

Increasing numbers of sudden death in children and young adults— Kawasaki's disease, Behcet disease, Goodpasture's disease, Stevens-Johnson syndrome, Takayasu arteritis, infantile arteritis nodosa, or a good old immunopathological vasculitis?

Viera Scheibner, PhD

178 Govetts Leap Rd.

Blackheath NSW 2785 Australia

Phone: +61 247 878 203 Fax+61 247 878 988

Email: Viera.Scheibner@gmail.com

Abstract

Increasing numbers of sudden cardiac deaths, in which aneurysms of the large arteries play an important role, are being reported all over the world, but especially in industrially developed countries. Even though orthodox medicine is at a loss to understand and explain (another of the 'mysteries') these increases, the problem has previously been described as an acute febrile vasculitis of infancy and childhood. In 1967, Tomisaki Kawasaki described these conditions as a possible new disease affecting infants and young children since the 1960s. Since then, the problem has been reported all over the world and given a number of names depending on which organs, besides the heart, are affected. However, the common underlying condition is immunopathological vasculitis. This article presents and reviews the relevant published studies, which collectively reveal that vaccines and other pharmacological agents are the primary causal factors. To educate clinicians, the emphasis is on case histories. As the age of the recipients of a variety of vaccines increases, so does the age at which Kawasaki disease results in sudden deaths. It is a time bomb that can only be stopped by abandoning mass vaccination and reconsidering the full extent of medication-related iatrogenic harm.

© Copyright 2009, Medical Veritas International Inc. All rights reserved

Keywords: Kawasaki's disease, Kawasaki syndrome, Behcet disease, Goodpasture's disease, Stevens-Johnson syndrome, Takayasu arteritis, infantile arteritis nodosa, vasculitis, sudden cardiac death, vaccines, mercury poisoning, coronary artery aneurysms, immunological disorders, periarteritis nodosa

1. Introduction

Recent media reports on an epidemic of sudden deaths in children and young adults of heart failure prompted me to look up my file on Kawasaki's Disease. Kawasaki's disease (KD) is defined as an acute febrile vasculitis of infancy and childhood, first described as such by Tomisaku Kawasaki in Japanese in 1967 and in the English language in 1974. Soon, the disease became recognized as a leading cause of acquired heart disease in childhood all over the industrially developed world.

Kawasaki *et al.* (1974) wrote that KD may be a new disease which has been afflicting infants and young children in Japan since 1960. They defined it as an acute, febrile, mucocutaneous condition accompanied by swelling of cervical lymph nodes (tentatively called mucocutaneous lymph node syndrome MLNS). It may be misdiagnosed as scarlet fever, the Stevens-Johnson syndrome, or infantile periarteritis nodosa. They also wrote that KD is now well known to be widely occurring all over Japan with an increasing incidence each year. More than 6,000 cases have been reported as of 1973. [The occurrence subsequently reached tens of thousands]. One to two percent of the patients reportedly have died suddenly of cardiac failure. All the autopsies showed the pathology of infantile periarteritis nodosa-like arteritis accompanied by coronary thrombosis and aneurysms.

Not surprisingly, the KD was very quickly reported to occur also in many other countries and particularly so in the industrially developed countries.

Since medicine is a system of observation-based knowledge that is (and should be) based on case histories, this article re-

views the papers dealing with the individual cases of what has been described under a number of name definitions such as Kawasaki's disease (or Kawasaki disease or syndrome), Behcet disease, Goodpasture's disease, Stevens-Johnson disease, infantile arteritis nodosa, erythema multiforme and/or a variety of systemic vasculitides. All the above diseases and all systemic vasculitides are a group of immunological disorders that affect the cardiovascular and other systems of the body.

2. Overview of the published information on Kawasaki's Diseases and related conditions

An article by Anonymous in *Morbidity, Mortality Weekly Reports (MMWR)* described Kawasaki's Disease in the United States. Since 1975, 232 suspected cases of KD (also referred to as mucocutaneous lymph node syndrome (MCLS, MLNS or MCLNS) have been reported to the Center for Disease Control (CDC). KD was documented in 112 of 117 patients after ruling out other possible diagnoses. It was described as an acute febrile illness of prepubertal children associated with characteristic picture of erythema of the conjunctiva and mucous membranes of the upper respiratory tract, erythema and indurative edema of the peripheral extremities, often with maculopapular rash, [skin] desquamation, and usually lymphadenopathy, often confined to the anterior cervical chain, thrombocytosis (from 500,000 to 2,000,000/ cubic mm) and elevated white blood cell count, with erythrocyte sedimentation rates usually normal. Meningitis, arthralgia, arthritis, proteinuria, sterile pyuria, diarrhea, and elevated liver enzymes are also seen. Throat culture, antistreptolysin-O titres, streptozyme test, and culture and sero-

logical examination for rubeola, rubella, rickettsiae, and other infectious agents are usually negative. Deaths are almost always related to cardiac involvement, notably infarction secondary to diseased coronary arteries, or myocardial failure or arrhythmia due to myocarditis. Recently, infantile periarteritis nodosa (IPN) was shown to be a severe and often fatal form of Kawasaki disease occurring in the first few months of life. Cases of IPN have been described in the United States by pathologists for decades, suggesting that pathological entities described as Kawasaki Disease may have long existed but gone unrecognized. IPN may not have been observed in Japan prior to 1960, when cases of Kawasaki disease were first noticed. Conversely, it is very likely, that the first observations in the US of pathological entities, later described as KD, also date back to the 1960s rather than ‘decades ago’. A habit of introducing new names for existing diseases may cloud the issues of disease definition and diagnosis.

Since 1975, the CDC has received a steadily increasing flow of reports of small children with KD. Just as in Japan, where it is epidemic, the Kawasaki disease in the US has not appeared to be limited by geographic, seasonal, socioeconomic, or environmental barriers. In addition to Japan and the US, cases have also been diagnosed in Korea, Taiwan, the Philippines, Australia, Canada, Mexico, England, Scotland, Belgium, the Netherlands, Spain, Italy, Greece, West Germany, Sweden, and Turkey. It was also reported with disproportionate frequency in Hawaii. Japanese investigators have compiled detailed information on more than 10,000 cases. They have also reported small geographical clusters, recurrences, and second cases within families.

The article also asserted that the etiology of KD has not been determined.

Carter *et al.* (1976) described a case of a 5-months old white baby boy born and living in Adelaide, which they defined as a town in Australia enjoying a high standard of living and temperate climate. The boy died after a 2-week illness which showed all the cardinal diagnostic signs of MCLS as defined by the Japanese Ministry of Health and Welfare. The additional finding was in the spleen, which showed striking changes not previously described. The spleen was five times the normal weight, soft, friable, and coated in many areas with a thin fibrous exudate. Histologically, the follicles had no obvious germinal centers but tended to merge with the surrounding pulp, which showed diffuse proliferation of unidentifiable monocytes (similar to those in the vascular lesions seen elsewhere in the body) plus obvious plasmacytoid and plasma cells. Occasional binucleated or multinucleated cells were present. The capsule was widened, frayed, and moderately infiltrated by similar cells extending into a thin, fibrous pericapsular exudate, which also contained proliferated mesothelial cells. Even though the authors presupposed an infectious origin of this syndrome, they also wrote that bacteriological cultures of post-mortem blood and spleen were negative and no virus was isolated from bowel and cerebrospinal (CNS) fluid.

Burke and Rennebohm (1981) described an eye involvement in KD. Besides quoting others who established the symptoms of KD, they added Germain and his associates’ (1980) observations of mild anterior uveitis during the acute stage of the disease. They conducted their own prospective study of the inci-

dence and nature of uveitis in KD and a retrospective study of children who had had KD, to determine whether any had evidence of past or present anterior uveitis months after the acute illness seemed to have resolved.

The results showed that eighty percent of the prospectively studied children with KD displayed mild anterior uveitis as the only abnormal eye finding other than transient bulbar conjunctival injection, which was present in 100 % of their cases. Three of the eight uveitis patients had tiny keratic precipitates. Two of the three patients had more than 10 keratic precipitates in each eye and only these two patients were treated with topical corticosteroid and cycloplegic drugs. All 145 of the prospectively studied patients had normal eye examinations without evidence of synechiae, glaucoma, or recurrent anterior uveitis. The time interval between KD and the follow-up examination ranged from 6 to 24 months (average 15.3 months).

All uveitis cases appeared completely resolved within two to eight weeks from the onset of the illness. The incidence of uveitis in 15 children studied retrospectively was considered unknown because none of them underwent biomicroscopy during their acute illness.

Burke and Rennebohm (1981) also wrote that despite the pathogenesis of KD being unknown, a systemic vasculitis appears to play an important role. Microvessel and small artery inflammation is thought to cause the acute phase signs and symptoms. It starts with bulbar conjunctival injection and vasculitis, then progresses to involve medium and large vessels, typically causing arteritis and aneurysm formation of the coronary arteries. Two of their 10 prospectively studied children had echocardiographic and angiographic evidence of coronary artery aneurysms.

Polomeno *et al.* (1981) added eight patients with KD associated anterior uveitis at the two pediatric hospitals in Montreal to the list of the patients who developed this eye disorder. Their age range was between 4 months and 7 years. They fulfilled the diagnostic criteria for KD and all had conjunctival injection. The uveitis was bilateral in 7 KD patients, and unilateral in the remaining patient. One patient had keratic precipitates. The uveitis responded to topical steroids and mydriatics in six patients. The uveitis lasted 4 days to a few weeks. There was no recurrence 2 months and 2 years later. They concluded that the finding of uveitis indicates that KD is a self-limiting, immunologically mediated, vascular disease triggered by an unidentified agent. They did not disclose the vaccination status of their patients. However, their ages were within the usual most intensely vaccinated age group.

Lee *et al.* (1989) wrote that severe renal complications of KD are rare, although pyuria and proteinuria are well-documented manifestations. They reported on a 3 months old boy with KD and nephrotic syndrome (NS) during the acute phase of the illness. This previously healthy three months old boy was admitted to the National University Hospital in Singapore, with a high spiking fever of 5 days duration, with associated irritability, poor feeding and diarrhoea. Soon, he developed symptoms of typical KD, which included generalized erythematous maculopapular rash, erythema of the oral mucosal membranes, dry fissured lips, bilateral non-purulent conjunctivitis, and subsequent desquamation of the finger tips. On the sixth day of illness, he developed generalized edema and neph-

rotic syndrome was confirmed by the presence of massive proteinuria and hypoalbuminemia, without hypertension, azotemia or hematuria. Four days after cessation of steroid administration, a recurrence of fever and a rash, consisting of pustular and necrotic lesions, developed. A skin biopsy showed a superficial perivascular infiltration of inflammatory cells, hyperplasia of the epidermis with intraepidermal and spongiform pustules, and edema of the papillary dermis. Steroids administration recommenced and his symptoms improved. However, on 34th day of illness, the patient collapsed suddenly. Cardiac arrest occurred and, after resuscitation, an ECG showed evidence of massive anterolateral infarct, with raised ST segments in leads I, II, V2-V6, and T wave inversion in leads III and AVR. Two hours later, a further cardiac arrest occurred and the patient could not be resuscitated. The authors quoted a number of other published cases of renal involvement in KD.

Vaccination status of the baby was not revealed, but his age is strongly indicative of him having received his first dose of the routine vaccines before developing the symptoms of KD.

Cheek (1975) commented on Kawasaki's mucocutaneous lymph node syndrome as possibly caused by a heavy metal poisoning. His reasons were that he noticed similarities between the symptoms suffered by Kawasaki disease patients and the so-called pink disease linked with known metabolic effects produced by mercury in infants with presumed inborn errors relating to catecholamine metabolism. He then listed a number of symptoms he considered common in both conditions, such as 1) sudden death; 2) nonpitting edema of the extremities; 3) erythema with desquamation of the extremities; 4) macular erythematous rash spreading across the body; 5) the enlargement of lymph glands; 6) albuminemia; 7) alteration of the conjunctiva; 8) majority of patients under 2 years; and 9) thromboses with occasional gangrene and necrosis of various parts of the body. He wondered whether samples of blood and urine have been analyzed from the patients described by others to exclude toxic levels of heavy metals.

Dr. Kawasaki's answer to Cheeks (1975) suggestion was interesting: he assured Dr. Cheek that while considering the acrodynia [mercury poisoning], which has been very rare in Japan, due to non-usage of mercury-containing products such as teething powder, other mercury-containing products such as killed vaccines and chemical preservatives and foods containing mercury are being checked.

[Since some vaccines still contain mercury compounds (i.e., Thimerosal), it is not surprising that their recipients develop signs of mercury poisoning].

Furusho *et al.* (1984) reported on their research into the ability of a high-dose intravenous gammaglobulin (IVGG) for KD to prevent the coronary artery lesions, in a multicentre controlled trial of IVGG plus aspirin versus aspirin alone (aspirin being the conventional treatment for KD), 45 and 40 patients in each group, respectively. The development of coronary artery dilatation was monitored by echocardiography. Within 29 days of the onset of the disease, this lesion had developed in 19 cases (42 %) in the aspirin group and in 6 cases (15 %) in the IVGG group. Thirty to sixty days later the coronary artery dilatation persisted in 14 and three cases, respectively. The authors concluded that IVGG seems to reduce the frequency of coronary artery abnormalities in patients with KD. Then, they repeated

the often-repeated statement that the cause of KD disease is unknown, but it is generally agreed that immunological mechanisms play a part. An immunological mechanism has also been proposed for idiopathic thrombocytopenic purpura (ITP), the cause of which is also considered unknown.

However, unless and until the researchers start looking in the right direction of the administered vaccines, the cause of KD and most cases of ITP will remain unknown. Withholding information on the vaccination status amounts to withholding vital information; it is unscientific to say the least.

This is the case because vaccines are known to cause immunological injuries, and more particularly vasculitis, which is the underlying problem, anyway. This was known and confirmed already in 1966 when Bishop *et al.* reported on a case of diffuse vasculitis and death in a 45-year old white male inmate of a local penal farm in Arkansas, after hypervaccination with pertussis vaccine. This case is not only instructive in fully understanding the effect of pertussis vaccine but also in the ignorance and lack of care for the wellbeing of a patient by those who conducted the procedure. While writing that severe complications have been observed in animals, such as amyloidosis in horses after intensive vaccination with diphtheria toxin, and vasculitis, glomerulonephritis and granuloma of the spleen in rabbits after repeated injections of horse serum, and joint as well as cardiac vascular lesions after injections of polysaccharide from *Klebsiella pneumoniae*, they also wrote that reports of complications in man are scarce. [While I agree that the reports of severe vaccine complications in man may be scarce, it does not mean that the occurrence of severe reactions is scarce]. One week after the last (8th) injection of pertussis vaccine, the inmate developed night sweats, anorexia, fever and weakness, lymphadenopathy and joint swelling and pain. Bishop *et al.* (1966) wrote, "Treatment with penicillin and tetracycline gave no improvement" [given the known cause of the observed pathology, i.e., vaccination, there was no reason to expect any improvement after antibiotics administration]. After three-week course of prednisone, his condition gradually worsened, and, late in May, cough, occasional haemoptysis and cramping epigastric pain, associated with nausea and vomiting, developed. About two months later, the inmate died. The autopsy showed that most organs were affected. This article should be a compulsory reading for every person who vaccinates, because the pathological findings amply describe the usual pre- and post-mortem findings in vaccine recipients. This case is also an instructive demonstration of the validity of the 'biological gradient' as one of the nine points of Bradford-Hill (1965).

Ono *et al.* (1985) carried out a study to clarify the changes in granulocyte function and circulating immune complexes in 32 children (all boys, aged 1 to 6 years) with Kawasaki disease. They were divided into two groups, those with or without coronary aneurysms (CAs). In the group with CAs, impairment of both granulocyte chemotaxis and phagocytosis was found, together with higher circulating immune complexes and normal intracellular killing activity. In the group without CAs, impaired phagocytosis was observed, but with normal granulocyte chemotaxis, circulating immune complexes, and intracellular killing activity. No correlation was observed between granulocyte chemotaxis and circulating immune complexes. The authors concluded that the impairment of granulocyte chemotaxis and

CICs might yield pertinent information as to the degree of severity of vasculitis in Kawasaki Disease.

Nagata *et al.* (1993) investigated the etiology of KD and looked into the cell surface phenotypes of mononuclear cells and enterocytes in the jejunal mucosa. In a case control study, 16 Japanese KD patients and 10 controls with diarrhea due to cow's milk protein intolerance were used. Both HLA-DR+CD3+ and DR+CD4 cells were significantly increased in the lamina propria of KD patients in the acute phase, compared with controls and the patients with cow's milk protein intolerance. CD8 cells were significantly reduced in both the epithelium and the lamina propria of KD patients in the acute phase compared with both controls and the patients with cow's milk intolerance diarrhea.

Yamashiro *et al.* (1996) studied the microbiota of the small intestine in 15 Japanese KD patients. The range of bacterial species adhering to the lumen of the jejunum of KD patients was quite different from that of controls – a wider variety of bacteria were isolated from jejunal biopsies in the acute phase of KD as compared with those from control children. Gram-positive cocci were isolated from KD patients predominantly. Notably, five kinds of streptococci and two kinds of staphylococci were isolated only from KD patients.

They concluded that it is possible that the gastrointestinal tract (GI) could be one of the primary sites of entry of bacterial toxins in KD patients. The GI tract is more exposed to causative foreign antigens than the throat, because of its broader exposure to a variety of foreign antigens. It is well known that T cells activation by exotoxins having superantigenic properties require expression by MHC class II molecules on antigen-presenting cells. The small intestine is a superantigen-presenting organ because it has a vast surface area exposed to various antigens, and large numbers of MHC class II molecules are present on the surface of antigen-presenting cells such as epithelial cells.

[Vaccines of all kind represent foreign superantigens and, together with antibiotics, they are quite capable of altering the gut microbiota, killing the beneficial species and allowing the toxigenic types to multiply and replace the beneficial ones].

Shulman and Rowley (1986) investigated whether KD has a retroviral etiology. They quoted Leung *et al.* (1983) who reported profound immunoregulatory abnormalities present in the acute stage of KD. The excessive activated T4+/Ia+ helper cell activity, reduced T8+ cells, and raised spontaneous secretion of IgG and IgM suggested to the authors that a lymphotropic agent such as a retrovirus might be implicated in the etiology of KD. The authors maintained that their preliminary results supported this hypothesis.

Levin *et al.* (1985) studied platelet immune complex interaction in pathogenesis of Kawasaki disease and childhood periarteritis in 19 children with Kawasaki disease and five with polyarteritis. All KD patients developed thrombocytosis in the second and third weeks of illness, reaching maximum in three to four weeks, before thrombocyte numbers falling rapidly in the fifth week. The peak platelet count was significantly correlated (P less than 0.005) with the subsequent development of coronary aneurysms. The rise of 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 suggesting an immune complex. Immune complexes detected by precipitation with polyethylene glycol, a coolant used in a number of vaccines, also appeared in the circulation as the platelet count increased. These complexes induced platelet aggregation, and there was a significant correlation between the concentration of IgG and IgA in the polyethylene glycol precipitated material and the platelet aggregation 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. The authors concluded that their findings imply that different mechanisms have a role in distinct phases of KD. The initial feverish phase (likely infective) is probably followed by an immune complex vasculitis that occurs when antibodies to the initiating agent appear in the circulation. The IC's aggregate platelets and induce release of serotonin. Platelet derived vasoactive mediators may increase vascular permeability and facilitate further deposition of complexes in the tissues. Of the patients with polyarteritis, four developed thrombocytosis and one thrombocytopenia.

It is interesting that the authors still maintained that the cause of KD is unknown despite ample published evidence of vaccines (and serum sickness) causing formation of circulating immune complexes.

Burns *et al.* (1986) concluded that lymphotropic viruses, such as Epstein-Barr virus and cytomegalovirus with affinity for endothelial and lymphoid cells might explain the vasculitis and immunological abnormalities in KD. They can alter the balance between helper and suppressor T cells, infect epithelial cells and cause B-cell activation.

Melish *et al.* (1989) published an important paper on absence of significant RNA-dependent DNA polymerase activity in lymphocytes from patients with Kawasaki syndrome. In one case, syncytium formation was observed in a co-culture from HB-ALL. Electron microscopic examination of this culture showed viral particles, subsequently identified as measles virus by specific immunofluorescence and radioimmuno-precipitation assays. The patient had been vaccinated with measles-mumps-rubella trivalent vaccine 8 days before onset of the disease. The authors concluded that the agent was measles vaccine virus. Using standard methods for reverse transcriptase detection, they were unable to demonstrate a retroviral etiology for KS. They concluded that if a retrovirus is involved in the causation or the pathogenesis of this disease, techniques more sensitive than the assays presently available would be required to establish its presence.

Then, the authors, surprisingly, wrote the following comment: "Our experience with recovery of measles virus and its demonstration within cultured lymphocytes by electron microscopy emphasizes the danger of assuming that agents recovered from patients with KS may have a causative role. Therefore, we believe that the etiology of KS remains unknown." It does not make sense to me: what was the danger? Moreover, if care should be exercised in assuming that the present measles vaccine virus was the causative agent in KS, then it is equally valid to advise caution when assuming that it was not the causative agent. What was that vaccine measles virus doing in the culture? Why were they testing for this virus if it was irrelevant? Importantly, the patient in question was vaccinated with MMR

vaccine 8 days before onset of KD. This is very close to the critical day 7 (Scheibner 2004). The way these statements are written makes me suspicious that the authors were under pressure not to incriminate the administered vaccine.

Bannister *et al.* (1989) looked at 13 serum samples from nine children with KD and 23 controls. The results of screening for antibodies to hog cholera virus, border disease of sheep, bovine diarrhea virus, and equine arteritis virus were negative. However, sera from two children with KS were cytotoxic; a possible link with cytotoxin from *Propionibacterium acnes* was considered.

Levin *et al.* (1991) summarized recent advances in KD [21]. Detailed epidemiological studies on KD disease have been undertaken in many countries such as Japan with over 80 thousand cases reported, and in many other developed countries. Children aged 6 months to 5 years were predominantly affected, with a peak incidence being between 9 to 11 months. It was established that KD occurs in siblings of affected patients more frequently than in general population. However, they also wrote that the lack of the secondary cases, coupled with unresponsiveness to antibiotics, precludes the infectious origin. They thought that there might be some hope in linking KD with *P. acnes* (as discussed above).

The authors also rejected the ideas of the association of KD with a retrovirus despite the observed abnormalities of cellular immunity and concluded that the detected reverse transcriptase activity may be due to cellular polymerases.

Takahashi (1998) discussed the history of KD with its many twists and turns. At the time of Kawasaki's original description of the disease in 1967, it was perceived as self-limiting benign febrile exanthema. Soon after this paper appeared came the startling revelation that some children, after recovering from the acute disease, died suddenly of thrombotic occlusion of coronary artery aneurysms. Post mortem examination usually showed thickened coronary artery walls caused by fibrinointimal proliferation with almost total obliteration of the left coronary artery. Infiltration of lymphocytes and plasma cells in the arterial walls suggests ongoing inflammation. "Is this just the tip of the iceberg?" asked the author. The obvious correct simple answer is "Yes". With the passage of time, many of those individuals who developed KD in early childhood will be dying suddenly of the delayed consequences of vaccine damage to the cardio-vascular system.

Data showing endothelial dysfunction were also beginning to accumulate. Takahashi (1998) quoted a number of papers in which the authors (such as Mitani *et al.* 1995) demonstrated impairment of endothelium dependent vasodilation despite angiographically normal appearance in 8 patients who had recovered from KD. Takahashi (1998) also referred to Dhillon *et al.* (1996) who have demonstrated by high-resolution ultrasound imaging and Doppler study of peripheral arteries of patients who recovered from KD that there is impairment of flow-mediated vasodilation of upper extremity arteries compared with that in normal children, suggesting that endothelial dysfunction is present even in the arteries remote from the coronary arteries.

Despite marked divergence in the manner of the initial endothelial injury and in the age of the patients, there appears to be a common final pathway resulting in marked fibrinoid hyperplasia.

In these vasculopathies, the abilities of normal endothelium to inhibit thrombus formation, leukocyte adhesion, and smooth muscle cell migration and proliferation are lost. As in the other entities, it is likely that in the patients with late phase KD, a yet undefined signaling cascade induces production of a variety of growth-stimulating polypeptides by platelets, macrophages, and smooth muscle cells and expression of adhesion molecules by endothelial cells, resulting in cellular proliferation, migration and production of extracellular matrix. Some of these peptides may also cause vasoconstriction under some circumstances. Saji *et al.* (1993) demonstrated platelet-derived growth factor B-chain protein in the endothelial cells and macrophages within immunostained skin biopsy specimens from patients with KD. Takahashi (1998) also quoted Ayusawa *et al.* (1995) who demonstrated a high level of soluble endothelin-1 not only in the acute phase of Kawasaki disease but also in the early convalescent phase in some patients. In addition to these mitogenic factors, IL-4, known to be a major contributor to late-phase inflammatory reactions, may play a role. The conclusion was that although IVGG has been effective in extinguishing the fire during the acute phase, it has failed to snuff out the smoldering vasculitis in the later stages of the disease.

Takahashi (1998) asked an important question: What would be the possible mechanism of sudden death in these cases? His answer was that widespread intimal changes in the intramyocardial coronary branches might create patchy areas of ischemia. Electron microscopy of myocardial biopsy specimens obtained a long time after acute KD show a spectrum of ultrastructural changes suggestive of chronic cellular ischemia despite lack of stenosis in the epicardial coronary arteries.

Animal experiments showed heightened response to beta-2 receptor stimulation, resulting in greater accumulation of cyclic adenosine monophosphate and calcium ion transient. In the context of myocardial ischemia, such adrenergic stimuli could precipitate ventricular arrhythmia.

[In the context of the growing numbers of sudden deaths in young people, the extent of deleterious reactions to vaccines is reaching catastrophic proportions; moreover, early deaths are lowering the overall healthy life expectancy].

The presence of vasculitis attracted the attention by several researchers, however, even that failed to turn their attention to vaccines. The only additional phenomenon noticed by the authors was that the age distribution of KD changed, with increasing delayed sudden cardiac deaths confirming that histological abnormalities are still present in the coronary arteries several years after the acute KD illness in early childhood.

In summary, all this information points in the direction of vaccines:

1. The age distribution (3 months to 13 years, which coincides with the general period of intensified vaccination);
2. The lack of seasonality, geography limitation, and socio-economic, and environmental barriers [vaccines are administered all year round and to all babies]; and
3. Perhaps the most interesting ever present finding is thrombocytosis (an elevated level of thrombocytes, 500,000 to 2,000,000/cubic mm) which is also a ubiquitous finding in the so-called shaken baby syndrome (SBS), these are vaccine deaths for which the innocent caregivers are blamed: for more detail see Scheibner (2004) and importantly, in

most cases of SBS, the final cause of death is cardiac arrest.

eSilva *et al.* (2001) set out to determine cardiovascular risk profiles of patients with Kawasaki disease and to relate them to a noninvasive measure of endothelial function. The assessment was performed in 24 patients and 11 normal controls. Their findings pointed to the tendency of the Kawasaki patients to have a more adverse cardiovascular risk profile potentially indicative of an increased predisposition to premature atherosclerotic changes.

Amsel *et al.* (1986) established that DPT vaccine causes myocarditis. They described a case of a 3 months old infant who developed myocarditis several hours after the second diphtheria-tetanus-pertussis vaccine injection. The child appeared normal and playful until 12 hours after administration of the second DPT vaccine dose, when it became irritable and experienced mild respiratory difficulties. An X-ray examination showed a generalized cardiac enlargement. The infant remained severely distressed for 48 hours, after which time a moderate gradual improvement was noticed. The serum creatine phosphokinase activity rose abruptly to 348 IU/L on the second day after hospital admission, indicating myocardial damage. The temperature was 38.5 °C, pulse rate 200 beats/min, and respiration rate 150/min. His color was ashen, and mild edema of the extremities was evident. A diagnosis of heart failure probably secondary to myocarditis was made. The infant was placed on oxygen, digitalized intravenously, and diuretics were given. The heart rate dropped smoothly back to expected levels for his age. Subsequently, he made what was described as an uneventful recovery. Serial chest x-ray examination showed progressive resolution of the cardiac enlargement. [In this regard, IDCM, idiopathic dilated cardiomyopathy has also become an increasingly common diagnosis based on post-mortems on young persons who die unexpectedly of a “heart attack” and, in some instances, highly elevated levels of mercury have been found in the heart muscle.] The ECG showed persistent widespread non-specific ST and T wave changes, but returned back to normal four months later. At seven months of age the baby was given oral polio vaccine, allegedly without adverse reaction. DPT boosters were not administered.

Amsel *et al.* (1986) believed that the above reaction was causally associated with DPT vaccine, the pertussis or diphtheria components being the possible provocation of the cardiac damage.

The observation of Amsel *et al.* (1986) makes sense since subsequent papers on KD started describing the syndrome as hypertrophic cardiomyopathy. Mortensen *et al.* (1986), who described endomyocardial biopsy in children with cardiac hypertrophy, wrote that heart muscle disease is not an uncommon disease in children. In a cooperative international study concerning the occurrence of sudden death in 186 previously non-operated children nearly one third of the cases had morphological signs suggesting various cardiomyopathies or specific heart muscle disease. In the majority of these children a heart disease had been known or suspected. It would be interesting to do a follow up of Amsel *et al.*'s patient as an adult. Reactions such as this are often considered as fully healed after the major symptoms clear. However, future events have demonstrated otherwise. This is well documented in an article by Takahashi

(1998) who wrote, “At the time of Kawasaki’s original description of the disease in 1967, it was perceived to be a self-limiting benign febrile exanthem. Soon thereafter came the startling revelation that some children, after recovering from the disease, died suddenly of thrombotic occlusion of coronary artery aneurysms”.

Rowley *et al.* (1987) reported on four patients with Kawasaki disease in whom characteristic coronary artery abnormalities developed after illnesses that did not meet the usual diagnostic criteria. An additional patient lacked history of acute manifestations of KD, but severe KD-like arterial changes were noted at autopsy. Fever was present in four of the five patients, in three lasting 7 to 14 days; three of four patients had desquamation of the fingers and toes 10 to 14 days after onset of illness, and the fifth had similar desquamation several months prior to death. In addition, 22 other children were seen with KD with coronary artery abnormalities during the same 2-year period as the previously described patients. For the five cases, these clinicians reported:

“Patient 1. This was a 7-months old white infant boy who had a 5-day history of fever (up to 39.5°C) and irritability. He had initially been considered to have hepatitis because of SGPT activity 235 IU/L and serum bilirubin concentration 1.1 mg/dL, but these returned to normal despite persistent fever. Bacterial cultures of blood, urine, and cerebrospinal fluid (CSF) were negative. Left posterior adenopathy and red, fissured lips were noted. It is also of note that the platelet count was 761,000, indicating thrombocytosis.

Patient 2 was a 4-months old white infant girl with a 7-day history of fever (40°C) and 1-day history of bulging fontanelle and diffuse erythematous rash. There was a borderline ventricular dilatation and platelet count up to 820,000 after 1 week. An echocardiogram showed a small pericardial effusion and aneurysms of the left anterior coronary arteries. After aspirin administration, fever subsided and the bulging fontanelle normalized. One year later she had persistent saccular aneurysms at the origin of the coronary artery and diffuse dilation of the left main coronary artery.

Patient 3 was a 6-months old Iranian girl, 2 weeks after an illness characterized by fever for 7 days, erythematous lips without fissuring, and swelling of the hands and feet. There was no conjunctival injection, lymphadenopathy, or other (than diaper) rash. Desquamation of fingers was noted. Echocardiogram revealed fusiform dilation of the left anterior descending coronary artery. Three months later the right coronary aneurysm had resolved and the dilation of the left anterior descending artery had improved.

Patient 4 was a 12-months old boy 3 weeks after illness manifested by two days of fever and 5 days of conjunctival injection. There was no rash or lymphadenopathy. Desquamation developed on the lateral sides of both feet and one hand two weeks later. Echocardiography showed dilation of the left main and right coronary arteries, and a large aneurysm persisted 1 month later.

Patient 5 was a 2½-year old Hispanic boy who was in an apparent good health until 5 days before admission, when he had a sore throat, occasional vomiting, without fever or other symptoms. On the day of admission, labored breathing was noted.

The temperature was 37.9 °C, 3/6 systolic murmur was heard at the left lower sternal border, the abdomen was distended, liver palpable 6 cm below the right costal margin, there was a generalized seizure and, finally, he had cardiorespiratory arrest. There was marked hemolysis. Chest radiograph showed generalized cardiomegaly with pulmonary edema and bilateral pleural effusions. An ECG showed a slightly prolonged PR interval, diffuse T wave changes, right axial deviation, and probable left ventricular hypertrophy. Echocardiogram showed a dilated left atrium and left ventricle, significant aortic regurgitation, abnormal mitral valve motion without insufficiency and normal coronary arteries. EEG showed diffuse nonspecific slowing. On hospital day 19, the patient died due to a multiple organ system failure and cardiorespiratory arrest.

An autopsy showed major pathological changes of the heart: fibrous scarring throughout the ventricular myocardium, cellular infiltrate of mononuclear cells (lymphocytes), multiple infarcts, marked intimal thickening of the heart muscle and blood vessels (the normal intima of the major coronary arteries was replaced by loosely textured myxoid fibrous tissue, in most cases destroying elastic lamina and reducing the lumen to slit-like or punctate space.”

Perhaps the most important paper which contributed to elucidation of aetiology and pathognomy of KD is that of Burgner *et al.* (1996) who described what they called a “delayed diagnosis of Kawasaki disease presenting with massive lymphadenopathy and airway obstruction” in a “previously well and fully inoculated 4-year-old white boy” who presented with a 10 day history of sore throat and fever unresponsive to antibiotics. The additional value of this paper is in revealing the positive vaccination status of the patient, even though the authors failed to recognize its etiological importance themselves. The rest of the overall symptomatology was very much the same as in other KD cases, but there was a massive lymphadenopathy as the overriding clinical feature. As the disease progressed, rash, palmar erythema, non-purulent conjunctiva, palm and groin erythema and scalded skin on the buttocks, together with pronounced thrombocytosis (537,000) and leukocytosis developed. Intravenous immunoglobulins and low-dose aspirin apparently resulted in immediate improvement of the symptoms.

Burke *et al.* (1997) described two cases (a 4-year old white boy and a 20-months old white boy) exhibiting major pathology of many organs but particularly of the heart and blood vessels. They wrote that cardiac complications of Kawasaki disease occur in approximately 25 % of patients who received no treatment. The initial phase of cardiac involvement is epicarditis with the subsequent formation of epicardial coronary aneurysms. However, diffuse narrowing of epicardial coronary by a healed vasculitis has rarely been reported, and has generally been described as mild. Death in their two patients was due to diffuse fibrinointimal proliferation involving all epicardial arteries resulting in more than 75 % luminal narrowing throughout the coronary system.

The heart of the first child weighed 155 g (the normal weight 53-115 g) for body weight of 27 kg. The left ventricular lateral wall was 6 mm thick with gross evidence of fibrosis or necrosis. The coronary arteries were diffusely thickened and the adventitial surfaces a dull whitish gray.

Histologically, there was diffuse fibrointimal proliferation, with focal destruction of the media and scattered inflammatory infiltrates in the intima, media and adventitia. There was focal acute and organizing thrombus.

The second child had similar pathology and thrombocytosis (666,000).

Despite administration of hyper immune gamma globulin therapy, the child died 1 year after the initial illness, after experiencing an episode of cyanosis and limpness. [This reminds me of the hypotonic hypo-responsive episode, which is considered a recognized reaction to, both the Thimerosal-preserved and phenol (phenoxyethanol)-preserved acellular pertussis vaccines. Let's not forget that DPT and/or DaPT are always administered with polio vaccine which may contain formaldehyde as a preservative; neither of the above preservatives are innocuous and all cause serious reactions] It would be interesting to follow up such babies for cardiac involvement both immediately and later on during their lives].

Smith and Goldwater (1993) wrote that KD is characterized by persisting fever of at least 5 days duration and four of five clinical features: 1) bilateral conjunctival injection; 2) oropharyngeal changes including injection, strawberry tongue and red fissured lips; 3) changes in the extremities such as edema and/or erythema of the hands and/or feet; and peri-inguinal desquamation; 4) The major morbidity associated with KD is the development of coronary artery aneurysms (CAA) or ectasia. This occurs 10-20 days after the onset of illness in approximately 20 % cases and may result in ischemia, infarction and sudden death. Coronary aneurysms may develop in the presence of only two to four diagnostic criteria, particularly in younger age groups. No adequate explanation for the predilection of coronary artery damage in KD has been proposed.

The average age of patients at admission was 3.2 years (median age 2.7 years), with 38% and 85% of cases being less than 2 and 5 years old, respectively, with a peak at 1-3 years. They also wrote that cardiovascular manifestations of KD result in cardiac artery aneurysms (CAAs), myocarditis, transient valvular incompetence, pericardial effusion and conduction defects, with myocarditis clinically apparent in 20-30 % of cases, with chest x-rays revealing cardiac enlargement, echocardiographic evidence of decreased myocardial function, or symptomatic congestive heart failure.

Peripheral arterial aneurysms occur less frequently, and periarthritis in KD had been described recently, indicating inflammation of veins as well as arteries. CAAs have been described on the fifth day of fever, but are usually observed at between 10 and 20 days. Giant CAAs occur in 3-8 % of untreated patients and these are associated with a 5 % mortality rate. Intimal thickening in KD can result in thrombosis and ischemia and may occur without aneurysm formation.

The lack of use of echocardiographic evaluation did not allow the authors to establish the relationship between fever duration and the highest platelet count to aneurysm risk. Cardiac murmurs were recorded in 18 cases (33 %). They were all considered transient. The authors asserted that they only rarely persist for longer periods of time.

The use of IVGG in KD is associated with a marked anti-inflammatory effect, improved myocardial function, and increase in suppressor T cells, a reduction in circulating activated

helper T cells, a decrease in spontaneous IgG and IgM synthesis; and a reduction in serum IL-1beta; persistence of their high levels following IVGG treatment is associated with an increased aneurysm risk. The authors proposed a new hypothesis of pathogenesis of KS that incorporates mechanisms of vessel pathology resulting from the release of endothelin and recognized mediators of endothelial damage, including tumor necrosis factor-alpha and interleukin-1beta.

Brecker *et al.* (1988) described a case of KD in an adult, a 43-year old male ambulance driver. At the age of eight, he suffered a systemic febrile illness with generalized lymphadenopathy, a mucocutaneous eruption, and alopecia. He recovered and remained well until 1974, when, at the age of 30, he was admitted to hospital with an acute anteroseptal myocardial infarction confirmed on serial electrocardiogram and by cardiac enzyme activity. He recovered and remained well until 1986, when he was referred to the Brompton Hospital for investigation of atypical chest pain. An ECG was consistent with an old anteroseptal myocardial infarction. Echocardiogram showed two circular echodense areas of approximately 1 cm in diameter in the region of the proximal left and right coronary arteries. A circular thin rim of calcification just distal to the tip of the coronary ostium was found. There was also a similar fine, eggshell, rim of calcification around the proximal right coronary artery. The authors concluded that there was also a strong circumstantial evidence of a childhood illness suggestive of Kawasaki disease. Their conclusions were supported by the unusual appearance of the aneurysms.

Kato *et al.* (1992) described adult survivors of childhood KD who had coronary artery disease that could be ascribed to KD. In response to questionnaires sent to cardiologists throughout Japan, 21 patients (17 men and 4 women), aged 20-63 years) with coronary lesions and a definite or suspected history of KD were reported. Five patients had presented with acute myocardial infarction, six with previous myocardial infarction, nine with angina pectoris and one with dilated cardiomyopathy. In addition, 16 patients had obstructions in two or more coronary arteries. Three had died and 18 were alive with serious sequelae (mitral regurgitation, arrhythmias, congestive heart failure). Based on these, childhood KD should be included in the differential diagnosis of coronary artery disease in young adults.

Nigro *et al.* (1994) wrote about active or recent parvovirus B19 infection in children with Kawasaki disease. They concluded that a high frequency of all major criteria for diagnosis of KD (60%), anemia (60%), coronary aneurysms (30%), and arthropathy (30%) was found in children with B19-associated KD, then B19 may have a pathogenic role to play in the development of Kawasaki disease, with other predisposing factors. Since parvovirus 19 is a contaminant of many vaccines, such as polio, their findings make sense.

Which vaccines are the most likely culprits in KD? According to both direct and circumstantial evidence, it is any vaccines, but mainly DPT and MMR and especially their diphtheria and rubella components due to their mass administration. However, let's not forget that tetanus toxins derange the central controls of many functions, including heart beat and temperature.

Last, but not the least: medical research has demonstrated time and again that vaccines have a damaging effect on the vascular system.

Sams *et al.* (1976) wrote that patients with leukoclastic vasculitis have purpuric, palpable lesions, most commonly in lower part of the legs. Systemic involvement, and more particularly of the kidneys, is found frequently. Characteristic pathology includes necrosis of small vessels within the dermis, infiltration by polymorphonuclear leukocytes within and around the vessel walls, hemorrhage and occasionally thrombosis, granular deposits of immunoglobulins and complement in vessel walls. A number of etiological agents and situations have been implicated and include infection: viral (influenza), bacterial (*Streptococcus*), foreign protein: serum sickness, hyposensitization antigen, chemicals: insecticides and herbicides, petroleum products, medications: aspirin, phenacetin, phenothiazine, penicillin, sulfonamides, iodides, tetracycline, and a variety of autoimmune diseases (systemic lupus erythematosus, hemolytic anemia, periarteritis nodosa, chronic ulcerative colitis), Hodgkin's disease, carcinoma and hepatitis. They also wrote that, in many instances, the vasculitis has cleared with removal of the suspected agent, but many researchers are reluctant to subject their patients to rechallenge. This is interesting because there is no reluctance to subject babies and adults to further doses of the incriminating vaccines and, after this effective rechallenge, there is still a reluctance to admit the causal connection. Even repetition of the same symptoms in other patients is a valid rechallenge. In the case of vaccines, it means tens of thousands of cases of the repetition of the same pathology. Insect bites, which do not seem to pose the same obstacle to recognizing causality, are also mentioned as the cause of vasculitis. [Why should vaccines be exempted?]

The authors further wrote that pathogenic mechanisms causing tissue lesions of leukoclastic vasculitis have not been clearly elucidated, but there is considerable experimental data that permit to draw a compelling hypothesis. Current evidence suggests that this form of vasculitis is an immune complex disease (type III immunological reaction), thus placing it in the same category as systemic lupus erythematosus. [I disagree that "it is presumed that antibodies are formed to some antigens, the nature of which is usually unknown". Quite to the contrary, the nature of such antigens is usually well-known despite denials of the most obvious. Even though temporal association is one of the nine points of Bradford Hill, nowadays it is usually handled as irrelevant. It is easy to perform tests in which the animals would be injected with the same vaccines as were given to the patients with vasculitis. This has been done, especially with pertussis vaccine, which has generally been used to induce the so-called experimental allergic encephalomyelitis. Until the researchers do this, the discussions such as above, with clear intention to muffle the issue, are inappropriate.]

In summary, vaccine-precipitated immune complexes have been implicated in vascular damage.

Reik (1980) wrote that there is a general agreement that the postinfectious and postvaccinal disorders of the nervous system represent an "allergic" phenomenon. The numerous nervous system abnormalities which follow antecedent infections and inoculations appear to share a common pathogenesis involving the immune system.

Pathologically, a small vessel vasculopathy involving arterioles and capillaries as well as venules in both gray and white matter is the earliest and most consistent change. Perivascular

demyelination appears to develop subsequently. Delayed hypersensitivity to myelin basic protein may not adequately account for these changes. Humoral immunity may be involved instead. Current hypotheses concerning their pathogenesis focus on the cellular immune system and an attack on the myelin sheath with subsequent demyelination. Such hypotheses have developed largely as a result of the clinical and histopathological similarities between these human disorders and experimental allergic neuritis (EAN) and experimental allergic encephalomyelitis (EAE) in laboratory animals, both of which appear to result from delayed hypersensitivity to myelin basic protein. They gain support from the demonstration of both sensitized lymphocytes in patients with Guillain-Barré syndrome or Bell's palsy capable of demyelinating peripheral nerves in cultures and of lymphocyte sensitization to nerve tissue antigen in a variety of postinfectious disorders.

A series of medical educational articles were written in the seventies and eighties. Fauci (1983) summarized the phenomenon of vasculitis in his article "Vasculitis" in the *Journal of Allergy and Clinical Immunology* as part of continuing medical education self-assessment program. He wrote that vasculitis is a clinicopathological process characterized by inflammation and damage to blood vessels; most of the vasculitis syndromes are mediated at least in part by immunopathogenic mechanisms, foremost of which is the immune complex model whereby antigen-antibody complexes either circulate and deposit in the vessel walls or are formed in situ at the area of tissue damage. Then he wrote "It is important to point out that although circulating immune complexes can be demonstrated in most of the vasculitic syndromes, and evidence for deposition of complexes in various tissues exists, the causal role that those mechanisms play in the inflammatory response of involved vessels remains unclear."

Fauci (1983) admitted that hepatitis B antigen-associated systemic vasculitis is generally accepted as the prototype of immune complex-mediated vasculitis in which an exogenous antigen has been implicated. In addition to the classic immune-complex-mediated vasculitis, other types of immunopathogenic mechanisms may be involved in damage to vascular tissue. One of these is cell-mediated immune reactivity which is not a well-documented form of vascular tissue damage. Tissue-injury mediated directly via antibodies with specificity against the vessel itself, or via cytotoxic effector cells in antibody-dependant cellular cytotoxicity can potentially play a role in vascular damage, although this is not very well documented.

Fauci (1983) categorized systemic vasculitis into the following five categories:

1. Systemic necrotizing vasculitis (polyarteritis nodosa group);
2. Hypersensitivity vasculitis;
3. Wegener's granulomatosis;
4. Giant cell arteritides; and
5. Other vasculitic syndromes.

Category 1 included: classic polyarteritis nodosa; allergic angiitis and granulomatosis; and polyangiitis overlap syndrome.

Category 2 included: Henoch-Schonlein purpura; serum sickness and serum sickness-like reactions; other drug-related vasculitides; vasculitis associated with infectious diseases; vasculitis associated with neoplasms (most lymphoid); vasculitis

associated with connective tissue diseases; vasculitis associated with other underlying diseases; congenital deficiencies of the complement system; and erythema elevatum diutinum.

Category 4 included cranial and temporal arteritis and Takayasu's arteritis.

Category 5 included mucocutaneous lymph node syndrome (Kawasaki's disease); Behcet's disease; thromboangiitis obliterans (Buerger's disease) and miscellaneous vasculitides.

Practically all organs are affected in the number of different vasculitides, with emphasis on individual organs. This resulted in the introduction of a variety of names for a variety of organs that are most involved.

Wees *et al.* (1981) described sural nerve biopsy in systemic necrotizing vasculitis. They studied 17 patients with polyarteritis nodosa in 11, rheumatoid arthritis in five and systemic lupus erythematosus in one, and established that

1. Polyneuropathy is the most common manifestation of peripheral neuropathy in polyarteritis nodosa;
2. Peripheral neuropathy is more common in systemic necrotizing vasculitis than physical evaluation alone would suggest; and
3. Abnormal sural nerve conduction is a prerequisite to the demonstration of vasculitis on biopsy of this nerve.

They also wrote that classical polyarteritis is a systemic necrotizing vasculitis of small and medium-sized arteries. Occasionally, in rheumatoid arthritis and systemic lupus erythematosus, similar vasculitis may occur, the pathology of which is indistinguishable from that of polyarteritis nodosa. When peripheral neuropathy is caused by necrotizing vasculitis, it is called vasculitis neuropathy.

The treatments with cyclophosphamide and high-dose corticosteroids were largely unsuccessful – all their patients, whether treated or not, eventually died.

Most authors dealing with the KD agree that not all cases of vasculitis affect the heart or coronary arteries. In many cases, KD affected only kidneys or digestive system. In many cases there are no aneurysms, no conjunctivitis, no polymorphous exanthem, erythema, strawberry red tongue, swelling of extremities, inflammatory changes of the lips and oral cavity or acute nonpurulent cervical adenopathy and lymphatic involvement. Many authors wrote about atypical KD. The only pathology occurring in all cases is vasculitis. Most authors also agree that KD is of basically immunological nature and so is the vascular damage.

Goolsby (1989) described the development of erythema nodosum after Recombivax[®] HB hepatitis b vaccine. He wrote that although Heptavax[®] B (Hepatitis B vaccine, as prepared from human serum) has been reported to be associated with erythema nodosum, the same reaction has not been described with recombinant hepatitis B vaccines. However, he had a case of a 43-year old woman who received her first dose of recombinant HB in November 1988. Four days later, several painful nodules developed in the anterior tibial portion of each leg. There was no evidence of the injury, fever, chills, cough, arthralgia, diarrhea, abdominal pain, sore throat, night sweats, weight loss, fatigue, or cat scratch or bites. The patient reported no use of sulfa drugs, oral contraceptives, penicillins or phenytoin in the recent past [this does not preclude the possibility that

she could have used such drugs in the more distant past]. Her medical history included asthma, pulmonary interstitial fibrosis in 1981, eczema, and pneumonia. Her long-term medications were terbutaline, an albuterol inhaler, and sustained-release theophylline.

A punch biopsy of a lesion on the right leg confirmed the diagnosis of erythema nodosum. A chest x-ray showed nonspecific chronic interstitial reticulonodular markings without hilar adenopathy. Pulmonary-functional testing showed severe obstruction with decreased forced vital capacity and forced expiratory volume in one second. Other tests were considered normal, including bacteriology. The IgE concentration was elevated at 1387 IU/ml.

The lesions disappeared gradually over several weeks. Prednisone was given for interstitial fibrosis. Three weeks after beginning a course of steroids, the patient received her second dose of Recombinant HB. Three days later, the erythema nodosum recurred and gradually resolved without recurrence. The author then wrote that the recombinant HB is produced by inserting plasmid containing the gene for 'adw' subtype of the hepatitis B surface antigen into the yeast *Saccharomyces cerevisiae*. It is adsorbed with aluminum hydroxide and preserved with Thimerosal. The author concluded that it is probably the hepatitis antigen itself and not the components used to prepare the vaccine that caused the symptoms. In this case, the causal link to the vaccine was confirmed by challenge-rechallenge point of Bradford-Hill.

Mader *et al.* (1993) described three cases of systemic vasculitis following influenza vaccination. They wrote that the most common form of systemic vasculitis is leukoclastic/hypersensitivity vasculitis, which results from an immunopathological response to antigen. In this context, infectious agents such as hepatitis, echo virus and cytomegalovirus have been associated with various forms of necrotizing vasculitis, due to an immunological host reactivity to the exogenous antigen, in contrast to direct invasion by the organism. They wrote that then it is not unexpected that a vaccine that consists of attenuated or killed organisms selected specifically to induce an immune response would on occasion induce an aberrant hypersensitivity state. Notably, the so-called attenuated and inactivated viruses and bacteria can revert to their original virulence when introduced into the bodies of the recipients of such products. [Then, of course, we can perhaps talk about an overwhelming infection introduced into the body via vaccine injections into the blood stream. The presence of aberrant hypersensitivity state then makes sense: bypassing the normal portals of entry, the vaccines elicit anaphylaxis, sensitization, and increased susceptibility to the disease and to atypical forms of the disease. For example, atypical measles is a well-defined and well-researched entity. It does not result in development of natural immunity and carries a 12% to 15% mortality rate].

Mader *et al.* (1993) also wrote that with the widespread use of influenza vaccine, an increasing number of adverse events are being documented. Several cases of vasculitis have been documented with the administration of this vaccine. They then proceeded to describe three cases of vasculitis associated with flu vaccine and reviewed the literature concerning the induction of necrotizing vasculitis by this then Thimerosal-preserved vaccine.

In case 1, a 60-year old man developed polymyalgia rheumatica one week after flu vaccination. His symptoms resolved within 10 days. One week after the second flu injection he experienced fever of up to 39 °C. Dry cough, chills, bilateral calf pain, fatigue and rigors. He also experienced a migratory maculopapular rash of his limbs. Discontinuation of the treatment with broad-spectrum antibiotics, and high doses of corticosteroids resulted in recurrence of his symptoms. A deep skin biopsy from the rash revealed perivascular mononuclear infiltrate and fibrinoid necrosis with polymorphonuclear infiltrate and altered elastic lamina of medium-sized vessels. There were red tender nodules on both anterior tibia and the 3rd right finger. Chest radiograph revealed a resolving upper lobe infiltrate. A presumptive diagnosis of vasculitis was made.

The second case, a 66-year old, otherwise healthy woman, developed severe myalgia of both calves, fever up to 39 °C, night sweats, malaise and fatigue two weeks after flu vaccination. A kidney biopsy showed fibrinoid necrosis of medium-size vessels and necrotizing glomerulonephritis. A calf biopsy showed necrosis and an inflammatory infiltrate within a medium-size artery.

Case 3 was a 50-year old male who developed palpable, purpuric lesions over his lower extremities and the ulnar surfaces of the forearm two weeks after receiving the flu vaccine. He also experienced pain in the proximal interphalangeal joints of the left 2nd and 3rd digits unassociated with swelling or erythema. A skin biopsy of one of the purpuric lesions revealed focal areas of necrosis and neutrophilic infiltrate in the epidermis. Fibrinoid necrosis of the vessels was seen in the papillary and upper reticular dermis with a perivascular infiltrate of neutrophils and nuclear dust as well as some lymphocytes and, in the focal area, eosinophils."

In the above series of patients, which also includes thirteen other patients, the main focus of attack of vasculitis were kidneys, lungs, optic nerve, muscles, and skin.

It would be interesting to do a follow up of the patients, whether still alive or dead, for possible later development of cardio-vascular problems (in the deceased this could have been the cause of death).

Castresana-Isla *et al.* (1993) dealt with erythema nodosum and so-called Takayasu's arteritis after vaccination with plasma-derived hepatitis B vaccine. Even though the plasma-derived hepatitis B is not used anymore, the historic value of this article has not been diminished. They described a case of one of health workers in the Security hospital in Costa Rica. A 29-year old woman was vaccinated with three 20-microgram doses of the plasma derived hepatitis b vaccine on August 26, September 1 and December 30 1985. She developed fever after the last two injections and in March 1986 developed painless papules on both lower limbs that disappeared after two weeks without treatment. In June 1986, she developed myalgia, arthralgia and fever of 38.5°C. In August 1986 she presented with painful erythematous nodules over her lower limbs as well as acrocyanosis. Even though the usual laboratory tests appeared normal, she had anti-HBs titer of 290 UI/l by immunoradiometric assay (protective response is equal to or above 10 UI/l). These symptoms disappeared with aspirin, but in December 1986, she was admitted to another hospital with another episode of erythema nodosum and hepatic abnormality was diagnosed

(liver granuloma). Tuberculosis etiology was suspected and ethambutol, rifampin and isoniazide treatment was started. In June 1987, she was readmitted in hospital with persistent low-grade erythema nodosum, arthralgia and upper extremity claudication. Diminished arterial pulses in her right upper extremity and absent arterial pulses in her left upper extremity were established. Her left carotid pulse also was diminished and left carotid and left subclavian bruits were perceived. An arteriographic study showed 50% stenosis of the left subclavian artery. Other arteries were also affected, with moderate narrowing of the left axillary artery. Treatment with prednisone and azathioprine was followed by re-establishment of normal values as above, but tapering off and discontinuance of the treatment resulted in re-appearance of some symptoms. In July 1988, all treatment was suspended and she was asymptomatic in December 1989.

Kelsall *et al.* (1997) described microscopic polyangiitis involving skin and joints after influenza vaccination in a 34-year old man, who received a trivalent influenza vaccination with an intention to minimize the risk of influenza infection; he was healthy and there was no other indication for vaccination. He remained well for two weeks until three days before hospital admission with nausea, vomiting, and watery nonbloody diarrhea. Symptoms abated and he returned back to work. Three days later, discomfort developed in the scrotum, which then became erythematous and swollen for 4 hours. Nine hours later the scrotum was necrotic and surgical debridement revealed necrosis of skin and subcutaneous fat of the shaft of the penis, scrotum, inguinal region and abdominal wall up to 2-3 cm above the symphysis pubis. In the 12 hours after surgery he developed erythematous and purpuric papulae and plaques over his knees (both knees were swollen and warm), buttock, back, antecubital fossae, and dorsal surfaces of his upper arms. He had no other prior influenza vaccination and there was no history of hepatitis, connective tissue disease, HIV risk factor, or allergy. The initial diagnosis of necrotizing fasciitis was precluded by a negative gram stain in tissues and provisional diagnosis of systemic vasculitis was made. He was treated with broad-spectrum antibiotics. Pulse steroids were then initiated with 1g of methylprednisone intravenously daily for three pulses followed by prednisone orally. Within 24 hours the purpura was resolving, but he developed diffuse swelling around the entire circumference of his neck without airway compromise. A CT-scan revealed increased density and edema consistent with panniculitis in subcutaneous fat and in fat in tissue planes separating neck muscle bundles. He also developed episcleritis four days after admission. These manifestations resolved within 3-5 days.

Pathology of debrided tissue and punch biopsies of skin lesions revealed necrotizing vasculitis of small and medium sized vessels extending from the superficial dermis to the deepest parts of the specimens. Variable size zones of necrotic tissue surrounded each involved vessel from the skin specimen derived from the inguinal region, despite all standard biopsies being negative. [Standard biopsies are as a rule performed for a given type and number microorganisms and not aimed at establishing what is actually in the samples].

In the discussion, the authors wrote that side effects from influenza vaccination include mild and transient systemic flu-like symptoms and local pain at the injection site. They also

wrote that more serious side effects are rare, of which the best known is an increased incidence of Guillain-Barré syndrome after 1976-77 swine flu vaccination; then they wrote the ubiquitous disclaimer that there has been no clear association with subsequent vaccine preparations. [Obviously, the association was clear, these reactions having occurred repeatedly after, but not before, vaccination in tens of thousands of people, but the open acceptance of the most obvious causal factor was unclear. However, to his credit, Kelsall *et al.* (1997) also listed references to further 16 cases of vasculitis after flu vaccine described by other authors.]

Tugal-Tutkun *et al.* (1995) conducted immunopathogenic study of the conjunctiva in patients with Behcet disease (BD). They wrote that even though conjunctiva is not primarily involved in patients with uveitis due to BD, it might reflect the immunopathology process when inflammation is induced by biopsy of conjunctiva. Conjunctival specimens obtained 48 hours after a 2mm biopsy of the epibulbar conjunctiva in 26 Turkish patients with inactive ocular BD and 9 Turkish patients with inactive idiopathic uveitis were studied by immunoperoxidase using a panel of mononuclear antibodies: anti-CD1, -CD3, -CD4, -CD5, -CD145, -CD22, -CD25, and -CD67, HLA-DR, E-selectin, intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM)-1.

Immunopathology of the conjunctival specimens obtained at the time of first biopsy was not significantly different between the BD and the idiopathic uveitis group. However, the second biopsy specimens of the patients with BD showed significantly greater numbers of T cells (CD3+ and CD4+) and granulocytes (CD67+) as well as HLA-DR+ and ICAM-1 + cells in the substantia propria. Vascular endothelium of the conjunctiva in BD patients had significantly more pronounced expression of the adhesion molecules, E-selectin, and ICAM-1. None of the conjunctival specimens in either group showed VCAM-1 positivity.

These results show that a more intense antigen-independent inflammation develops with recruitment of both neutrophils and T lymphocytes of helper/inducer phenotype in the conjunctiva of BD patients in response to surgical trauma. The authors concluded that this might also suggest a critical role for these adhesion molecules in the initial events of inflammation.

In conclusion, Behcet disease is a multisystem vasculitis with ocular, skin, joints and oral cavity involvement and recurrent symptoms. It was originally described as a syndrome that affects mainly people living around the Mediterranean basin, Middle East (Turkey) and Japan. However, it soon became diagnosed in many other areas all over the world. It affects men a little more often than women. The mean age at onset is the third decade. Infectious agents, immune mechanisms, and genetic factors are implicated in the etiopathology of the disease. Eyes, skin, joints, the oral cavity, blood vessels, and central nervous system are usually involved, although less frequently the heart, lung, kidney, genital system, and gastrointestinal tract may be affected (Kaklamani *et al.* 1998).

Stanley *et al.* (1991) studied the relationship between chronic cardiomyopathy and muscle weakness or acute coma in children with a defect in carnitine uptake. They established that patients with severe carnitine deficiency suffered progressive cardiomyopathy, with or without chronic muscle weakness. Other patients presented with episodes of fasting hypoglycemia

during the first 2 years of life before cardiomyopathy had become apparent. [Carnitine is a small, water-soluble molecule required for the oxidation of long chain fatty acids by mitochondria.]

More recent papers on KD have increasingly recognized that this disease is a form of systemic vasculitis.

Grunebaum *et al.* (2002) wrote about the role of anti-epithelial cell antibodies in KD, based on in vitro and in vivo studies. They defined KD as a systemic vasculitis with cardiac and noncardiac complications. It is diagnosed predominantly in early childhood and is characterized by the presence of prolonged fever, conjunctivitis, lymph node enlargement and rash. If not treated promptly (most effectively, with intravenous immunoglobulins), cardiovascular complications are common and many patients develop noncardiac manifestations such as uveitis, pneumonitis, arthritis or nephritis. They also wrote that pathogenesis of KD is still not completely understood but many suggested that abnormal endothelial functions are central for disease development and for late sequelae. [Let's pause here a little: so, all this sophisticated knowledge about the immune system and its components led to nothing more than what was published in the 1960s of the twentieth century.]

However, Grunebaum *et al.* (2002) contributed to resolution of the mystery by studying the role of anti-endothelial cell antibodies (AECA) in KD. They wrote that AECA are found among many KD patients. Studies showed that KD patients have increased in situ expression and elevated serum levels of cytokines, interleukins, adhesion molecules and growth factors, reflecting endothelial cells (EC) activation and regeneration and histological and ultrastructural changes characteristic of EC injury. The ability of intravenous Ig to block the EC changes may explain their therapeutic effect in KD. However, the cause of endothelial dysfunction is unclear. Certain clinical and epidemiological features of KD have suggested that allergens, infections or toxins may initiate the disease, yet extensive research has failed to clearly identify such an agent. [My answer to this is that even when the researchers reveal the vaccination status of the KD patients before developing the disease, they fail to see the causal connection, and/or may dispute it. The reasons are political rather than scientific, because many authors (such as Reik 1980) clearly stated that vasculitis is caused also by vaccinations.]

Then Grunebaum *et al.* (2002) continued that profound disturbances of immunoregulation exceeding those accompanying most other febrile childhood illness, indicate that a major immune fault is detrimental for KD development. The immune dysfunction includes abnormal apoptosis of circulating neutrophils or mononuclear cells; endothelial tissue infiltration by inflammatory cells; the presence of circulating immune complexes and diverse autoantibody production. However, they also added that none of these immune abnormalities was shown to be central in the pathogenesis of KD. Several studies were able to demonstrate the presence of increased anti-endothelial cell antibodies (AECA) titers in 26 % to 72 % of the patients with KD. Correlation between AECA levels and disease activity and the decline in AECA titers after treatment suggests that AECA may be important in the development of autoimmune and vasculitis diseases and in KD. They then wrote that "Indeed, several in vitro studies reported that sera of patients with KD induced

activation or damage to EC, although there were conflicting data concerning the ability of AECA to affect resting vs. pre-stimulated cells." Then they also wrote that there is still some debate about the actual role of AECA in KD development. In order to assess directly the role of AECA in KD, the authors employed an experimental model of active immunization previously used to evaluate the pathogenic role of several autoantibodies. The results provided evidence that AECA derived from a patient with KD can induce the production of mouse AECA followed by clinical and histological abnormalities similar to those observed in KD. Three months after the first injection, significantly higher titers of murine AECA were evident in five of the mice injected with KD-AECA, compared to the levels in mice subjected to N-Ig. The mice AECA titers peaked one month later and did not decline significantly until the mice were sacrificed. Proteinuria was noted 4 months after vaccination in the urine of all the mice in which murine AECA were found, while none of those injected with the KD-AECA that did not develop murine AECA or with N-Ig had any abnormal urinary findings. There was also a significant diffuse fluorescent staining in the renal mesangium of the mice that developed murine AECA, which was not evident in the kidneys of the mice vaccinated with N-Ig. However, hematoxylin-eosin preparation of the aorta, heart, liver, kidney or the lung did not disclose any vasculitis, and no increased immuno-fluorescence was detected in these tissues.

Falcini *et al.* (2003) described a case of a three and a half months old baby boy who was admitted to the hospital in Italy with dyspnea, malaise, irritability in August 2001. One week before, he had an upper respiratory infection treated with amoxicillin and inhaled steroids; the day before admission he presented with high grade fever (up to 40 °C).

On day 5 from admission, a diffuse maculopapular rash all over the body appeared, including the scalp. Initially, most laboratory tests were near normal, except for erythrocyte sedimentation rate, C-reactive protein, and platelet count of over 500. Initially, an electrocardiogram did not show any abnormality, while the EEG showed diffuse slow waves and abdominal ultrasound confirmed hepatosplenomegaly and excluded the presence of other masses. However, repeat testing showed more abnormalities and the child was transfused. Post-transfusion tests showed the presence of multiple lymph nodes in the retroperitoneal, cervical and axillar areas, lung infiltrates, the presence of myelocytes, promyelocytes and histiocytes. During anesthesia for bone marrow biopsy, the boy underwent cardiac arrest. ECG then showed inverted T waves and echo color Doppler of two giant aneurysms. KD was suspected and treatment with intravenous immunoglobulins was given. Anticoagulation with low heparin was also instituted. High dose of aspirin was started after fever dropped to normal values. The patient improved dramatically and became alert. Blood tests progressively improved and the child was discharged in good condition.

Cheung *et al.* (2004) findings support the possibility of ongoing low-grade inflammation after the acute phase of KD in patients with coronary aneurysms. This low-grade inflammation may have a role in increasing systemic arterial stiffness.

Kimura *et al.* (2004) dealt with the suppression of Th1 and Th2 cytokine production and wrote that when T helper (Th)

cells are activated they mainly differentiate into two functionally distinct subsets, Th1 and Th2 cells. Transcriptional factors, T-beta and GATA-3 play important roles in the differentiation of Th1 and Th2 subsets, respectively. Th1 cells play an important role in cellular immunity by secreting IL-2 and IFN-gamma, and Th2 cells have the helper function for the development of antibody producing B cells by secreting IL-4, IL-5, IL-6, and IL-10.

In KD, histopathological findings indicate panvasculitis with endothelial necrosis and infiltration of mononuclear cells (MNC) into small- and medium-sized blood vessels. Although activation of immune systems and production of various cytokines have been reported, the role of T cells and the functional state of Th1 and Th2 cells in KD are still controversial. [One wonders why the authors did not inject their rats with the same vaccines as given to their human patients?]

Jefferys (2001) warned about vaccination with increasing numbers of vaccines. He wrote that “Multiple vaccinations during a short space of time could therefore increase the risk of immunogenic presentation of intracellular self-antigens by increasing the number of T cells undergoing apoptosis. These possibilities do not seem to have been specifically investigated in animals. Before any vaccination program is declared safe, the potential disruption in normal T cell homeostasis – and any resultant adverse outcomes – must be fully assessed. For infants whose immune system is still maturing, such ill-understood issues should be a public health priority.” These comments have a universal validity in any vaccine discussion.

Indeed, Geier *et al.* (2008) in their latest article confirmed that administration of rotavirus vaccine with a multitude of other vaccines resulted in significant increases in the total number of intussusceptions and cases of Kawasaki disease, according to VAERS system.

Takehita *et al.* (2005) investigated whether an imbalance exists in the production between antiangiogenic and angiogenic growth factor in patients with KD. The results showed that an imbalance does exist in the production between vascular endothelial growth factor (VEGF) and endothelial cells (EC) in patients with KD while also suggesting that KD patients with a high VEGF/ES (vascular endothelial growth factor/endostatin) ratio have a significantly greater risk of coronary artery lesions (CAL) involvement.

Carlton-Conway *et al.* (2005) wrote that KD is a systemic vasculitis and may affect the cerebral function acutely. In their research, they measured a number of behavioral and social parameters within a cohort of KD patients. Parents of children with past diagnosis of KD were recruited to complete several behavior screening questionnaires. Sixty-five sets of questionnaires relating to the patient cohort were eligible for inclusion. Two control groups were used, a hospital (HC) control and a sibling control (SC) group.

Forty percent of KD disease group showed elevated internalizing scores in the clinical or borderline-clinical range. This compared with 18% of hospital controls and 13 % sibling controls. Additionally, the KD group experienced greater overall total difficulties when compared with the controls. The KD group had more somatic problems and withdrawal traits, conduct and social interactions as well as more thought problems. Positron emission tomograms were performed on nine patients

to investigate severe behavioral problems. Three patients showed minor changes, possibly showing a resolving cerebral vasculopathy. The problems were significant enough to warrant consultation with an educational psychologist, a clinical psychologist or a GP.

As always, there is more to the issue of systemic vasculitis. Behcet (1937) described the clinical triad of relapsing iritis, ulcers of the mouth and genitalia, and other cutaneous lesions. However, the first researcher to describe these symptoms was Bluthe (1908). Subsequently, others, such as O’Duffy *et al.* (1976), described central nervous system (neurological) involvement in Behcet syndrome. Their 25 patients had headache and fever during or preceding exacerbations of the CNS, and all had cerebrospinal pleocytosis (WBC count from 6 to 490/cubic mm) with predominant lymphocytosis. Clinical findings included corticospinal disease, cerebellar ataxia, pseudobulbar palsy and transient ocular palsies. Of the three patients who died, one died from a presumed myocardial infarction.

Moore and Cupps (1983) dealt with neurological complications of vasculitides as a group of disorders sharing the histological features of inflammation and necrosis of blood vessels. They wrote that neurological dysfunction occurs in 80 % of patients with polyarteritis nodosa and fewer than 10 % of patients with hypersensitivity vasculitis. The mechanism of neurological dysfunction in the vasculitides is tissue ischemia. The clinical effects of ischemia vary, and symptoms may be transient or prolonged. Mononeuritis multiplex polyneuropathy and stroke are frequent complications, but encephalopathies, cranial neuropathies and brachial plexopathies are seen as well. The occurrence of symptoms late in the course of the disease suggests ischemia resulting from healed scarred vessels, as well as from their acute inflammation which is considered to be the case in Takayashu’s arteritis and possibly in polyarteritis nodosa.

The authors wrote that immunological mechanisms that produce the histological changes of vasculitis are incompletely understood; however, in experimental models the role of immune complexes has revealed the necessary conditions for immune-complex mediated vasculitis. 1) Soluble immune complexes formed under conditions for slight antigen excess with a size less than 195, 2) increased vascular permeability from filtration of immune-complexes by the elastic lamina of arteries or the basement membrane of venules, 3) activation of complement with subsequent attraction of polymorphonuclear leukocytes to the site of immune complex deposition, and 4) release of proteolytic enzymes by polymorphonuclear leukocytes with destruction of vascular structures and loss of functional integrity. In humans, immune complex deposition probably initiates vascular inflammation in hypersensitivity vasculitis and in the polyarteritis nodosa (PAN) group of systemic necrotizing vasculitides. Other biological mechanisms, such as hepatitis B surface antigen, bacterial antigens, immunoglobulins b1C, and C-reactive protein, have been demonstrated in the cutaneous lesions of hypersensitivity vasculitis.

Cell-mediated immune mechanisms are important as well, as indicated by the presence of granulomata. Macrophages can be activated by phagocytosis of immune complexes, by Fc receptor interaction with immune complexes, or by lymphokines released by antigen-sensitized T-lymphocytes. These activated

macrophages can then release lysosomal enzymes that damage the vessel wall. Vessel necrosis can also be caused by direct infiltration or invasion of the vessel walls by atypical or neoplastic lymphoid cells characteristic of lymphomatoid granulomatosis. Other potential mechanisms of blood vessel inflammation and damage are cellular immune mechanisms mediated by either thymus-derived T cells or other soluble products, autoantibodies directed against vascular determinants, and cytotoxic mechanisms such as antibody-dependent cellular cytotoxicity or natural killer (NK) cell activity.

Tissue ischemia is recognized as the universal common denominator of the vasculitides. Even after the acute inflammation has resolved, ischemia may be sustained by fibrotic narrowing of the vessel wall. The effects of ischemia on the nervous system range from subtle alterations in cellular metabolism and slowed impulse propagation and synaptic transmission, to frank infarction.

Variability in clinical expression can be explained by the acuteness of the ischemia, the extent of collateral circulation, and the degree of tissue sensitivity to hypoxia and ischemia. Asymptomatic ischemia of the nervous system is common in systemic necrotizing vasculitis.

Some vasculitides affect only the central nervous system, others both the peripheral and central nervous system. Some vessels are affected early in the course of the disease, others only later. The reason for this variability is unknown. Central nervous system abnormalities occur in 20 % to 40 % of patients. Two common presentations are diffuse encephalopathy affecting cognitive function or level of alertness, and focal or multifocal disturbances of the brain or spinal cord. Both are caused by vasculitis. The onset can be insidious but can evolve in one day. Focal or generalized seizures may occur. Hypertension sometimes accompanies or follows the encephalopathy and, if severe, may exacerbate functional effects of marginal ischemia. The symptoms may resolve spontaneously over days or weeks, and with appropriate treatment, recurrence is unusual. Focal symptoms are caused by stroke and are sudden in onset.

Strokes may appear in the cerebral hemispheres, but cerebellar and brainstem strokes may occur as well. They may be hemorrhagic (subarachnoid or intraparenchymal) or ischemic. Vascular scarring is indicated when CNS abnormalities occur later in the course of the systemic necrotizing vasculitis. Blurred vision and visual loss are frequent complaints. Vasculitis of the optic nerve, chiasm, and tract, the occipital cortex, and cranial nerves III, IV, and VI are well documented. Abnormal laboratory findings often include elevation of the erythrocyte sedimentation rate (ESR), leukocytosis, anemia, thrombocytosis, hematuria, proteinuria, circulating immune complexes, and low titers of rheumatoid factor. Eosinophilia is generally not present in classic PAN. Thirty percent of patients with a systemic vasculitis of the PAN group have a hepatitis B antigenemia. Antinuclear antibodies are not a feature of the primary vasculitis, although 20 % of patients may have low titers and a nonspecific pattern.

In patients with CNS disease, nonspecific slowing of the encephalogram is frequent. Computed tomography (CT) findings are normal in diffuse encephalopathy, but scanning may show areas of hypodensity or hemorrhage in patients with stroke. Allergic angiitis and granulomatosis are distinctive for a

history of allergic diathesis, invariable lung involvement, and peripheral eosinophilia. Fibroid necrosis with eosinophilic and granulomatous tissue reactivity is present not only in small and medium-sized muscular arteries, but also in capillaries and venules. Neurological complications are similar in their frequency and pattern to those in classic PAN.

Neurological involvement is not common in hypersensitivity vasculitis, with the exception of serum sickness. The neurological complications of serum sickness include encephalopathy, seizures, coma, peripheral neuropathies, and brachial plexopathy. They may accompany cutaneous vasculitis, postinfectious vasculitis and vasculitis with cryoglobulinemia. Subarachnoid hemorrhage and stroke have been reported in Henoch-Schoenlein purpura. The common features of these disorders are cutaneous lesions, usually palpable purpura of the legs, and venulitis. Features that distinguish these diseases are a known underlying cause (a drug induced allergic vasculitis, postinfectious vasculitis), systemic involvement (serum sickness), colicky abdominal pain (H-S purpura), and associated cryoglobulinemia (essential mixed cryoglobulinemia). Hypergammaglobulinemia may be present, IgG in serum sickness and IgA in H-S purpura. Serum complement levels may be low or normal. Skin biopsies show small vessel inflammation; immunoglobulins and complement sometimes occur in the vessel wall.

In the acute stage there is polymorphonuclear leukocyte infiltration of venules with leukoclasia (presence of nuclear debris). Mononuclear cell infiltrations are present later. Arteries and capillaries may also be affected.

The first goal of therapy is to identify and remove any known sensitizing agents. Moore and Cupps (1983) wrote that treatment with corticosteroids may mask smoldering inflammation process; if no response is observed, cytotoxic drugs should be considered instead.

Cadman *et al.* (1976) added pulmonary manifestations including hemoptysis in a 22-year old female patient with other symptoms of the Behcet syndrome (arthralgia, conjunctivitis, ulcers in the mouth and vagina, and petechial lesions on the lower extremities).

Moore and Cupps (1983) also dealt with Wegener's granulomatosis, which is a systemic necrotizing vasculitis of the respiratory tract, with or without renal involvement (glomerulonephritis). Initial symptoms are related to the upper respiratory system and skin lesions often involve ulcerations and papules. Arthralgias are present in more than half of the patients, but true arthritis is unusual. This disease entity includes a fibrinoid necrosis of small arteries and veins. Granulomata are well formed and contain many giant cells. Healing is associated with fibrosis.

Neurological abnormalities include diabetes insipidus, and focal lesions of the brain and spinal cord. Cranial nerve involvement also occurs. Diabetes insipidus has been documented 9 months prior to the onset of Wegener's granulomatosis. Aseptic meningitis can have an explosive onset, but milder symptoms may be missed in an acutely ill patient. Both cranial and peripheral neuropathies may occur transiently, resolving over a period of hours. Sometimes there are mild cognitive alterations (particularly memory) and seizures, strokes, and encephalopathy are late complications of an untreated disease.

Primary granulomata of neural tissue are less common but include isolated granulomas of cranial nerves, intracerebral granulomas and focal lesions of the parietal bone. Visual loss may also occur. Thrombosis and hemorrhage of a medium-sized intracranial artery may result in a stroke.

The authors also elaborated on so-called Takayasu's arteritis (aortic arch syndrome, pulseless disease), which is a large-vessel arteritis with a predilection for the aortic arch and its branches. It is most common in young women. The presenting complaints are usually vascular insufficiency to limbs or organs. Bruits in the neck or supraclavicular region are heard in 96 % of patients. Congestive heart failure is present in about a third, and angina pectoris in 12 % of patients. Hypertension is present in about 50 % of patients. Arteriosclerosis disease may develop years later in previously damaged vessels.

Carotid occlusion results in neurological dysfunction in Takayasu's disease and may occur later in the disease. Presenting symptoms may be headache and vertigo and focal abnormalities (paresis, sensory loss and aphasia) occur less often. Visual changes, syncope, dizziness, sensory changes are also characteristic. Syncope attacks may be caused by a hypertensive carotid sinus reflex. The course of the neurological disease is variable, but the authors have seen three young patients with profound hemiplegia regain considerable function over 1 to 2 years. This is of particular interest in relation to Gardasil[®] (cervical cancer) vaccine: many young girls developed syncope, dizziness, transient blindness and hemiplegia within minutes of the cervical cancer vaccine injections.

Boucher *et al.* (1998) described serous retinal detachments associated with Goodpasture's syndrome. GS is a rare autoimmune disorder in which IgG antibodies are directed against the alpha 3 chain of type IV collagen resulting in pulmonary haemorrhage and renal failure. Circulating anti-basement-membrane antibodies are usually demonstrated and a lung or kidney biopsy usually shows linear immunofluorescent staining for IgG along the basement membrane. Inciting factors in the onset of the disease may be infection, cigarette smoking, and exposure to industrial solvents. The prognosis is guarded, with pulmonary hemorrhage or renal failure as the cause of death.

This information is also relevant to the babies that died from vaccines. Unfortunately, in many cases both ophthalmologists and judges have mistaken retinal detachments with physical traumatic injuries in many cases of shaken baby syndrome (SBS).

Later on, Efthimiou *et al.* (1986) described five patients with BS presenting with hemoptysis and recurrent radiographic opacities, with a review of 23 similar cases. Typical pulmonary disease was associated with active disease at other sites, although the patients often only complained of hemoptysis. Male patients predominated, with thrombophlebitis and deep vein thrombosis being more common. Immunopathological evidence suggested that the underlying pathogenesis is a pulmonary vasculitis, which may result in arterial and venous thromboses, pulmonary infarction, pulmonary hemorrhages and pulmonary arterial aneurysms formation.

Circulating immune complexes were also found in association with pulmonary disease.

In at least 11 patients, pulmonary hemorrhage was the probable cause of death. All deaths occurred within six years of the first episode.

Akoglu *et al.* (1987) described a case of a 32-year old woman who experienced cough and dyspnea for three months. Three years previously she developed genital ulcers and oral aphthous lesions and had been diagnosed with incomplete Behcet disease. She also had hypoplastic bone marrow and disseminated intravascular coagulation which developed in the terminal stage of her disease. They characterized this case as incomplete Behcet syndrome with unusual manifestations.

Among other basically vascular disorders, it seems appropriate to mention, at least briefly, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome). According to Fauci (1983), hypersensitivity vasculitis may affect any organ system, but, in this disorder, the skin involvement dominates the clinical picture. The skin lesions can be pruritic and acutely painful, with a stinging or burning sensation. Lesions may occur on the face or other parts of the body, such as feet and ankles, mucosal membranes, ears, conjunctiva, they may be edematous, hemorrhagic into skin/purpura, in the form of papulae/petechiae, necrotic ulceration, vesicles/bullae, nodules. There may or may not be other symptomatic complaints.

Yetiv *et al.* (1980) wrote about etiological factors of the Stevens-Johnson Syndrome. Many factors have been proposed as having an etiological role in its pathology. These have ranged from drugs (several hundred listed in the world literature) to various biological agents including viruses, bacteria, Mycoplasma, herpes simplex, and fungi, deep radiation therapy, collagen vascular diseases, malignancies and even pregnancy and certain foods.

It is not without interest, that they also wrote that in the Johns Hopkins group of 46 cases, ten (22 %) had a history of recurrent and chronic bacterial infections beginning early in life, with an impressive frequency of abnormalities of the immune system.

Delattre *et al.* (1987) published an abstract of their lecture (published in Neurology) erythema multiforme (EM) and erythema multiforme bullosa (Stevens-Johnson syndrome EMB) complicating treatment with phenytoin or radiation therapy of intracranial tumors. Hypersensitivity and immune depression were the main factors.

Goldstein *et al.* (1987) wrote that toxic epidermal necrolysis (TEN) or Lyell's syndrome, holds a unique place among dermatological diseases for its frightening, rapid progression and all too often tragic outcome. Lack of understanding of the pathogenesis of this disease, coupled with its infrequency and the lack of objective laboratory criteria for its diagnosis, have created considerable confusion and controversy.

Guillaume *et al.* (1987) described their findings in relation to 87 cases of toxic epidermal necrolysis (Lyell's syndrome) between 1972 and 1985. The culprit drugs included the following: sulfonamides (sulfamethoxazole and trimethoprim in particular), anticonvulsants (barbiturates and carbamazepine only), non-steroidal anti-inflammatory drugs (mainly the phenylbutazone derivatives), allopurinol, chlormezazone, and aspirin, antipyretics and antibiotics being infrequently implicated.

Roujeau *et al.* (1987) concluded that epidermal necrosis reminded them of allogenic skin graft rejections suggesting that it is an immunological reaction mediated by "aggressor lymphocytes" sensitized to epidermal cells.

Huff and Weston (1989) conducted a prospective study of erythema multiforme in 22 subjects who experienced more than one episode. They believed that, based on their findings, the recurrent EM is a distinct group of EM that is related etiologically to recurrent herpes simplex virus (HSV) infections.

Roujeau *et al.* (1990) wrote that, although recognized previously, toxic epidermal necrolysis (TEN) was described in 1956 by Lyell as a syndrome characterized by extensive detachment of the epidermis. Necrolysis denotes necrosis and detachment of the epidermis on its whole thickness. Toxic means severe constitutional symptoms and complications, and applies to the drug origin in most, if not all, cases.

Chan *et al.* (1990) carried out a study to estimate the incidence of erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) requiring hospitalization and determination of the culprit drugs. A total of 61 suspect cases were identified from the computerized hospital records. Overall, their data suggested that cases of EM, SJS, and TEN sufficiently severe to require hospitalization are infrequent among outpatients using well-established drug therapies. A continuing challenge is the evaluation of these severe cutaneous reactions associated with newly marketed or less frequently prescribed drug therapies.

Strom *et al.* (1991) set out to determine the incidence of SJS from computerized Medicaid billing records from 1980 to 1984, from the states of Michigan, Minnesota and Florida. Penicillins, especially aminopenicillins, were frequently used in 19 patients judged to be true cases of SJS. They concluded that it was an uncommon condition.

Williams and Lehner (1977) analyzed the series of 17 patients with typical Behcet syndrome (BS) pathology and found immune complexes in their sera. Immune complexes were more common in patients with the neuro-ocular type of BS than in those with mucocutaneous type, and in those with herpetiform ulcers than with those with major or minor aphthous ulcers. Immune complexes were also associated with active disease.

Sakane *et al.* (1982) found functional aberrations of T-cell subsets in patients with BS. They wrote that although originally characterized by the triad of oral ulcers, iritis, and genital ulcers, BS is now recognized as a systemic inflammatory disease of unknown etiology. They also wrote that some evidence suggests that immunological abnormalities are important in its pathogenesis. Many of the clinical features of BS are caused by autoimmunity, including finding of elevated immunoglobulins, immunoglobulin-binding to oral mucosa, and antibodies that react with fetal oral mucosal tissue.

Tanaka *et al.* (1983) established increased solubilization of immune complexes by the sera from the patients with BD. The presence of circulating immune complexes reported in patients with BD suggests that immunological abnormalities may be related to the pathogenesis of this disease.

Peces *et al.* (1984) described a case of a 36-year old white man with BD who developed nephrotic syndrome and chronic renal failure. The renal biopsy confirmed renal amyloidosis, and the potassium permanganate staining indicated that the amyloid

was of the AA protein type. They considered their report to be the first of BD with amyloidosis and chronic renal failure in maintenance hemodialysis.

Mishima *et al.* (1985) wrote that even though the pathogenesis of BD is still unknown, clinical findings following the ocular attacks in the fundus show hemorrhage and exudates caused by thromboangiitis. They also mentioned a number of reports on the role of fibrinolytic enzyme system in the disease. They studied the plasminogen activator levels in plasma samples of 37 BS patients and established a significant decrease in plasminogen activator activity by the euglobulin-lysis-time method, the amyloid-activity level (Testzyn method), and the fibrin-plate method.

Kaneko *et al.* (1985) studied natural killer (NK) cell numbers and function in peripheral lymphoid cells in Behcet disease. NK activity in the peripheral blood of BD patients was significantly lower than that of patients in the inactive stage and normal controls. Their results suggested that the patients with active BD lack a factor which activates NK cells.

Kaneko, Takahashi *et al.* (1985) established that patients with BD show an intense delayed hypersensitivity (DH) reaction to a group of streptococcal bacteria. Deposits of IgM and positive fluorescence of anti-streptococcal group D serum were found in vessel walls and sites infiltrated by inflammatory cells. Cytological analysis has revealed that the inflammatory infiltrating cells are mainly composed of activated T-cells and macrophages in association with natural killer cells. These results suggested that DH reactions with antigen-antibody mediated cytotoxicity might play an important role in causing lesions of BD.

Pivetti-Pezzi *et al.* (1995) dealt with Behcet's disease in Italian children. In the last 25 years, 211 patients with Behcet's disease have been observed, most of whom have not developed ocular signs. Ophthalmic and other clinical symptoms only occurred in 16 children and 122 adult patients affected by BD and they were studied to delineate the clinical features of BD in childhood and investigate the differences between the expression of the disease in children and adults. Pediatric onset of BD was found in 7.6 % of all the cases with male/female ratio of 1.28:1. They wrote that the complete type of the disease was observed in 50 % of the children. No statistically significant differences were noted between children and adults in the incidence of oral aphthae, genital ulcers, skin lesions, arthritis, gastrointestinal involvement, while the neuropsychiatric symptoms appeared more frequently in children (25 % against 16.4 %) as was the presence of HLA-B51. Thrombophlebitis was associated with the onset of disease in adult age. Uveitis alone or in combination with other major symptoms was the presenting sign in a higher percentage of children, and diffuse uveitis was the most common ocular inflammation. Children more frequently developed cataract, maculopathy, subretinal neovascularisation, retinal detachment and neuropsychiatric problems. Both adult and young male patients have shown a lower age at onset and a higher rate of optic atrophy than females. Ocular involvement in children may be very severe, as was confirmed by the high frequency of diffuse uveitis and ocular complications. Both young and adult males alike exhibited an earlier onset of the disease and a worse ocular prognosis.

In discussion, the authors wrote that although Behcet's disease is quite rare in Italy, it is one of the most frequently encountered systemic disease in patients with diffuse uveitis. Since not all symptoms occur simultaneously, the onset may be quite insidious. Frequently, the children display only the mucocutaneous lesions, while the other manifestations of the disease, especially ocular and neuropsychiatric may appear later (after a mean time of 14.2 years in the present survey).

The therapeutic approach for pediatric Behcet disease is limited by the young age which may discourage the use of drugs with short, medium and long-term toxic effects. Immunosuppressants are used preferentially to steroids because of fewer side effects.

Honma *et al.* (1987) studied biopsy specimens from 18 patients with Behcet's syndrome by electron microscopy with particular attention to the appearance of the lymphocyte-macrophages infiltrate into the interlobules of subcutaneous fat in erythema nodosum-like lesions. Electron microscopic evaluation revealed vacuolization changes of fat cells with detachment of their cell membranes from the basal lamina that permitted lymphocytes and macrophages to enter into this developed space. The detachment of fat cells from the basal lamina precedes invasion by lymphocytes which in turn attracts macrophages into the space. This eventually leads to fat-cell lysis accompanied by activation of macrophages, which causes further inflammation, completing the picture of panniculitis in the erythema nodosum-like lesions in Behcet's syndrome.

Biousse *et al.* (1998) provided a practical review of the ophthalmological manifestations of intracranial vascular abnormalities. They reviewed and described ocular manifestations of the most common intracranial vascular abnormalities: intracranial aneurysms, carotid-cavernous fistulas, arteriovenous malformations, and cavernous malformations. They concluded that unruptured aneurysms can compress the third cranial nerve and the anterior visual pathways. Ruptured aneurysms and subarachnoid hemorrhages can result in Terson syndrome and papilloedema. Direct and indirect carotid-cavernous fistulas most commonly cause the classical triad of proptosis, conjunctival chemosis, and cranial bruit can masquerade as chronic conjunctivitis. Arteriovenous malformations, with or without hemorrhage, may compress portions of the retrochiasmal pathways, causing visual field loss. Cavernous malformations, when in the brainstem, commonly cause abnormalities of supranuclear, nuclear, and fascicular ocular motility.

The authors concluded that the ophthalmologist might be the first physician to encounter clinical manifestations of intracranial vascular abnormalities that may herald devastating neurological complications. Prompt diagnosis facilitates appropriate management and therapy.

Visual complications are a not an infrequent source of morbidity in those patients surviving acute intracranial bleeding.

[In my opinion, the fact that quite a large percentage of controls also displayed behavioral problems indicates to me that seemingly healthy people used as controls, may have undiagnosed or mild behavioral problems which go undetected simply because so many people are damaged by vaccines and that there is a continuum and overlap of a range of damage done by vaccines to their recipients. I have a reasonable suspicion that children in all groups were given vaccines and simply devel-

oped also other, different, or milder reactions and damage. The true controls should have been totally unvaccinated individuals.]

Matsubara *et al.* (2006) dealt with the development of serum IgM antibodies against superantigens of *Staphylococcus aureus* and *Streptococcus pyogenes* in Kawasaki's disease. The intent was to serologically determine the association of microbial superantigens and the pathogenesis of KD. They measured serum IgG and IgM antibodies against staphylococcal enterotoxin A (SEA), SEB, SEC, toxic shock syndrome toxin-1, and streptococcal pyrogenic exotoxin A (SPEA), by an enzyme-linked immunosorbent assay on 293 serum samples from 65 KD patients on clinical days 1-28 as well as on 120 control samples.

The administration of immunoglobulin products, which contain high concentration of IgG antibodies against all superantigens, directly elevated antitoxin IgG antibodies against all the superantigens in KD patients. In contrast, antitoxin IgM antibodies were not detected in immunoglobulin products. Actually, the authors found a significant elevation of IgM antibodies against SEA in KD patients in the first, second, third, and fourth weeks, compared to the controls. Significant differences of IgM antibodies were also true for SEB, TSST-1, and SPEA throughout the first to fourth weeks, and, for SEC, throughout the second to fourth weeks. The prevalence in KD patients having high IgM titers to the 5 superantigens was increased with the clinical weeks, and reached 29-43 % of KD subjects at the fourth week. They claimed theirs to be the first study that described kinetics of IgM antibodies against superantigens and clarified the serological significance throughout the clinical course of KD. The authors also claimed that their study suggests that multiple superantigens (microbial toxins) are involved in the pathogenesis of KD. They have not mentioned that vaccines are also superantigens and that they contain a number of microbial toxins.

They also wrote that in any case, the specific organisms may not be as important as a common mechanism of stimulation to develop the immune system. [This may explain why efforts to find a unifying etiological association, or a consistent TCR V-beta repertoire, have been unsuccessful to date. Had any authors ever looked into the effect of vaccines, they would have found the unifying etiological association.]

One can ask a relevant question: Why didn't any authors inject their laboratory animals with exactly the same vaccines as were injected into the KD patients before they developed KD? That would once and for all resolve the question of etiology of this important group of immune-mediated diseases.

Weinstein (2006) described a case of a previously healthy 22-months old girl of Asian heritage who presented with a ten-day history of high fever and a 3-day history of non-purulent conjunctivitis, erythema and swelling of her left upper arm and right side of her neck, and reddened swollen palms. "Her immunizations, including BCG (bacilli Calmette-Guerin) vaccination given at 9 months of age, were up to date". Beside typical symptoms of KD, she also had marked erythema, induration and small areas of vesiculation on her left upper arm that corresponded to the area of her BCG vaccine.

Laboratory investigations showed mildly abnormal values and KD was diagnosed and intravenous gamma globulin therapy and a high-dose ASA therapy were started. The patient became afebrile and the clinical signs resolved within 24 hours.

An echocardiogram showed ectasia of the right coronary artery. She was discharged with 40 mg of ASA daily; echocardiogram 4 weeks later appeared normal.

Wolff *et al.* (2007) described a case of a 24-year old white man presented to hospital with a 3-week illness with fever, headache, nausea, sore throat and cough, non-suppurative conjunctivitis, significant cervical lymphadenopathy, oral changes and fissured tongue and labial non-suppurative conjunctivitis, significant cervical lymphadenopathy, oral changes and fissured tongue and labials, and extremity edema, followed by 5 days later by arthralgia. Two weeks later, the patient noted an erythematous, diffuse shin rash beginning on his torso and spreading to his extremities. At a local hospital, he was diagnosed with scarlet fever and placed on penicillin, although a throat culture was negative for Streptococcal species. His skin desquamated from his fingernails and progressing centrally. The patient was placed on cephalexin and referred to a larger hospital. He was previously healthy and reported no drug allergies. [Perhaps the fact that his father suffered upper respiratory infection was of some significance: both father and son could have received the flu injections; it was the winter time. One developed URI and the other KD. This is only a conjecture, but I consider it a reasonable conjecture.]

The patient's symptoms were considered compatible with systemic vasculitis, the most interesting being, in my opinion, the right knee effusion without warmth or erythema, and pain with active motion of the wrists, hips, knees, and ankles. These symptoms may indeed be the only symptoms in some KD cases.

KD was diagnosed based on the absence of infection, failure to improve with antibiotics, and the presence of all diagnostic criteria.

3. Conclusion

In conclusion: had any of the above authors injected the laboratory animals with the same vaccines as those received by KD patients before they developed the disease, they would have not only produced a classical KD, but would have established with certainty the real cause of KD—vaccination. The more recent authors have failed to contribute to the issue of the cause of Kawasaki Disease; they as a rule have not even disclosed the vaccination status of their patients; the only contribution, compared with the earlier authors, is that they now talk about the intricacies and some finer points of the immune system. The simple correct observation would have been more productive.

Moreover, even though very few authors even mentioned the vaccination status of their patients with KD, notwithstanding directly linking vaccines causally to KD, the circumstantial evidence clearly shows the link. Firstly, it is the ages of the very young patients; the onset of KD always closely following the vaccination schedule. There were no data on the occurrence of KD in babies younger than 3 months. Secondly, KD is an immunologically-mediated disease since, as a rule, the administration of immunoglobulin has a positive effect on the symptoms. Thirdly, it has been demonstrated that vaccines such as DPT and those containing the rubella component, seriously affect the heart and the vascular system. Fourthly, one can see the internal consistency of the close fit in the ages of the victims of KD

with the time of intensified vaccination of infants. This is very much the same as with the causal relationship between SV40 contamination of polio vaccines and the age-related epidemics of certain brain and other cancers in the victims who were given the contaminated vaccines first as school children and later on as babies.

References

- [1] Akoglu T, Paydas S, Sarpel S, Tunali N, Tuncer I. 1987. Incomplete Behcet's syndrome with unusual manifestations. *Ann Rheum Dis*; 46:632–3.
- [2] Amsel SG, Hanucoglu A, Fried D, Wolyvovic M. 1986. Myocarditis after triple immunisations. *Arch Dis Childhood*; 61:403–5.
- [3] Anonymous. 1978. Kawasaki disease – United States. *MMWR*; 27(2):9.
- [4] Anonymous. 1990. Criteria for diagnosis of Behcet's disease. *Lancet*; 336:1078–80.
- [5] Bannister BA, Edwards S, Iyata G. 1989. Aetiology of Kawasaki disease. *Arch Dis Childhood*; 64:397–8.
- [6] Behcet H. 1937. Ueber rezidivierende, aphthose, durch ein virus verursachte heschwure am mund, am auge und dem genitalien. *Dermat. Wochenschr.*; 105:1152–9.
- [7] Biousse V, Mendicino ME, Simon DJ, Newman NJ. 1998. The ophthalmology of intracranial vascular abnormalities. *Am J Ophthalmol*; 125:527–44.
- [8] Bishop WB, Carlton RF, Sanders LL. 1966. Diffuse vasculitis and death after hyperimmunization with pertussis vaccine. *New Engl J Med*; 274(11):616–9.
- [9] Bluthe L. 1908. Zur Kenntnis des rezidivierendem Hypopyons. Inaugural Thesis. Heidelberg.
- [10] Boucher MC, El Toukhy, Cormier G. 1998. Bilateral serous detachments associated with Goodpasture's syndrome. *Can J Ophthalmol*; 33:46–9.
- [11] Brecker, SJD, Gray HH, Oldershaw PJ. 1988. Coronary artery aneurysms and myocardial infarction: adult sequelae of Kawasaki disease? *Br Heart J*; 59) 509–12.
- [12] Burgner D, Festa M, Isaacs D. 1996. Lesson of the week: delayed diagnosis of Kawasaki disease presenting with massive lymphadenopathy and airway obstruction. *BMJ*; 312:1471–2.
- [13] Burke MJ, Rennebohm RM. 1981. Eye involvement in Kawasaki Disease. *J Paed Ophthalmol and Strabismus*; 18(5):7–11.
- [14] Burns JC, Geha RS, Schneeberger EE, Newburger JW, Rosen FS, *et al.* 1986. Polymerase activity in lymphocyte culture supernatants from patients with Kawasaki disease. *Nature*; 223:814–6.
- [15] Cadman EC, Lundberg WB, Mitchell MS. 1976. Pulmonary manifestations in Behcet syndrome. *Arch Intern Med*; 136:944–7.
- [16] Carlton-Conway D, Ahkluwalia R, Henry L, Michie C, Wood L, Tulloch R. 2005. Behavioural sequelae following acute Kawasaki disease. *BMC Pediatrics*; 5 (14):Biomedcentral.com1471–2431.
- [17] Carter RF, Hayes M. 1976. Rickettsia-like bodies and splenitis in Kawasaki Disease. *Lancet*; 4 Dec.:1254–5.
- [18] Castresana-Isla CJ, Herrera-Martinez G, Vega-Molina J. 1993. *J Rheumatol*; 20:1417–8.
- [19] Chan H-L, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, Walker M. 1990. The incidence of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol*; 126:43–7.
- [20] Cheek DB. 1975. Comment on mucocutaneous lymph node syndrome: could it be a heavy metal poisoning? *Pediatrics*; 56(2):335–6.
- [21] Cheung YF, Ho MHK, Tam SCF, Young TC. 2004. Increased high sensitivity C reactive protein concentrations and increased arterial stiffness in children with a history of Kawasaki disease. *Heart*; 90:1281–5.

- [22] Delattre JY, Safai B, Posner JB. 1986. Erythema multiforme and Stevens-Johnson syndrome complicating treatment of intracranial tumors. *Neurology* 36(Suppl 1):287.
- [23] Efthimiou J, Johnston C, Spiro SG, Turner-Warwick M. 1986. Pulmonary disease in Behcet's syndrome. *Q J Med; NS* 58, (227):259-280.
- [24] eSilva AA, Maeno Y, Hashimi A, Smallborn JF, Silverman ED, McCrindle BW. 2001. Cardiovascular risk factor after Kawasaki disease: a case-control study. *J Pediatr*; 138:4000–5.
- [25] Falcini F, Simonini G, Calabri GB, Cimaz R. 2003. Multifocal lymphadenopathy associated with severe Kawasaki disease: a difficult diagnosis. *Ann Rheum Dis*; 62:688–9.
- [26] Fauci AS. 1983. Vasculitis. *Continuing Medical Education. J Allergy Clin Immunol*; 72 (3):211–23.
- [27] Furusho K, Nakano H, Tamura T, Manabe Y, Kawarano M *et al.* 1984. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*; 10 Nov.:1055–7.
- [28] Geier DA, King PG, Sykes LK, Geier MR. 2008. RotaTeq vaccine adverse events and policy considerations. *Med Sci Monit*; 14 (3):PH9–16.
- [29] Germain BF, Moroney JD, Guggino GS *et al.* 1980. Anterior uveitis in Kawasaki disease. *J Pediatr*; 97(5):780.
- [30] Goldstein SM, Wintroub BW, Elias PM, Wuepper KD. 1987. Toxin epidermal necrolysis. Unmuddying the waters. *Arch Dermatol*; 123:1153–6.
- [31] Goolsby PL. 1989. Erythema nodosum after Recombivax HB hepatitis B vaccine. *New Engl J Med*; 321 (17):1198–9.
- [52] Grunnebaum E, Blank M, Cohen S, Afek A, Kopolovic J, Meroni PL, *et al.* 2002. The role of anti-endothelial cell antibodies in Kawasaki disease—in vitro and in vivo studies. *Clin Exp Immunol*; 136:233–40.
- [33] Guillaume J-C, Roujeau J-C, Revuz J, Penso D, Touraine R. 1997. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol*; 123:1166–70.
- [34] Honma T, Bang D, Saito T, Nakagawa S, Ueki H, Lee S. 1987. Ultrastructure of lymphocyte-mediated fat-cell lysis in erythema nodosum-like lesions of Behcet's syndrome. *Arch Dermatol*; 123:1650–4.
- [35] Huff JC, Westion WL. 1989. Recurrent Erythema Multiforme. *Medicine*; 68(3):133–40.
- [36] Jefferys R. 2001. T cells and vaccination. *Lancet*; 357:1451.
- [37] Kaklamani VG, Vaiopoulos G, Kaklamani PG. 1998. Behcet disease. *Semin Arthritis and Rheum*; 27:197–217.
- [38] Kaneko F, Takahashi Y, Muramatsu R, Adaschi K, Miura Y, *et al.* 1985. Natural killer cell numbers and function in peripheral lymphoid cells in Behcet's disease. *Br J Dermatol*; 113:313–8.
- [39] Kaneko F, Takahashi Y, Muramatsu Y, Miura Y. 1985. Immunological studies on aphthous ulcer and erythema nodosum-like eruptions in Behcet's disease. *Br J Dermatol*; 113:303–12.
- [40] Kato H, Inoue P, Kawasaki T, Fujiwara H, Watanabe T, Toshima. 1992. Adult coronary artery disease probably due to childhood Kawasaki disease. *Lancet*; 3490:1127–9.
- [41] Kawasaki T. 1967. Acute febrile MCLNS: clinical observations of 50 cases (in Japanese). *Jpn J Allergol*; 16:178–222.
- [42] Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa A. 1974. A new infantile acute febrile mucocutaneous lymph-node syndrome (MLNS) prevailing in Japan. *Pediatrics*; 54:171–6.
- [43] Kelsall JT, Chalmers A, Sherlock CH, Tron VA, Kelsall AC. 1997. Microscopic polyangiitis after influenza vaccination. *J Rheumatol*; 24:1198–202.
- [44] Kimura J, Takada H, Nomura A, Ohno T, Mizuno Y, Kushura K, *et al.* 2004. Th1 and Th2 cytokine production is suppressed at the level of transcriptional regulation in Kawasaki disease. *Clin Exp Immunol*; 137:444–9.
- [45] Lee BW, Yap HK, Yip WCL, Giam YC, Tay JSH. 1989. Nephrotic syndrome in Kawasaki disease. *Aust Paediatr J*; 25:241–2.
- [46] Levin M, Holland PC, Nokes TJC, Novelli V, Mola M *et al.* 1985. Platelet immune complex interaction in pathogenesis of Kawasaki disease and childhood polyarteritis. *BMJ*; 290:1456–60.
- [47] Leung DYM, Chu ET, Wood N, Grady S, Meade R, Geha RS. 1983. Immunoregulatory T cell abnormalities in mucocutaneous lymph node syndrome. *J Immunol*; 130:2002–4.
- [48] Levin M, Tizard EJ, Dillon MJ. 1991. Kawasaki disease: recent advances. *Arch Dis Childhood*; 66:1369–74.
- [49] Luke RG. 1998. Chronic renal failure – a vasculopathic state. *New Engl J Med*; 339(12):841–3.
- [50] Mader R, Narendran A, Lewtas J, Bykerk V, Goodman RCJ, Dickson JR, Keystone EC. 1993. Systemic vasculitis following influenza vaccination – report of 3 cases and literature review. *J Rheumatol*; 20:1429–31.
- [51] Matsubara K, Fukaya T, Miwa K, Shibayama N, Nigami H, Hari-gaya H *et al.* 2006. Development on serum IgM antibodies against superantigens of *Staphylococcus aureus* and *Streptococcus pyogenes* in Kawasaki disease. *Clin Exp Immunology*; 143:427–34.
- [52] Melish ME, Marchette NJ, Kaplan JC, Kihara S, Ching D, Ho DD. 1989. Absence of significant RNA-dependent DNA polymerase activity in lymphocytes from patients with Kawasaki syndrome. *Nature*; 337:288–290.
- [53] Mishima H, Masuda K, Shimada S, Toki N, Taushima H, Gocho M. 1985. Plasminogen activator activity levels in patients with Behcet's syndrome. *Arch Ophthalmol*; 103:935–6.
- [54] Moore PM, Cupps TR. 1983. Neurological complications of vasculitis. *Ann Neurol*; 14:155–267.
- [55] Mortensen SA, Baandrup U, Wennevold. 1986. Endomyocardial biopsy in children with cardiac hypertrophy. *Acta Paediatr Scand*; 75:81–5.
- [56] Nagata S, Yuichiro Y, Maeda M, Yoshikazu O, Yabuta K. 1993. Immunohistochemical studies on small intestinal mucosa in Kawasaki disease. *Pediatric Research*; 33(6):557–63.
- [57] Nigro G, Zerbini M, Krzyzstofiak A, Gentilomi G, Porcaro MA, Mango T, Musiani M. 1994. Active or recent parvovirus B19 infection in children with Kawasaki disease. *Lancet*; 343:1260–1.
- [58] O'Duffy JD, Goldstein NP. 1976. Neurologic involvement in seven patients with Behcet disease. *Am J Med*; 61:170–8.
- [59] Ono S, Onimaru T, Kawakami K, Hokonohara M, Miyata K. 1985. Impaired granulocyte chemotaxis and increased circulating immune complexes in Kawasaki disease. *J Pediatr*; 106(4):567–70.
- [60] Peces R, Riesgo I, Oriega F, Velasco J, Grande JA. 1984. Amyloidosis in Behcet's disease. *Nephron*; 36:114–7.
- [61] Pivetti-Pezzi P, Accorinti M, Abdulaziz MA, La Cava M, Torella M, Riso D. 1995. Behcet disease in children. *Jpn J Ophthalmol*; 39:309–14.
- [62] Polomeno RC, Jacob J-L, Chad Z, Lapointe N. 1981. Anterior uveitis and Kawasaki disease. *Ibid*:11–12.
- [63] Reik L. 1980. Disseminated vasculomyelinopathy: an immune complex disease. *Ann Neurol*; 7:291–6.
- [64] Roujeau J-C, Huynh TN, Bracq C, Guillaume J-C, Revuz J, Touraine R. 1987. Genetic susceptibility to toxic epidermal necrolysis. *Arch Dermatol*; 123:1171–3.
- [65] Roujeau J-C, Guillaume J-C, Fabre J-P, Penso D, Flechet M-L, Girre J-P. 1990. Toxic epidermal necrolysis (Lyell syndrome). *Arch Dermatol*; 126:37–42.
- [66] Rowley AH, Gonzalez-Crussi F, Gidding SS, Duffy CE, Shulman ST. 1987. Incomplete Kawasaki disease with coronary artery involvement. *J Pediatr*; 110:409–13.
- [67] Sakane T, Kotani H, Takada S, Tsunematsu T. 1982. Functional aberration of T cell subsets in patients with Behcet's disease. *Arthritis and Rheumatism*; 25 (11):1343–51.

- [68] Sams WM, Thorne EG, Small P, Mass MF, McIntosh RM, Standford RE. 1976. Leukoclastic vasculitis. *Arch Dermatol*; 12:219–22.
- [69] Scheibner V. 2004. Dynamics of critical days as part of the dynamics of non-specific stress syndrome discovered during monitoring with Cotwatch breathing monitor. *J ACNEM*; 23 (3):10–14.
- [70] Shulman ST, Rowley AH. 1986. Does Kawasaki disease have a retroviral aetiology? *Lancet*; 6 Sep.:545–6.
- [71] Smith PK, Goldwater PN. 1993. Kawasaki disease in Adelaide: a review. *J Paediatr Child Health*; 29:126–31.
- [72] Stanley CA, DeLeeuw S, Coates PM, Vianey-Liaud C, Divry P, et al. 1991. Chronic cardiomyopathy and weakness or acute coma in children with a defect in carnitine uptake. *Ann Neurol*; 30:709–16.
- [73] Strom BL, Carson JL, Halpern AC, Schinnar R, Snyder ES, Shaw M, et al. 1990. A population-based study of Stevens-Johnson syndrome. *Arch Dermatol*; 127:831–8.
- [74] Suzuki A, Tozard EJ, Hooch V, Dillon MJ, Haworth SG. 1990. Kawasaki disease: echocardiographic features in 91 cases presenting in the United Kingdom. *Arch Dis Childhood*; 65:1142–6.
- [75] Takahashi M. 1998. The endothelium in Kawasaki disease: The next frontier. *J Pediatr*; 133:1277–9.
- [76] Takeshita S, Kawamura Y, Takabayashi H, Yoshida N, Nonoyama S. 2005. Imbalance in the production between vascular endothelial growth factor and endostatin in Kawasaki disease. *Clin Exp Immunology*; 139:575–9.
- [77] Thanopoulos BD, Rokas S, Frimas CA, Mantagos P, Beratis NG. 1989. Cardiac involvement in postnatal rubella. *Acta Paediatr Scand*; 78:141–4.
- [77] Tanaka K, Kajiyama K, Kameda S, Nishigouri S, Yamada I, Sawae Y. 1983. Increased solubilization of immune complexes by the sera from patients with Behcet's disease. *Tohoku J exp Med*; 140:363–8.
- [78] Tugal-Tutkun I, Urgancioglu M, Foster CS. 1995. Immunologic study of the conjunctiva in patients with Behcet disease. *Ophthalmology*; 102:1660–8.
- [79] Wees SJ, Sunwood LN, Shin Joong Oh. 1981. Sural nerve biopsy is systemic necrotizing vasculitis. *Am J Med*; 71:525–32.
- [80] Weinstein M. 2006. Inflammation at a previous inoculation site: an unusual presentation of Kawasaki disease. *CMAJ*; 174(4):459–60.
- [81] Williams O, Lehner T. 1977. Immune complexes in Behcet's syndrome and recurrent oral ulceration. *BMJ*; 28 May:1387–9.
- [82] Wilson CA, Choromokos EA, Sheppard R. 1988. Acute posterior multifocal placoid pigment epitheliopathy and cerebral vasculitis. *Arch Ophthalmol*; 106:796–802.
- [83] Wolff AE, Hansen KE, Zakowski L. 2007. Acute Kawasaki disease: not just for kids. *J Gen Intern Med*; 22(5):6814.
- [84] Yamashiro Y, Nagata S, Ohtsuka Y, Oguchi S, Shimizu T. 1996. Microbiologic studies on the small intestine in Kasawaki disease. *Pediatric Research*; 39(4):622–4.
- [85] Yetiv JZ, Bianchine JR, Owen JA. 1980. Etiologic factors of the Stevens-Johnson syndrome. *Southern Med J*; 73 (5):599–602.