BLOWING IN THE WIND

The mysterious Kawasaki disease might cross the Pacific on air currents high in the atmosphere.

BY JENNIFER FRAZER

The desperately ill baby had been airlifted in from Wyoming, recalls Jane Burns, thinking back to 1981 and her third year as a paediatric resident at the University of Colorado School of Medicine in Denver. Twenty-one days later, the little girl's skin rashes were mostly gone, but the accompanying fever was still raging, and Burns had no idea why.

"I think this is Kawasaki disease," said Richard Anderson, an infectious-disease fellow at the school, who had also examined the tiny patient.

Burns was stunned. Kawasaki disease was uncommon even in Japan, where it had been first identified in the early 1960s, and was almost unheard of in the United States. It was also utterly mysterious — some kind of inflammation in the blood vessels that primarily targeted children under the age of five and produced a variety of dramatic symptoms (see 'Mysterious malady'). Burns had heard of the disease only because she had encountered two Kawasaki disease patients in the previous year. And now Anderson was telling her she'd just got a third.

Less than 12 hours later, the baby was dead.

"I was so completely amazed by this disease that had now come and got me for a third time that I did the post mortem with the pathologist," says Burns. "And I'll never forget opening up her chest and looking at her heart and seeing the aneurysms sitting there."

These balloon-like bulges are common enough in the blood vessels of adults, especially those with risk factors such as diabetes or high blood pressure. But in a once-healthy infant? For Burns, now a paediatrics researcher at the University of California, San Diego (UCSD), and director of the Kawasaki Research Center at the UCSD Children's Hospital, the baby's death was a turning point. She has been studying Kawasaki disease ever since, whenever she can find funding. And she is not alone. "Kawasaki disease is something that has been fascinating people in infectious disease since it was described," says Ian Lipkin, an epidemiologist and director of the Center for Infection and Immunity at Columbia University in New York. "It smells like an infectious disease; we've just never been able to catch the culprit."

Epidemiologists now have a new place to look: on winds blowing from central Asia. A team of medical and climate scientists, including Burns, argue in last November's issue of

Seasonal winds from central Asia could be bringing Kawasaki disease into Japan.

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Scientific Reports[1] that the agent of Kawasaki disease is not only reaching Japan from the Asian mainland by this route, but it seems to be crossing the Pacific Ocean to infect children in Hawaii and the North American mainland.

If windborne spread turns out to be true, the Kawasaki disease agent will be the first viable human disease pathogen proved to cross thousands of kilometres of ocean by natural means (as opposed to carriage on planes or ships). And it may not be the last: researchers are beginning to ask whether the wind might also be a factor in the spread of influenza.

FIRST SIGNS

Japanese paediatrician Tomisaku Kawasaki saw his first case of the disease in 1960. He had no idea what it was. But it was so striking that he made diagrams and kept detailed records of the symptoms.

"He had this joke that he filed it in a folder called GOK, which was God Only Knows," says Burns.

Kawasaki published the first formal description of the malady in 1967 in Japanese[2]. Since then, there have been three major outbreaks in Japan: peaking in April 1979, May 1982 and March 1986. And the number of cases has been rising steadily each year (see 'Seasonal cycle'), despite Japan's falling birthrate. Today, the average annual incidence of about 12,000 cases in Japan rivals that of the earlier outbreaks at their peaks. Even in San Diego, Burns sees 80 to 100 new cases a year.

It is hard to say how widespread the disease actually is, because outside Japan the diagnosis is probably missed as often as not; children get mysterious rashes all the time. But the consequences can be serious. The kind of aneurysms that Burns saw in the 1981 autopsy occur in a quarter of untreated cases, and kill about 1 patient in 100. In addition, the body's attempts at repair can cause a build-up of scar tissue or narrowing of the arteries.

"Damage can be completely silent for decades until it's not," Burns says. "And the presentation can be with a massive heart attack in these young adults, who just have no idea why this is happening to them."

Genetics seems to play a big part, she says. Asian children are more susceptible than those in other ethnic groups. The immune system is deeply involved as well. The disease is characterized by widespread inflammation, which eventually focuses on the smooth muscle cells found in the walls of medium-sized arteries, in the heart and elsewhere, and can lead to aneurysms. The only effective treatment is intravenous injection of human immunoglobulin G, the major antibody fraction in blood, which — for reasons that are still not completely understood — lowers the probability of aneurysms from 25% to 1–5%.

Yet the cause of the disease remains GOK: for decades, researchers have looked for the Kawasaki disease agent among viruses, bacteria and every other category of pathogen, to no avail. Lipkin has been collaborating with Burns on this search for 20 years, applying each new molecular diagnostic tool as it came along and coming up empty-handed each time. Burns herself spent much of the 1980s investigating an initially promising link between Kawasaki disease and carpet cleaning, only for it to lead nowhere.

In the mid-2000s she started looking at a possible connection between Kawasaki disease and climate, along with Daniel Cayan, a meteorologist at the Scripps Institution of Oceanography at UCSD. Their first success came when they analysed the incidence of Kawasaki disease in Japan by prefecture, using Burns's contacts in the country to access detailed records of nearly 85,000 patients between 1987 and 2000. A trend was clear: cases were sharply seasonal, peaking in the winter and early spring, and again in early summer, which suggested that an environmental factor was involved[3].

Funding ran out and that lead went cold. But then in 2007, Cayan heard a lecture by Xavier Rodó, director of the Catalan Institute of Climate Sciences in Barcelona, Spain, who was on sabbatical at UCSD. Rodó had experience in figuring out how climate affects infectious diseases such as cholera, and had designed mathematical and statistical tools to pick out variables that might have low signal-to-noise ratios, or that might be intense but brief.

After the lecture, Rodó recalls, Cayan told him about Burns and her access to the extraordinary database of Japanese Kawasaki disease patients. "He said many people have had a go at this disease but no one really found anything that significant," says Rodó — a challenge too good to refuse.

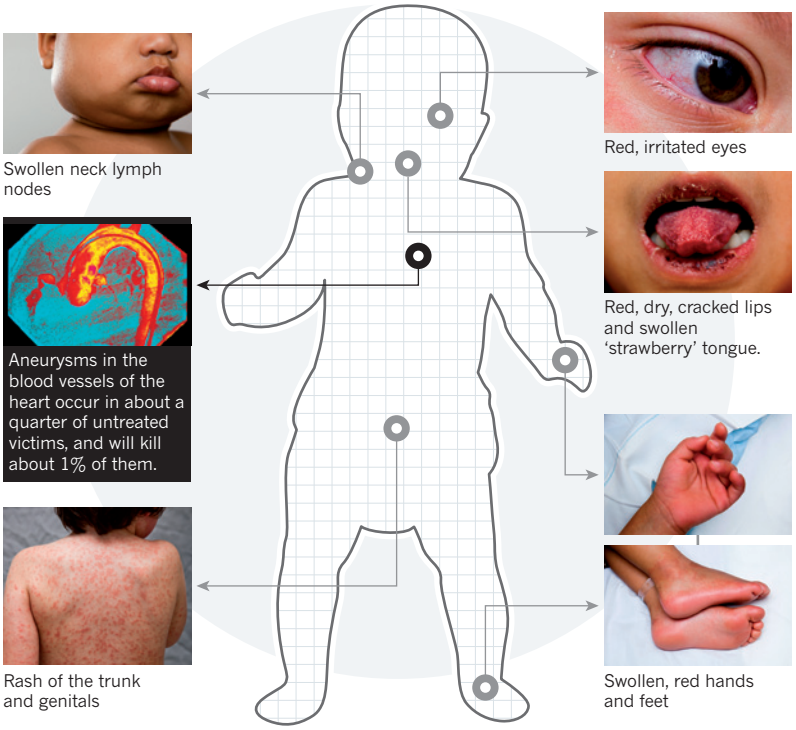
Adding Japanese records of more than 247,000 patients to his programs, Rodó let the software plough through a plethora of climate variables, including temperature, precipitation and humidity. One trend popped out: when the winds blew from central Asia across Japan, the number of Kawasaki disease cases skyrocketed. All three major outbreaks in Japan had followed this pattern, and it was also evident in the normal disease seasons. When the winds shifted to blow from the Pacific, cases dropped[1]. And when winds from central Asia made their way to Hawaii or California, cases spiked there too.

"I must say I was really shocked and surprised," says Rodó. The climate–disease correlation had fallen out with remarkable ease. And, the implication — that a human disease agent might still remain active after riding the winds all the way across the Pacific — was unprecedented.

Certainly the group's analysis would fly in the face of conventional wisdom if the disease agent proves to be a living organism, says Burns. Microbiologists have generally assumed that ultraviolet radiation and the near-cryogenic temperatures at high altitude will annihilate any infectious microbes before they can make it across an ocean. But maybe not, she says. "My background is molecular virology.

MYSTERIOUS MALADY

Kawasaki disease, discovered in Japan in 1960, is a widespread inflammation of the body's medium-sized blood vessels that affects mainly children under the age of five. The cause is unknown. But the symptoms, which also include fever, are striking.



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When I preserve my viruses in the lab, what do I do? I desiccate them and freeze them at –80 °C. Well, hello! Those are the conditions up in the troposphere."

Besides, says Burns, wind is often full of dust. "If you take a dust particle and look at it under the electron microscope, it's like a whole universe," she says. "It's got nooks and crannies and valleys and peaks", any of which could shelter a microbe or two from solar ultraviolet.

It's certainly the case that wind can carry pathogens short distances, says Arturo Casadevall, a microbiologist at the Albert Einstein College of Medicine in New York. He points to coccidioidomycosis, or valley fever, a human fungal disease that often appears in the US Southwest after dust storms or when earthquakes shake spores from the soil into the air. And over longer distances, there is evidence that the fungus *Aspergillus sydowii* rides west on dust storms from Africa to cause disease in sea fans in the Caribbean[4].

Dale Griffin, an environmental and public-health microbiologist at the US Geological Survey in Tallahassee, Florida, has studied African dust storms close up. On cruises to the waters over the Mid-Atlantic Ridge, Griffin has taken air samples just above the boat and cultured hundreds of microorganisms, including two fungal plant pathogens, the bacterium *Pseudomonas aeruginosa*, which can cause fatal infections in burn victims, and *Brevibacterium casei*, which can cause blood infections.

He estimates that about 10–20% of the dust-storm culture samples are pathogens. Griffin, who has also collaborated on a project that cultured microorganisms from samples collected at an altitude of 18 kilometres in the stratosphere[5], believes that Rodó and his colleagues have made a strong case that Kawasaki disease is riding the wind. "It's not surprising to me that an agent that has yet to be identified could be moving in the atmosphere — with dust or without dust," he says. "We also know there are many, many species that are very tolerant and can make long journeys in the atmosphere."

FINDING THE CULPRIT

Casadevall agrees that the case for wind-borne Kawasaki disease is strong, but goes on to emphasize that correlation is not causation, a point also raised by researchers sceptical of the theory. "In the past, people have made claims about this sort of thing, but it's all circumstantial," says Donald Aylor, a plant pathologist at the Connecticut Agricultural Experiment Station in New Haven, who has studied the wind dispersal of plant pathogens and pollen for 35 years. Even if the wind is blowing in a certain direction when a particular disease shows up, he says, it can be difficult to prove that a wind-blown pathogen is to blame. And when the pathogen is a total unknown, as in Kawasaki disease, the difficulties are even greater, he says. "You would have to ask yourself what else was happening during the time that the Kawasaki outbreak was happening. I mean, there could be a million things, right?"

The best way to counter this objection, Burns and her collaborators know, is to find the airborne pathogen. With Lipkin, they set up an experiment to filter the air over Japan at various altitudes during a period when the agent was suspected to be present, and then to sequence the DNA of everything on the filter — an approach known as 'metagenomics'.

In early March 2011, a Spanish engineer wearing a protective suit to prevent contamination went up in an aircraft that carried an air-filter built by Rodó's lab in Barcelona. The craft followed a route mapped out by Rodó using real-time wind data. When it returned, the samples were packed in dry ice and shipped to Lipkin's lab at Columbia. The timing was particularly fortunate as the route had criss-crossed Japan's Fukushima region. Just a week later, after nuclear reactors there were damaged in the earthquake and tsunami on 11 March, the winds would be full of radioactivity.

> "IT SMELLS LIKE AN INFECTIOUS DISEASE; WE'VE JUST NEVER BEEN ABLE TO CATCH THE CULPRIT."

At Columbia, where the metagenomic analysis is being carried out by biologist Brent Williams, progress has been slow because of the minuscule amounts of DNA present in air samples taken at high altitude. But the work is beginning to pay off, says Lipkin. Williams has found candidates for the Kawasaki agent — although Lipkin declined to discuss them before publication — and will soon be progressing to immunoassays. In these, antibodies generated to proteins predicted to be expressed by the suspected disease agent will be mixed with serum samples from children who have had Kawasaki disease and from controls who have not. If the antibodies interact significantly more strongly with the Kawasaki disease samples than with the controls, the team can be more confident that its suspected Kawasaki agent is the real thing.

The next step will be to look for DNA sequences in the blood samples of affected children that match the DNA detected in the air samples. "That would also be strong circumstantial evidence that would give us confidence that we're on the right track," Lipkin says.

With the identification of a causative agent, many more questions about Kawasaki disease could be addressed. Where is the agent's natural reservoir and is there an animal host? Why did this agent only emerge to cause disease in the 1950s and 60s? And why is its incidence rising?

And, of course, what other diseases are blowing in the wind? Taiwanese scientists, noting that outbreaks of avian influenza often occur downwind of dust storms, found influenza virus in air samples, and found that concentrations of the virus spiked when dust storms blew in from central Asia[6]. So, says Burns, "why don't we acknowledge the possibility that agents important for human health could be travelling on these wind currents?" ■

Jennifer Frazer *is a Colorado-based science writer and blogger for* Scientific American.

1. Rodó, X. *et al. Sci. Repts* **1,** http://dx.doi.org/10.1038/srep00152 (2011).
2. Kawasaki, T. *Arerugi* **16,** 178–222 (1967) (in Japanese).
3. Burns, J. C. *et al. Epidemiology* **16,** 220–225 (2005).
4. Shinn, E. A. *et al. Geophys. Res. Lett.* **27,** 3029–3032 (2000).
5. Smith, D. J., Griffin, D. W. & Schuerger, A. C. *Aerobiologia* **26,** 35–46 (2009).
6. Chen, P.-S. *Environ. Health Perspect.* **118,** 1211–1216 (2010).

SEASONAL CYCLE

The number of Kawasaki disease cases in Japan (red) is slowly rising, for unknown reasons, but is strongly correlated with the average velocity of winds coming from the northwest (blue) — the direction of central Asia.

SOURCE: REF. 1