Kawasaki Disease Before Kawasaki at Tokyo University Hospital

Noriko Shibuya, MD*; Kazuhiko Shibuya, MD‡; Hitoshi Kato, MD‡; and Masayoshi Yanagisawa, MD§

ABSTRACT. *Objective.* **Kawasaki disease (KD) was first reported by Tomisaku Kawasaki in 1967 in Japan. Large-scale nationwide epidemiologic surveys have been conducted continuously by the Japan Kawasaki Disease Research Committee; however, there were very few reports of KD before 1967. This study was performed to clarify when KD appeared in Japan.**

Design. **We investigated the medical charts of patients who had been hospitalized at Tokyo University Hospital between 1940 and 1965.**

Results. **We identified 10 patients whose clinical signs fulfilled the criteria for KD. The ages of the patients ranged from 8 months to 5 years, and their final diagnoses were Stevens-Johnson syndrome, allergic toxic erythema, Izumi fever, scarlet fever, and cervical lymphadenitis. These 10 patients presented between 1950 and 1964, and no confirmed cases were seen between 1940 and 1949.**

Conclusions. **Our findings suggested that KD patients were rare before 1950 in Japan.** ***Pediatrics*** **2002; 110(2). URL: http://www.pediatrics.org/cgi/content/full/110/2/e17;** ***Kawasaki disease, Stevens-Johnson syndrome, allergic toxic erythema, Izumi fever, scarlet fever.***

ABBREVIATION. KD, Kawasaki disease.

It has been >30 years since 50 patients with Kawasaki disease (KD) were first reported by Tomisaku Kawasaki in 1967 in Japan.[1] Today, KD is a well-known acute febrile disease of young children all over the world with notable cardiac complications of coronary aneurysm. In Japan, nationwide epidemiologic surveys have been conducted continuously by the Japan Kawasaki Disease Research Committee.[2] These surveys indicated that the number of KD patients has gradually increased since the late 1960s, and that after 3 nationwide epidemics in 1979, 1982, and 1986, there are 6000 to 8000 new cases annually. However, there were only 88 cases reported before 1964, and it is not clear when KD first emerged in Japan. A case of Feer disease in 1952 may have been the first case of KD in Japan.[3] Feer disease was later regarded as acrodynia or "pink disease," which is caused by mercury poisoning.[4]

From the *Department of Pediatrics, Sanno Hospital, Tokyo, Japan; ‡Department of Pediatrics, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; and §Department of Pediatrics, National Children's Medical Center, Tokyo, Japan.

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Reprint requests to (N.S.) Department of Pediatrics, Sanno Hospital, 8–10-16 Akasaka, Minato-ku, Tokyo 107-0052, Japan. E-mail: nshibuya@iuhw.ac.jp

Although KD has been reported all over the world, the disease is overrepresented among Asian populations, especially Japanese, and disease susceptibility may be influenced by genetic and possibly cultural factors.[5] The causative agent of KD has not yet been determined; thus, it is important to clarify when KD emerged and what kind of environmental changes took place for young children at that time in Japan.

In this report we investigated the medical charts of patients who had been hospitalized at Tokyo University Hospital, the oldest national hospital in Japan and probably the only Japanese hospital where medical charts have been preserved intact for over a century. We determined from the charts whether the patients' clinical signs fulfilled the diagnostic criteria for KD, because KD is only a clinical diagnosis.

MATERIALS AND METHODS

Among the patients who had been hospitalized at Tokyo University Hospital between 1955 and 1965 (group I), we selected those who were diagnosed with allergic toxic erythema, periarteritis nodosa, or Stevens-Johnson syndrome. We selected these 3 diseases because not only do they resemble KD in presentation, but they are also multi-etiologic, and their diagnoses are often indistinct. Moreover, our purpose with group I was to confirm the existence of KD at our hospital as KD patients were beginning to be reported at other hospitals during this period.

Next, we investigated charts between 1940 and 1954 (group II) to clarify when KD emerged in Japan. We selected cases that were diagnosed as the diseases listed in Table 1.

We investigated patients' symptoms and signs, laboratory data, and clinical courses. We examined whether their signs fulfilled the diagnostic criteria for KD, particularly the principal signs approved by the Kawasaki Disease Research Committee.[6]

RESULTS

Group I (1955–1965)

Seven hundred to 900 patients were hospitalized each year, and a total of 9001 patients were hospital-

TABLE 1. Diagnoses Investigated in Medical Charts Between 1940 and 1954

Atypical scarlet fever
Atypical measles
Cervical lymphadenitis
Endocarditis
Eruptions with unknown cause
Erythema multiform
Feer disease
Fever of unknown origin
Infectious mononucleosis
Izumi fever
Leptospirosis
Mucocutaneous-ocular syndrome
Scarlet fever (under 3 y)
Sepsis
Still's disease

ized at the pediatric ward of Tokyo University hospital during this period (Table 2). The patients diagnosed with allergic toxic erythema, Stevens-Johnson syndrome, and periarteritis nodosa totaled 27, 8, and 2, respectively. We investigated these 37 patients by comparison of their signs with the principal signs of KD. The patients who had 5 of the principal signs recognized today as KD totaled 3 of 27 diagnosed as allergic toxic erythema, 2 of 8 Stevens-Johnson syndrome, and 0 of 2 periarteritis nodosa patients (Table 3).

Case 1

A 3-year-old boy had fever on October 8, 1964. On the second day, right cervical lymphadenopathy was noted. On the third day, skin rash started from the hands and spread gradually. On the fourth day, he had left cervical lymphadenopathy and was hospitalized. On admission, he had apparent conjunctivitis, and his lips were markedly red and dry. Round-shaped erythema was seen on his trunk, and the palms and soles were markedly red. On the sixth day, he developed jaundice and hepatomegaly, and was thus suspected to have Weil's disease. He was infused with Weil convalescent serum, but because serologic tests were not compatible with Weil's disease, his final diagnosis was Stevens-Johnson syndrome.

Case 2

A 3-year-old girl had fever on April 3, 1963. On the fourth day, erythema appeared on her hands and feet. On the fifth day, erythema spread to her trunk and face. She complained of oral pain and was suspected of having Behcet disease. She was hospitalized on the seventh day when she had conjunctivitis, injected lips, strawberry tongue, and cervical lymphadenopathy. There was no record of any mucosal lesions with vesicles or crusts. She showed freshly red erythematous lesions on her trunk and extremities. The palms and soles were red and swollen. She had transient arthritis of the fingers around the 11th day. Fever subsided on the 14th day, and her final diagnosis was Stevens-Johnson syndrome.

Case 3

A 3-year-old boy had fever and left cervical lymphadenopathy on October 21, 1959. On the third day, urticarial rash appeared. On the fifth day, he was admitted to a dental clinic, and the next day he was referred to Tokyo University hospital with a diagnosis of sepsis. On admission, he had conjunctivitis, red, dry and fissured lips, and cervical lymphadenopathy (7×5 cm) with redness and pain. He also had urticarial rash on the trunk and extremities. The erythema disappeared but transient measles-like erythema appeared on the 10th day. Fever subsided on the 11th day but transient fever was seen for the next 2 days. On the 15th day, membranous skin desquamation was seen on the fingertips. On the 20th day, he developed arthralgia of the knees and was given steroids as a treatment for rheumatic fever. It seemed that steroid treatment was effective. His final diagnosis was allergic toxic erythema and cervical lymphadenitis.

Case 4

An 8-month-old boy had fever and erythema on November 18, 1958. He was suspected to have scarlet fever and was hospitalized on the third day. On admission, he had severe conjunctivitis, and markedly red and dry lips. His palms and soles were red, and there was scarlet fever-like erythema on the trunk. Fever subsided on the eighth day, and there was no record of skin desquamation. His final diagnosis was allergic toxic erythema.

Case 5

A 2-year-old girl had fever on June 21, 1956. On the second day, she had cervical pain. On the third day, eruptions appeared on her dorsal feet. On the fourth day, erythema appeared on her face, and her lips became red and dry. She was hospitalized on the sixth day. On admission, she had conjunctivitis, red, dry and fissured lips, strawberry tongue, and cervical lymphadenopathy. Distal parts from the wrists and ankles were diffusely red and swollen. There was freshly red multiform erythema on the trunk and extremities. She showed consciousness disturbance with nuchal rigidity around the eighth day and was diagnosed as having encephalopathy by electroencephalography. Fever subsided on the 11th day and her condition improved. Membranous skin desquamation from the fingertips started on the 14th day. Her final diagnosis was allergic toxic erythema.

All of these 5 patients had leukocytosis and marked elevation of erythrocyte sedimentation rate. None of them proved to have *Streptococcus* by throat culture, and all were resistant to antibiotic therapy. All recovered completely and were discharged from hospital. We have no data on them after discharge.

Group II (1940–1954)

A total of 7618 patients were hospitalized at the pediatric ward of Tokyo University Hospital during this period (Table 4). Among these patients, 144 were diagnosed with the diseases listed in Table 1. Two patients were diagnosed with leptospirosis, both of

TABLE 2. Patients Hospitalized at Tokyo University Hospital Between 1955 and 1965

Diagnosis	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	Total
Allergic toxic erythema	1	5	3	3	2	4	5	2	1	1	0	27
Stevens-Johnson syndrome	0	0	1	0	0	0	1	1	3	1	1	8
Periarteritis nodosa	0	2	0	0	0	0	0	0	0	0	0	2
Total	1	7	4	3	2	4	6	3	4	2	1	37
Total patients hospitalized	705	723	887	899	898	864	871	800	757	764	833	9001

TABLE 3. Patients Who Had 5 Principal Signs of KD (Group I)

No.	Year	Age	Sex	Final Diagnosis	Principal Signs							
					Fever (Days)	Extremity Changes			Rash	Conjunctivitis	Oral Changes	Cervical Lymphadenopathy
						Erythema	Edema	Desquamation				
1	1964	3 y 3 mo	M	Stevens-Johnson syndrome	20	+	NR	NR	+	+	+	+
2	1963	3 y 3 mo	F	Stevens-Johnson syndrome	13	+	+	NR	+	+	+	+
3	1959	3 y 9 mo	M	Allergic toxic erythema	10	NR	NR	+	+	+	+	+
4	1958	8 mo	M	Allergic toxic erythema	7	+	NR	NR	+	+	+	−
5	1956	2 y 4 mo	F	Allergic toxic erythema	10	+	+	+	+	+	+	+

NR indicates no record.

TABLE 4. Patients Hospitalized at Tokyo University Hospital Between 1940 and 1954

Diagnosis	1940	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954	Total
Atypical scarlet fever	0	0	0	0	0	0	3	0	0	0	0	0	1	0	0	4
Atypical measles	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2
Cervical lymphadenitis	0	1	0	1	1	0	0	1	0	1	1	0	0	0	1	6
Endocarditis	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
Eruptions with unknown cause	2	0	1	1	1	0	2	2	1	0	0	0	0	3	1	14
Erythema multiforme	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Fever with unknown origin	5	9	6	6	0	1	0	0	1	0	1	0	0	0	0	29
Infectious mononucleosis	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	2
Izumi fever	0	0	0	0	0	0	0	0	0	0	1	2	5	3	3	14
Leptospirosis	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Scarlet fever (under 3 y)	12	2	4	7	4	0	3	1	0	1	1	1	1	1	3	41
Sepsis	5	2	2	3	0	0	1	1	2	2	3	0	0	1	0	22
Still's disease	2	0	0	0	2	0	0	0	0	1	0	1	0	0	0	6
Total	27	15	13	18	8	1	9	5	4	6	9	6	7	8	8	144
Total patients hospitalized	846	813	838	771	557	201	280	320	315	360	355	410	450	505	597	7618

TABLE 5. Patients Who Had 5 Principal Signs of KD (Group II)

No.	Year	Age	Sex	Final Diagnosis	Principal Signs							
					Fever (Days)	Extremity Changes			Rash	Conjunctivitis	Oral Changes	Cervical Lymphadenopathy
						Erythema	Edema	Desquamation				
6	1954	9 mo	F	Izumi fever	20	+	NR	+	+	+	+	+
7	1953	4 y 0 mo	M	Izumi fever	14	NR	+	+	+	+	+	+
8	1953	1 y 1 mo	M	Izumi fever	9	+	+	+	+	NR	+	+
9	1951	2 y 10 mo	M	Scarlet fever	15	+	+	+	+	+	+	+
10	1950	5 y 8 mo	M	Cervical lymphadenitis	10	NR	NR	NR	+	+	+	+

NR indicates no record.

whom had Weil's disease. There were no patients diagnosed with either mucocutaneous-ocular syndrome or Feer disease. There were 5 patients who had >5 principal signs of KD (Table 5). Three of the 5 patients were diagnosed with Izumi fever, a disease which was later presumed to be *Yersinia* infection.[7]

Case 6

A 9-month-old girl had fever and red face on July 10, 1954. On the third day, she had lymphadenopathy. On the fourth day, her conjunctivas became markedly red. On the fifth day, her hands and feet became freshly red. On the ninth day, measles-like erythema appeared. She was hospitalized on the 12th day when she had erythema, conjunctivitis, and strawberry tongue. Fever was resistant to antibiotics and subsided on the 21st day. The final diagnosis was Izumi fever.

Case 7

A 4-year-old boy had fever and generalized rash on July 29, 1953. On the second day, his hands became swollen and he was hospitalized. On admission, he had erythema, conjunctivitis, and cervical lymphadenopathy. He had low-grade fever from the fourth to ninth day, but had high fever with urticarial rash from the 10th to 14th day. Skin desquamation from the trunk and fingers started on the 13th day. Fever subsided on the 15th day, and his final diagnosis was Izumi fever.

Case 8

A 13-month-old boy had fever on April 12, 1953. On the third day, he was diagnosed as having cervical lymphadenitis. On the fourth day, he had eruptions on the neck and chest. On the 5th day, his palms and soles became red. On the seventh day, he was hospitalized with neck stiffness and drowsiness. On admission, his palms and soles were markedly red. His lips were also markedly red and he had cervical lymphadenopathy. Fever subsided on the 10th day, and his general condition improved. On the 14th day, skin desquamation from the fingertips was noted. He was finally diagnosed as having Izumi fever because of a biphasic fever and atypical rash including extremity changes.

Case 9

A 2-year-old boy had fever and swelling of dorsal hands and feet on May 7, 1951. On the second day, he had eruptions on the trunk and legs. On the fourth day, erythema increased, and cervical swelling was noted. On the fifth day, his lips became dry and fissured so that he had difficulty in eating because of pain. He was hospitalized on the eighth day, when he had erythema and swelling on the hands and feet, conjunctivitis, dry lips with scabbing, and lymphadenopathy. Fever subsided on the 15th day when membranous skin desquamation from the fingertips was noted. Heart murmur was ausculted on the 19th day, but electrocardiogram findings were normal. His final diagnosis was scarlet fever, but throat and blood culture failed to detect *Streptococcus.*

TABLE 6. Laboratory Data of the Probable KD Cases

No.	Year	Day of Lab Test	WBC Count	ESR/Hour	Throat Culture	Blood Culture
1	1964	4	16 300	76	*Streptococcus* (−)	NR
2	1963	7	33 900	90	NR	Negative
3	1959	6	33 400	118	*Staphylococcus* (+)	Negative
4	1958	3	20 500	70	*Streptococcus* (−)	Negative
5	1956	6	16 200	105	*Micrococcus* (+)	Negative
6	1954	10	28 600	NR	Negative	Negative
7	1953	2	12 300	21	*Staphylococcus* (+)	NR
8	1953	7	36 400	NR	NR	NR
9	1951	8	20 000	48	Negative	Negative
10	1950	6	13 300	35	NR	Negative

WBC indicates white blood cells; NR, no record; ESR, erythrocyte sedimentation rate.

Case 10

A 5-year-old boy had fever and left cervical lymphadenopathy on September 9, 1950. On the third day, the right cervical lymph node became swollen. He was hospitalized on the fifth day, when he had conjunctivitis, freshly red and erosive lips, lymphadenopathy, and erythema. Fever subsided on the 12th day. He was diagnosed as having purulent lymphadenitis and the doctor's comment on the chart says, "The rash might have been because of drug allergy, although the conjunctivitis cannot be explained."

All 5 patients except case 10 had apparent extremity changes. All had leukocytosis and were resistant to antibiotic therapy. All patients recovered completely and were discharged from the hospital. We have no data on them after discharge. Laboratory data of these 10 cases are summarized in Table 6.

There was one more patient whom we strongly suspected to have been KD, although she did not fulfill the criteria. She was a 9-month-old infant diagnosed with Izumi fever in 1952. As she was hospitalized at another hospital during the acute phase, we do not know her complete clinical findings. She had a biphasic fever for 15 days, rash, jaundice, and skin desquamation from the fingertips to palms. There was also a chart statement saying "The site of BCG vaccination was reddish and swollen to ~4 cm in diameter, followed by abscess formation," which is a characteristic sign of KD.

From 1940 to 1949, we found 3 cases that we suspected may have been KD; all of these had a diagnosis of scarlet fever (Table 7).

Case 12

A 13-month-old boy had fever and erythema on July 13, 1946. He was hospitalized on the third day when he had "scarlet fever-like" erythema on the whole body. His palms and soles were markedly red. He had strawberry tongue, but no conjunctivitis or red lips. Fever subsided on the 12th day. Skin desquamation was observed except on the hands and feet.

Case 13

A 22-month-old girl had fever on July 6, 1942. She had erythema on the second day. She was hospitalized on the third day when she had "scarlet fever-like" erythema and strawberry tongue. Her pharynx was markedly injected. She did not have conjunctivitis or red lips. On the fifth day, cervical lymphadenopathy was noted. On the seventh day, multiple abscesses with fluctuation appeared on her head. On the eighth day, fever subsided and skin desquamation was seen on the 11th day. Her white blood cell count on admission (third day) was 7600.

Case 14

A 2-year-old girl had fever and red face on December 22, 1940, and she was hospitalized at Tokyo University Hospital on the same day. She had exanthema and conjunctivitis, and her pharynx was markedly injected. She had no apparent strawberry tongue or lymphadenopathy. Fever subsided on the 12th day, and skin desquamation was seen on the 14th day. Her aunt had scarlet fever and was hospitalized until the beginning of December, then lived with her.

These 3 patients recovered completely and were discharged from the hospital.

DISCUSSION

We investigated the medical charts of patients who had been hospitalized at Tokyo University Hospital between 1940 and 1965 and identified 10 patients who had 5 principal signs of KD (Table 3). These 10 patients were admitted between 1950 and 1964, and none were found from 1940 to 1949. These cases were distributed from April to November, and no cases were found in winter. However, the number of cases was too small to say anything about seasonal distribution. The ages of these 10 patients ranged from 8 months to 5 years, compatible with the ages at which KD predominantly strikes. Their final diagnoses were Stevens-Johnson syndrome, allergic toxic erythema, Izumi fever, scarlet fever or cervical lymphadenitis. However, most were first diagnosed as having other diseases, and their final diagnoses were reached by ruling out several other diseases, suggesting difficulty in understanding their symptoms.

There was a discussion about the differences between Stevens-Johnson syndrome and KD when KD was first described.[8] Stevens-Johnson syndrome is characterized by multiform skin and mucous membrane lesions with vesicles, crusts or ulcers. There were no such lesions apparent in cases 1 and 2. Transient jaundice, as in case 1, is occasionally observed in KD patients,[8] and both cases 1 and 2

TABLE 7. Suspected KD Cases Between 1940 and 1949

No.	Year	Age	Principal Signs									WBC Count	Throat Culture
			Fever (Days)	Extremity Changes			Rash	Conjunctivitis	Oral Changes			Cervical Lymphadenopathy		
				Erythema	Edema	Desquamation			Lips	Tongue	Pharynx			
12	1946	1 y 1 mo	11	+	NR	−	+	−	NR	+	+	−	21 500	NR
13	1942	1 y 10 mo	7	NR	NR	+	+	−	NR	+	++	+	7600	NR
14	1940	2 y 0 mo	11	NR	NR	+	+	+	NR	−	++	−	NR	Diphth B (−)

WBC indicates white blood cell; NR, no record.

showed extremity changes, suggesting they were more likely to have had KD.

Allergic toxic erythema is not a distinct clinical entity, and most of the patients with this diagnosis had a mixture of erythematous diseases of unknown origin. Thus, it is possible that the patients who met the criteria for KD actually had KD.

Izumi fever is a disease first described as a scarlet fever-like febrile disease in Japan in 1929.[9] There were many mass outbreaks of Izumi fever shortly after World War II in Japan, but the outbreaks decreased rapidly after 1955.[7] The latest mass outbreak occurred in 1981, and because the pathogen was found to be *Yersinia pseudotuberculosis* at that time, the previous patients were presumed to have had the same pathogen.[7] There is a strong resemblance between *Yersinia* infection and KD symptoms, and some patients with *Yersinia* infection met the criteria for KD and even demonstrate coronary aneurysms.[10,11] However, there is still controversy as to whether *Yersinia* is the cause of KD. In our study, we found 3 patients with Izumi fever who met the KD criteria. We have no means of testing for pathogens or of obtaining any serologic data from these patients. However, because KD is only diagnosed clinically, we considered these to be cases of KD. It is possible that there were more KD patients misdiagnosed with Izumi fever in this period.

Scarlet fever also resembles KD in symptoms. Case 9 demonstrated all 6 principal signs of KD, and the absence of organisms in throat culture and the resistance to antibiotic therapy indicated that the disease was not attributable to streptococcal infection. Three cases of scarlet fever between 1940 and 1949 were confusing probably because scarlet fever was a much more serious illness in former times. Differential diagnosis usually can be made by the presence of conjunctivitis, extremity changes, or lymphadenopathy. Case 12 had extremity changes, but other symptoms were typical for scarlet fever. Case 13 had cervical lymphadenopathy, but with multiple abscesses as a secondary disease, which her lymphadenopathy could be attributable to. Also, her white blood cell count was not compatible with KD. Case 14 had conjunctivitis but other symptoms such as erythema, marked pharyngitis were typical for scarlet fever. She also had familial infection of scarlet fever. Thus, we concluded that it was more likely that these 3 cases had scarlet fever than KD. A cautious approach is necessary when examining the charts of scarlet fever patients.

Case 10 was diagnosed as cervical lymphadenitis with allergic erythema. However, the patient had apparent conjunctivitis and the lips were "freshly red, somewhat erosive" (in German). Although there was no record of extremity changes, it is easier to understand each sign as part of the KD signs.

KD was first described in 1967 in Japan.[1] The Japan Kawasaki Disease Research Committee has conducted 15 nationwide surveys on KD at 2-year intervals from 1970 to 2000, and the total number of patients reported by the surveys is 169 117.[12] However, there have been few reports of cases now assumed to have had KD before 1967. A case of Feer

disease in 1952,[3] a case of muco-cutaneous syndrome, and a case of Izumi fever in 1953 were thought to be the earliest case reports of KD in Japan.[13,14] In our study, we found KD cases identified by fulfilling the criteria as early as 1950, but we found no such cases from 1940 to 1949. Additional investigations would be necessary to find earlier KD, but we presume that numbers of KD patients were very few, if any, before 1950. It is likely that a small number of KD patients emerged in the 1950s and then increased in nationwide epidemics toward the 1970s.

Although some infectious agent is suspected, the cause of KD remains unknown. However, we may find clues through investigating what happened around the time at which KD broke out.

There is controversy as to whether KD was a new disease that emerged in Japan. A comment in the *Journal of Pediatrics* in 1999 suggested that the article by Fanney on the cases of Stevens-Johnson syndrome in 1949 might be the first reported cases of KD.[15,16] Another discussion took place about the similarity between KD and infantile periarteritis nodosa,[17] and some early cases of infantile periarteritis nodosa were indicated to be cases of KD before those reported by Fanney.[18]

On the assumption that Fanney's or other IPN cases were the first reported cases of KD in the world, no cases were reported in Japan before World War II; thus, it is possible that some pathogen responsible for KD might have been introduced into Japan sometime after World War II. Also, rapid changes in lifestyle after the war, such as food, clothing, or housing, might have contributed to aberrant reactions against the pathogen. Alternatively, it is hard to ignore the clinical similarities between KD and *Yersinia* infection. It was reported that a KD patient with coronary artery aneurysm demonstrated not only positive serologic findings, but was also positive culture for *Y pseudotuberculosis* [19]. As there are epidemiologic differences between Izumi fever and KD and because the serologic data of KD patients were contradictory to *Yersinia* infection,[20] the pathogen may be different. However, it is still possible that the causal agent of KD and *Y pseudotuberculosis* share a common pathogenicity. Improvements in sanitation may have given rise to some interactions among pathogens. For example, the incidence of *Yersinia* infection that was predominantly transmitted via well water decreased rapidly in the 1950s. This might create another environment where other organisms could survive, or a decrease in the chances of exposure to antigens such as *Yersinia* may have led to changes in the host defense mechanisms that conferred increased susceptibility to KD.

Additional investigations into the environmental changes around young children in this period will provide new insights into the pathogenesis of KD.

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