

The Narratives of Kawasaki Disease

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SUMMARY: Kawasaki disease is a rash/fever illness of early childhood in which coronary artery aneurysms (CAA), sometimes fatal, may develop in up to 25 percent of untreated children. Because its etiology and pathophysiology are unknown and no diagnostic laboratory test exists, diagnosis is made via a list of clinical signs; however, a significant number of children fail to meet the clinical criteria and go on to develop CAA. We suspected a connection between these missed cases and the continuing difficulty in identifying the etiological agent(s) and mechanisms for CAA. In search of that connection, we launched a historical investigation into the institutionalization of the clinical criteria, and explored how this process influenced the framing of research questions. Our findings suggest that the canonization of the Kawasaki disease case definition was as much due to the enshrinement of the historical narrative as to compelling scientific findings. The Kawasaki disease narrative encompasses interrelated issues of definition, discovery, and naming; these, in turn, have profoundly influenced diagnosis, treatment, and research. “Atypical” cases, despite being at risk for CAA, often fail to receive prompt diagnosis and treatment; consequently, research has been limited to the population that meets the diagnostic criteria for Kawasaki disease, rather than including those who are at risk of CAA. Although clinical concerns prompted this investigation, it nevertheless has important implications for the history of medicine: it provides an illustration of how a historical interrogation of a syndrome’s construction can free medical researchers to pursue novel approaches. Equally important, it demonstrates how historians can make unique contributions as collaborators in clinical care and medical research.

KEYWORDS: Kawasaki disease, syndrome classification, diagnostic criteria, coronary artery aneurysms, infantile periarteritis nodosa, pediatric vasculitis

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Kawasaki disease is a rash/fever illness of early childhood in which coronary artery aneurysms (CAA), sometimes fatal, may develop in up to 25 percent of untreated children. The incidence is highest in Japan, with an annual rate of 130–140 per 100,000 in children under five years of age.¹ In comparison, incidence for under-fives in the continental United States varies between 9 and 20/100,000, and, among Japanese Americans living in Hawaii, between 120 and 130/100,000.² Because the etiologic agent(s) and pathophysiological mechanisms of Kawasaki disease remain unknown, and because there is no diagnostic laboratory test, diagnosis relies on the observation and recognition of clinical signs that comprise the Kawasaki disease case definition.

With the establishment of intravenous immunoglobulin (IVIG) as an effective therapy,³ prompt diagnosis has become essential for timely therapy to ensure a good cardiac outcome.⁴ A significant number of children, however, fail to meet the clinical criteria, receive delayed treatment, and develop CAA. We hypothesized that there might be a connection between these missed cases and the continuing frustration of researchers trying to identify the etiological agent(s) and mechanisms responsible for CAA. In order to identify what that connection might be, we launched a historical investigation into the construction of the clinical criteria and the process of their canonization.

The illness is named after the Japanese pediatrician Tomisaku Kawasaki, who in 1967 described fifty cases of infants with persistent fever accompanied by rash, lymphadenopathy, edema, conjunctival injection, redness and cracking of the lips, “strawberry tongue,” and convalescent desquamation⁵ (see Table 1).

1. H. Yanagawa, Y. Nakamura, M. Yashiro, et al., “Results of the Nationwide Epidemiologic Survey of Kawasaki Disease in 1995 and 1996 in Japan,” *Pediatrics*, 1998, 102: e65–e72.

2. Marian Melish, personal communication, April 2000.

3. K. Furusho, T. Kamiya, and H. Nakano, “High-Dose Intravenous Gamma Globulin for Kawasaki Disease,” *Lancet*, 1984, 2: 1055–58; Jane W. Newburger, Michael Takahashi, Jane C. Burns, et al., “The Treatment of Kawasaki Syndrome with Intravenous Gamma Globulin,” *New England J. Med.*, 1984, 315: 341–47.

4. Although arteriography (available in the 1970s) and echo imaging (beginning in the early 1980s) are important tools for the detection of CAA, they are not useful for prevention since they can detect CAA only after it occurs.

5. Tomisaku Kawasaki, “Acute Febrile Muco-Cutaneous Lymph Node Syndrome in Young Children with Unique Digital Desquamation: Clinical Observation of 50 Cases” [in Japanese], *Aterugi [Jpn. J. Allergology]*, 1967, 16 (3): 178–222; H. Shike, J. C. Burns, and C. Shimizu, English translation of Dr. Tomisaku Kawasaki’s original report of fifty patients in 1967 [in Japanese], *Pediatr. Infect. Dis. J.*, 2002, 21 (11): 993–95, esp. p. 993 (Additional files available on Article Plus: Part 1: <http://ipsapp006.lwwonline.com/content/getfile/1980/99/2/6840/articleplus.pdf>; Part 2: <http://ipsapp006.lwwonline.com/content/getfile/1980/99/2/6841/articleplus.pdf>) (accessed on 11 February 2004).

Table 1. Kawasaki's Sign Complex (1967)

1. Even with the use of various antibiotics, fever higher than 38°C persists longer than 6 days. 50 cases (100%)
2. Bilateral bulbar conjunctiva presents injection. 49 cases (98%)
3. Erythematous rash seen particularly on bilateral palm and/or bilateral sole, but never forms vesicles. 43 cases (86%)
4. Redness, dryness, erosion, cracking, sometimes bleeding and hemorrhagic scab on lips and sometimes diffuse injection of oral mucosa and strawberry tongue are recognized. 48 cases (96%)
a. No formation of vesicles, ulcers, pseudomembrane or aphtha.
5. Acute swelling of neck lymph node(s) (equal or bigger than the head of thumb). 33 cases (66%)
a. Never develop to pyesis.
6. Bilateral hands and feet present vaso-neurogenic edema. 22 cases (44%)
7. Desquamation starts from nail-skin junction of fingers and toes, mostly from the second week of the disease. 49 cases (98%)
8. More than half of the cases are under age of 2 years. 27 cases (54%)
9. No recurrence.
10. Resolves without intervention; no sequela.

No contagion between siblings observed.

Adapted from Tomisaku Kawasaki, "Acute Febrile Muco-Cutaneous Lymph Node Syndrome in Young Children with Unique Digital Desquamation: Clinical Observation of 50 Cases" [in Japanese], *Averugi [Jpn. J. Allergology]*, 1967, 16 (3): 178-222.

The typical history of Kawasaki disease provides a narrative that emphasizes Kawasaki's careful clinical observations and his subsequent classification of clinical signs into a distinct syndrome. It relates the story of how he identified what he and his supervisor and colleagues at the Red Cross Hospital considered to be a novel childhood illness. Kawasaki labeled the illness "mucocutaneous lymph node syndrome" (MLNS or MCLS). Initially he assumed that the syndrome was self-limiting and benign, requiring no special intervention; however, the death of a number of patients reported in early surveys persuaded him to acknowledge a connection between the illness and coronary artery abnormalities. Simultaneously with Kawasaki's discovery, a team of American pathologists identified a fatal cluster of childhood CAA as a distinct syndrome that they labeled "infantile polyarteritis nodosa" (IPN). Within a decade, pathologists determined that IPN and fatal cases of MCLS were identical; soon after, MCLS and IPN were renamed Kawasaki disease, in honor of its discoverer.⁶

6. We too have contributed to this view: see Jane C. Burns, Howard I. Kushner, John F. Bastian, et al., "Kawasaki Disease: A Brief History," *Pediatrics*, 2000, 106: e27-e34.

Deconstructing this narrative exposes a number of issues about claims of disease “discovery” processes, the construction of syndromes, the naming of diseases, and the consequences of all of these for medical research and clinical practice.⁷ It also serves to destabilize epidemiological assumptions and other knowledge claims about Kawasaki disease, and it opens up important possibilities for clinical research because it calls into question assumptions that have framed the identification, treatment, and search for the etiology of CAA in children since the 1960s.⁸ Further, it demonstrates the utility of the history of medicine for alerting medical investigators to new research questions.

By the mid-1970s, medical interest in MCLS/MLNS was heightened due to the occurrence of a Kawasaki disease epidemic in Japan, as well as the recognition of the risk of associated CAA. By this time, Kawasaki, who had built his career around the syndrome, had become its spokesperson in Japan and beyond. Medical experts from Japan and the United States formed strong professional and personal alliances, and the Japan Kawasaki Research Center became an international clearing house, publishing pamphlets and bibliographies and organizing national and international meetings on Kawasaki disease. At the center of it all was Tomisaku Kawasaki, who increasingly became its icon. Presentations at professional meetings since the 1980s often begin with a slide of the presenter standing next to Dr. Kawasaki: the speaker uses the photograph as if to imply that the talk has received an endorsement from the discoverer of Kawasaki disease.

What concerns us here is the impact of that iconography on diagnosis, treatment, and research. What constitutes evidence for diagnosis and

7. In *Making Sense of Illness*, Robert Aronowitz shows how the “celebratory view of Lyme disease’s ‘discovery’ has co-opted the earlier history in a variety of ways”—but he adds that saying this does not necessarily “diminish the considerable achievements of the Lyme-disease investigators” (Robert Aronowitz, *Making Sense of Illness* [Cambridge: Cambridge University Press, 1998], pp. 57–82, quotation on pp. 81–82).

8. Our data consist of historical records of clinical cases and autopsy reports, interview data, and observational notes. Because the syndrome was only recently recognized, firsthand accounts are available from those involved in its “discovery.” We conducted a series of focused interviews with pediatricians, pathologists, and medical researchers from Japan, North America, and Europe; the topics covered in these open-ended interviews included a recollection of their earliest clinical observations of possible cases, their histories of research into the characteristics and the etiology of the syndrome, and their professional conversations about it. To provide a context for the interview data, we also observed practicing physicians, including members of our team, as they considered and eliminated Kawasaki disease and other possible diagnoses. In addition, the observational data were placed in the context of our historical understanding derived from the review of existing written sources.

treatment with a relatively expensive intervention in a condition where it might be unnecessary for 75 percent of the diagnosed? What factors delay diagnosis and treatment in other children who subsequently develop CAA? Which patients are included in the population that is the focus of etiological research?

The answers to these questions are bound up with specific historical inquiries about the nature of the syndrome. Did Kawasaki discover a “new” syndrome, or merely describe the clinical signs of an existing condition? If the disorder that he described is clinically similar to, but ultimately different from, the fatal vasculitis formerly known as IPN, it might help explain why the risk of developing CAA is more than twice as high in children with atypical presentations as among those who meet the syndrome criteria.⁹ For more than forty years researchers have attempted and failed to locate the etiological agents and pathophysiological mechanisms that result in CAA.¹⁰ To what extent may this be the result of the rule that the Kawasaki disease clinical sign complex must be present (even if CAA develops) for inclusion in a research protocol? Why have researchers not included all patients who go on to develop CAA, whether or not they meet the Kawasaki disease case definition? These are clinical and medical research questions that deserve historical investigation.

We are interested in the history of Kawasaki disease because our investigation persuades us that today’s unchallenged diagnostic and clinical assumptions rest on yesterday’s unresolved contests. This realization can free investigators to ask new questions and to explore neglected avenues, which may provide insights and clues for the construction of new strategies for hypothesis development, in the quest to identify the possible mechanisms and agents that result in this sometimes fatal childhood vasculitis.

9. Howard I. Kushner, John F. Bastian, Christena H. Turner, and Jane C. Burns, “Rethinking the Boundaries of Kawasaki Disease: Toward the Next Case Definition,” *Perspect. Biol. & Med.*, 2003, 46: 216–33.

10. Despite numerous promising leads and impending breakthroughs, no responsible agent has been identified. At one time or another a variety of infectious bacterial, viral, and rickettsial organisms have been suspected, as have immunological agents such as bacterial toxin-mediated superantigens. Additional candidates have included heavy metals (mercury) and allergens such as anionic detergents in carpet cleaners and house-dust mites. See A. J. Lloyd, C. Walker, and M. Wilkinson, “Kawasaki Disease: Is It Caused by an Infectious Agent?” *Brit. J. Biomed. Sci.*, 2001, 58: 122–28.

Syndromes, Spectrums, and Naming

Our investigation is informed by a number of medical histories. The history of the Tourette syndrome (TS) has a number of parallels with that of Kawasaki disease.¹¹ This history reveals an unstable classification, with clinical signs and symptoms that varied in service to the dominant psychiatric paradigm and were as informed as much by politics as by pathology. As a number of TS clinical researchers concede, persistent disagreements over what constitute the signs and symptoms of TS (its phenotype) continue to frustrate attempts to locate its underlying pathogenesis (causes).¹²

These contests are due in large measure to the fact that TS is a syndrome rather than a disease. Measles, polio, and sickle-cell anemia are *diseases* because a tentative diagnosis based on signs and symptoms is confirmed or rejected through a laboratory test indicating infection by a pathogen or the presence of a genetic mutation. In contrast, the cause of a *syndrome* remains unknown.¹³ The diagnosis of syndromes depends on the identification of a list of possible combinations of signs and symptoms displayed by a patient within a certain time period; the list is tentative, and disagreement often surfaces over which signs and symptoms are crucial to diagnosis.¹⁴ As a result, the identification of a syndrome often varies over time and by geographic location.¹⁵

Recognition of the tentativeness of a syndrome can be productive, because it authorizes researchers and clinicians to question underlying assumptions about the signs and symptoms and to provide alternative hypotheses for the etiology of idiopathic disorders. Atypical cases often provide insight into possible etiological and pathological features. What is seen as a single clinical entity may result from a variety of different underlying mechanisms, or one underlying mechanism may manifest itself in a variety of different signs and symptoms.

11. Howard I. Kushner, *A Cursing Brain? The Histories of Tourette Syndrome* (Cambridge: Harvard University Press, 1999).

12. See James F. Leckman, Bradley S. Peterson, George M. Anderson, et al., "Pathogenesis of Tourette's Syndrome," *J. Child Psychol. & Psychiatry*, 1997, 38: 119–42, on pp. 122–23. For a similar view, see Roger Kurlan, "Future Direction of Research in Tourette Syndrome," *Neurol. Clin.*, 1997, 15: 451–56.

13. Morely C. Sutter, "Assigning Causation in Disease: Beyond Koch's Postulates," *Perspect. Biol. & Med.*, 1996, 39: 581–92, on pp. 584–85.

14. Kushner, *Cursing Brain?* (n. 11), pp. 4–6; Ian Hacking, *Rewriting the Soul: Multiple Personality and the Sciences of Memory* (Princeton: Princeton University Press, 1995), pp. 8–38.

15. Terra Ziporyn, *Nameless Diseases* (New Brunswick, N.J.: Rutgers University Press, 1992), pp. 1–2.

Kawasaki disease, despite its name, is a syndrome. Acknowledging this may liberate researchers from assuming that they are looking at only one scenario leading to CAA. We will therefore explore the extent to which epidemiological results and research questions are constrained by the current requirement that studies limit their subjects to those that fulfill the specific Kawasaki disease case definition.

The issue of inclusion and exclusion is illuminated by the history of poliomyelitis, where the exclusive focus on paralysis misled researchers. As we now recognize, only 1–2 percent of those infected developed the paralytic signs, 3–4 percent displayed nonspecific illness, while the vast majority (95 percent) remained asymptomatic. In 1910 and again in 1917, the epidemiologist Wade Hampton Frost reported that during epidemic outbreaks, while many children reported flulike symptoms and signs, only a minority developed paralysis; this could have alerted researchers to a possible spectrum of outcomes, but in the 1910s and 1920s epidemiology was viewed by virologists as soft science. Instead, researchers led by Simon Flexner at Rockefeller pursued a nasal passage route of a respiratory infection. The Rockefeller teams even managed to create a virus strain that infected primates, providing seeming confirmation of their theoretical assumptions. Only in 1931, when John R. Paul and James D. Trask at Yale decided to review the earlier literature on polio epidemics, was Frost's earlier study rediscovered. Building on Frost's work, the Yale team demonstrated that poliomyelitis was transmitted through an enteric route, only sometimes resulting in paralysis.¹⁶

As in the history of polio, investigations of the etiology of Kawasaki disease may be constructing a misleading disease spectrum. Unlike polio research, Kawasaki disease research may have been confounded by an early focus on benign cases because of the enshrinement of Kawasaki's persuasive clinical classification. Atypical cases have been excluded because they do not fit the specific criteria for epidemiological inclusion, even though they result in the condition that treatment and research aim to prevent.

The adoption of the nomenclature and construction of Kawasaki disease is also consequential. As the medical historian and internist Robert Aronowitz has noted, practitioners and researchers often assume that "the name of a new disease is of little consequence beyond who might get the credit for the discovery. . . . The particular identity that a disease has . . . is neither a necessary nor an inevitable consequence of

16. Margaret L. Grimshaw, "Scientific Specialization and the Poliovirus Controversy in the Years before World War II," *Bull. Hist. Med.*, 1995, 69: 44–65.

biological processes, but rather is contingent on social factors. Knowing the details of a disease's particular social construction matters because it is only with that knowledge that we can make sense of disease. . . ."¹⁷ Thus, we will explore the extent to which adopting the name "Kawasaki disease" has enabled and constrained both epidemiological claims and research findings related to the etiology of CAA.¹⁸

We will examine historical evidence for three distinct, but interrelated, clinical and research questions: (1) Does Kawasaki disease occur across a spectrum from benign to fatal outcome? (2) Is Kawasaki disease a new clinical entity? and (3) How and why was a sometimes fatal condition named after an individual who initially argued that such an outcome was impossible? Our analysis is purposely topical, overlapping, and retrospective rather than strictly chronological. When it comes to histories of syndromes, chronological approaches tend to reinforce the authority of the present consensus, thereby framing what is seen as historically relevant by what is currently believed. We adopt a topical strategy in order to question the dominant view that Kawasaki disease is a single disease with a linear history: our investigation exposes multiple intersecting histories rather than a unified narrative.

We begin with how Kawasaki disease came to be understood as synonymous with IPN, a rare, almost always fatal, childhood form of vasculitis; as a result of this merger, investigators neglected the possible distinctions between fatal and nonfatal cases of Kawasaki disease. In the section entitled "The Histories of CAA," we look back to the period prior to the discovery and classification of Kawasaki disease to examine how IPN was understood as a distinct entity. Because IPN was almost always fatal, the search for its causes and pathophysiology was the concern of pathologists. In contrast, Japanese pediatricians encountered an outbreak of a generally benign rash/fever syndrome in the clinic and looked for clues to its etiology in pediatric illnesses with similar sign presentations. The section entitled "From Stevens-Johnson Syndrome to Kawasaki's MCLS" recounts how and why Japanese physicians initially were persuaded that

17. Aronowitz, *Making Sense of Illness* (n. 7), p. 11; and see also pp. 57–83.

18. Similar issues have been raised in a number of recent histories of heart disease, including Christopher Lawrence, "'Definite and Material': Coronary Thrombosis and Cardiologists in the 1920s," in *Framing Disease: Studies in Cultural History*, ed. Charles E. Rosenberg and Janet Golden (New Brunswick, N.J.: Rutgers University Press, 1991), pp. 50–82; Robert A. Aronowitz, "From the Patient's Angina Pectoris to the Cardiologist's Coronary Heart Disease," in *Making Sense of Illness* (n. 7), pp. 84–110. The history of rheumatic fever also illuminates a number of issues related to KD, and we explore these later in this article.

this outbreak resembled a hypersensitive reaction to inoculations or antibiotics, and why they did not at first focus on possible coronary artery sequelae. This returns us to the issue of “naming.” Kawasaki disease was classified and named without consideration of the risk of CAA, even though by the time the nomenclature was adopted it was apparent that CAA and death were possible for some of the afflicted. Research remained restricted to a specific epidemiological definition that excludes patients with CAA who fail to meet the Kawasaki disease diagnostic criteria. This history may help explain why it has been so difficult for researchers to locate the etiology and pathophysiology of pediatric CAA.

The Merger of Kawasaki Disease and IPN

In his exploration of the history of Lyme disease, Aronowitz examines the extent to which claims about the novelty of this illness required the construction of an artificial distinction from erythema chronicum migrans (ECM), which had been identified earlier in Sweden and Austria. Although Aronowitz does not insist that the American Lyme disease is synonymous with ECM, he does suggest that the claim for the distinctiveness of Lyme disease was prompted as much by political as by scientific reasons: “Although researchers presented Lyme disease’s rheumatological identity as self-evident objective fact, it can more profitably be viewed as having been constructed from interacting biological and social factors.”¹⁹ The same might be said for the construction of Kawasaki disease. The difference is that unlike Lyme disease, where the etiologic agent and pathophysiological mechanisms have been identified, Kawasaki disease remains a medical mystery.

Kawasaki made three claims: (1) there were no sequelae, (2) the illness “resolves without intervention,” and (3) the syndrome constituted a new, as yet unidentified, illness. As we shall see, almost no one believes any of these claims today. Thus, it is widely accepted that 25 percent of afflicted children develop CAA if untreated; that timely intervention with IVIG will prevent CAA; and, based on the assumption that Kawasaki disease and IPN are synonymous, that Kawasaki disease/IPN cases can be found as early as the 1870s.

Kawasaki was well aware that children with signs similar to those he was observing sometimes had vasculitis and several of them died; nevertheless, he insisted that these cases were not part of the syndrome. When he reexamined a 1962 autopsy report of a child at the Red Cross Hospital

19. Aronowitz, *Making Sense of Illness* (n. 7), p. 67.

who had died as a result of CAA,²⁰ he concluded that the fatal outcome was not related to the syndrome he was uncovering.²¹ In 1965 Noboru Tanaka, then head of pathology at the Red Cross Hospital, performed an autopsy on another child, whom Kawasaki had previously diagnosed as having MCLS. Tanaka's autopsy revealed coronary artery thrombosis, and he wrote in the autopsy report: "Clinical Diagnosis: Muco-cutaneous ocular syndrome, sudden death, unknown etiology."²² Kawasaki disagreed with Tanaka's interpretation, and published a two-part article in 1970 rejecting the association of his disease with this case of fatal cardiac complications.²³

Kawasaki's claims were also contested by Takajiro Yamamoto, who had been independently gathering similar cases in the late 1950s and early 1960s. In 1968, Yamamoto and his colleagues at Tokyo's St. Luke's Hospital published a report of twenty-three patients, of whom eleven (48 percent) had abnormalities detected by electrocardiogram.²⁴ However, Kawasaki insisted that these cardiac abnormalities were distinct from MCLS, whose course was always benign.²⁵

Despite Kawasaki's resistance to the link between MCLS and fatal sequelae, the reports by Yamamoto, Tanaka, and others led to the inclusion of a request in a 1970 national epidemiological survey that clinicians report any fatal outcomes occurring in MCLS patients. The result of that

20. Ika Chen, N. Kuribayashi, and N. Tanaka, "An Autopsy Case of Infantile Polyarteritis Nodosa, with Particular Findings in Coronary Arteries" [in Japanese], *Nihon Byouri Gakkaishi [Japn. Path. Org.]*, 1962, 51: 541–42.

21. Noboru Tanaka, interviewed by J. F. Bastian, J. C. Burns, H. I. Kushner, and C. H. Turner, San Diego, Calif., 1–2, 4, 7 December 1999; T. Kawasaki, T. Sakata, and M. Kubo, "Two Autopsy Cases of Periarthritis Nodosa and Its Clinical Aspects" (paper delivered at the 17th Eastern Japan Meeting on Pediatrics, no 7., Chiba, 30 October 1966).

22. N. S. Tanaka, Autopsy Report SN-1369, Japan Red Cross Hospital, 22 February 1965.

23. T. Kawasaki, N. Kubo, . . . and N. Tanaka, "Two Autopsy Cases of Infantile Periarthritis Nodosa and Their Clinical Characteristics—in Relation to Acute Febrile MCLS" (in 2 parts) [in Japanese], *Chiryō [J. Therap.]*, 1970, 52 (3,4): 633–44, 811–18; Kawasaki listed Tanaka, a coauthor of the Chen paper (n. 20) and then head of pathology at the Red Cross Hospital, as a contributing author, even though Tanaka disagreed with the paper's conclusion (Tanaka interview [n. 21]). See also N. Tanaka, S. Naoe, and T. Kawasaki, "Pathological Study on Autopsy Cases of MCLS in Childhood—Particularly in Relation with Periarthritis Nodosa-like Arteritis" [in Japanese], *Nisseki Chuo Byoin Iho [Med. J. Jpn. Red Cross Central Hosp.]*, 1972, 1: 85–94.

24. Takajiro Yamamoto, T. Oya, A. Watanabe, et al., "Clinical Aspects of Acute Febrile MCLS (Kawasaki): One Type of Broad Definition of 'MCOS' or Erythema Multiform (Stevens-Johnson)" [in Japanese], *Shonika Rinsho [Jpn. J. Pediatr.]*, 1968, 21: 291–97.

25. Interview with Takajiro Yamamoto and T. Kawasaki, by J. Burns, H. Kushner, T. Matsubara, and C. Turner, Tokyo, 8 December 1998.

request was the discovery that ten more children had died suddenly from thrombosis of coronary artery aneurysms.²⁶ This finding was used to establish coronary vasculitis as a complication of MCLS. While the Japan MCLS Research Committee (JRC) did not change the criteria for diagnosis, it did list the coronary complications as an occasional finding for the second national survey conducted in 1972.²⁷

Notwithstanding the emerging epidemiological evidence, Kawasaki continued to express doubts about the extent to which CAA was part of the syndrome's spectrum, and he maintained the view that he had discovered a new and distinct syndrome.²⁸ Part of his reluctance may have been due to the fact that if coronary artery abnormalities and consequent fatalities were shown to be part of MCLS, the syndrome might have been reclassified as part of an IPN spectrum. Yet, his insistence was also informed by his careful observation and classification of more afflicted MCLS patients than any other practitioner in the world. This experience persuaded him that IPN and MCLS were different disorders.²⁹

IPN became recognized as a distinct clinical entity only in 1963, even though there were numerous published case reports of the illness going back to the late 1930s.³⁰ By the late 1940s, reports of children dying from what was then called pediatric poly- (or peri)-arteritis nodosa (PN) began to appear more frequently in the medical literature.³¹ Polyarteritis

26. Japan MCLS Research Committee, *Diagnostic Guidelines of Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome* (Tokyo, 1970).

27. Japan MCLS Research Committee, *Diagnostic Guidelines of Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome* (Tokyo, 1972). Yamamoto explained that the committee again wanted the reporting of MCLS to remain specific and to exclude similar diseases: Yamamoto/Kawasaki interview (n. 25). See also H. Yanagawa, M. Yashiro, Y. Nakamura, et al., "Results of 12 Nationwide Epidemiological Incidence Surveys of Kawasaki Disease in Japan," *Arch. Pediatr. & Adolesc. Med.*, 1995, 149: 779–83. The JRC feared that if cardiac complications were a diagnostic criterion or were emphasized as a feature, then physicians might mistakenly report cases of acute rheumatic fever as MCLS.

28. T. Kawasaki, interview by J. Burns, H. Kushner, T. Matsubara, and C. Turner, Tokyo, 5–7 December 1998.

29. *Ibid.*

30. M. Viola Rae, "Coronary Aneurysms with Thrombosis in Rheumatic Carditis," *Arch. Path.*, 1937, 24: 369–76; Samuel Spector, "Scarlet Fever, Periarteritis Nodosa, Aneurysm of Coronary Artery with Spontaneous Rupture, Hemopericardium," *Arch. Pediatr.*, 1939, 56: 319–24.

31. H. A. Wilmer, "Two Cases of Periarteritis Nodosa Occurring in the First Month of Life," *Bull. Johns Hopkins Hosp.*, 1945, 77: 275–86; J. C. Bertrand, D. Fuks, and D. Nielson, "Periarteritis Nodosa en un Niño," *Archivos Argentinos de Pediatría*, April 1943, 293–309; E. P. Scott and C. C. Rotondo, "Periarteritis Nodosa: Report of Two Cases, One Compli-

nodosa had long been recognized as a baffling condition of unknown etiology, invariably fatal, seldom diagnosed during life.³²

By the early 1950s a growing number of pediatric cases of polyarteritis nodosa were being reported by North American, German, French, Swedish, Argentine, Cuban, and Japanese physicians.³³ These reports indicated that pediatric patients displayed similar, but varying, pathology and histology, and that the vasculitis and aneurysms were generally limited to the coronary arteries, particularly in infants—unlike polyarteritis nodosa in adults.³⁴ Moreover, most, but not all, of the young children diagnosed with polyarteritis nodosa displayed a relatively consistent array of clinical

cated by Intrapericardial Hemorrhage,” *J. Pediatr.*, 1944, 25: 306–10; C. M. Pickard, J. G. Owen, and G. J. Dammin, “Aneurysms of the Coronary Arteries Due to Polyarteritis Nodosa Occurring in an Infant: Report of a Case with Coronary Artery Thrombosis,” *J. Lab. & Clin. Med.*, 1947, 32: 1513–14; W. Sinclair, Jr., and E. Nitsch, “Polyarteritis Nodosa of the Coronary Arteries: Report of a Case in an Infant with Rupture of an Aneurysm and Intrapericardial Hemorrhage,” *Amer. Heart J.*, 1949, 38: 898–904.

32. First described by Adolph Kussmaul and Rudolf Maier in 1866, the condition typically was diagnosed at autopsy: arterial aneurysms and lesions produced by extensive infiltration of arterial walls by inflammatory cells. See A. Kussmaul and R. Maier, “Über eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht” [About a not yet described and unique kind of artery sickness], *Deutsches Archiv für klinische Medizin*, 1866, 1: 484–517; Erika Dressler, “The Creation of a Syndrome: From Periarteritis Nodosa to Necrotizing Angiitis” (M.A. thesis, San Diego State University, 1999).

33. L. Adelson, “Periarteritis Nodosa in Infancy: Report of a Case Following Allergic Reactions to Penicillin,” *J. Pediatr.*, 1951, 39: 346–53; R. R. Martelle, “Coronary Thrombosis in a Five-Month-Old Infant,” *J. Pediatr.*, 1955, 46: 322–26; H. Munro-Faure, “Necrotizing Arteritis of the Coronary Vessels in Infancy: Case Report and Review of the Literature,” *Pediatrics*, 1959, 23: 914–26; W. M. Block and F. M. Skopec, “Polyarteritis Nodosa in a Four-Month-Old Infant,” *J. Iowa Med. Soc.*, 1966, 56: 945–48; G. Kemp and F. Roth, “Zur Periarteritis Nodosa im Kindesalter,” *Zeitschrift für Kinderheilkunde*, 1954, 75: 60–79; J. Canet, P. Lancret, G. Pensel, et al., “La péri-artérite noueuse du nourrisson,” *Annales de Pédiatrie*, 1963, 47: 604–13; M. Bohman, “Periarteritis Nodosa in an Infant of Three Months,” *Acta Paed.*, 1954, 43: 374–78; J. C. Ponce, “Periarteritis nodosa y trombopenia en un lactante,” *Archivos Argentinos de Pediatría*, 1953, 39: 48–54; J. M. Portuondo and Castro, “Formas clinicas de la periarteritis nudosa,” *Revista Medica Cubana*, 1953, 64: 24–38; K. Hanawa, “Two Cases of Pericardial Hematoma in Infancy” [in Japanese], *Shonika Shinryo* [*Jpn. J. Pediatr. Pract.*], 1959, 22: 820; I. Nagamatsu, M. Shizuka, A. Watanabe, and S. Yoshino, “Coronary Artery-Localized PN in a 2-Year-Old Child” [in Japanese], *Shonika Rinsho* [*Jpn. J. Pediatr.*], 1967, 20: 198–203.

34. P. M. Zeek, C. C. Smith, and J. C. Weeter, “Studies on Periarteritis Nodosa: III. The Differences between the Vascular Lesions of Periarteritis Nodosa and Hypersensitivity,” *Amer. J. Path.*, 1948, 24: 889–917; H. M. Keith and A. H. Baggenstoss, “Primary Arteritis (Periarteritis Nodosa) among Children,” *J. Pediatr.*, 1941 18: 494–506.

signs and symptoms that varied considerably from the signs and symptoms in adult polyarteritis nodosa.³⁵

In 1963, American pathologists F. Barry Roberts and George H. Fetterman, both at the University of Pittsburgh, concluded that pediatric cases of polyarteritis nodosa appeared to constitute “a rather constant clinical syndrome,” which they named “infantile polyarteritis nodosa” (IPN).³⁶ Based on reports of fatal cases of pediatric polyarteritis nodosa, they constructed a set of commonly occurring clinical signs and laboratory findings, including prolonged fever, rash, conjunctivitis, cough, congestive heart failure, abnormal central nervous system signs, hypertension, pericardial effusion, gangrene of extremities, abnormal urinary sediment, cardiomegaly, and abnormal EKG. Identification of IPN required that these clinical signs and laboratory findings be combined with postmortem findings of coronary artery lesions³⁷ (see Table 2).

In 1973 Zenshiro Onouchi at Kyoto University Hospital joined Tanaka in concluding that a review of autopsy reports and clinical cases demonstrated that “MCLS is a mild form of IPN.”³⁸ Again Kawasaki disagreed. In his first English-language paper on MCLS/MLNS, published in *Pediatrics* in 1974, he wrote that “the clinical pattern of MLNS is also different from that of polyarteritis nodosa in infancy”; he agreed, however, that “the *pathological finding* in 13 autopsied cases of MLNS seems to be consistent with those of polyarteritis nodosa.”³⁹ Thus, while *fatal* cases of MLNS and IPN were pathologically similar, Kawasaki was reaffirming his belief that nonfatal ones—like the fifty that he classified in 1967—were and should be understood as distinct from fatal cases.

Three years later, American pathologists Benjamin H. Landing and Eunice Larson published a retrospective study concluding that IPN and fatal MCLS were the same illness. Although this publication became early

35. Martelle, “Coronary Thrombosis” (n. 33); P. M. Zeek, “Periarteritis Nodosa: A Critical Review,” *Amer. J. Clin. Path.*, 1952, 22: 77–90; R. J. Johansmann and P. Zeek, “Periarteritis Nodosa in a Week-Old Infant,” *Arch. Path.*, 1954, 58 (3): 207–13; E. Liban, Z. Shamir, and S. Schorr, “Periarteritis Nodosa in a Nine-Month-Old Infant,” *Amer. J. Dis. Child.*, 1954, 88: 210–15.

36. F. Barry Roberts and George H. Fetterman, “Polyarteritis Nodosa in Infancy,” *J. Pediatr.*, 1963, 63: 519–28, quotation on p. 528.

37. *Ibid.*, p. 527.

38. Z. Onouchi, K. Tanaka, M. Shinkawa, et al., “A Study of Mucocutaneous Lymphnode Syndrome and Its Cardiac Lesions” [in Japanese], *Nippon Shonika Gakki Zasshi*, 1973, 77: 320–26.

39. T. Kawasaki, F. Kosaki, S. Okawa, et al., “A New Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome (MLNS) Prevailing in Japan,” *Pediatrics*, 1974, 54: 271–76, quotation on p. 272 (*italics added*).

Table 2. Sign/Symptom Complex of Infantile Polyarteritis Nodosa

Clinical manifestations:

1. Prolonged/intermittent fever
2. Erythematous macules, erythema multiforme, or urticaria
3. Conjunctivitis
4. Cough/grunting or grunting respirations
5. Congestive heart failure
6. Abnormal CNS signs
7. Hypertension
8. Pericardial effusion
9. Gangrene of extremities

Laboratory Findings:

1. Abnormal urinary findings
2. Chest radiogram abnormalities of lung parenchyma or cardiomegaly
3. Abnormal ECG

Adapted from F. Barry Roberts and George H. Fetterman, "Polyarteritis Nodosa in Infancy," *J. Pediatr.*, 1963, 63: 519–28.

proof that Kawasaki's syndrome and IPN were the same disorder, Landing and Larson were more circumspect, because, as they admitted, "none of the 20 patients with IPN totally fulfills the Kawasaki criteria."⁴⁰ Thus, they concluded that "the clinical and pathological data presented justify the opinion that *the predominant form of IPN*, with severe and aneurismal involvement of the major coronary arteries, and *fatal MCLS* are clinically and pathologically indistinguishable."⁴¹ However, their evidence can just as well support the opposite conclusion, that *only* fatal MCLS and IPN were identical; therefore, they could reasonably have affirmed Kawasaki's initial and persistent belief that IPN and nonfatal MCLS were different disorders that sometimes, but not always, shared a number of presenting clinical signs.⁴²

As a result of the publication of Landing and Larson's paper, a worldwide medical consensus emerged that Kawasaki's syndrome and IPN were the same disorder. Clinicians and researchers now assumed that

40. Benjamin H. Landing and Eunice J. Larson, "Are Infantile Periarteritis Nodosa with Coronary Artery Involvement and Fatal Mucocutaneous Lymph Node Syndrome the Same? Comparison of 20 Patients from North America with Patients from Hawaii and Japan," *Pediatrics*, 1977, 59: 651–62, quotation on p. 653.

41. *Ibid.*, p. 655 (italics added).

42. It is worth noting that 10 percent of Kawasaki's original fifty cases do not fit any of the current case definitions of KD. See Burns, commentary on the translation of Kawasaki (n. 5).

Kawasaki disease is a spectrum, ranging from those with a benign outcome to those who develop fatal coronary artery abnormalities. Kawasaki continued to express ambivalence. In 1980 he and Yoshio Yanese, also at the Red Cross Hospital, wrote that “it is impossible to decide whether IPN and MCLS are the same disease.”⁴³ In our 1998 interviews with Kawasaki, he reiterated his belief that Kawasaki disease and IPN might be separate diseases.⁴⁴ In a recent publication, he repeated his belief that Kawasaki disease and IPN are separate disorders.⁴⁵

The Histories of CAA

The assumption that IPN is the fatal form of Kawasaki’s MCLS sign complex has led some researchers to reconstruct reports in medical literature of infant deaths involving CAA prior to 1967 as likely instances of Kawasaki disease.⁴⁶ Where the clinical picture is unclear or contradicts the accepted Kawasaki disease case definition, other observers have argued that clinicians made incomplete or defective diagnoses, missing clinical signs that today would have been noted.⁴⁷ But when the historical record is called upon, only one case is cited for the period prior to the late 1930s: an 1871 report of a British child who died of a CAA, which, according to pathologist K. Aterman, is “probably one of the earliest recorded incidences” of Kawasaki disease.⁴⁸ This claim ultimately is based on the assumed identity of Kawasaki’s syndrome and IPN, but given the fact that the patient also presented with meningitis and intercurrent pneumonia, it strains speculation to conclude that the child’s “scarlatinal dropsy” is evidence of the Kawasaki disease clinical sign complex. A search of the clinical literature of the Americas, Europe, and Japan yields no other reports until the late 1930s.

Of course, until the late nineteenth century, infant and childhood mortality was so common and the treatment of illness and postmortem

43. T. Kawasaki and Y. Yanese, “MCLS and IPN” [in Japanese], *Syounika [Pediatrics]*, 1980, 21: 697–704, quotation on p. 697.

44. Kawasaki interview (n. 28).

45. T. Kawasaki, “Kawasaki Disease: A New Disease?” *Acta Paed. Taiwan*, 2001, 42: 8–10.

46. Stanford Shulman, “The First Reported Case of Kawasaki Disease,” *J. Pediatr.*, 1999, 135: 532.

47. N. Shibuya, K. Shibuya, H. Kato, and M. Yanagisawa, “Kawasaki Disease before Kawasaki at Tokyo University Hospital,” *Pediatrics*, 2002, 110 (2, part 1): e17–e24; K. Aterman, “A Possible Early Example of Mucocutaneous Lymph Node Syndrome,” *J. Pediatr.*, 1978, 92: 1027–28.

48. Aterman, “Possible Early Example” (n. 47), p. 1027. The case was reported in Samuel J. Gee, “Aneurysms of Coronary Arteries in a Boy,” *St. Barth. Hosp. Rep.*, 1871, 7: 148.

examinations of these deaths so rare, that it is possible that similar cases would have escaped professional notice. Moreover, there are a number of childhood rash/fever diseases, including scarlet fever, acute rheumatic fever, and acro-dynia, whose clinical presentations include signs associated with Kawasaki disease. Only with the widespread use of antibiotics—first sulfa drugs in the late 1930s, and then penicillin in the post-World War II era—might a separate syndrome like Kawasaki disease become evident, because the fever and other clinical signs associated with Kawasaki disease do not respond to antibiotic interventions. Assuming that Kawasaki disease, as we now know it, existed prior to the 1950s, the historical record of medical concern is far more likely to yield fatal cases of vasculitis than reports of a generally self-limiting collection of clinical signs.

Unlike the situation in Europe and America, in Japan there were no reported fatal cases of pediatric CAA until the late 1950s. Our interviews with senior Japanese pediatricians and pathologists who were active in the pre- and postwar periods indicated that none of them had seen a child who remotely fit the pathology of IPN; nor had they encountered children with clinical signs that resemble what today is classified as Kawasaki disease until the 1950s.⁴⁹ Epidemiological data from Japan appear consistent with the introduction of a new disease.⁵⁰ The novelty of

49. All those we interviewed agreed that in the mid-1950s there was a sudden and increasing number of reports of children presenting with rash/fever illnesses, all of whom appeared very sick, but almost all of whom recovered without (or despite) clinical interventions. Japanese physicians believed they were seeing an illness new to Japan and possibly elsewhere. Kawasaki's mentor, ninety-two-year-old Jushichiro Naito, a retired professor of pediatric infectious disease and a practitioner since 1931, claimed that he had never seen any patients who "remotely" resembled those treated by his student Kawasaki, and he insisted there was no evidence whatsoever that this illness was present in Japan prior to World War II: J. Naito, interview by J. Burns, H. Kushner, C. Turner, and T. Matsubara, Tokyo, 8 December 1998. When Zenshiro Onouchi, now chair of pediatrics at Kyoto University School of Medicine, was a young physician, he "went around and asked the other older doctors who had long clinical experience and none of them could remember anything like this" (Z. Onouchi, interview by J. Burns, H. Kushner, C. Turner, and T. Matsubara, Kyoto, 10 December 1998). Pediatric pathologist and leading KD expert Shiro Naoe concedes that KD may have been "a new disease," but is more persuaded that it could have existed "in the past, but was so rare it would be impossible to find a pattern"; the "important question," according to Naoe, "is why did it start to cluster. Why did the incidence suddenly increase around the same time that Dr. Kawasaki started working" (S. Naoe, interview by J. Burns, H. Kushner, T. Matsubara, and C. Turner, Tokyo, 7 December 1998).

50. Nationwide hospital surveys showed a KD incidence among children below the age of five of less than 1 per 100,000 in 1964. This rate then increased rapidly throughout the 1960s and 1970s; following three nationwide epidemics in 1979, 1982, and 1986, the rate

these presentations is supported by a recent retrospective examination of the 7,618 pediatric patients admitted to Tokyo University Hospital from 1940 to 1965: the authors found no patients admitted from 1940 to 1949 who met the clinical criteria of Kawasaki disease, but they identified ten likely cases for the 1950–64 period.⁵¹

If IPN represents the fatal end of the Kawasaki disease spectrum, one might expect to uncover some evidence of nonfatal cases accompanying the increasing number of infant deaths with CAA reported in Europe and the Americas in the 1940s and 1950s. Japanese epidemiological studies of Kawasaki disease since the 1970s indicate that about 2 percent of all untreated Kawasaki disease patients die from CAA;⁵² therefore, for every death there should have been approximately fifty very sick children who recovered, some with noticeable sequelae. If fatal cases represented only the tip of an illness spectrum, there may have been a growing epidemic of Kawasaki disease in the Americas and in Europe beginning in the late 1930s to the mid-1960s. It is difficult, but not impossible, to imagine that these cases escaped the gaze of pediatricians. Could it be that a common form of pediatric CAA is possible without the signs and clinical course we now connect to Kawasaki disease?

Alternatively, it is possible that the agent(s) responsible for CAA became less virulent, resulting in more benign cases, and, as a result, in alterations of presenting clinical signs. Such a scenario has been laid out for the history of rheumatic fever by the pediatrician and medical historian Peter English. English shows how the clinical signs and reported symptoms associated with rheumatic fever changed dramatically in a relatively short time span from the late nineteenth to the mid-twentieth century. Along with these alterations, the site of inflammation moved from the joints (rheumatism), heart lining (pericarditis), and heart valves (endocarditis) to the heart muscle (myocarditis). Parallel to these changes in presentation and sites of inflammation, English traces a decline in virulence and the transformation of rheumatic fever from a fatal disease of early childhood to a chronic condition of adulthood.

began to level off at approximately 100 per 100,000. See H. Yanagawa, Y. Nakamura, et al., "Changes in the Epidemic Patterns of Kawasaki Disease in Japan," *Pediatr. Infect. Dis. J.*, 1999, 18: 64–66; Yanagawa et al., "Results of 12 Nationwide Epidemiological Incidence Surveys" (n. 27); Yanagawa et al., "Results of the Nationwide Epidemiologic Survey" (n. 1).

51. Those who met the criteria had been diagnosed with Stevens-Johnson syndrome (SJS), allergic toxic syndrome, Izumi fever (caused by *Yersinia pseudotuberculosis*), scarlet fever, or cervical lymphadenitis; Shibuya et al., "Kawasaki Disease before Kawasaki" (n. 47).

52. Burns et al., "Kawasaki Disease" (n. 6), pp. e28–e29; Yanagawa et al., "Results of 12 Nationwide Epidemiological Incidence Surveys" (n. 27).

Epidemiological data suggest that these alterations took place prior to effective antibiotic treatment. English speculates that they may be connected to the impact of earlier treatments, beginning with the salicylates in the late nineteenth century that altered bacterial action on the joints and led to subtle mutations in the streptococcus, perhaps leading to a decline in the chorea associated with rheumatic fever. Each subsequent intervention—sulfonamide, steroids, and penicillin—had its own effect on the bacteria (Group A beta-hemolytic streptococcus, or GABHS), and thus on the bacteria's evocation of immune response, which is the mechanism (molecular mimicry) responsible for damage to the heart. This complex interaction, according to English, resulted in a transformation of the clinical signs and symptoms associated with rheumatic fever.⁵³

Although the agent or agents responsible for pediatric CAA are unknown, imagining a similar scenario for IPN/Kawasaki disease raises a number of interesting research questions and avenues of possible investigation. Was there a more virulent form of pediatric CAA whose agent mutated over time, becoming less virulent and manifesting itself with slightly different clinical signs? What does such a hypothesis suggest about revisiting the possibility that the Kawasaki disease agent may be bacterial? Are fatal cases simply different from the nonfatal cases, although sharing a number of similar clinical signs? Was Kawasaki correct in insisting that fatal cases of CAA are different from the sign complex he identified? Given the failure of so many talented researchers to identify the etiology and pathological mechanism of both Kawasaki disease and CAA, it could be useful for investigators to acknowledge all these possibilities and to develop appropriate research protocols.

From Stevens-Johnson Syndrome to Kawasaki's MCLS

The dominant view of Europeans and Americans until the 1960s was that the sign complex similar to that now associated with Kawasaki disease was a subcategory of Stevens-Johnson syndrome (SJS), an idiopathic rash/fever complex often seen as a result of hypersensitivity (possibly to serum, antibiotics, vaccinations, or other medications).⁵⁴ When clusters

53. Peter C. English, *Rheumatic Fever in America and Britain: A Biological, Epidemiological, and Medical History* (New Brunswick, N.J.: Rutgers University Press, 1999), esp. pp. 6–14; idem, "Emergence of Rheumatic Fever in the Nineteenth Century," in Rosenberg and Golden, *Framing Disease* (n. 18), pp. 20–32.

54. SJS was described in 1922 by pediatricians A. M. Stevens and F. C. Johnson of Columbia University and Bellevue Hospitals. The syndrome generally begins suddenly, with a high fever lasting up to two weeks. Its most notable signs are severe purulent

of nonfatal cases were first noticed in Japan, they were referred to as mucocutaneous ocular syndrome (MCOS). The afflicted infants presented with ocular signs sometimes designated conjunctivitis, and sometimes conjunctival injection.⁵⁵ Similarly, SJS was identified as the culprit for the clinical signs in some American reports of pediatric polyarteritis nodosa in the late 1940s.⁵⁶

By the 1950s, however, the connection between similar fatal pediatric cases and hypersensitivity became explicit. Researchers at the University of Heidelberg wrote in 1954 that their clinical experience and literature review convinced them that pediatric polyarteritis nodosa had increased with the introduction of antibiotics.⁵⁷ By the 1960s, SJS was probably the most frequent diagnosis of the clinical sign cluster that resembled Kawasaki's MCLS.⁵⁸

conjunctivitis and red, raised, oval erythema of the trunk, arms, and thighs, which becomes vesicular. Patients also present with cracked, bleeding, encrusted lips and ulcerative stomatitis. In some cases the conjunctivitis is so severe that it results in blindness. See A. M. Stevens and F. C. Johnson, "A New Eruptive Fever Associated with Stomatitis and Ophthalmia," *Amer. J. Dis. Child.*, 1922, 24: 26–33; W. L. Weston, "What Is Erythema Multiforme?" *Pediatr. Ann.*, 1996, 25: 106–9.

55. "Conjunctivitis" denotes inflammation (associated with SJS), while "conjunctival injection" refers to dilation of the vessels of the conjunctiva (associated with KD); but on cursory examination it is easy to confound the two. The distinction is important, because it suggests a very different pathophysiology in the latter case where the vessels, as with coronary arteries in CAA, are dilated. It was not until the 1990s that a biopsy study of the conjunctiva in acute KD patients established that there is no inflammatory infiltrate in the conjunctiva in this disease. See J. C. Burns, J. D. Wright, J. W. Newburger, et al., "Conjunctival Biopsy in Patients with Kawasaki Disease," *Pediatr. Pathol.*, 1995, 15: 547–53.

56. Kushner et al., "Rethinking the Boundaries" (n. 9), pp. 220–21; A. F. Portman, Autopsy Record 10074, University Hospitals of Cleveland, 7 April 1948; Sinclair and Nitsch, "Polyarteritis Nodosa" (n. 31); G. C. Fanney, "Erythema Multiforme Exudativum: Stevens-Johnson Syndrome. Cardiovascular and Central Nervous System Involvement," *J. Pediatr.*, 1949, 34: 195–203.

57. F. Von Schmid and A. Weiss. "Die Periarteriitis Nodosa beim Kinde," *Monatsschrift für Kinderheilkunde*, 1954, 102: 442–48.

58. This can be seen in a 1966 report by Iowa pediatrician Walter Block and pathologist Francis Skopec of a four-month-old infant who died of a CAA after a diagnosis of SJS; Block and Skopec eventually classified the child as afflicted with IPN: Block and Skopec, "Polyarteritis Nodosa" (n. 33). Japanese pediatrician Yamamoto remembered that when he was a visiting professor at Roosevelt Hospital and Cornell University Medical Schools in New York City in 1963, one of the first cases he observed during rounds was a three-year-old Japanese male with fever and rash. The child's clinical features looked very much like those Yamamoto had been seeing in Japan, which later he and Kawasaki would identify as MCLS; the consensus of the American physicians, he recalled, was that the child had Stevens-Johnson syndrome: Yamamoto/Kawasaki interview (n. 25).

Like their American colleagues, many Japanese pediatricians were initially persuaded that these idiopathic rash/fever illnesses were most likely variations of SJS.⁵⁹ Records from pediatric cases at Tokyo University Hospital indicate that five of ten cases of probable Kawasaki disease in the period 1950 to 1964 were diagnosed as SJS and/or allergic toxic erythema, which is sometimes classified as a subcategory of SJS.⁶⁰

It was in this context that in 1960 S. Itoga and M. Yamagishi, pediatricians from Keio University, reported that since 1954 they had treated twenty cases of a nonfatal childhood illness. Their search of the literature for similar cases persuaded them that their patients presented with a form of SJS, which they labeled “Mucocutaneous Ocular Syndrome” (MCOS). They wrote that MCOS “is an acute febrile disease that specifically affects the skin, mucosal membrane, and eyes,” and was therefore a variation of SJS; treated with steroids, all the children’s clinical signs resolved.⁶¹

The following year (1961) Kawasaki saw his first case of a child whose clinical signs closely resembled those reported by Itoga and Yamagishi; the patient, a four-year-old male, recovered spontaneously from his illness and was discharged as “diagnosis unknown.”⁶² Within a year Kawasaki had treated seven cases and reported them as “non-scarlet fever syndrome with desquamation” at a regional pediatric association meeting.⁶³ By 1964, he had gathered twenty cases that he and his clinical supervisor, Fumio Kosaki (director of pediatrics at Red Cross Hospital), reported at a pediatric meeting in Matsumoto.⁶⁴ Like Itoga and Yamagishi, Kosaki and Kawasaki labeled these cases as “Mucocutaneous Ocular Syndrome (MCOS).”

59. Alternatively, Toshio Fujikawa suggested in 1952 that the signs resembled acro-dynia, a disorder brought on by mercury in teething powders: T. Fujikawa, “A Case of Feer Disease” [in Japanese] *Shonika Shimryo [Jpn. J. Pediatr. Pract.]*, 1952, 16: 281.

60. Shibuya et al., “Kawasaki Disease before Kawasaki” (n. 47), pp. 18–19.

61. S. Itoga and M. Yamagishi, “Steroid Treatment for Muco-cutaneous Ocular Syndrome of Children” [in Japanese], *Chiryō [J. Therap.]*, 1960, 42: 1174–79, quotation on p. 1174. All of the children were between two months and seven years old, with 95 percent under two years. All presented with fever, rash, mucosal, and ocular (conjunctival) signs. None were found to have any bacterial infection, and all survived without any observed sequelae.

62. Kawasaki interview (n. 28).

63. T. Kawasaki, “Non-Scarlet Fever Desquamative Syndrome” [in Japanese], *Chiba Med. J.*, 1962, 38: 3–4.

64. F. Kosaki and T. Kawasaki, “Twenty Cases of Oculo-muco-cutaneous Syndrome,” Presentation no. 33 at 15th Eastern Japan and 9th Central Japan Meetings on Pediatrics, Matsumoto, Japan, October 1964.

By 1967, when he published his now-landmark study in the *Japan Journal of Allergology*, Kawasaki had rejected the MCOS designation.⁶⁵ He concluded his paper with a detailed discussion distinguishing his sign complex from Itoga's. Conceding that the cases reported by Itoga and Yamagishi "closely resemble ours in many aspects," he pointed to "important clinical differences"; in particular, he emphasized that twice as many of his patients (66 percent) presented with lymphadenopathy.⁶⁶ He rejected Itoga's designation of MCOS because it was historically confusing and clinically nonspecific.⁶⁷ Thus, Kawasaki asserted that Itoga's clinical imprecision, combined with his adoption of the acronym MCOS, revealed that he had failed to recognize the emergence of a new syndrome.

The rejection of the identifier "MCOS," along with the detailed critique of Itoga's study, served to reinforce Kawasaki's claims of discovery. Ironically, he had originally selected a descriptive title for his 1967 article that elevated ocular signs over lymphadenopathy, much as Itoga's earlier MCOS label had done—namely, "Febrile Oculo-oro-acrodesquamatus Syndrome with or without Acute Non-suppurative Cervical Lymphadenitis in Infancy and Childhood: Clinical Observation of 50 Cases." Kawasaki, most likely by oversight, left this title on the English abstract. Thus, by a kind of archaeology, the original title appears, as if revealing the ancient foundation supporting a putatively novel construction. When questioned about the reasons for this last-minute alteration, he recalled:

In Japan it is customary to submit your article to the chief of your section after you have written the manuscript so I submitted it to Dr. Fumio Kosaki, director of the Dept. of Pediatrics. At that time the Japanese title and the English title were the same. Dr. Kosaki said that the title was too long and too detailed. He made the Japanese title shorter and more concise but the long

65. Kawasaki, "Acute Febrile Muco-Cutaneous Lymph Node Syndrome" (n. 5).

66. *Ibid.*, p. 212 (all quotes in this note are from this page). None of Kawasaki's patients developed skin blisters. All of Itoga's cases presented with desquamation, but Kawasaki reported that "desquamation in our syndrome is extremely unique," because it was localized at "the nail-skin junction" of "the fingers and feet." While Itoga reported "conjunctivitis or conjunctivitis-like finding" in all cases, Kawasaki found "congestion of both bulbar conjunctivae." Unlike Itoga, Kawasaki found no mucosal bleeding, ulcers, thrush, or aphthous erosion, but he reported that his patients presented with "dryness, erythema, erosion, and cracking of the lips and diffuse hyperemia affecting the entire oral mucosa." Additionally, children diagnosed with SJS were typically older than Kawasaki's patient cohort.

67. Kawasaki pointed out that MCOS had been used synonymously with erythema multiforme exudativum (Stevens-Johnson syndrome), or divided into subtypes known as erythema multiforme and ectodermosis erosivea. Different authors had used MCOS to describe varying combinations of clinical signs.

English title remained and was published. No one at that time imagined that the article would receive international attention so the English title and abstract remained as it was.⁶⁸

Of course, if Kawasaki and Kosaki had retained the original title and nomenclature, however clumsy and long, the resemblance to MCOS would have been more obvious. This would have had two important consequences. First, the similarity to Itoga's designation would have become a more important part of the historical narrative; and second, the role of conjunctival injection might have become the focus for research.

The retention of the original name, with its greater emphasis on ocular signs than on lymphadenopathy, might also have suggested a stronger role, perhaps even as codiscoverers, for those contemporaries of Kawasaki who had been describing and publishing papers about the illness with this in mind, including Tanaka and Yamamoto. Tanaka, as discussed above, had made a direct connection between IPN and Kawasaki's patients as early as 1965, and he continued to press this view for the next two decades. Yamamoto had studied under Kosaki. In 1966, the year before Kawasaki published his study, Yamamoto presented a paper at a national pediatric conference describing the syndrome.⁶⁹ In our interviews, Kawasaki said that he did not know about Yamamoto's work at the time, but there may have been a connection between the two through their mutual mentor, Kosaki. Kosaki's dual role as Kawasaki's supervisor and as Yamamoto's medical school advisor put him in a position to be aware of the work of both of these young pediatricians. In any case, Kawasaki sent preprints of his 1967 article to Yamamoto, and in our interviews with him Yamamoto jokingly pointed out that he received preprints from both Kosaki and Kawasaki as well as from the journal itself.⁷⁰ Whether or not Kosaki played any role in trying to ensure an earlier publication date for his subordinate's work is impossible to know, but it is clear that these two were only months apart in the publication of their observations.

By 1968 Yamamoto had connected the sign complex with coronary artery abnormalities. He rejected the idea that Kawasaki was describing a necessarily self-limiting illness that was new and distinct: it is "reasonable,"

68. Kawasaki to Jane Burns, 30 June 2002, personal communication.

69. The abstract of Yamamoto's presentation was published the following year: T. Yamamoto, T. Oya, A. Watanabe, et al., "Clinical Observations of 'MCOS' or Erythema Multiforme (Stevens-Johnson)" [in Japanese], *Shonika Shinryo* [*Jpn. J. Pediatr. Pract.*], 1967, 30: 1544.

70. Yamamoto/Kawasaki interview (n. 25).

wrote Yamamoto in 1968, “to categorize this syndrome,” as Itoga had, “as a mucocutaneous ocular syndrome (MCOS) . . . complicated with myocarditis.”⁷¹ Itoga’s was “the first paper,” wrote Yamamoto, “which reported this syndrome.”⁷²

A few Japanese physicians, especially those connected to the influential Tokyo University Medical School (Todai), found it difficult to acknowledge that a general practitioner at a community hospital had identified a new clinical syndrome.⁷³ The opposition to Kawasaki’s claims, however, was neither organized nor sustained. Whatever skepticism remained was erased by the findings of epidemiological surveys conducted in 1970 and 1972, which concluded that Kawasaki’s clinical description constituted a distinct syndrome.⁷⁴ Ironically, the case definition used in the first national survey identified conjunctival injection as a primary criterion, but relegated lymphadenopathy to a secondary sign.⁷⁵ Subsequent case definitions, however, elevated lymphadenopathy to the primacy laid out in Kawasaki’s 1967 article.⁷⁶ Thus, illness was officially classified according to Kawasaki’s sign complex, and the nomenclature MLNS or MCLS was adopted. The renaming of the syndrome as Kawasaki

71. T. Yamamoto and J. Kimura, “A Case Report of Acute Febrile MCLS (Kawasaki)—A Subtype of MCOS or Erythema Multiforme (Stevens-Johnson)—Complicated with Myocarditis” [in Japanese], *Shonika Rinsho* [*Jpn. J. Pediatr.*], 1968, 21: 336–39, quotation on p. 336.

72. T. Yamamoto, “Recent Experience with Patients with Skin, Mucous, and Ocular Lesions” [in Japanese], *Chiryō* [*J. Therap.*], 1968, 50: 1919–34, quotation on pp. 1932–33.

73. H. Minagawa and his colleagues were persuaded that Kawasaki’s MLNS was hypersensitivity to inoculation and therefore acute erythema multiforme, or SJS. See H. Minagawa, “Recent Experience with Patients with Skin, Mucous, and Ocular Lesions” [in Japanese], *Chiryō* [*J. Therap.*], 1968, 50: 1919–34, quotation on p. 1920. “This syndrome is named or categorized as MCLS (Kawasaki),” wrote Jyunichi Sugiura of Kiryu Kousi Sougou Hospital in 1969, but it is simply an “enlarged definition of Mucocutaneous Ocular syndrome or an atypical type of Stevens-Johnson syndrome” (J. Sugiura, “A MCLS (Kawasaki) Case with Myocarditis” [in Japanese], *Shonika Rinsho* [*Jpn. J. Pediatr.*], 1969, 22: 221–23, quotation on p. 221). Also see Kathryn Holcomb, “Where Was Kawasaki Disease before Kawasaki? The Stevens Johnson Syndrome Puzzle” (M.A. thesis, San Diego State University, 1999).

74. Since Fujikawa’s 1952 observation (see n. 59), others in both Japan and the West have linked acrodynia, caused by mercury contained in teething powder, to MCLS/MLNS: D. B. Cheek, “Comment on Mucocutaneous Lymph Node Syndrome: Could It Be a Heavy Metal Poisoning?” *Pediatrics*, 1975, 56: 335–37; Goro Nishida, “Mercury Poisoning and MLNS,” *Pediatrics*, 1976, 58: 138.

75. Japan MCLS Research Committee, *Diagnostic Guidelines of Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome* (Tokyo, 1970).

76. Japan MCLS Research Committee, *Diagnostic Guidelines*, 1972 (n. 27); Japan MCLS Research Committee, *Diagnostic Guidelines of Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome*, 2nd ed. (Tokyo, 1974).

disease served to transform the sign complex into a prerequisite for diagnosis and treatment. Even though lymphadenopathy was present in only two-thirds of Kawasaki's cases and even less frequently among patients treated outside Japan, many physicians who had learned the MCLS or MLNS label assumed that the presence of swollen lymph nodes was more important than conjunctival injection for a diagnosis of Kawasaki disease.

This emphasis on lymphadenopathy has had consequences for research. Investigations of the etiology of pediatric polyarteritis nodosa in the 1940s and 1950s and of IPN in the 1960s had focused on conjunctival injection and conjunctivitis. In contrast, research on the etiology of Kawasaki disease has tended to focus on possible agents that produce fever, rash, and lymphadenopathy along with conjunctival injection, edema, and desquamation. Yet increasing evidence suggests that the two most important signs leading to CAA are fever and conjunctival injection.⁷⁷

Thus, nomenclature has influenced diagnosis and treatment in an important way. It was not inevitable that Kawasaki's views would triumph, or that this nomenclature would frame pediatric CAA. The reasons for this result lie as much in historical circumstance as they do in scientific discovery. In the end they cannot be separated from the circumstances that transformed MCOS into Kawasaki's MCLS.

Naming Kawasaki Disease

Kawasaki's 1967 designation—"Pediatric acute febrile mucocutaneous lymph node syndrome with characteristic desquamation of fingers and toes"—proved too wordy, and in subsequent publications the acronyms MLNS and/or MCLS were adopted by both Kawasaki and those who wished to refer to his syndrome. In Japan the acronyms "MLNS and MCLS (Kawasaki)" slowly gave way to the eponym "Kawasaki disease." In 1976, the Japanese MCLS study group adopted the name "*Kawasaki Byo*," or Kawasaki disease.⁷⁸ However, the Japanese word *byo* shares with its English counterpart "disease" the ambiguous signification of either a precise medical definition or a colloquial synonym for illness or sickness. In our interviews with Japanese physicians, they explained that it was very difficult to use the more technical Japanese term *shokogun*, or "syndrome," in speaking to parents and families, whereas *byo* was a common

77. Anne H. Rowley, "Incomplete (Atypical) Kawasaki Disease," *Pediatr. Infect. Dis. J.*, 2002, 21: 563–66.

78. T. Kawasaki, S. Kusakawa, and I. Shigematsu, eds., *Progress of Research on Kawasaki Disease (M.C.L.S.)* (Tokyo: Kindai Shuppan Publications, 1976).

word that allowed physicians and the families of patients to communicate more easily about the condition from which their children suffered.⁷⁹

There are a variety of reasons that Kawasaki alone was credited with the discovery of the new syndrome MCLS. His persistence and personality played a key role.⁸⁰ No one, with the possible exception of Tanaka, cared enough to dispute his primacy in identification of the syndrome. Circumstantial evidence suggests that he and his clinical director Kosaki were not passive observers about who should receive recognition for this “discovery.” Although Kawasaki’s careful elaboration of his findings was no doubt persuasive, others, including Itoga, Yamamoto, and Tanaka, had made equally important contributions, the latter two having connected the sign complex with coronary artery abnormalities. Kawasaki discounted Itoga’s report, portraying it as inexact and confused.⁸¹ Itoga never responded to Kawasaki’s critique and appears to have had no further academic interest in this syndrome.

Yamamoto may have had an even better claim to primacy than Itoga: the abstract of his 1966 presentation was in press and would appear almost simultaneously with Kawasaki’s article.⁸² Yet, he seemed unperturbed that with Kosaki’s aid and urging, Kawasaki’s study was published first. Kawasaki recruited Yamamoto, Tanaka, and other potential rivals as coauthors of articles on aspects of MCLS that promoted his role as the central player. He even persuaded Yamamoto to join him in articles focusing on the difference between MCLS and SJS, despite Yamamoto’s endorsement of the label MCOS as the best designation.⁸³

79. In 1995 the Japan Kawasaki Research Center, directed by Kawasaki, published a comprehensive bibliography: Y. Nakamura, H. Yanagawa, H. Kato, et al., *A Bibliography of Kawasaki Disease* (Tokyo: Japan Kawasaki Research Center, 1995). Often, the English translations of pre-1973 Japanese titles have the term “Kawasaki disease,” when the original Japanese titles actually used the terms “MCLS” or “MCLS (Kawasaki),” meaning the syndrome described by Kawasaki.

80. “Kawasaki overwhelmed the bureaucrats,” according to Naoe, because he did not fit the bureaucratic mentality that informed much of the Japanese medical establishment, where there was “only one form of intelligence” (Naoe interview [n. 49]).

81. Kawasaki, “Acute Febrile Muco-Cutaneous Lymph Node Syndrome” (n. 5), p. 212.

82. Yamamoto et al., “Clinical Observations” (n. 69). Perhaps this is why Kawasaki and Kosaki chose to publish in a journal that focused on allergies rather than delaying the time of publication by selecting a more mainstream pediatric journal.

83. For instance, in 1968 Kawasaki organized a symposium to discuss MCLS. The participants, aside from Yamamoto, challenged his claims that the MLNS sign complex constituted a distinct syndrome. Kawasaki asked Yamamoto to write the summary, add his own conclusion, and be listed as single author of the journal article that reported the meeting: Yamamoto, “Recent Experience” (n. 72). Similar stories emerged from our interview with Yamamoto and Kawasaki in December 1998 (n. 25).

Tanaka presented a different type of challenge. Kawasaki had listed him as a coauthor of a paper whose conclusion, despite Tanaka's explicit objection, contradicted his view that fatal MCLS and IPN were identical.⁸⁴ Although Tanaka subsequently published a series of articles detailing his early identification of CAA with MCLS and his disagreements with Kawasaki, he pursued no new research or pathologic studies on the topic. His lone resistant voice increasingly appeared more as a demand for credit than as an alternative to what Kawasaki had described.

The fact that Kawasaki's description of MCLS received a positive response from American and European clinicians added to his cachet in Japan. This first came from Hawaii, with its large population of Japanese Americans. In 1971 Eunice Larson, a pediatric pathologist at Kauaikeolani Children's Hospital in Honolulu, performed an autopsy on a ten-month-old Japanese American infant who had died of coronary artery thrombosis. Baffled by the case, Larson subsequently sent the autopsy report to her former professor, Benjamin Landing, at Children's Hospital of Los Angeles, who replied that during a recent trip to Japan (1972) he had learned of a syndrome described by Kawasaki that resembled the clinical signs of her patient.⁸⁵ Larson then altered her diagnosis on the autopsy to "infantile coronary periarteritis disease (Kawasaki disease) with generalized necrotizing vasculitis [and] thrombosis of coronary arteries."⁸⁶

Larson was unaware that two of her colleagues, pediatrician Marian Melish and rheumatologist Raquel Hicks, had been observing similar clinical cases.⁸⁷ The combination of Landing's letter to Larson and a visit from a Japanese physician distributing the 1972 Japanese case definition with photographs persuaded Melish and Hicks that the children they were seeing fit the syndrome described by Kawasaki.⁸⁸ Together with Larson, they wrote an abstract concluding that their cases were indeed MCLS as described in Japan, and that the syndrome could, as Larson's

84. Tanaka interview (n. 21).

85. Eunice Larson, Autopsy Report 71-16, Kauaikeolani Children's Hospital, 20 April 1971, revised 3 May 1973; E. Larson, interview by J. F. Bastian, J. C. Burns, H. H. I. Kushner, and C. H. Turner, San Diego, Calif., 11 November 1999. Landing had trained a number of prominent Japanese pediatric pathologists.

86. Larson attached a copy of the English abstract of Dr. Kawasaki's 1967 article and noted on the revised report that "Dr. Landing suggested the diagnosis": Larson, Autopsy Report 71-16 (n. 85); B. Landing, interview by J. F. Bastian, J. C. Burns, H. I. Kushner, and C. H. Turner, San Diego, Calif., 14 August 1999.

87. M. Melish, interview by J. Bastian, J. Burns, H. Kushner, and C. Turner, San Diego, Calif., 4 April 2000; R. Hicks, interview by J. Bastian, J. Burns, H. Kushner, and C. Turner, San Diego, Calif., 26 May 2000.

88. M. Melish to T. Kawasaki, 15 March 1974; T. Kawasaki to J. Burns, 30 April 2000.

case demonstrated, result in coronary artery aneurysms and death.⁸⁹ The three credited Kawasaki with having identified the syndrome.

In 1976 an editorial in the British journal *Lancet* urged following the lead of “the Japanese M.C.L.S. study group” by adopting the “name Kawasaki disease in place of M.C.L.S., thus accepting it as a nosological entity,” even though the writer conceded that “the aetiology of M.C.L.S. is obscure.”⁹⁰ As Landing and Larson noted the next year, “different acronymic terms (MCLS and MLNS) and the eponym Kawasaki disease” were used by different authors.⁹¹ To avoid confusion, they suggested, it would be “useful to agree on a name for the disorder,” and they proposed that “the acronymic term MCLS be retained, or that the eponym, Kawasaki disease, which recognizes the great contribution of Japanese workers to the current knowledge of the disorder, be employed in the medical literature.”⁹²

Meanwhile, at the Centers for Disease Control (CDC) in Atlanta, David Morens, a young Epidemic Information Service (EIS) officer, began a campaign to convince his skeptical superiors that MCLS was indeed a separate syndrome. Morens had worked as a pediatric resident at Kauaikeolani Children’s Hospital and had seen some of the first recognized American cases while under Melish’s supervision. Convinced of the importance of this syndrome, he continued to pursue his interest in it at the CDC. He adopted the Japanese Research Committee’s 1974 criteria as the official CDC research case definition of MCLS.⁹³ In order to make his case for the importance of the disorder, Morens unilaterally made the decision to change the label of the syndrome to “disease” and to adopt the eponym “Kawasaki”:

I went back to CDC and made my decision. The one thing that caused a lot of controversy later . . . was that I called it Kawasaki disease, and not Kawasaki

89. M. E. Melish, R. M. Hicks, and E. Larson, “Mucocutaneous Lymph Node Syndrome in the U.S.,” *Pediatr. Res.*, 1974, 8: 427A; M. E. Melish, R. M. Hicks, and E. J. Larson, “Mucocutaneous Lymph Node Syndrome in the United States,” *Amer. J. Dis. Child.*, 1976, 130: 599–607.

90. “Kawasaki Disease,” *Lancet*, 1976, 1: 675–76.

91. Landing and Larson, “Are Infantile Periarthritis Nodosa . . . ?” (n. 40), p. 659.

92. *Ibid.*, p. 661.

93. Morens made only one minor change to the criteria, and that was the addition of a statement reminding clinicians that KD was a diagnosis of exclusion: The diagnosis of KD is considered confirmed by the presence of fever of at least five days’ duration plus four of the remaining five criteria, and the inability to explain the illness by some other known disease process. See David M. Morens and R. J. O’Brien, “Kawasaki Disease in the United States,” *J. Infect. Dis.*, 1978, 137: 91–93; David Morens, interview by H. I. Kushner, Bethesda, Md., 12 August 1999.

syndrome. . . . All these people at CDC didn't believe there's any such thing. If I call it a syndrome, I'm handing them ammunition to say, yeah, even by your own definition in your name, you're calling it a constellation of nonspecific features—signs and symptoms. To call it a disease was essentially making an assertive statement that this is a distinct pathological entity. So I just did it!⁹⁴

Some, like Melish, resisted the disease label, but had no reservations about extending recognition to Kawasaki and referring to the illness as either “Dr. Kawasaki’s” MCLS or Kawasaki Syndrome (KS).⁹⁵ Kawasaki also questioned the disease label, recently explaining: “because the etiology of Kawasaki disease (KD) is still unknown, KD cannot yet be called a disease entity but is still regarded as a clinical entity. Consequently it can be said that only when the etiology is discovered will KD be seen as a disease entity.”⁹⁶ Disease or syndrome, Kawasaki’s name was permanently attached to childhood CAA. One of the problems with adopting eponyms for syndrome designations may be that the intention to honor a medical pioneer results in an overvaluation of initial, but necessarily tentative, sign criteria.

Although Morens insisted that his case definition was designed to be an epidemiological tool and not to be adopted for diagnostic purposes as a clinical tool, it was, nevertheless, institutionalized in diagnostic handbooks—including the *Redbook*, the official publication of the Academy of Pediatrics Committee on Infectious Diseases; R. D. Feigin and J. D. Cherry’s *Textbook of Pediatric Infectious Diseases*; the American Heart Association’s *Guidelines of the Diagnosis of Kawasaki Disease*; and J. T. Cassidy and R. E. Petty’s *Textbook of Pediatric Rheumatology*.⁹⁷ As a result, the CDC case definition became and remains the foundation for a new clinical and research paradigm, and the syndrome previously known as MCLS is today known around the world as Kawasaki disease⁹⁸ (see Table 3).

94. Morens interview (n. 93).

95. Melish interview (n. 87). CDC publications have recently returned to using the label “Kawasaki syndrome,” but the overwhelming and general use now has become “Kawasaki Disease.”

96. Kawasaki, “Kawasaki Disease” (n. 45), p. 8.

97. American Academy of Pediatrics, *Redbook-2000: Report of the Committee on Infectious Diseases*, 25th ed. (Elk Grove Village, Ill.: American Academy of Pediatrics, 2000), pp. 360–63; R. D. Feigin and J. D. Cherry, *Textbook of Pediatric Infectious Diseases* (Philadelphia: Saunders, 1981), 2 (36): 1637–38; J. T. Cassidy and R. E. Petty, *Textbook of Pediatric Rheumatology* (Philadelphia: Saunders, 2001), pp. 360–64.

98. The 2003 *Redbook* acknowledges that children presenting with “incomplete or atypical Kawasaki syndrome” when accompanied by appropriate laboratory findings, are candidates for treatment with IVIG. The latest edition of the *Redbook* has also replaced the label “Kawasaki disease” with “Kawasaki syndrome.” American Academy of Pediatrics,

Table 3. Clinical Manifestations of Kawasaki Disease (*Redbook-2000*)

5 days of fever AND 4 of the 5 following criteria:

1. Discrete bulbar conjunctival injection without exudate
 2. Erythematous mouth and pharynx, strawberry tongue, and red cracked lips
 3. A polymorphous generalized erythematous rash
 4. Changes in the peripheral extremities consisting of induration of the hands and feet with erythematous palms and soles
 5. Cervical lymphadenopathy (> 1.5 cm), usually unilateral
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Adapted from American Academy of Pediatrics, *Redbook-2000: Report of the Committee on Infectious Diseases*, 25th ed. (Elk Grove Village, Ill.: American Academy of Pediatrics, 2000), pp. 360–61.

Conclusion

Although researchers have attempted to uncover the etiology of Kawasaki disease since the 1960s, we appear to be no closer to an answer. Among those who assume there is an infectious agent, disagreement continues over whether that agent is bacterial or viral, and whether or not it acts as a superantigen. Immune response remains a crucial arena of investigation; yet no robust hypothesis has convincingly linked the sign complex and immune cascade with the development of CAA. Part of the reason that a breakthrough has been so difficult may be the fact that since the 1960s, research has been constrained by a set of assumptions informed by a historical narrative that became dogma by the 1980s. As we have attempted to show, this dogma results from only one of the possible readings of an incomplete historical record, rather than from a robust scientific investigation. Remembering that Kawasaki disease is a historically contested syndrome may have a liberating impact on the search for its etiology.

We make no claims about the true identity or etiology of Kawasaki disease, but our history has questioned a number of presumptions about Kawasaki disease—including its identity with IPN, its spectrum from benign to fatal, its existence in the West prior to the late 1930s, its precision of clinical description, and its naming. Destabilizing the Kawasaki disease narrative creates the possibility of reexamining the claims about its epidemiology, clinical course, and, ultimately, its etiology. It also

Redbook. 2003: Report of the Committee on Infectious Diseases, 26th ed. (Elk Grove Village, Ill.: American Academy of Pediatrics, 2003), pp. 392–95, see esp. p. 392.

reveals that the narrative has authorized treating this syndrome as a single “disease” because it tends to transform a set of tentative and contested clinical signs into a diagnostic canon. This process has, in turn, restricted the research population to those who meet the clinical case criteria, while excluding many of those who present with the pathology that the signs are meant to identify. The reasons for this exclusion are historical and political (in the widest sense of the term). Historical analysis of the reasons can affect the future of diagnosis and treatment of Kawasaki disease, and may also allow for the development of a more inclusive protocol for research on its etiology and pathophysiology. We have made several specific suggestions for developing this protocol.⁹⁹

Although our examination has focused on Kawasaki disease, it has implications for a variety of other baffling syndromes whose clinical signs have become canonized while their etiology has eluded researchers. As we have demonstrated, the power of historical narrative lies not only in its ability to understand the unfolding of a separate medical history, but also in its power to determine that history itself. We believe that historical investigations of the construction of syndromes can elicit useful issues for the development of research hypotheses. In this way, the history of medicine can become an important tool in the medical researcher’s armamentarium.

99. Kushner et al., “Rethinking the Boundaries” (n. 9), pp. 227–29.