30 Loskutoff DJ, Edgington T. Synthesis of a fibrinolytic activator and inhibitor by endothelial cells. *Proc Natl Acad Sci USA* 1977;**74**:3903-7.
31 Holmberg L, Lecander I, Persson B, Åstedt B. An inhibitor from placenta specifically binds urokinase and inhibits plasminogen activator released from ovarian carcinoma in tissue culture. *Biochim Biophys Acta* 1978;**544**:128-37.
32 Lecander I, Roblin R, Åstedt B. Differential inhibition of two molecular forms of melanoma cell plasminogen activator by a placental inhibitor. *Br J Haematol* 1984;**57**:407-12.
33 Verheijen JH, Chang GTG, Kluft C. Evidence for the occurrence of a fast-acting inhibitor for tissue-type plasminogen activator in human plasma. *Thromb Haemost* 1984;**51**:392-5.
34 Juhan-Vague I, Moerman B, De Cock F, Aillaud MF, Collen D. Plasma levels of a specific inhibitor of tissue-type plasminogen activator (and urokinase) in normal and pathological conditions. *Thromb Res* 1984;**33**:523-30.
35 Wijngaards G, Groeneveld E. Temporarily increased inhibition by plasma of plasminogen activator activity in severely ill patients [abstract]. *Haemostasis* 1982;**12**:106.
36 Nilsson IM, Tengborn L. Impaired fibrinolysis. New evidence in relation to thrombosis. In: Jespersen J, Kluft C, Korsgaard O, eds. *Clinical aspects of fibrinolysis and thrombolysis*. Esbjerg: South Jutland University Press, 1983: 273-91.
37 Loskutoff DJ, van Mourik JA, Erickson LA, Lawrence D. Detection of an unusually stable fibrinolytic inhibitor produced by bovine endothelial cells. *Proc Natl Acad Sci USA* 1983;**80**:2956-60.
38 Emeis JJ, van Hinsbergh VWM, Verheijen JH, Wijngaards G. Inhibition of tissue-type plasminogen activator by conditioned medium from cultured human and porcine vascular endothelial cells. *Biochem Biophys Res Commun* 1983;**110**:392-8.
39 Levin EG. Latent tissue plasminogen activator produced by human endothelial cells in culture: evidence for an enzyme-inhibitor complex. *Proc Natl Acad Sci USA* 1983;**80**:6804-8.
40 Wiman B, Ljungberg B, Chmielewska J, Urdén G, Blombäck M. The role of the fibrinolytic system in deep venous thrombosis [abstract]. *Haemostasis* 1984; **14**:175.
41 Nilsson IM. Coagulation, fibrinolysis and venous thrombosis. *Triangle* 1977; **16**:19-27.
42 Rosing DR, Redwood DR, Brakman P, Astrup T, Epstein SE. Impairment of the diurnal fibrinolytic response in man. Effects of aging, type IV hyperlipoproteinaemia, and coronary artery disease. *Circ Res* 1973;**32**:752-8.
43 Bick RL. Clinical relevance of antithrombin III. *Semin Thromb Hemost* 1982; **8**:276-86.
44 Griffin JH. Clinical studies of protein C. *Semin Thromb Hemost* 1984;**10**:162-6.
45 Pennica D, Holmes WE, Kohr WJ, *et al*. Cloning and expression of human tissue-type plasminogen activator cDNA in E coli. *Nature* 1983;**301**:214-21.
46 Sue-Ling HM, Davies JA, McMahon MJ, *et al*. Indicators of depressed fibrinolytic activity in prediction of post-operative deep vein thrombosis [abstract]. *Haemostasis* 1984;**14**:176.
47 Verheijen JH, Rijken DC, Chang GTG, Preston FE, Kluft C. Modulation of rapid plasminogen activator inhibitor in plasma by Stanozolol. *Thromb Haemost* 1984;**51**:396-7.

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Platelet immune complex interaction in pathogenesis of Kawasaki disease and childhood polyarteritis

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Abstract

The role of platelets in the pathogenesis of vasculitis and the formation of coronary artery aneurysms was studied in 19 children with Kawasaki disease and five with polyarteritis. All patients with Kawasaki disease developed thrombocytosis in the third week of illness. The peak platelet count was significantly correlated ($p < 0.005$) with the subsequent development of coronary artery aneurysms. The rise in platelet count was associated with the appearance in the circulation of a factor that induced aggregation and serotonin release in normal platelets. This factor was shown to be of high molecular weight, and its activity was lost at low pH—features suggestive of an immune complex. Immune complexes, detected by precipitation with polyethylene glycol, also appeared in the circulation as the platelet count increased. These complexes induced platelet aggregation, and there was a significant correlation ($p < 0.001$) between the concentrations of IgG and IgA in the polyethylene glycol precipitated material and the platelet aggregating activity. Similar platelet aggregating activity was also detected in patients with polyarteritis but followed a different time course, persisting in the circulation for several months in association with continued disease activity.

These findings imply that different mechanisms have a role in distinct phases of Kawasaki disease. The initial feverish phase (probably infective) is probably followed by an immune complex vasculitis that occurs when antibodies to the initiating agent appear in the circulation. The immune complexes aggregate platelets and induce release of serotonin. Platelet derived vasoactive mediators may increase vascular permeability and facilitate further deposition of complexes in the tissues.

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Introduction

Kawasaki disease, or the mucocutaneous lymph node syndrome, is an acute, feverish illness affecting young children, with prominent mucocutaneous and cardiovascular manifestations.[1] Since its description in 1967 many thousands of cases have been seen in Japan, and the disease is recognised increasingly often in many other countries.[2 3]

Kawasaki disease is often a benign and self limited illness. Arteritis affecting the extraparenchymal muscular arteries is, however, common and results in the development of coronary artery aneurysms in 20-60% of cases.[4-6] Death due to coronary artery thrombosis, myocardial infarction, or aneurysm rupture occurs in 1-2·8% of patients in the first three months of the illness,[2 4-6] and there are reports of sudden death due to myocardial infarction occurring months to years after the initial illness.[7]

Coronary artery aneurysms and myocardial infarction are most commonly detected after the second week of the illness and usually occur at a time when the fever and mucocutaneous manifestations are subsiding and the child appears to be convalescing.[8] Thrombocytosis also occurs at this time, with the platelet count often exceeding 1000×10^9/l.[2] This puzzling temporal association of thrombocytosis with the development

of coronary artery aneurysms and thrombosis led us to investigate the role of platelets in the pathogenesis of Kawasaki disease and also in the related disorder, childhood polyarteritis.

Patients and methods

Nineteen children fulfilling the criteria for Kawasaki disease laid down by the mucocutaneous lymph node syndrome study group[9] were studied after admission to the Hospital for Sick Children, London, between June 1981 and June 1983. Five other children were studied in whom polyarteritis had been diagnosed on the basis of multisystem disease and the exclusion of other known infective, neoplastic, and immunological diseases. The diagnosis of polyarteritis was confirmed arteriographically in two of these patients and histologically in another two. Table I shows clinical details of both groups of patients.

TABLE I—*Clinical features of patients with Kawasaki disease or polyarteritis*

	Kawasaki disease (n = 19)	Polyarteritis (n = 5)
Median (range) age (years)	1·3 (0·3-3·3)	6·7 (1·6-14)
No of boys	12	1
Median (range) duration of symptoms (days) before admission to:		
Local hospital	6 (1-15)	32 (14-180)
Hospital for Sick Children	13 (6-23)	183 (30-260)
No of children with:		
Fever > 38°C	19	5
Polymorphous rash	19	1
Mucous membrane changes	18	2
Conjunctival hyperaemia	17	0
Cervical lymphadenopathy	18	1
Generalised lymphadenopathy	0	2
Oedema and erythema of hands and feet	18	1
Vasculitic skin ulcers	0	3
Coronary aneurysms	7	0
Heart affected in other ways	2	3
Affected kidneys	8	4
Hypertension	8	4

Venous blood was collected from patients on admission and twice each week throughout the illness. Citrated plasma (one volume 3·8% trisodium citrate to nine volumes blood) was prepared within one hour after collection by centrifugation at 1300 *g* for 15 minutes, and both serum and plasma were stored at −70°C until required. Similar samples were obtained from 30 healthy controls. Serial platelet counts were performed twice a week.

DETECTION OF PLATELET AGGREGATING ACTIVITY

Platelet aggregating material was detected in serum with a modification of the platelet aggregating titre of Pentinnen and Myllyla.[10] Platelets were prepared from the blood of a group O Rh negative donor by centrifuging blood, collected into one tenth the volume of acid citrate dextrose, at 140 *g* for 15 minutes. The platelet rich plasma was layered on to a gradient of 10% and 25% metrizamide (Nyegaard Sigma) and centrifuged at 1000 *g* for 15 minutes. The plasma and 10% metrizamide were removed from above, and the 25% metrizamide from below, the layer of platelets. The platelets were recovered from the interface, resuspended in calcium free phosphate buffer pH 5·9, washed three times in the same way, and finally resuspended in calcium free phosphate buffer pH 7·4. Volumes of patients' or controls' serum of 100 μl were serially double diluted in barbitone buffered saline pH 7·4 in U bottomed microtitre plates. Washed platelets, 50 μl, were then added to each well. After incubation at 4°C for 18 hours agglutination of platelets was detected macroscopically against a direct light source. Heat aggregated IgG was used as a positive control and buffered saline as a negative control, and normal control sera were included in each plate. Results were expressed as the $\log^2$ multiple of the highest titre at which aggregation was detected in normal serum.

In eight patients platelet aggregating activity was also determined in plasma using a Payton dual channel aggregometer coupled to a Rikadenki recorder. Test plasma 200 μl was added to 200 μl washed normal platelets (final platelet count 150-300 × 10^9/l) in an aggregometer cuvette. The mixture was stirred at 900 rpm for five minutes and the aggregation recorded. We determined the effect on aggregation of prostacyclin 10 ng/l, albumin 2 g/l, 5 mM edetic acid, and 2·5 mM calcium solution. Plasma from a control was tested simultaneously in each experiment.

RELEASE OF SEROTONIN

The effect of patients' or controls' plasma on serotonin release from normal platelets was assessed as follows: platelets from a control were washed with metrizamide and labelled at room temperature with serotonin, labelled with carbon-14, (5-hydroxytryptamine, side-chain-2-^{14}C) creatinine sulphate (Amersham International), specific activity 222 × 10^7 Bq (60 mCi)/mmol, final concentration 0·84-0·95μM. Labelled platelets 200 μl were added to test or control plasma 200 μl to give a final platelet count of 200-300 × 10^9/l. The proportion (%) of ^{14}C labelled serotonin released into the surrounding medium after stirring for three minutes in the aggregometer was determined as follows: 100 μl of the platelet suspension was added to 400 μl 1·5% formaldehyde at 0°C and centrifuged for 30 seconds in an Eppendorf microcentrifuge; supernatant 200 μl was transferred to scintillation fluid 2·5 ml for counting on an LKB β-counter.

ISOLATION OF PLATELET AGGREGATING MATERIAL

Serum or plasma from two patients with Kawasaki disease and one with polyarteritis, each of whom had a greatly raised platelet aggregating titre, was fractionated by sucrose density gradient ultracentrifugation. The test samples were diluted with 12 volumes of phosphate buffered saline pH 7·2 and ultracentrifuged at 150 000 *g* for 18 hours at 4°C in an MSE 65 prepsin ultracentrifuge on a linear 10-40% sucrose gradient. IgG and IgM were used as external markers. Fractions were collected by downward displacement, diluted to the original volume with phosphate buffered saline, and then tested for platelet aggregating activity on both the platelet aggregating titre test and aggregometry. Fractions were also prepared after acidification to pH 3·0 and 0·1M glycine hydrochloride. Fractions prepared at low pH were neutralised with 0·2M potassium phosphate before assay.

POLYETHYLENE GLYCOL PRECIPITATION OF IMMUNE COMPLEXES

Serum was incubated with polyethylene glycol (2% final concentration) at 4°C for 12 hours. The precipitate was washed with 2% polyethylene glycol, resuspended in the original volume of phosphate buffered saline, and tested for platelet aggregating activity.

The IgG, IgA, IgM, and IgE content of the polyethylene glycol precipitate was measured by an enzyme linked immunosorbent assay (ELISA) technique.[11] After incubating the precipitate with specific anti-immunoglobulin labelled with peroxidase the unbound antibody was measured by its binding to immunoglobulin coated ELISA plates. Standard curves were determined using known quantities of immunoglobulin for each ELISA plate.

Results

SERIAL PLATELET COUNTS

All 19 children with Kawasaki disease developed thrombocytosis (platelet count > 500 × 10^9/l) in the second and third weeks of illness as the fever and mucocutaneous manifestations subsided. Figure 1 shows the course in a representative patient and figure 2 serial platelet counts for all 19 patients. After reaching a peak in the third or fourth week (often exceeding 1000 × 10^9/l) the platelet count fell rapidly in the fifth week and then declined gradually towards normal in the subsequent weeks.

Cross sectional echocardiography was undertaken each week in all patients with Kawasaki disease,[8] and the peak platelet count was significantly higher ($p < 0·005$; Student's *t* test) in those who developed aneurysms than in those who did not (fig 3).

Of the patients with polyarteritis, four developed thrombocytosis and one thrombocytopenia. The platelet counts in the patients with polyarteritis, however, showed a persistent mild increase for many months rather than the transient rise seen in Kawasaki disease.

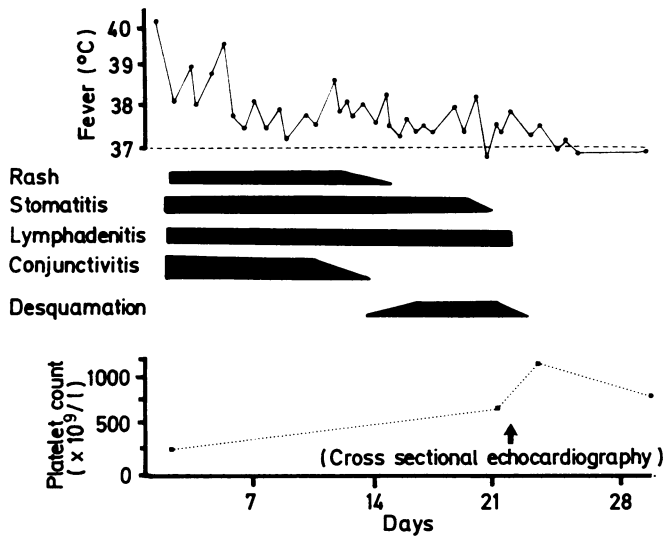

FIG 1—Temporal relations of clinical manifestations of Kawasaki disease to rise in platelet count in a single representative patient. Thrombocytosis occurred in the third and fourth weeks of illness, as fever subsided.

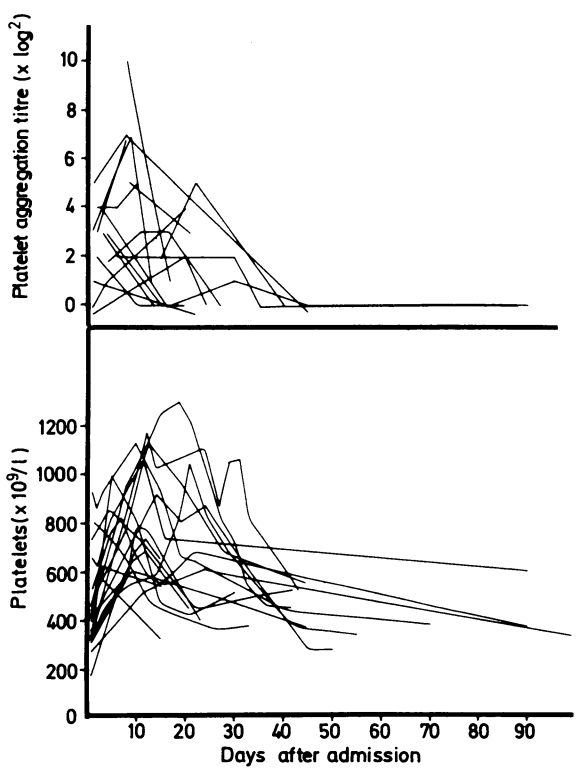

FIG 2—Time course of platelet count (bottom) and platelet aggregating titre (top) after admission in patients with Kawasaki disease.

DETECTION OF PLATELET AGGREGATING ACTIVITY

The rise in platelet count was closely associated with a rise in serum platelet aggregating activity (as detected by platelet aggregating titre) in patients with Kawasaki disease (fig 2) and in four of the five with polyarteritis. The peak level of platelet aggregating material coincided with a peak in the platelet count, and platelet count and platelet aggregating titre were significantly correlated ($p < 0.001$; Spearman rank test). In contrast with the transient rise in platelet aggregating material seen in Kawasaki disease, the increase in platelet aggregating titre persisted in the patients with polyarteritis, often for many months in association with continued disease activity.

Plasma from each of the eight patients tested (four with polyarteritis and four with Kawasaki disease) aggregated washed normal platelets on stirring in the aggregometer. Figure 4 shows a typical example. The aggregation was blocked by the addition of prostacyclin (10 ng/l) or edetic acid (5mM) but was unaffected by the addition of albumin. Increasing the calcium concentration to 2·5mM enhanced the aggregation. No aggregation was detected on addition of normal control plasma to either normal or patients' washed platelets.

RELEASE OF SEROTONIN

Plasma from two patients with polyarteritis and three with Kawasaki disease was tested and in each case induced release of ^{14}C labelled

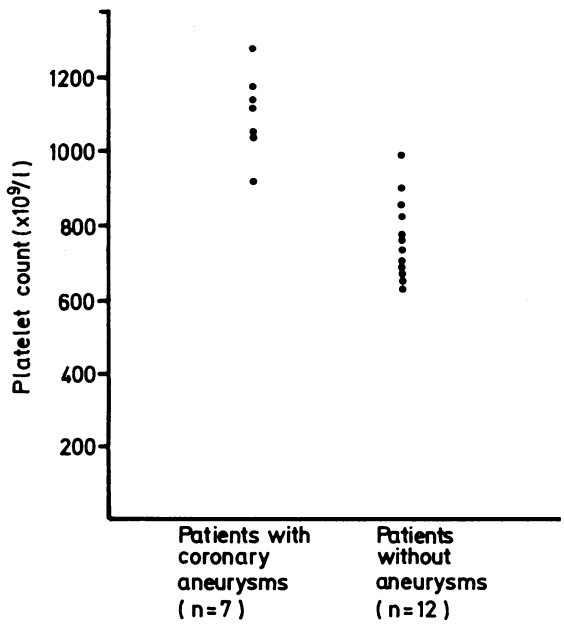

FIG 3—Peak platelet count in patients with and without coronary artery aneurysms detected on cross sectional echocardiography. Patients with coronary artery aneurysms had a significantly higher peak platelet count ($p < 0.005$); Student's t test).

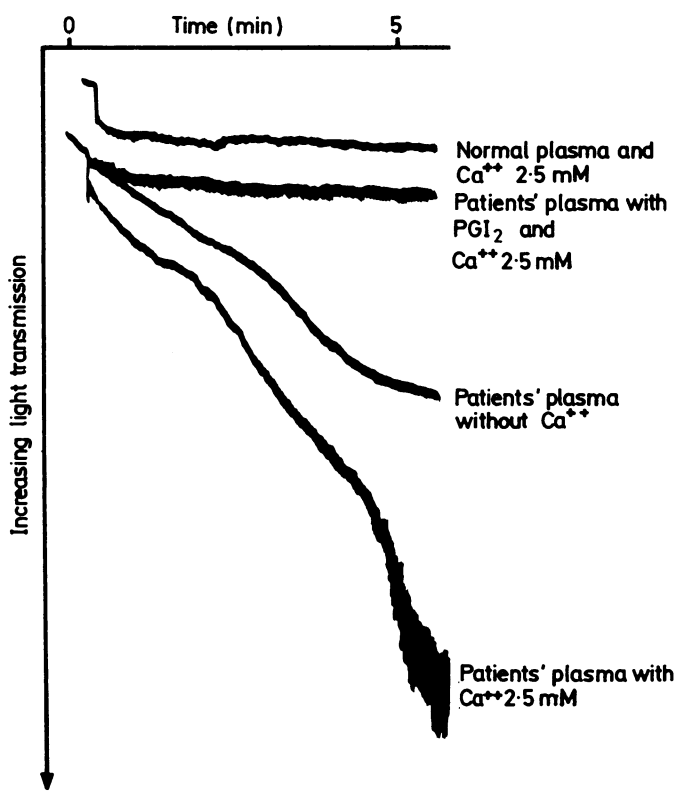

FIG 4—Aggregation on addition of plasma from normal controls and patients with Kawasaki disease or polyarteritis to washed normal platelets.

serotonin from labelled normal platelets (table II), whereas release did not occur using normal plasma.

ISOLATION OF PLATELET AGGREGATING MATERIAL

The fractions of serum and plasma from patients with Kawasaki disease or polyarteritis prepared by sucrose density gradient ultracentrifugation were tested for platelet aggregating activity by both the platelet aggregating titre test (serum) and aggregometry (plasma). Aggregating activity was detected in the high molecular weight fractions (>19 S) prepared at neutral pH. Fractions prepared under dissociating conditions for immune complexes at pH 3 contained no aggregating activity (fig 5).

TABLE II—*Release of serotonin, labelled with carbon-14, from labelled platelets induced by plasma from normal subjects or patients with polyarteritis or Kawasaki disease*

	Serotonin release (%)
Pooled normal plasma	<1
Normal control plasma	<1
Plasma from patients with Kawasaki disease:	
(Case 1)	27
(Case 2)	21
Plasma from patients with polyarteritis:	
(Case 1)	20
(Case 2)	28
(Case 3)	39

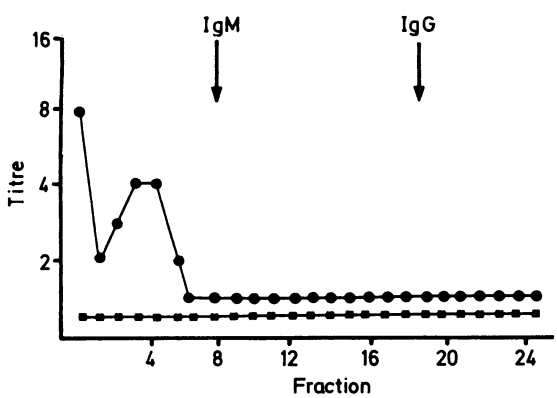

FIG 5—Fractionation of serum from patients with Kawasaki disease by sucrose density gradient ultracentrifugation. IgM and IgG were used as molecular weight markers. Aggregating activity was detected in fractions 1-6 (molecular weight >IgM) separated at pH 7 (●—●). No aggregating activity was detected in fractions prepared at pH 3 (■—■).

The precipitate of serum from patients with Kawasaki disease or polyarteritis obtained after incubation with 2% polyethylene glycol induced platelet aggregation when tested by the platelet aggregating titre test in the presence of calcium (n=5). IgG immune complexes were raised in 13 (68%) of 19 tests in patients with Kawasaki disease. There was a highly significant correlation ($p < 0.001$; Spearman rank correlation) between the rise in platelet aggregating titre and the rise in IgG complexes (fig 6). IgA complexes were detected in 85% of patients with Kawasaki disease, and there was a significant correlation between the presence of IgA complexes and the rise in platelet aggregating titre ($p < 0.001$). A similar correlation was not observed for IgM (raised in 10 patients (55%)) or IgE complexes.

All patients with polyarteritis had appreciably raised concentrations of IgG, IgA, and IgM complexes. The concentrations of IgG and IgM complexes were significantly higher in the patients with polyarteritis than in those with Kawasaki disease.

Discussion

The pathogenesis of Kawasaki disease remains unknown despite its worldwide occurrence and the intensive investigation of many thousands of cases. The clinical features of the illness,

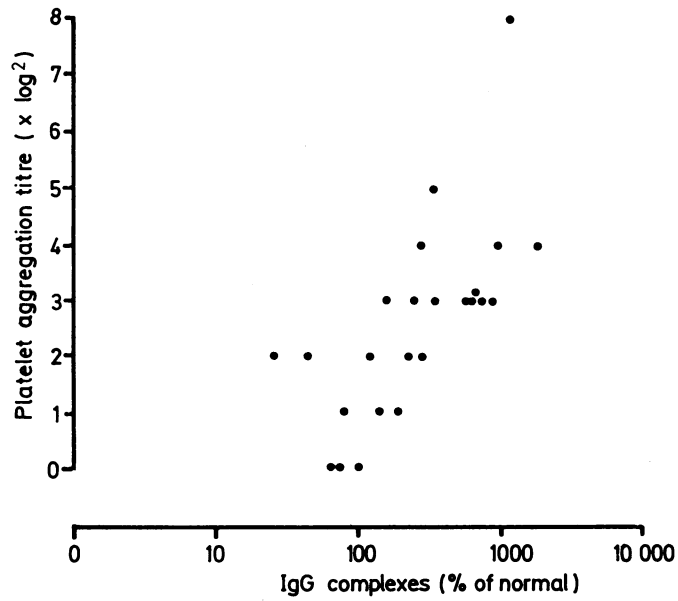

FIG 6—Correlation between platelet aggregating titre and IgG immune complexes in patients with Kawasaki disease or polyarteritis ($p < 0.001$; Spearman rank correlation).

with fever, leucocytosis, and raised acute phase reactants, suggest an infective process, a possibility that is supported by the occurrence of epidemics,[12] geographical and temporal clustering,[13] seasonal variation,[12 13] and occasional simultaneous occurrence in siblings.[14] Despite recent reports, however, implicating a variant strain of the aerobic organisms *Propionibacterium acnes* transmitted by a mite[15] and earlier studies suggesting infection with rickettsia like organisms[16 17] attempts to isolate the causative agent have been unsuccessful. Furthermore, the failure to respond to antibiotics (including those active against rickettsia and anaerobes), the lack of case to case transmission,[12 13] and the progression of the disease despite negative cultures suggest that factors other than infection play a part.

An alternative hypothesis is that the disease is due to an immunological reaction to either a ubiquitous micro-organism or some other environmental agent. This is supported by the systemic vasculitis, a reported association with atopy, raised IgE concentrations,[18] and the presence of immune complexes,[18-20] which have been detected in some but not all studies.[21]

A role has been suggested for platelets in the pathogenesis of the lesions in the coronary arteries and other vessels: platelets are hyperaggregable in both acute and convalescent phases of the disease,[22 23] and circulating in vivo platelet aggregates have been detected[22] as have raised plasma concentrations of β thromboglobulin,[22] platelet factor 4,[22] and thromboxane B2.[24] The mechanisms by which platelets take part and their relation to the immunological or infective processes have not been documented previously.

Our findings suggest that both infective and immunological processes are important in the pathogenesis of Kawasaki disease but that they occur at different phases of the illness and that interaction between immune complexes and platelets may be important in mediating the vascular complications.

The thrombocytosis occurring in the third to fifth weeks of the illness is associated with the appearance in the circulation of material that induces aggregation and release of serotonin from normal platelets and is highly correlated with both the platelet aggregating titre and the subsequent development of coronary artery aneurysms. The platelet aggregating material is of high molecular weight (> 19 S), and labile at low pH, all features suggesting an immune complex. Immune complexes also appear in the circulation simultaneously with the platelet

aggregating activity, and there is a highly significant correlation between the amount of IgG and IgA that can be precipitated with polyethylene glycol and the platelet aggregating activity. Similar platelet aggregating material is also detected in patients with polyarteritis but follows a different time course, persisting in the circulation for months or years in association with continued disease activity.

These findings suggest that Kawasaki disease has three distinct pathophysiological phases. During the first fever, lymphadenopathy, and mucocutaneous manifestations occur, the platelet count is normal, and neither platelet aggregating activity nor immune complexes are detectable in the circulation. In the second, in the third to fifth weeks, when the fever and systemic symptoms are subsiding and desquamation has started, a dramatic rise in the platelet count occurs and platelet aggregating material and immune complexes become detectable. (It is during this phase that aneurysms are most often detected and death from coronary artery thrombosis is most likely to occur.[7 8]) Finally, the platelet count decreases and platelet aggregating material and immune complexes become undetectable. Patients who have survived the first two phases generally recover, but those with coronary artery aneurysms remain at risk from late complications of myocardial infarction or coronary thrombosis.

Although the features of the first two weeks of Kawasaki disease suggest an infective origin for this feverish phase, the subsequent temporal relations are similar to those of experimental immune complex vasculitis, in which platelets play an important part in starting the vascular damage.[25-27] In the serum sickness model (in which the coronary artery is often affected) antigen antibody complexes are formed in the second week after injection of heterologous protein and interact with platelets to cause aggregation and release of vasoactive mediators such as histamine and serotonin.[28] These mediators increase vascular permeability and permit deposition of immune complexes in the subendothelial tissues.[25 26] The pathogenic importance of platelet derived vasoactive substances has been shown by the enhancing effect of histamine or serotonin on immune complex deposition in the tissues[27] and the inhibition of immune complex deposition and tissue damage by platelet depletion and histamine or serotonin antagonists.[25-27] Ultimately, continued production of antibodies results in elimination of the antigen and resolution of the vasculitis.

The association of thrombocytosis with the presence of circulating platelet aggregating material is paradoxical. Aggregated or damaged platelets are normally rapidly removed from the circulation by the reticuloendothelial system, and thus thrombocytopenia rather than thrombocytosis might have been the expected consequence. In animal models saturation of the reticuloendothelial system appreciably delays the clearance of injected colloidal carbon aggregates.[29] Similar observations have been made in patients with immune complex diseases in whom delayed reticuloendothelial system clearance of heat damaged or IgG coated red cells has been shown.[30 31] Small immune complexes may saturate the reticuloendothelial system and prevent the clearance of larger immune complexes[32] or platelet aggregates. Thrombocytosis may therefore be an indication of saturation of the reticuloendothelial system by immune complexes, a possibility substantiated by the positive correlation between platelet count and immune complex titres. An additional possibility is that thrombopoiesis may be stimulated by a product released from aggregated platelets, such as platelet derived growth factor.

The question of whether Kawasaki disease, infantile polyarteritis, and adult polyarteritis represent different diseases or overlapping end results of the same process has caused considerable debate.[33] Our findings suggest that interactions between immune complexes and platelets are important in both disorders. In contrast, however, with the transient rise and fall of platelet aggregating complexes in Kawasaki disease, in polyarteritis the platelet aggregating immune complexes persist in the circulation for months or years, in association with active disease. Whether this persistence is due to a defect in immune elimination of antigen or to a continuing antigenic exposure is not known. A key question requiring further study is whether Kawasaki disease is due to a single (infective) antigen or an immune response to various antigens and whether these antigens are distinct from those in polyarteritis.

Finally, the pathogenic mechanisms we have described have several clinical and therapeutic implications. Patients with the highest platelet counts also have the highest titres to immune complexes and are most likely to develop coronary artery aneurysms. The peak platelet count may therefore be a marker of severe disease and could be used to identify a group of patients requiring more aggressive treatment. Antiplatelet agents may be beneficial in reducing not only the risk of thrombosis but also the severity of the vasculitis.

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References

1 Kawasaki T. Acute febrile mucocutaneous lymph node syndrome with specific exfoliation of the fingers and toes. *Arerugi* 1967;**16**:178-223.
2 Morens DM, Anderson LJ, Hurwitz ES. National surveillance of Kawasaki disease. *Pediatrics* 1980;**65**:21-5.
3 Novelli VM, Marshall WC, Hendrickse W, Levin M, Smallhorn J, Gailbraith A. Kawasaki disease in London. *Lancet* 1983;ii:172.
4 Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. *Pediatrics* 1979;**63**:175-9.
5 Kato H, Koike S, Yamamoto M, Ito Y, Yano E. Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. *J Pediatr* 1975;**86**:892-8.
6 Meade RH, Brandt L. Manifestations of Kawasaki disease in New England outbreak of 1980. *J Pediatr* 1982;**4**:558-62.
7 Tanaka N. Kawasaki disease in Japan: relationship with infantile periarteritis nodosa. *Pathology and Microbiology (Basel)* 1975;**43**:204-18.
8 Novelli VM, Galbraith A, Robinson PJ, Smallhorn JF, Marshall WC. Cardiovascular abnormalities in Kawasaki disease. *Arch Dis Child* 1984;**59**:504-9.
9 Kawasaki T. Clinical features of Kawasaki syndrome. *Acta Paediatrica Japonica* 1983;**25**:3-13.
10 Penttinnen K, Myllyla G. Interaction of human blood platelets, viruses and antibodies. I. Platelet aggregation test with micro equipment. *Annales Medicinae Experimentalis et Biologiae Fenniae* 1968;**46**:188-92.
11 Voller A, Bidwell D, Bartlett A. Enzyme-linked immunosorbent assay. In: Rose RN, Freidman H, eds. *Manual of clinical immunology*. 2nd ed. Washington DC: American Society for microbiology 1980:359-71.
12 Dean AG, Melish ME, Hicks R, Palumbo NE. An epidemic of Kawasaki syndrome in Hawaii. *J Pediatr* 1982;**4**:552-7.
13 Yanagawa H, Shigematsu I. Epidemiological features of Kawasaki disease in Japan. *Acta Paediatrica Japonica* 1983;**2**:18-31.
14 Tominaga M, Ohshima K, Yanagawa H. Epidemiological study of family occurrence of MCLNS. *Pediatrics of Japan* 1977;**18**:59-63.
15 Kato H, Fujimoto T, Osamu I, *et al*. Variant strain of propionibacterium acnes: a clue to the aetiology of Kawasaki disease. *Lancet* 1983;ii:1383-7.
16 Hamashima Y, Kishl K, Tasaka K. Rickettsia-like bodies in infantile mucocutaneous lymph node syndrome. *Lancet* 1973;ii:42.
17 Hamashima Y, Tasaka K, Hisayoshi F, Hoshino T, Shunji M, Kao T. Kawasaki's disease—its pathological features and possible pathogenesis. *Acta Paediatrica Japonica* 1983;**25**:32-41.
18 Kusakawa S, Heiner DC. Elevated levels of immunoglobulin E in acute febrile mucocutaneous lymph node syndrome. *Pediatr Res* 1976;**10**:108-11.
19 Fossard C, Thompson RA. Mucocutaneous lymph-node syndrome (Kawasaki disease): probable soluble complex disorder. *Br Med J* 1977;i:883.
20 Fujimoto T, Kato H, Ichinose E, Sasaguri Y. Immune complex and mite antigen in Kawasaki disease. *Lancet* 1982;ii:980-1.
21 Damiano A, Zulaica D, Cuadrado E, Ochao M. Immunologic findings in Kawasaki disease. *Ann Intern Med* 1981;**94**:138-9.
22 Shirahata A, Nakamura T, Asakura A. Studies on blood coagulation and antithrombotic therapy in Kawasaki disease. *Acta Paediatrica Japonica* 1983;**25**:104-15.
23 Yamada K, Shirahata A, Shinakai A, Meguro T. Haematological studies on acute febrile mucocutaneous lymph node syndrome with special reference to the platelet—the thrombus formation and aetiology of MCLNS. *Acta Paediatrica Japonica* 1977;**81**:1263-71.
24 Inamo Y. Studies on plasma thromboxane B2 levels in patients with Kawasaki disease: as an indicator of coronary aneurysm formation. *Acta Paediatrica Japonica* 1983;**25**:154-9.
25 Cochrane CG. Mechanisms involved in the deposition of immune complexes in tissues. *J Exp Med* 1971;**134**:755-8.
26 Kniker WT, Cochrane CG. The localization of circulating immune complexes in experimental serum sickness. *J Exp Med* 1968;**127**:119-35.
27 Cochrane CG. Studies on the localization of antigen-antibody complexes and other macromolecules in vessels. II. Pathogenetic and pharmacodynamic studies. *J Exp Med* 1963;**118**:503-13.
28 Gocke DJ, Osler AG. In vitro damage of rabbit platelets by an unrelated antigen-antibody reaction. I. General characteristics of the reaction. *J Immunol* 1965;**94**:236-46.
29 Haakenstad AO, Mannik M. Saturation of the reticuloendothelial system with soluble immune complexes. *J Immunol* 1974;**112**:1939-48.
30 Frank MM, Hamburger MI, Lawley TJ, Kimberly RP, Plotz PH. Defective reticulo-endothelial system Fc-receptor function in systemic lupus erythematosis. *N Engl J Med* 1979;**300**:518-23.
31 Lockwood CM, Worlledge S, Nicholas A, Cotton C, Peters DK. Reversal of impaired splenic function in patients with nephritis or vasculitis by plasma exchange. *N Engl J Med* 1979;**300**:524-30.
32 Benacerraf B, Sebestyen M, Cooper NS. The clearance of antigen antibody complexes from the blood by the reticuloendothelial system. *J Immunol* 1959;**82**:131.
33 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* 1977;**59**:651-62.

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