Kawasaki Disease: A Brief History

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ABSTRACT. Tomisaku Kawasaki published the first English-language report of 50 patients with Kawasaki disease (KD) in 1974. Since that time, KD has become the leading cause of acquired heart disease among children in North America and Japan. Although an infectious agent is suspected, the cause remains unknown. However, significant progress has been made toward understanding the natural history of the disease and therapeutic interventions have been developed that halt the immune-mediated destruction of the arterial wall. We present a brief history of KD, review progress in research on the disease, and suggest avenues for future study.

Kawasaki saw his first case of KD in January 1961 and published his first report in Japanese in 1967. Whether cases existed in Japan before that time is currently under study. The most significant controversy in the 1960s in Japan was whether the rash and fever sign/symptom complex described by Kawasaki was connected to subsequent cardiac complications in a number of cases. Pathologist Noboru Tanaka and pediatrician Takajiro Yamamoto disputed the early assertion of Kawasaki that KD was a self-limited illness with no sequelae. This controversy was resolved in 1970 when the first Japanese nationwide survey of KD documented 10 autopsy cases of sudden cardiac death after KD. By the time of the first English-language publication by Kawasaki in 1974, the link between KD and coronary artery vasculitis was well-established.

KD was independently recognized as a new and distinct condition in the early 1970s by pediatricians Marian Melish and Raquel Hicks at the University of Hawaii. In 1973, at the same Hawaiian hospital, pathologist Eunice Larson, in consultation with Benjamin Landing at Los Angeles Children's Hospital, retrospectively diagnosed a 1971 autopsy case as KD. The similarity between KD and infantile periarteritis nodosa (IPN) was apparent to these pathologists, as it had been to Tanaka earlier.

What remains unknown is the reason for the simultaneous recognition of this disease around the world in the 1960s and 1970s. There are several possible explanations. KD may have been a new disease that emerged in Japan and emanated to the Western World through Hawaii, where the disease is prevalent among Asian children. Alternatively, KD and IPN may be part of the spectrum of the same disease and clinically mild KD masqueraded as other diseases, such as scarlet fever in the preantibiotic era. Case reports of IPN from Western Europe extend back to at least the 19th century, but, thus far, cases of IPN have not been discovered in Japan before World War II. Perhaps the factors responsible for KD were introduced into Japan after the World War II and then reemerged in a more virulent form that subsequently spread through the industrialized Western world. It is also possible that improvements in health care and, in particular, the use of antibiotics to treat infections caused by organisms including toxin-producing bacteria reduced the burden of rash/fever illness and allowed KD to be recognized as a distinct clinical entity.

Itsuzo Shigematsu, Hiroshi Yanagawa, and colleagues have conducted 14 nationwide surveys in Japan. These have indicated that: 1) KD occurred initially in nationwide epidemics but now occurs in regional outbreaks; 2) there are ~5000 to 6000 new cases each year; 3) current estimates of incidence rates are 120 to 150 cases per 100 000 children <5 years old; 4) KD is 1.5 times more common in males and 85% of cases occur in children <5 years old; and 5) the recurrence rate is low (4%). In 1978, David Morens at the Centers for Disease Control and Prevention published a case definition based on Kawasaki's original criteria. The Centers for Disease Control and Prevention developed a computerized database in 1984, and a passive reporting system currently exists in 22 states. Regional investigations and national surveys suggest an annual incidence of 4 to 15 cases per 100 000 children <5 years of age in the United States.

The natural history of KD reveals that coronary artery aneurysms occur as a sequela of the vasculitis in 20% to 25% of untreated children. Echocardiography can be successfully used to detect coronary artery dilatation and aneurysms in virtually all patients. Patients with no acute phase coronary artery changes detected by echocardiogram are clinically asymptomatic at least 10 years later. The Japanese Ministry of Health has established a registry of 6500 children who will be followed longitudinally to determine the natural history of the illness. No similar registry of patients exists in the United States.

Studies of KD pathogenesis show a progression of arterial lesions accompanying KD vasculitis and a number of immunoregulatory changes, including a deficiency of circulating CD8+ suppressor/cytotoxic T cells; an abundance of circulating B cells spontaneously producing immunoglobulins; and circulating, activated monocytes. Biochemical and immunologic evidence suggests endothelial cell activation and injury. Although the cause of KD remains unknown, clinical trials have established effective therapies, despite the absence of a proven cause. Intravenous immunoglobulin (IVIG) plus aspirin lowers the rate of coronary artery aneurysms from 20% to between 3% and 5%. In 1988, the Committee on Infectious Diseases of the American Academy of Pediatrics endorsed IVIG treatment as recommended therapy for KD. Questions remain regarding treatment of patients who fail to respond to an initial dose of IVIG. The role of

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Received for publication Dec 14, 1999; accepted Feb 25, 2000.
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steroids or other antiinflammatory agents in the treatment of KD is controversial.

Areas for further research include: 1) a more sensitive case definition that includes laboratory and echocardiographic data, as well as clinical signs and symptoms; 2) development of a diagnostic test based on the biology of inflammation and acute endothelial cell damage that, in the absence of the causative agent, could be used to identify children with KD; 3) studies of index cases and their families to identify relevant genetic factors; and 4) long-term follow-up of patients into their third and fourth decades with monitoring for late cardiovascular sequelae. ***Pediatrics*** **2000;106(2). URL: http://www.pediatrics.org/cgi/content/full/106/2/e27;** ***vasculitis, coronary artery aneurysms, pediatric cardiology.***

ABBREVIATIONS. KD, Kawasaki disease; MCOS, mucocutaneous ocular syndrome; IPN, infantile periarteritis nodosa; IgA, immunoglobulin A; IVIG, intravenous immunoglobulin.

In 1974, Dr Tomisaku Kawasaki first reported in English his original series of 50 Japanese patients who manifested a constellation of signs and symptoms that would later bear his name.[1] In the intervening 25 years, Kawasaki disease (KD) has been reported in children of most racial and ethnic groups throughout the world and is now the leading cause of acquired heart disease in children in the United States and Japan.[2,3] Although an infectious agent is suspected, the cause of this puzzling disease remains unknown. Over the last 25 years, however, significant progress has been made toward understanding the pathogenesis of the vasculitis, the natural history of the disease, and therapeutic interventions that halt the immune-mediated destruction of the arterial wall. This review will highlight the insights that have been gained and the challenges that remain in our study of this disease.

Emergence of KD in Japan

Kawasaki saw his first case of KD in January 1961 when he was a staff pediatrician at the Red Cross Hospital in a suburb of Tokyo (T. Kawasaki, personal communication, 1998). The patient, a 4-year-old boy, recovered spontaneously from his illness and was discharged as "diagnosis unknown"(Fig 1). It was not until Kawasaki saw his second case 1 year later that he began to suspect the emergence of a disease that had not been previously described in Japan. In fact, cases now thought to be KD were documented in Japan as early as the 1950s.[4–7] Whether cases existed in Japan before that time is currently under investigation as part of the Kawasaki Disease History Project.[8] Initially, Kawasaki believed that the clinical syndrome was a benign, self-limited process with no sequelae. He reported the first 7 cases as "non-scarlet fever syndrome with desquamation" at a 1962 meeting of the Chiba District Pediatric Group of the Japanese Pediatric Association in Chiba. By 1964, he had gathered 22 cases and these he presented as mucocutaneous ocular syndrome (MCOS) at the annual meeting of the East Japan/Chubu Pediatric Group. Despite the accumulation of cases, many clinicians continued to believe that KD was not a new disease entity, but rather an atypical form of Stevens-Johnson syndrome (T. Kawasaki, personal communication, 1998). In 1965, Dr Noboru Tanaka, then head of the Department of Pathology at the Red Cross Hospital, performed an autopsy on a child previously diagnosed by Kawasaki as having MCOS. The child had died suddenly and unexpectedly and at autopsy Tanaka discovered coronary artery thrombosis. Tanaka, thus, was the first pathologist to recognize the serious and sometimes fatal cardiac complications of the disease. Despite the autopsy evidence, most clinicians rejected the claim of Tanaka that the disease called MCOS could be associated with fatal cardiac complications (N. Tanaka, personal communication, 1999). At the urging of Dr Fumio Kosaki, then head of the Department of Pediatrics at Red Cross Hospital, Kawasaki published his series of 50 patients in an allergy journal to avoid conflict with individuals in the pediatric establishment who disagreed with his claim that he was describing a previously unknown and unique condition.[9]

The publication of the article by Kawasaki engendered considerable excitement and controversy throughout the Japanese medical community. Probably the most significant clinical debate that ensued was over the possible link between the rash and fever sign/symptom complex Kawasaki had so carefully documented and the cardiac complications of this condition. The first clinician to suspect cardiac involvement in nonfatal cases of KD was Dr Takajiro Yamamoto, head of the Department of Pediatrics at St Luke's Hospital in Tokyo (T. Yamamoto, personal communication, 1998). He, like Kawasaki, had been independently gathering cases in the late 1950s and early 1960s. In December 1966, one of his patients presented with the clinical stigmata of typical KD and had a gallop rhythm associated with congestive heart failure. In 1968, Yamamoto and colleagues[10] published a report of 23 patients, of whom 11 (48%) had abnormalities detected by electrocardiogram. These results persuaded Yamamoto that cardiac involvement was a common feature of this syndrome.[11]

It is possible that Yamamoto was the first physician to recognize KD in the United States, when, as a visiting professor at New York Cornell Hospital in 1963, he observed a patient with the KD sign/symptom complex while attending Professors' Rounds led by Dr Heinz Eichenwald, then acting Chairperson of the Department of Pediatrics (T. Yamamoto, personal communication, 1998; H. Eichenwald, personal communication, 1999). Because of Yamamoto's experiences with similar patients in Japan, he recognized the clinical features of the condition that would later become known as KD.

Not until 1970, however, was it possible to shed new light on the debate about the cardiac sequelae of KD. The first Japanese nationwide epidemiologic survey of KD was conducted in that year by Dr Itsuzo Shigematsu (Chief of the Department of Epidemiology, Institute of Public Health, Tokyo) and colleagues. At the urging of Tanaka, the questionnaire asked about cardiac complications associated with the clinical syndrome. With this extensive sur-

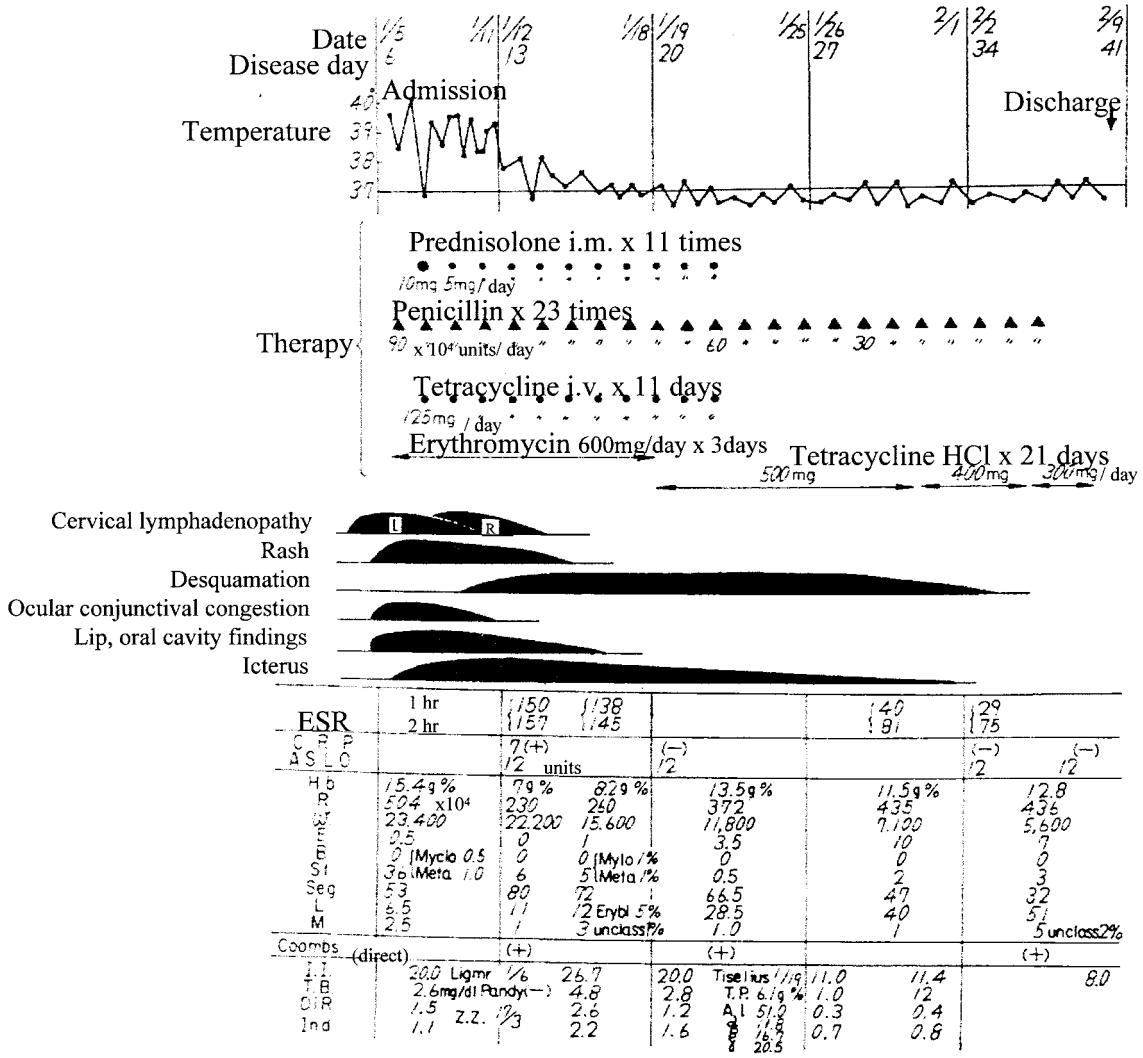

Fig 1. Clinical description of the first case of Kawasaki. The patient was a 4-year-old Japanese boy who was hospitalized on the sixth day of illness in January 1961 with fever and associated signs and symptoms. An unusual feature of this patient was the Coombs-positive hemolytic anemia that Kawasaki never saw again in subsequent patients with the clinical syndrome. Temperatures are in degrees centigrade. im indicates intramuscularly; iv, intravenously; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASLO, antistreptolysin O; Hb, hemoglobin concentration; R, red blood cell count; W, white blood cell count; E, eosinophils; B, basophils; St, immature neutrophils (stabs); Seg, neutrophils; L, lymphocytes; M, monocytes; II, icterus index; TB, total bilirubin; Dir, direct bilirubin; Ind, indirect bilirubin. Adapted from Kawasaki (N. Tanaka, personal communication, 1999); translation by Chisato Shimizu.

vey, the number of cases and the range of variation in the condition raised the discussions about the disease to new levels of sophistication. Confirming the earlier arguments of both Tanaka and Yamamoto, it became clear that cardiac involvement, as a sequela of severe vasculitis, was part of the spectrum of KD. By the time of the first English-language publication of Kawasaki's original 50 patients in 1974, the link between KD and coronary artery vasculitis had been well-established.

A separate debate during these early days of KD research involved pathologists who saw a similarity between infantile periarteritis nodosa (IPN) and fatal KD and questioned whether these were the same disease. As a result of the 1970 national survey in Japan, 10 autopsy cases of sudden death after KD were compiled, and it became apparent that there were good reasons to pursue links to IPN.[12] Tanaka et al[13] published a discussion of the possible link between the 2 disease entities in 1972. Following his lead, Dr Zenshiro Onouchi, then a staff pediatrician at Kyoto Municipal Medical School, and his pathology colleagues presented further autopsy data suggesting that the fatal syndrome IPN might be a severe form of KD.[14]

Emergence of KD in the United States

What we now know as KD was also being noticed in Hawaii at the same time that it was being described in Japan. In the early 1970s, 2 young faculty members in the Department of Pediatrics at the University of Hawaii began to see children with an unusual constellation of fever, rash, and red mucous membranes. Dr Marian Melish, a specialist in pediatric infectious diseases, and Dr Raquel Hicks, a pediatric rheumatologist, were puzzled by this illness that occurred predominantly among Asian children, most of them Japanese Americans (M. Melish, personal communication, 1999). These cases reminded Melish of 2 patients who she had seen in the late

1960s, while at the University of Rochester. Both children had a clinical syndrome compatible with what we now call KD. They were presented at Pediatric Grand Rounds as patients with fever of unknown origin that spontaneously resolved (M. Melish, personal communication, 1999).

In the fall of 1973, Melish and Hicks saw photographs of children with KD from Japan and immediately recognized their new disease. Melish contacted Kawasaki shortly thereafter, and it became clear that the syndrome independently documented by Melish and Hicks was identical to the newly described syndrome in Japan.[15]

In the United States, as in Japan, the emergence of KD was characterized by separate paths of discovery for clinicians and pathologists. In April 1971, Dr Eunice Larson, a pediatric pathologist at Kauikeolani Children's Hospital in Honolulu, performed an autopsy on a 10-month-old Japanese American infant who died of coronary artery thrombosis after resolution of an illness later recognized as KD (B. Landing and E. Larson, personal communications, 1999). This case was retrospectively diagnosed as KD in 1973, when Larson consulted Dr Benjamin Landing, her former mentor and Pathologist in Chief at Los Angeles Children's Hospital. Landing had recently returned from a trip to Tokyo, where he had learned of KD and reviewed histologic sections from patients with fatal arteritis. Landing reviewed the slides from Hawaii and recognized the pathologic changes of KD. In 1976, the clinical and pathologic aspects of KD in Asian/Pacific Islander children from Hawaii were published.[16] The similarity between KD and IPN was immediately apparent to these pathologists as well. In a review of autopsy cases of KD and IPN from Japan and the United States, Landing and Larson[17] extended the observations of Tanaka and argued that the 2 diseases were indistinguishable to the pathologist.

KD Around the World

The reason for the simultaneous recognition of this disease around the world in the 1960s and 1970s remains unknown. There are several possible explanations. KD may have been a new disease that emerged in Japan and emanated to the Western world through Hawaii, where the disease became prevalent among Asian children. Alternatively, KD and IPN may be part of the spectrum of the same disease and clinically mild KD masqueraded as other diseases, such as scarlet fever in the preantibiotic era. Case reports of IPN from Western Europe extend back to at least the 19th century, but, thus far, cases of IPN have not been discovered from Japan before World War II.[18] Perhaps the factors responsible for KD were introduced into Japan after the war and then reemerged in a more virulent form that subsequently spread through the industrialized Western world. It is also possible that improvements in health care and, in particular, the use of antibiotics to treat infections caused by organisms including toxin-producing bacteria reduced the burden of rash/fever illness and allowed KD to be recognized as a distinct clinical entity.

Understanding the Epidemiology

In 1970, a meeting of Japanese physicians and epidemiologists was organized by the Japanese Ministry of Health and was led by Shigematsu and colleagues[19] to design a case definition for KD and to conduct a nationwide survey of the disease. A color brochure with pictures of the clinical features of KD and a brief questionnaire were distributed to all hospitals with at least 100 beds and a department of pediatrics. A total of 631 hospitals responded and >3000 cases were reported dating back to the early 1950s. To date, 14 nationwide surveys have been conducted by Dr Hiroshi Yanagawa (Chief of the Department of Public Health, Jichi Medical School, Tochigi) and colleagues in Japan.[3,20–23] From this enormous database, we have learned that: 1) recognized cases of KD occurred initially in nationwide epidemics (1979, 1982, and 1986) but now occur only in limited, regional epidemics, 2) there are ~5000 to 6000 newly diagnosed cases per year in Japan, 3) current estimates of incidence rates are between 120 and 150 cases per 100 000 children <5 years old, 4) the disease is 1.5 times more common in males than in females and 85% of cases occur in children <5 years old, and 5) the recurrence rate is low (4%).

Although it is beyond the scope of this review to summarize the international literature on KD, reports from around the world suggest that where there are children, there is KD.[24] Whether the global recognition of KD represents the emergence of a new disease in these countries or simply represents the unmasking of a disease process that was hidden in other disease categories must ultimately await elucidation of the causative agent.

In the United States, a modified case definition based on Kawasaki's original clinical criteria, and with the exclusion of other plausible causes of fever (Table 1), was created in 1978 by Dr David Morens, then an officer of the Epidemiologic Investigation Service at the Centers for Disease Control and Prevention.[25] Beginning in 1984, a computerized database was created at the Centers for Disease Control and Prevention. A passive reporting system for KD in 22 states is currently in place,[26] but poor compliance with reporting procedures has prevented an accurate estimate of the number of cases diagnosed each year. However, local investigations in different regions of the continental United States coupled with national surveys suggest an annual incidence of 4 to

TABLE 1. Diagnostic Criteria for Kawasaki Disease*

The diagnosis of Kawasaki disease is considered confirmed by the presence of fever and 4 of the remaining 5 criteria and if the illness cannot be explained by some other known disease process.

1. Fever ≥5 d
2. Bilaterial conjunctival injection
3. Changes of the mucous membranes of the upper respiratory tract: injected pharynx, injected, fissured lips, strawberry tongue
4. Changes of the peripheral extremities: peripheral edema, peripheral erythema, periungual desquamation
5. Polymorphous rash
6. Cervical adenopathy

* Adapted from Morens and O'Brien.[25]

15 per 100 000 children <5 years old.[27–32] Although KD has been reported in most ethnic groups, the disease is over represented among Asian American populations.[27,28,33–35] In Hawaii, the annual incidence for Japanese Americans is estimated at 135/100 000 children <5 years old (M. Melish, personal communication, 1999). These data suggest that in Asians, disease susceptibility may be influenced by genetic and possibly cultural factors. As in Japan, ~85% of patients are <5 years old, the disease is more common in males, and regional epidemics have been observed.[27,28,33–35]

Understanding the Natural History

Large series of patients from Japan have established the following features of the natural history of KD: 1) coronary artery aneurysms occur as a sequela of the vasculitis in 20% to 25% of untreated children[36]; 2) echocardiography can be successfully used to detect coronary artery dilatation and aneurysms in virtually all patients[37,38]; and 3) patients with no coronary artery changes detected by echocardiogram during the acute phase are clinically asymptomatic at least 10 years later.[39] For patients who develop coronary artery lesions during the acute disease, ~20% will develop coronary artery stenosis[39] and may subsequently require treatment for myocardial ischemia including percutaneous transluminal angioplasty, coronary artery stenting and bypass grafting, and even cardiac transplantation.[40] The significance of myocardial fibrosis detected on endomyocardial biopsy as long as 11 years after disease[41] and impaired vasodilatory capacity of coronary[42–44] and peripheral arteries[45] as long as 15 years after KD in patients without evidence of coronary artery abnormalities during the acute disease is uncertain.

To determine the long-term outcome for children after KD, the Japanese Ministry of Health has established a registry of ~6500 children with a history of KD who are being evaluated longitudinally.[46,47] Thus far, no excess mortality has been attributed to KD after the acute phase of the disease. Unfortunately, no similar registry of patients has been established in the United States, where a priori risk of cardiovascular disease in adulthood is much higher than in Japan and different environmental, cultural, and genetic factors may influence the outcome of children after the coronary artery vasculitis associated with KD.

Understanding the Pathogenesis

Careful descriptive studies of autopsy cases have suggested the following progression of the arterial lesions in KD based on the duration of illness before death.[48,49] Stage I (0–9 days) is characterized by perivasculitis of small arteries. Pericarditis, myocarditis, inflammation of the atrioventricular conduction system, and endocarditis with valvulitis are also present. Stage II (12–25 days) is characterized by pan-vasculitis of medium-sized, muscular arteries with aneurysm formation and thrombosis. Myocarditis, pericarditis, and endocarditis with valvulitis may also be present. During stage III (28–31 days), myointimal proliferation in the coronary and other medium-sized arteries is prominent, and acute inflammation disappears from the microvasculature. In stage IV (after 40 days), scarring of arteries with stenosis may occur.

The acute vasculitis of KD is associated with a number of immunoregulatory changes. Dr Donald Leung, then an assistant professor at Harvard Medical School, was the first to demonstrate the deficiency of circulating CD8+ suppressor/cytotoxic T cells and the abundance of circulating activated B cells engaged in the spontaneous production of immunoglobulins.[50] Dr Susumu Furukawa (then Professor of Pediatrics at Juntendo University Medical School) and coworkers[51,52] studied the activation of circulating monocytes during the acute phase. Activation of cellular elements of the immune system is likely to be fueled by proinflammatory cytokines, which are elevated during the acute phase.[53–55] Several lines of evidence suggest that genetic influences on the magnitude and nature of the immune response may underlie the susceptibility to KD.[56,57]

Biochemical and immunologic evidence suggest endothelial cell activation and injury. Increased expression of cell adhesion molecules may increase the recruitment of immune effector cells at the luminal surface of the arteries.[58,59] Other likely mechanisms of endothelial cell injury include antibodies directed against activated endothelial cells[60] and increased levels of vascular endothelial cell growth factor, which may also be important in vessel repair.[61]

Dr Anne Rowley (Professor of Pediatrics, Northwestern University) and colleagues[62] are investigating the role of the immunoglobulin A (IgA) immune response in KD patients. They propose a mucosal portal of entry for the agent, which then elicits a specific IgA response. The role of IgA-secreting B cells detected in some autopsy tissues is currently under investigation.

Search for the Causative Agent

The cause of KD remains unknown, although an infectious agent is likely in view of the following observations: 1) a seasonal peak in the winter/spring months in most geographic areas, 2) epidemics with a clear epicenter, 3) the peak incidence in the toddler age group with only rare cases in infants <3 months old and in adults, suggesting a role for transplacental antibodies conferring protection coupled with asymptomatic infection in most individuals with development of protective antibodies, and 4) the similarity of many of the clinical features of KD to other infectious diseases, eg, adenoviral infection and scarlet fever. A long list of discarded pathogens is all that remains after 30 years of search for the causal agent of KD. Initially, standard microbiologic methods to isolate pathogens from different body fluids as well as animal inoculation of these specimens were used in an attempt to isolate an agent.[9,16] More recently, molecular methods to detect agent-specific nucleic acid in patient samples and subtractive hybridization using acute and convalescent patient samples to identify specific antiagent antibodies have not yet yielded answers[63] (J.C.B., unpublished data). Finally, the idea that bacterial toxins acting as superantigens

could trigger the cascade of events that lead to KD has been widely debated. This controversial hypothesis has been supported by some studies[64,65] and refuted by others.[66]

Research efforts have recently focused on identifying a diagnostic test for the disease in lieu of actually identifying the causative agent. This would be analogous to the use of the heterophil antibody test to diagnose infectious mononucleosis before the discovery of the Epstein-Barr virus. As part of this effort, studies are testing the hypothesis that measurement of metalloproteinases in acute serum might serve as a discriminatory diagnostic marker of KD.[67]

Therapy

In the original series of 50 patients, Kawasaki attempted therapy with different antibiotics (penicillins, chloramphenicol, and tetracycline), steroids, and aspirin without a dramatic effect on the clinical course of the disease.[9] After the publication of successful intravenous immunoglobulin (IVIG) therapy of idiopathic thrombocytopenic purpura in 1981,[68] 2 Japanese investigators, Dr Kensi Furusho (then Professor of Pediatrics, Kokura Memorial Hospital, Kitakysushu City) and Dr Susumu Furukawa (then Assistant Professor of Pediatrics, Juntendo University School of Medicine, Tokyo) independently tried high-dose IVIG therapy in acute KD patients (K. Furusho and S. Furukawa, personal communication, 1999).[69] Following the lead from the Japanese, a US multicenter study group was formed and 2 trials of high-dose IVIG therapy for acute KD were conducted in the United States. The results of these trials and further trials in Japan established that IVIG plus aspirin lowered the rate of coronary artery aneurysms from 20% to between 3% and 5%.[70–72] In addition, a single dose of 2-g IVIG/kg resulted in more rapid cessation of fever and improvement in laboratory parameters of systemic inflammation.[72] In 1988, the Committee on Infectious Diseases of the American Academy of Pediatrics endorsed IVIG treatment as recommended therapy for children with acute KD.[73] More recently, questions have arisen regarding treatment of patients who fail to respond with cessation of fever after the first dose of IVIG[74] and whether steroids or other antiinflammatory agents should play a greater role in the initial control of inflammation in these patients.[75,76]

Future Directions

Today, the Japan Kawasaki Disease Research Center in Tokyo, Japan, founded by Kawasaki in 1980, serves as an important resource for information about KD as well as a catalyst for Japanese and international research efforts and education. Clearly, the primary mystery of KD is the cause of the disease. Although an infectious agent is suspected, the culprit pathogen continues to elude investigators. Even in the absence of knowledge of the causative agent, a sensitive and specific diagnostic test would greatly aid studies of epidemiology, outcome, and treatment of KD.

We suggest that fruitful avenues for future research include the following: 1) detailed investigations of the global incidence of the disease, 2) institution of sentinel hospital surveillance for KD and creation of national registries, 3) a more sensitive case definition that includes laboratory and echocardiographic data as well as clinical signs and symptoms, 4) long-term follow-up of patients into their third and fourth decade with monitoring for late cardiovascular sequelae, 5) expanded studies of the pathology of arteries in patients dying of other causes after KD, 6) studies of index cases and their families to identify genetic factors that may influence disease susceptibility and outcome, 7) application of new molecular-based methods to search for the causative agent, 8) increased cooperation between clinicians and pathologists with creation of a centralized registry of autopsy tissues that could quickly and efficiently be accessed for testing new hypotheses, 9) development of a diagnostic test based on the biology of inflammation and acute endothelial cell damage that, in the absence of the causative agent, could be used to identify children with the disease, and 10) international, collaborative, multicenter prospective trials of additional antiinflammatory therapies for the acute disease and antithrombotic and thrombolytic therapies for children with aneurysms.

ACKNOWLEDGMENTS

This work was supported in part by the Kawasaki Disease Research Program; grant from the Chancellor's Associates, University of California, San Diego, School of Medicine; a translation grant from San Diego State University; and a travel grant from the Japan Kawasaki Disease Research Center.

We thank the interviewees who generously donated their time to this research effort: (in alphabetical order) Japan: Susumu Furukawa, Kenshi Furusho, Kenji Hanawa, Hirohisa Kato, Tomisaku Kawasaki, Shiro Naoe, Jushichiro Naito, Rokuro Okuda, Zenshiro Onouchi, Shizu Sakai, Itsuzo Shigematsu, Tomoyoshi Sonobe, Tamiko Takemura, Noboru Tanaka, Tadahiko Ueno, Takajiro Yamamoto, and Hiroshi Yanagawa; Europe: Anton Becker, Hans Cremer, Michael Dillon, and Eva Salo; and the United States: Heinz Eichenwald, Benjamin Landing, Eunice Larson, Marian Melish, David Morens, Lawrence Schonberger, and Samuel Spector.

We especially thank Noriko Sato at the Japan Kawasaki Disease Research Center for her administrative support and assistance in organizing interviews in Japan; Katherine E. Holcomb and Frederique C. deVries at the Kawasaki Disease History Project Office for administrative and technical support in the United States; and James G. Dobbins for his helpful comments.

REFERENCES

1. Kawasaki T, Kosaki F, Okawa S, et al. A new infantile acute febrile mucocutaneous lymph node syndrome (MCLS) prevailing in Japan. *Pediatrics*. 1974;54:271–276
2. Taubert KA, Rowley AH, Shulman ST. A nationwide survey of Kawasaki disease and acute rheumatic fever. *J Pediatr*. 1991;119:279–282
3. Yanagawa H, Nakamura Y, Ojima T, Yashiro M, Tanihara S, Oki I. Changes in epidemic patterns of Kawasaki disease in Japan. *Pediatr Infect Dis J*. 1999;18:64–66
4. Itoga S, Yamagishi M. Steroid treatment for mucocutaneous ocular syndrome in childhood [in Japanese]. *Chiryo (J Therapeutics)*. 1960;42:1174–1179
5. Hanawa K. Two cases of pericardial hematoma in infancy [in Japanese]. *Shonika Shinryo (J Pediatr Pract)*. 1959;22:820
6. Fujikawa T. A case report of Feer disease [in Japanese]. *Shonika Shinryo (J Pediatr Pract)*. 1953;16:281–283
7. Sakurai K. Mucocutaneous ocular syndrome: report of a case [in Japanese]. *Shonika Rinsho (Jpn J Pediatr)*. 1954;7:787–790
8. Kushner HI, Turner C, Burns JC, Bastian J. The worldwide emergence of Kawasaki disease. Presented at the 73rd Annual Meeting of the Amer-

ican Association for the History of Medicine; May 2000; Bethesda, MD
9. Kawasaki T. Pediatric acute mucocutaneous lymph node syndrome: clinical observation of 50 cases [in Japanese]. *Arerugi (Jpn J Allergy)*. 1967;16:178–222
10. Yamamoto T, Kimura J. Acute febrile mucocutaneous lymph node syndrome (Kawasaki): subtype of mucocutaneous ocular syndrome of erythema multiforme complicated with carditis [in Japanese]. *Shonika Rinsho (Jpn J Pediatr)*. 1968;21:336–339
11. Yamamoto T, Oya T, Watanabe A, et al. Clinical features of Kawasaki disease [in Japanese]. *Shonika Rinsho (Jpn J Pediatr)*. 1968;21:291–297
12. Kosaki F, Kawasaki T, Okawa S, et al. Clinicopathological conference on 10 fatal cases with acute febrile mucocutaneous lymph node syndrome [in Japanese]. *Shonika Rinsho (Jpn J Pediatr)*. 1971;24:2545–2559
13. Tanaka N, Naoe S, Kawasaki T. Pathological study on autopsy cases of MCLS in childhood—particularly in relation with periarteritis nodosa-like arteritis [in Japanese]. *Nisseki Chuo byoin Iho (Med J Jpn Red Cross Central Hosp)*. 1972;1:85–94
14. Tanaka K, Onouchi Z, Tomisawa M, et al. A study of Kawasaki disease: presentation of an autopsy case and relationship with infantile periarteritis nodosa [in Japanese]. *Nippon Shonika Gakkai Zasshi (J Jpn Pediatr Soc)*. 1973;77:397–411
15. Melish ME, Hicks RM, Larson E. Mucocutaneous lymph node syndrome in the US. *Pediatr Res*. 1974;8:427A. Abstract
16. Melish ME, Hicks RM, Larson EJ. Mucocutaneous lymph node syndrome in the United States. *Am J Dis Child*. 1976;130:599–607
17. Landing BH, Larson EJ. 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*. 1976;59:651–662
18. Kushner H, Holcomb KE. Where was Kawasaki disease before Kawasaki? Proceedings of the Sixth International Kawasaki Disease Symposium. *Pediatr Res*. 2000;47:560. Abstract
19. Shigematsu I. Epidemiology of mucocutaneous lymph node syndrome [in Japanese]. *Nippon Shonika Gakkai Zasshi (J Jpn Pediatr Soc)*. 1972;76: 695–696
20. Yanagawa H, Yashiro M, Nakamura Y, Kawasaki T, Kato H. Results of 12 nationwide epidemiological incidence surveys of Kawasaki disease in Japan. *Arch Pediatr Adolesc Med*. 1995;149:779–783
21. Yanagawa H, Yashiro M, Nakamura Y, Kawasaki T, Kato H. Epidemiologic pictures of Kawasaki disease in Japan: from the nationwide incidence survey in 1991 and 1992. *Pediatrics*. 1995;95:475–479
22. Yanagawa H, Nakamura Y, Yashiro M, Ojima T, Koyanagi H, Kawasaki T. Update of the epidemiology of Kawasaki disease in Japan: from the results of 1993–1994 nationwide survey. *J Epidemiol*. 1996;6:148–157
23. Yanagawa H, Nakamura Y, Yashiro M, et al. Results of the nationwide epidemiologic survey of Kawasaki disease in 1995 and 1996 in Japan. *Pediatrics*. 1998;102(6). URL: http://www.pediatrics.org/cgi/content/full/102/6/e65
24. Taubert KA. Epidemiology of Kawasaki disease in the United States and worldwide. *Prog Pediatr Cardiol*. 1997;6:181–185
25. Morens DM, O'Brien RJ. Kawasaki disease in the United States. *J Infect Dis*. 1978;137:91–93
26. The Council of State and Territorial Epidemiologists (CSTE), Reporting Requirements for Health Care Providers and Laboratories Diseases and Conditions Not Under National Surveillance. Available at: http://www.cste.org/ndtable 3a.html. Survey updated March 10, 1999
27. Shulman ST, McCauley JB, Pachman LM, Miller ML, Ruschaupt DG. Risk of coronary abnormalities due to Kawasaki disease in urban area with small Asian population. *Am J Dis Child*. 1987;141:420–425
28. Rausch AM, Kaplan SL, Nihill MR, Pappas PG, Hurwitz ES, Schonberger LB. Kawasaki syndrome clusters in Harris country, Texas, and eastern North Carolina: a high endemic rate and a new environmental risk factor. *Am J Dis Child*. 1988;142:441–444
29. Taubert KA, Rowley AH, Shulman ST. Seven-year national survey of Kawasaki disease and acute rheumatic fever. *Pediatr Infect Dis J*. 1994; 13:704–708
30. Davis RL, Waller PL, Mueller BA, Dykewicz CA, Schonberger LB. Kawasaki syndrome in Washington State: race-specific incidence rates and residential proximity to water. *Arch Pediatr Adolesc Med*. 1995;149: 66–69
31. Bronstein DE, Besser RE, Burns JC. Passive surveillance for Kawasaki disease in San Diego County. *Pediatr Infect Dis J*. 1997;16:1015–1018
32. Holman RC, Belay ED, Clarke MJ, Kaufman SF, Schonberger LB. Kawasaki syndrome among American Indian and Alaska native children, 1980–1995. *Pediatr Infect Dis J*. 1999;18:451–455
33. Morens DM, Anderson LJ, Hurwitz ES. National surveillance of Kawasaki disease. *Pediatrics*. 1980;65:21–25
34. Bell DM, Brink EW, Nitzkin JL, et al. Kawasaki syndrome: description of two outbreaks in the United States. *N Engl J Med*. 1981;304:1568–1575
35. Dean AG, Melish ME, Hicks R, Palumbo NE. An epidemic of Kawasaki syndrome in Hawaii. *J Pediatr*. 1982;100:552–557
36. Suzuki A, Kamiya T, Kuwahara N, et al. Coronary arterial lesions of Kawasaki disease: cardiac catheterization findings of 1,100 cases. *Pediatr Cardiol*. 1986;7:3–9
37. Yoshikawa J, Yanagihara K, Owaki T, et al. Cross-sectional echocardiographic diagnosis of coronary artery aneurysms in patients with mucocutaneous lymph node syndrome. *Circulation*. 1979;59:133–139
38. Capannari TE, Daniels SR, Meyer RA, Schwartz DC, Kaplan S. Sensitivity, specificity, and predictive value of two-dimensional echocardiography in detecting coronary artery aneurysms in patients with Kawasaki disease. *J Am Coll Cardiol*. 1986;7:355–360
39. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease: 10- to 21-year follow-up study of 594 patients. *Circulation*. 1996;94:1379–1385
40. Newburger JW, Burns JC. Kawasaki disease. *Vascular Med*. 1999;4: 187–202
41. Yutani C, Go S, Kamiya T, et al. Cardiac biopsy of Kawasaki disease. *Arch Pathol Lab Med*. 1981;105:470–473
42. Muzik O, Parion SM, Singh TP, Morrow WR, Dayanikli F, DiCarli MF. Quantification of myocardial blood flow and flow reserve in children with a history of Kawasaki disease and normal coronary arteries using positron emission tomography. *J Am Coll Cardiol*. 1996;28:757–762
43. Mitani Y, Okuda Y, Shimpo H, et al. Impaired endothelial cell function in epicardial coronary arteries after Kawasaki disease. *Circulation*. 1997; 96:454–461
44. Paridon SM, Galioto FM, Vincent JA, Thomasina TL, Sullivan NM, Bicker JC. Exercise capacity and incidence of myocardial perfusion defects after Kawasaki disease in children and adolescents. *J Am Coll Cardiol*. 1995;25:1420–1424
45. Dillon R, Clarkson P, Donald KE, et al. Endothelial dysfunction late after Kawasaki disease. *Circulation*. 1996;94:2103–2106
46. Nakamura Y, Yanagawa H, Kato H, Harada K, Kawasaki T. Mortality among patients with a history of Kawasaki disease: the third look. *Acta Pediatr Jpn*. 1998;40:419–423
47. Nakamura Y, Yanagawa H, Kawasaki T. Mortality among children with Kawasaki disease in Japan. *N Engl J Med*. 1992;326:1246–1249
48. Fujiwara H, Hamashima Y. Pathology of the heart in Kawasaki disease. *Pediatrics*. 1978;61:100–107
49. Tanaka N, Sekimoto K, Naoe S. Kawasaki disease: relationship with infantile periarteritis nodosa. *Arch Pathol Lab Med*. 1976;100:81–86
50. Leung DYM, Siefel RL, Grady S, et al. Immunoregulatory abnormalities in MCLNS. *Clin Immunol Immunopathol*. 1982;23:100–112
51. Furukawa S, Matsubara T, Jujoh K, et al. Peripheral blood monocyte/macrophage and serum tumor necrosis factor in Kawasaki disease. *Clin Immunol Immunopathol*. 1988;48:247–251
52. Furukawa S, Matsubara T, Motohashi T, Nakachi S, Sasai K, Yabuta K. Expression of Fc epsilon R2/CD23 on peripheral blood macrophages/monocytes in Kawasaki disease. *Clin Immunol Immunopathol*. 1990;56: 280–286
53. Matsubara T, Furukawa S, Yabuta K. Serum levels of tumor necrosis factor, interleukin 2 receptor, and interferon gamma in Kawasaki disease involved coronary artery lesions. *Clin Immunol Immunopathol*. 1990; 56:29–36
54. Maury CPJ, Salo E, Pelkonen P. Circulating interleukin-1 in patients with Kawasaki disease. *N Engl J Med*. 1988;319:1670
55. Ueno Y, Takano N, Kanegane H, et al. The acute phase nature of interleukin 6: studied in Kawasaki disease and other febrile illness. *Clin Exp Immunol.* 1989;76:337–342
56. Shulman ST, Melish M, Inoue O, Kato H, Tomita S. Immunoglobulin allotypic markers in Kawasaki disease. *J Pediatr*. 1993;122:84–86
57. Quasney MW, Zhang Q, Troupe C, et al. Genetic polymorphism in the regulatory region of the TNF-α gene in children with Kawasaki disease. *Pediatr Res*. 1999;45:171A. Abstract
58. Furukawa S, Imam K, Matsubara T, et al. Increased levels of circulating intercellular adhesion molecule 1 in Kawasaki disease. *Arthritis Rheum*. 1992;35:672–677
59. Nash MC, Shah V, Dillon MJ. Soluble cell adhesion molecules and von Willebrand factor in children with Kawasaki disease. *Clin Exp Immunol*. 1995;101:13–17
60. Leung DY, Collins T, Lapierre LA, Geha RS, Pober JS. Immunoglobulin M antibodies present in the acute phase of Kawasaki syndrome lyse cultured vascular endothelial cells stimulated by gamma interferon. *J Clin Invest*. 1986;77:1428–1435
61. Maeno N, Takei S, Masuda K, et al. Increased serum levels of vascular endothelial growth factor in Kawasaki disease. *Pediatr Res*. 1998;44: 596–599

62. Rowley AH, Eckerley CA, Jack HM, Shulman ST, Baker SC. IgA plasma cells in vascular tissue of patients with Kawasaki syndrome. *J Immunol*. 1997;159:5946–5955
63. Rowley AH, Wolinsky SM, Relman DA, et al. Search for highly conserved viral and bacterial nucleic acid sequences corresponding to an etiologic agent of Kawasaki disease. *Pediatr Res*. 1994;36:567–571
64. Abe J, Kotzin BL, Jujo K, et al. Selective expansion of T cells expressing T-cell receptor variable regions V beta 2 and V beta 8 in Kawasaki disease. *Proc Natl Acad Sci USA*. 1992;89:4066–4070
65. Leung DYM, Giorno RC Kazemi LV, Flynn PA, Busse JB. Evidence for superantigen involvement in cardiovascular injury due to Kawasaki syndrome. *J Immunol*. 1995;155:5018–5021
66. Pietra BA, De IJ, Giannini EH, Hirsch R. TCR V beta family repertoire and T cell activation markers in Kawasaki disease. *J Immunol*. 1994;153:1881–1888
67. Chua PK, Yu Q, Nerukar VR, et al. Elevated matrix metalloproteinase 9 (MMP-9) activity in Kawasaki syndrome. *Pediatr Res*. 1999;45:159A. Abstract
68. Imbach P, Barandun S d'Apuzzo V, et al. High-dose intravenous gamma globulin for idiopathic thrombocytopenic purpura in childhood. *Lancet*. 1981;1:1228–1230
69. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gamma globulin for Kawasaki disease. *Lancet*. 1984;2:1055–1058
70. Morikawa Y, Ohashi Y, Harada K, et al. A multicenter, randomized controlled trial of intravenous gamma globulin therapy in children with acute Kawasaki disease. *Acta Pediatr Jpn*. 1994;36:347–354
71. Newburger JW, Takahashi M, Burns JC, et al. Treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*. 1986;315:341–347
72. Newburger JW, Takahashi M, Beiser AS, et al. Single infusion of intravenous gamma globulin compared to four daily doses in the treatment of acute Kawasaki syndrome. *N Engl J Med*. 1991;324:1633–1639
73. American Academy of Pediatrics. Kawasaki disease. In: Peter G, ed. *1988 Red Book: Report of the Committee on Infectious Diseases*. 21st ed. Elk Grove Village, IL: American Academy of Pediatrics; 1988:251–254
74. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP, the Multicenter KD Study Group. Intravenous gamma globulin treatment and retreatment in Kawasaki disease. *Pediatr Infect Dis J*. 1998;17:1144–1148
75. Wright DA, Newburger JW, Baker A, Sundel RP. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. *J Pediatr*. 1996;128:146–149
76. Furukawa S, Matsubara T Umezawa Y, Motohashi T, Ino T, Yabuta K. Pentoxifylline and intravenous gamma globulin combination therapy for acute Kawasaki disease. *Eur J Pediatr*. 1994;153:663–667

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Pediatrics 2000;106;e27

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