinic owner doing research, Tintle "is quite unique," said Kerstin Lindblad-Toh, one of Tintle's research collaborators.

Lindblad-Toh is a professor in comparative genomics at Uppsala University in Sweden and scientific director of vertebrate genome biology at the Broad Institute of Massachusetts Institute of Technology and Harvard University. She is a co-author with Tintle and others on two groundbreaking studies of shar-pei genetics and disease. The [first study](#), published in 2011 in the journal *PLOS Genetics*, found that the same mutation that gives shar-pei their characteristic thick, wrinkled skin also predisposes the breed to a periodic fever syndrome.

The [second study](#), published this October in *PLOS ONE*, delves deeper into shar-pei disease to identify genetic variants associated with disease risk. The research shows that the same genetics underlie different clinical signs of inflammation, demonstrating that the periodic fevers are part of an autoinflammatory syndrome. The genetic information makes it possible to develop a DNA test to gauge individual dogs' risk of autoinflammatory disease — a test that may be commercially available in a matter of months.

"It's absolutely huge," Tintle said. "I'm so excited about this."

Pup drew young veterinarian's focused attention

Tintle never intended to fold research into her career, much less become an authority on one dog breed's health problems. "Never did I say, 'I want to grow up to be a shar-pei expert,'" she said.

But from the way she took care of her first shar-pei patient three decades ago, it was apparent that Tintle was not the type of doctor to let a puzzle go unsolved.

"She was so dedicated and put so much time in," said Helen Mandelcorn, who, with her husband Harvey, had acquired one of the first shar-pei to be imported from China to the United States. That dog, Pistol, was the mother of the feverish pup. Reflecting on Tintle's response to the case, Mandelcorn said, "I don't know if there was a human baby that (ever) got as much care and attention as this puppy got."

The puppy who took ill happened to be the one Mandelcorn had chosen to keep from the litter. Mandelcorn called the dog Chin-Chin, short for Chinoiserie. Asked whether she ever worried that her beloved Chin-Chin was in the care of an inexperienced veterinarian whom she'd never met, Mandelcorn said not at all.

On the contrary, she and her husband Harvey were impressed how much effort the tall, determined young veterinarian put into a patient whose owners she didn't know. "She didn't know our circumstances, she didn't know whether or not we were going to be able to pay our bill," said Mandelcorn. "From what I understand, unfortunately there are a lot of people who go to veterinarians and don't pay their bill. But she didn't hesitate to put herself out, and immediately, that gave us a really good feeling. Look, here's this young vet who's willing to take this on, and she doesn't know us from a hole in the wall. What if we'd said, 'Put this puppy down, we can't afford it?'"

Tintle treated Chin-Chin with antibiotic and anti-inflammatory medications and took the puppy home until the Mandelcorns returned. "Twenty-four hour care was not available to most general practitioners in 1981," Tintle explained. "It was not uncommon for us to take a patient home for overnight observation."

Chin-Chin's fever quickly resolved, but not knowing what caused it or whether the drugs were actually effective left Tintle dissatisfied. "Because I was a new vet, I didn't have a lot of preconceived notions of what could be causing this," she recalled. "I immediately began delving into what could be causing a high fever like this."

The Mandelcorns supported her quest, which involved a battery of tests for infectious and autoimmune diseases. During Chin-Chin's recuperation, they made the hour drive from their home in Westchester County to Tintle's clinic for periodic checkups, tests and treatment for other conditions that arose. During those visits, Tintle often took Chin-Chin home with her until the dog was ready to return to her owners.

By then, Tintle had fallen in love with the cuddly breed. "They were just the right size, just the right short coat and they were very intelligent," she said.

Seeing how taken she was with shar-pei, the Mandelcorns thought of a way to show their appreciation to the veterinarian. "At the time, shar-pei were selling for a few thousand dollars each, and we knew there was no way for her to afford a puppy on her salary as a starting veterinarian," Mandelcorn said, "so we said, 'Pick a puppy from the litter.'"

That gesture of gratitude would lay the course of Tintle's career.

'Before I knew it, I was running a study'

As a teenager, Tintle bred and showed Great Danes, so she was familiar with the world of breed enthusiasts. To learn more about shar-pei, she began attending shows to connect with shar-pei breeders. As owners heard of her interest and growing knowledge, they began coming to her clinic, some driving across states.

Other veterinarians with shar-pei patients, such as Vidt, the practitioner in suburban Chicago, reached out for consultations and to share observations and ideas.

Tintle learned that shar-pei are given to bouts of mysterious fevers that may spontaneously resolve.

Sometimes, their hocks swell painfully. They are prone to arthritis, dermatitis, otitis and kidney disease. Tintle suspected a systemic problem, perhaps an immunodeficiency of some sort.

She monitored the scientific literature, hoping and waiting for someone to explore the problem. No one did. She began calling around, trying to interest researchers in the issue. At first, she had no luck. Then she connected with immunologists at Cornell University, her alma mater, on a project exploring the pathogenesis of inflammatory bowel disease, a condition common in shar-pei. She would send the researchers blood samples from both sick and well dogs, trying to identify what was happening in the immune system. Tintle wasn't only the supplier of samples. She worked with the researchers to examine the results and design increasingly defined studies.

"Before I knew it," she said, "I was running a study."

Their work led to the discovery that the shar-pei, even when they weren't feverish, had high levels of interleukin-6, a chemical messenger associated with inflammation. This finding ([published](#) in July 1992 by the journal *Clinical Immunology and Immunopathology*) suggested that, indeed, the dogs had an underlying systemic disorder.

In 1984, a few years before she began research, Tintle opened her own clinic in Wurtsboro, N.Y. The clinic originated as a satellite of a mixed animal practice in Middletown owned by Tintle's husband, Dean — a Cornell classmate whom she married their senior year — and Dean's brother, Kevin. About 15 years ago, the Tintles separated the two practices and expanded the satellite clinic into a full-service small animal hospital. Dean joined the Wurtsboro practice full-time.

Today, Tintle's patients are almost exclusively shar-pei. "It's not unusual for me to see three to eight shar-pei a day," she said.

Shar-pei aren't inevitably sickly. Tintle's first pup, Rikki — the littermate of Chin-Chin — lived to be 16½. One of Tintle's patients lived to 18, an impressive age for any dog. But a practice of mostly shar-pei can be depressing at times.

"Every week, it seems like, I have a patient dying of something. It's very disturbing, to say the least," Tintle said. "These are young dogs. They should be living out normal lifespans. And a lot of times, there's no warning. You'll have a 2- or 3-year-old dog that seems healthy suddenly going into kidney failure."

An explanation for shar-pei's fragile health began to emerge in 1990 with the publication of an [article](#) in the *Journal of the American Veterinary Medical Association* by Dr. Stephen DiBartola of the Ohio State University College of Veterinary Medicine. DiBartola and collaborators described a familial renal amyloidosis of young shar-pei and reported that many of the dogs had a history of recurrent unexplained fever events. The study noted that the episodes resemble Familial Mediterranean Fever, a periodic fever disorder that also predisposes patients to the buildup of abnormal amyloid protein. Amyloidosis can affect any of a variety of organs or systems — heart, kidneys, liver, spleen, nervous system and gastrointestinal tract. The study begged the question: Might shar-pei fever syndrome be similar?

The answer, it turns out, is yes. Researchers now know that, like Familial Mediterranean Fever, Familial

Shar-Pei Fever, as the condition has come to be named, is inherited and characterized by attacks of inflammation.

Building on this concept, Tintle, Broad Institute geneticist Lindblad-Toh and colleagues found that a genetic mutation in shar-pei produces excess hyaluronan, a substance found throughout the body. Tintle describes it as “the body’s sculptural material that also functions as a molecule that signals damage.” As with so many things, while a certain amount of hyaluronan is essential and beneficial, an excess is detrimental. The health consequences are “practically limitless,” Tintle said.

Not all shar-pei are afflicted. Some, like normal dogs, have two copies of a genetic mutation affecting the production of hyaluronan; others have as many as 10, according to Lindblad-Toh. “It’s not a yes-no switch but a gradient,” she said. The more copies of the mutation, the researchers believe, the greater a dog’s risk of autoinflammatory fallout.

Complicating the picture, the researchers have found that while excess hyaluronan is related to the shar-pei’s wrinkles, you can’t necessarily predict by its wrinkles an individual dog’s risk. That’s why a DNA test from a blood sample to determine the number of variant copies is so eagerly anticipated.

The role of hyaluronan isn’t the whole story. The researchers recently found that a second genomic region influences a dog’s development of amyloidosis, which in shar-pei can lead to early death by kidney failure. More study is needed to determine the exact role of the modifier locus, but Tintle is hopeful it will explain why some dogs die young — and perhaps point to breeding approaches that promote healthier future generations of shar-pei.

Professional leadership another priority

The Cornell immunologist with whom Tintle first collaborated, Dr. Fred Quimby, tried years ago to talk her into pursuing a doctorate in immunology and making a full-time career of research. She does love research, and admits moments of regret for not following the call. But, she said, “I just like practice. ... I own my own veterinary hospital, so I have a lot more freedom in a lot of ways than I would working in academia.”

For her research collaborators, Tintle’s ease in both worlds is a boon. Lindblad-Toh, the Broad Institute geneticist, said: “It’s a pleasure to work with Linda. She’s always very curious and cares about the dogs, and also has a good sense for science to always record things carefully.”

She added: “There are veterinarians who are very helpful and collect samples, but when the samples leave their hands, it’s up to us. This (collaboration with Tintle) is a dialogue.” She estimated that on average, someone from her team communicates with Tintle weekly.

Beyond practice ownership and research, Tintle has still more commitments. She's created and sells a line of supplements for dogs with chronic inflammatory disorders. She recently wrapped up eight years on the dean’s advisory council at the Cornell veterinary college. She’s president of a local emergency animal hospital. She is president of the New York State Veterinary Medical Society. She’s is versed on an array of heavy topical issues in the profession, from student debt to foreign-school accreditation, from the under-representation of women in leadership positions to an apparent decrease in young

veterinarians aspiring to own hospitals.

And she manages to make time for personal pleasures, such as hiking and downhill skiing, as well as caring for two dogs, a cat and a flock of chickens.

One of Tintle's greatest admirers knows her not as a clinician-scientist but as a professional leader and role model. Dr. Donald F. Smith, a former dean of the Cornell University College of Veterinary Medicine, invited Tintle about a year ago to help him with an initiative to bring more female veterinarians into leadership roles and boost their numbers in practice ownership. While women make up more than half of U.S. veterinarians and comprise about 80 percent of current veterinary students, Smith said they hold about 20 percent of senior leadership positions in the American Veterinary Medical Association (AVMA).

Smith said he wanted Tintle involved because "She is a known leader. I really admire the way she thinks and how she motivates colleagues. She can assemble a group of people in a room around a complex situation, and they will find solutions."

He described her style as self-assured. "You can't be vague around Linda because she's very confident and focused," Smith said. "...She will not dance around issues."

For example, during a session on women's leadership he co-organized at the state veterinary conference in September, participants talked about the need for mentoring and leadership-skill development. Someone pointed out that the AVMA has just such a program involving some 12 recent graduates per year.

Tintle wasn't impressed. "We need more than 12 people," Smith recalls her saying in a crescendo. "We need 10 times that!" In fact, she said, "Why don't we have 300 people in a program developing leadership skills!"

Her direct and assertive manner does not appear to translate into ego, however. After her first paper on shar-pei was published in 2011, Tintle thought to email the Mandelcorns — the couple whose puppy Chin-Chin was Tintle's first shar-pei patient. The veterinarian thanked her former clients for their role in her work.

The recognition somewhat embarrasses Mandelcorn. "We always felt that our influence or contribution was so minimal, but it was so nice of her to acknowledge us this way," Mandelcorn said.

After all, as she and her husband see it, in tracking down the mysteries of shar-pei health, Tintle is, in a way, still taking care of their pup.

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