Clinical Pathology of the Jarisch-Herxheimer Reaction

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The Jarisch-Herxheimer reaction is a complication that can follow treatment of several infectious diseases. Its most severe form is in louse-borne relapsing fever; in this syndrome the reaction can cause death. Information from studies in Ethiopia during the past eight years is presented, and clinical, physiological, pathological, and immunological features of the reaction are described. Possible causative mechanisms of the reaction are discussed, especially in relation to the role of endotoxin, and an attempt is made to consider this reaction in relation to other endotoxin-associated states.

Medieval syphilis, the great pox, was a terrible disease with a high mortality rate. The beneficial effect of mercury was soon discovered, and in 1539, Ruy Diaz de Isla, a physician in Barcelona, noticed that the first application of mercury ointment to patients with "serpentine disease" was followed by an "ephemeral putrid or hectic fever which left them perfectly healed" [1]. Three hundred fifty years later, Jarisch recorded the fact (apparently well-known to contemporary syphilologists) that the spots of roseolar syphilis became clearer and more numerous after treatment with mercury [2]. In 1902 Herxheimer and Krause [3] pointed out that the reaction followed within 24 hr of the first application of an adequate dose of mercury, and that it was accompanied by a rise of temperature to 38 C, sweating, and anorexia. These investigators observed that the faster the reaction developed, the quicker it settled. The descriptions by these four men contain the essential features of what has become known as the Jarisch-Herxheimer reaction (JHR).

Similar reactions have been reported after treatment of other spirochetal infections (louse-borne relapsing fever [LBRF], Vincent's angina, rat bite fever, leptospirosis, and yaws), of some bacterial infections (brucellosis, tularemia, glanders, and anthrax), and of African trypanosomiasis, in which it is a serious hazard [4, 5].

Description of the JHR

The JHR is a distinct entity, characterized by a triad of events that follow the first adequate dose of a drug in a variety of infectious diseases. (1) The body temperature first rises and then falls. The rise in temperature is accompanied by a chill, distress, and a variety of other symptoms, and the fall by sweating. The changes are typically brisk "all-or-none" events. (2) The existing lesions are aggravated, as are the symptoms and signs: the flaring of the rash in secondary syphilis, increased mental disturbance in cerebral syphilis and trypanosomiasis, and myocardial failure in relapsing fever. (3) There are characteristic physiological changes, including early hyperventilation, vasoconstriction, and a rise in blood pressure and a later fall in blood pressure associated with vasodilation and low peripheral resistance.

The crisis that naturally terminates each febrile
< 2 hr. Procaine penicillin (3 × 10^6 units by im injection) is also effective; it clears the blood more slowly (8–9 hr) but produces a less severe reaction. Tetracycline has the added advantage of preventing relapses. Alteration of the dose of a given antibiotic does not alter the severity of the ensuing JHR.

LBRF has several features of interest to students of infectious disease. Spirochetes can be simply, if roughly, quantitated. It is still not clear whether the termination of spirochetemia in each remission is brought about by antibodies or is independent of their production; if the latter is the case, what factors limit spirochete populations? LBRF is one of the most severe febrile diseases, brief and predictable in its behavior, and so is eminently suitable for physiological studies. The rapid interplay of disorders of several organs and systems calls for continuous clinical vigilance and fine judgment. The crisis that follows treatment is the most dramatic example of the JHR and ought to provide a wealth of information on the pathogenesis of inflammation and shock. The studies that I shall describe, however, pose more questions than answers.

Characteristics of the JHR in LBRF

Clinical features. The reaction begins about 60 min after iv tetracycline has been given. There is a brief moment when the patient feels uncomfortable, anxious, and restless and may vomit or pass urine. A vigorous rigor then begins and lasts 10–30 min. The rigor is most distressing and frightening for the patient and may be accompanied by limb pains, diarrhea, vomiting, paroxysmal cough, disorientation, delirium, or even coma. After the rigor, the patient suddenly feels hot and soon breaks out into a profuse sweat, after which he feels comfortable and falls asleep, exhausted.

Physiological changes. During this reaction, the four phases of the classical human response to endotoxin can be clearly recognized [7, 8]: (1) the prodromal phase; (2) the chill phase, during which body temperature, blood pressure, and pulse and respiratory rates increase; (3) the flush phase, when blood pressure falls strikingly and the temperature reaches its peak of 40 C–42 C before starting to fall; and (4) the
phase of defervescence, which lasts for up to 12 hr. Patients can die in the chill phase of hyperpyrexia (none died in our series) or in the phase of defervescence (three of 64 in our series), most probably of myocardial failure, but the situation is complex.

Metabolic rate (as indicated by a rise in CO₂ output, O₂ uptake, and respiration) rises sharply and peaks with the rigor. This increase is due partly to the fever and partly to muscular activity, which is equivalent to the level of activity during a walk up a gradient. Ventilation is stimulated to cope with the demand for O₂, and the respiratory rate can rise to >80 breaths per min. However, ventilation is in excess of physiological demands, as shown by the low level of PaCO₂, and the presence of a third metabolic stimulus is suggested. There is evidence that this stimulus may be endotoxin.

Despite this overventilation arterial O₂ saturation remains low. The calculated values of pulmonary venous admixture show that pulmonary gas exchange is impaired; this problem is more pronounced during the rigor. The impairment might be due to impaired diffusion or to mismatched ventilation and perfusion. The outcome of this arterial hypoxia is lactic acidosis, which can be prevented by breathing 100% O₂.

Circulatory changes are equally striking. Early vasoconstriction, which is so characteristic of experimental endotoxin fever, was only occasionally detected by standard physiological techniques. This finding may have been rare because most patients were, in any case, peripherally constricted, and measurements of systemic vascular resistance were not made frequently enough. However, by use of a finger calorimeter and measurement of finger heat elimination, it was possible to demonstrate peripheral vasoconstriction before and during the rigor and vasodilation in the flush phase [9].

The arterial blood pressure, which is low in LBRF, rises sharply at or immediately before the rigor. This event may be due partly to the sudden increase in cardiac output as a result of muscular activity but probably also follows vasoconstriction caused by endotoxin or some other mediator. At the end of the rigor, blood pressure falls abruptly to dangerously low levels and remains low (although fluctuating) for at least 8 hr and often for two to three days. During or after the rigor, there is a marked fall in systemic vascular resistance, which does not return to pretreatment levels for 8 hr or to normal levels before the next day. This fall might well represent the effect of endotoxin causing hepatosplanchnic vasodilation. Cardiac output falls once the rigor is over but remains above normal until at least the next day.

During the phases of flush and defervescence, skin temperatures fluctuate wildly, a finding possibly representing the conflict between the need to lose heat and the need to maintain blood pressure. The first 8 hr after the rigor is a critical period for the patient. The cardiac output is strained to its limit, the circulating volume falls (D. A. Warrell, unpublished observation) because of dehydration, and death of spirochetes in the myocardium may precipitate or aggravate myocarditis, evidence of which was present in 38% of patients [10]. Signs of acute cardiac failure were detected in 9% of patients; this state responded promptly to iv administration of digoxin. Carefully controlled rehydration and treatment of cardiac failure if it develops is the crux of management after the flush phase.

Hematological events. Just before the rigor and the rise in temperature, the leukocyte count in the peripheral blood starts to fall sharply; the lowest point comes 2 hr later, at about the time spirochetes disappear [11]. Mainly polymorphonuclear leukocytes (PMNs) disappear, but the lymphocyte count falls, too. There is a clear relation between leukopenia and the rise in temperature. Polymorphs degranulate, and vacuoles appear in their cytoplasm and in the cytoplasm of monocytes.

Spirochetes start to disappear from the blood 15–30 min before leukocytes. Leukocytes are able to phagocytose dead spirochetes but not live ones. This sequence of events and the timing involved suggest that killed spirochetes are phagocytosed by granulocytes and monocytes, which become sequestered, degranulate, and release various mediators of inflammation, especially endogenous pyrogen. If endotoxin were released at this time, it might be expected to have a similar effect on leukocytes and body temperature.

Hemostasis. Studies of blood coagulation in our patients before treatment showed thrombocytopenia (92%) and prolonged prothrombin or partial thromboplastin times (50%). Fibrinogen
levels were high in 48% and low in 20% of the patients. Bleeding time was normal and clotting time was rapid. There was no correlation between these findings and spirochete densities. It is important to distinguish between the early petechial rash in LBRF and severe hemorrhage late in the disease. The petechial rash is found almost at the onset of the disease in about one patient in five. Petechiae are also present on the conjunctiva and on mucosal and serosal surfaces and may be accompanied by epistaxis; however, there is never severe hemorrhage at this stage. Borreliae are known to stick to endothelial surfaces, and it has been postulated that clumps of spirochetes become trapped in capillaries and damage them. Platelets may then adhere to the damaged endothelium and clumped spirochetes. In some forms of trypanosomiasis, which shares many of the features of relapsing fever, there is evidence for a factor that is released by trypanosomes and aggregates platelets. Either or both of these processes could account for thrombocytopenia, which is so characteristic from the onset of the illness. Late in the disease, there may be massive bleeding, especially on serosal surfaces and retroperitoneally; this bleeding is associated with hepatocellular failure and prothrombin deficiency.

In preliminary studies of patients undergoing the JHR [12], two of seven patients had changes in the levels of circulating platelets, fibrinogen, and fibrin degradation products; these findings were suggestive of a transient phase of disseminated intravascular coagulation (DIC).

Drs. David Dennis, S. Awoke, and E. B. Doberstyn have recently undertaken a much fuller (and currently unpublished) study of 29 patients with LBRF who are undergoing the JHR after treatment with erythromycin, which induces a slower reaction than tetracycline. These workers counted platelets and measured euglobulin clot lysis time, protamine sulfate, ethanol gelatin, and fibrin degradation products by countercurrent immunoelectrophoresis. They found that the platelet count fell further (mean, 5.2 × 10^9/mm^3 to 3.6 × 10^9/mm^3) and that the proportion of patients with circulating fibrin monomers increased during the JHR from 39% to 64% and with fibrin degradation products from 0 to 44%. They took this as evidence of a sudden increase of fibrinolysis during the JHR. There were, however, no changes in the levels of hemoglobin or fibrinogen or in the already prolonged prothrombin and partial thromboplastin times, nor did erythrocytes fragment. Direct biochemical proof of DIC was therefore lacking, and there was no clinical evidence for the development of this state during the JHR. It does not seem likely, based on this evidence, that DIC is essential to the pathogenesis of the JHR, but clearly it could pose a complicating threat.

In a postmortem study of six Ethiopians who died 4–12 hr after treatment, Judge et al. [13] considered that myocarditis was the most likely cause of death in each case. In addition, these authors found petechial hemorrhages in pulmonary alveoli. In no instance was there evidence of adrenal or renal cortical hemorrhage or necrosis. In five of the patients, a few adrenocortical sinusoids contained fibrin thrombi, and fibrin surrounded occasional adventitial vessels. In this study, too, evidence of DIC was minimal, and nothing suggested that it was the cause of death.

**Antibodies and complement.** The classical studies of Balteanu et al. [14] showed that the infusion of immune serum into patients with LBRF cleared the blood of spirochetes and induced the JHR. The same phenomenon has been shown in rabbits infected with *Spirillum minor* [15]. It is assumed, but by no means proved, that antibodies induce the natural remissions of LBRF, with their attendant reactions. Certainly, serum levels of IgM, which include specific antibody, increase with each wave of spirochetemia in experimental relapsing fever [16], but levels of IgG do not increase until the first wave of spirochetemia is cleared. Levels of agglutinating antibody peak after the crisis. I know of no studies in which the investigators have looked for evidence of antibody consumption during the JHR in LBRF.

Serum complement levels have been found to be consistently low in LBRF (mean C3, 77.3 mg/dl; mean C4, 32.8 mg/dl), a fact that is suggestive of complement activation (D. Dennis, R. L. Gillum, S. Awoke, and E. B. Doberstyn, personal communication). There was a suggestion of a further fall during the hours after treatment. At the moment, however, there is no firm information on the cause of complement activation, which could be due to any one of a number of events, including immune complex formation, endotoxin...
activation, or immune lysis of spirochetes. More detailed analysis of these preliminary studies is awaited.

Evidence for the presence of endotoxin. The four phases of the JHR (prodrome, chill, flush, and defervescence) recall experimental endotoxin fever but by no means exclude the possibility that, in the JHR, some other stimulus (such as phagocytosis) causes the release of a mediator common to both situations. Endogenous (or leukocyte) pyrogen is a likely possibility. Although severe hypotension is the rule after the JHR, our patients invariably had warm skin and a bounding pulse, and we never saw the cold, clammy, distressed, and thready patient typical of the individual with gram-negative septicemia.

From each of four patients, we took 100 ml of blood at the onset of the JHR; the next day we reinfused the blood into the patient from whom it had been obtained [9]. In one instance, this reproduced the typical physiological features of the JHR. Vasconstriction began 40 min after infusion and rigor after 60 min. The experiment indicated the presence of a circulating mediator of the JHR. This timing of the reaction is suggestive of the presence of endotoxin rather than that of leukocyte pyrogen. Careful examination of the observations, however, did suggest a brief moment of vasconstriction and a rise in arterial pressure and respiratory rate starting 10 min after reinfusion. This timing is suggestive of the presence of leukocyte pyrogen. Rectal and skin temperatures altered as they do in the JHR.

To examine further the nature of the circulating mediator of the JHR, we injected samples of plasma from patients with LBRF (centrifuged free of spirochetes) into pairs of rabbits and measured the rise in body temperature. Samples were taken before treatment, at the onset of the reaction, during rigor, and again the next day. All samples taken from febrile patients induced fever in rabbits; as little as 2 ml of plasma was sufficient. There were no constant differences in timing or degree of this febrile response that could be related to the timing of sampling. In particular, there was no evidence that plasma obtained at onset of the reaction contained measurably more mediator. Plasma taken on the day after the JHR, when the patients were afebrile, induced little or no fever in rabbits.

When pyrogenic samples of human plasma were incubated with normal rabbit plasma and injected into endotoxin-refractory rabbits, fever was not induced. These two experiments provide strong support for the view that in LBRF, there is a potent circulating endotoxin. There was no evidence of leukocyte pyrogen in the experiments with humans or in those with rabbits. This result was unexpected; perhaps we used too small a volume of plasma. For two reasons, however, it is by no means clear whether endotoxin release mediated the JHR. First, in rabbits, it was not possible to demonstrate an increase of circulating endotoxin at the time when spirochetes were being killed. Second, three of four patients who were reinfused with their own plasma after treatment failed to develop fever or any other manifestation of the JHR. It is quite possible, however, that at this stage the patients were tolerant of endotoxin, just as patients are after typhoid fever [17], but this hypothesis has not been formally tested.

Recently, Perine has used the limulus lysate assay to look for the presence of endotoxin in plasma from patients with LBRF. In three of 11 patients studied, results of the assay were positive, but only in samples of plasma taken during the phases of flush and defervescence.

It has long been known that petechiae are never seen during relapses. There is some evidence that antibody, cross-reacting between relapse strains, is responsible for this. It is interesting that antibody to endotoxin prevents DIC in rabbits [18].

There are suggestions in the literature that corticosteroids reduce the severity of the JHR in patients with syphilis. We investigated this possibility in patients with LBRF [8]. Two patients were infused with hydrocortisone at the rate of 20 mg/kg per hr, starting 1 hr before the injection of tetracycline. Hydrocortisone reduced fever in both patients (by 0.7 C and 1.5 C, respectively), but the JHR was not prevented, nor was the severity of any of the physiological or hematological changes reduced. The actual rise in temperature was greater than usual in these two patients, although the maximal temperature reached was not as great. These results do not necessarily mean that fever in LBRF before treatment and fever during the JHR are caused
by different mechanisms. It may simply be that steroids, in the dose used, can stabilize leukocyte or lysosome membranes up to a certain labilizing threshold and that this threshold is exceeded in the JHR. It is known that steroids do inhibit release of leukocyte pyrogen [19]. The experiment does not help to tell us whether the labilizing stimulus is phagocytosis, endotoxin, or some other process.

The JHR in Syphilis

The differences between the JHR in syphilis and the JHR in LBRF have been summarized [20]. In syphilis the incidence of the JHR after treatment varies directly with seropositivity and is greatest in the secondary stage and in general paralysis of the insane [21]. In syphilis the reaction is slower in onset and milder than it is in LBRF. The patient's temperature before treatment is usually lower, and there is no constant pattern of increasing fever: some patients show no increase, whereas others have increases of up to 2.7°C (one degree more than we ever recorded in LBRF). Identical physiological events take place, but these events are not as marked as those in LBRF. There is a suggestion that corticosteroids may modify the JHR in syphilis [22].

The essential difference is that, in syphilis, there is no phase of leukopenia; rather, there is only a phase of leukocytosis, which starts with the febrile response. The significance of this difference is discussed below.

Synthesis of Information on the Pathogenesis of the JHR and Suggestions for Further Research

The JHR begins with the death of spirochetes, which are then phagocytosed by PMNs, monocytes, and fixed reticuloendothelial cells. The simplest and still the most attractive and perhaps most important sequence of events follows directly from phagocytosis. There is ample experimental evidence (with organisms such as pneumococci) that sudden and massive intravascular phagocytosis is followed by leukocyte sequestration, the release of leukocyte pyrogen and other mediators of inflammation, and later by leukocytosis. Endogenous pyrogen causes fever, at least some of the circulatory changes we have described, and local inflammation. The snag to this hypothesis is that, so far, there is no direct evidence that leukocyte pyrogen is indeed released. Further research is needed to settle this point. In syphilis, in which the organisms are mainly in the tissues, the reaction is slower, leukocyte sequestration is unimportant, and leukocytosis and local inflammation dominate the picture.

There is no evidence for immune or allergic mechanisms in the JHR after treatment of LBRF or syphilis. The JHR is just as severe early in LBRF, when antibodies cannot be detected, as it is later. This fact suggests that, in the spontaneous JHR (which is often relatively mild), antibodies may kill spirochetes and contribute to phagocytosis and lysis but play little or no further part. We have never observed clinical features of immune complex disease, such as arthritis, episcleritis, glomerulonephritis, or cutaneous vasculitis, after the JHR. Nevertheless, immune complexes have not been looked for formally, and this search might be worthwhile.

In infections with Trypanosoma rhodesiense, however, urticaria, joint pains, and eosinophilia accompany the JHR, which follows treatment, and the titer of cytoplasmic antibodies falls for a period of several days [23].

Certainly in LBRF complement is activated, both during the disease and during the JHR, in a proportion of patients. Phagocytosis and endotoxemia (with or without DIC) are two possible explanations for this finding in the absence of evidence for immune activation. Further work is necessary to define the role of complement in the JHR.

Endotoxin might cause the clinical and hematological manifestations of the JHR in LBRF—if it is released; it seems important to repeat our rabbit assays of endotoxicity with use of ultracentrifuged plasma and without the addition of tetracycline to the pretreatment sample, thereby reexamining the question of endotoxin release during the JHR.

Two clinical observations suggest a role for endotoxin in the pathogenesis of the JHR. One is the four classical phases of the reaction; the other is the duration of leukopenia, which resembles that caused by the experimental injection of Escherichia coli (as compared with pneumococci or staphylococci) into rabbits [28].
The lack of agreement between the results of assays in rabbits and those of Perine's limulus assays makes one wonder whether these systems are detecting different qualities of endotoxin. Endotoxin detectable by limulus lysate appeared only after the reaction and in only one-third of the patients studied. Could it be that this assay is detecting gram-negative endotoxin entering the circulation across a gut wall anoxic from prolonged splanchnic pooling? There is clearly a need to isolate and define borrelial endotoxin. Endotoxin produces its physiological effects through other biochemical mediators, which remain to be defined in the JHR.

The endotoxin/leukocyte pyrogen hypothesis is particularly attractive in view of Murphy's demonstration [29] that the quantity of leukocyte pyrogen released by a given number of leukocytes is related to the dose of endotoxin with which the leukocytes have been incubated, only over a narrow range of extremely low doses. Beyond this point, leukocyte pyrogen release is maximal. This is essentially an all-or-none response and might explain the all-or-none characteristic of the JHR, the remarkable regularity of the pattern of fever and physiological changes, and the independence of the severity of the reaction from the stage of the disease.

Endotoxin might also be responsible for the observed complement changes and for the features suggestive of DIC; however, it is perhaps a little disturbing that, if endotoxin is so important, clear evidence of DIC is so hard to obtain and that the syndrome of severe gram-negative shock was never observed. Does this again point to a particular quality of endotoxin?

It is likely that several of the mechanisms discussed come into play during the JHR, perhaps not all of them in the same patient; it is too early to attempt to present a unified scheme for their pathways and interactions. However, it seems important to pursue this subject, because the JHR in LBRF is always severe and can be fatal, and, until its pathogenesis is resolved, it is unlikely that a way will be found to mitigate it.

We need a good model of the spirochetal JHR. Squirrels, rhesus monkeys, and patas monkeys are susceptible to *Borrelia*, and Judge et al. [30] have recently shown that the grivet monkey (*Cercopithecus aethiops*) infected with *Borrelia recurrentis* develops the JHR after treatment with tetracycline. Features of the reaction include leukopenia, fever, hyperpnea, and tachycardia.

The JHR in Relation to Other Clinical Syndromes Associated with Endotoxin

It might be valuable to look briefly at similarities and differences among four other endotoxin-associated clinical situations: (1) experimental injection of endotoxin into human volunteers; (2) gram-negative septicemic shock; (3) fulminating meningococcemia; and (4) dengue shock syndrome. (Although there is no evidence at all to associate dengue shock syndrome with endotoxemia, it does represent the purest form of shock and DIC.)

The doses of endotoxin currently used experimentally in man [24] produce the four-phase reaction seen in the JHR, with fever starting 90–120 min after injections. Leukopenia is occasionally noted, and leukocytosis, due to mobilization of bone marrow reserves of PMNs, is the rule. Shock and DIC do not develop. The subjects are healthy volunteers and are given small doses of endotoxin; thus these studies cannot imitate the effects of large doses of endotoxin in sick patients or in dogs, since the physiological responses of dogs to endotoxin are quite different from those of humans. In their classical studies, Altschule et al. [7] gave typhoid vaccine iv to induce therapeutic fever in patients with a variety of chronic diseases; this may be a better model of natural endotoxin-associated disease. They recorded prodromes as short as 30 min and many of the physiological changes seen in the JHR, although cardiac output fell in the chill phase (a fact which they attributed to excessive venous constriction). Of greatest interest to this discussion, however, was that several patients developed shock during the flush phase, with cold, pale, sweating skin, anxiety, dyspnea, and a falling cardiac output; this syndrome resembles much more that seen in gram-negative septicemia than that in the JHR.

“Gram-negative shock" is seen in patients with gram-negative septicemia or endotoxemia due to intestinal vascular stasis and ischemia associated with a variety of disorders such as burns or peritonitis. The patient is already sick, and the quantity of endotoxin in his blood may be large. There is no doubt that the development of the
cold, clammy shock syndrome carries a very high risk of mortality [25], but the pathogenic role of endotoxin itself is still not entirely clear. There is not yet a simple direct relation between septicemia and endotoxemia as detected by the limulus assay [26] or endotoxemia and shock [27], although 50% of patients with gram-negative septicemia have endotoxemia and 40% develop the shock syndrome. This syndrome differs from that in the JHR in that peripheral vasoconstriction is marked and vasoconstrictor drugs are of little use, but the essential feature of lowered total systemic vascular resistance is present, and there is a clear association with complement activation, thrombocytopenia, DIC, and fibrinolysis [27]. It seems likely that features of septicemia other than endotoxin are important in the pathogenesis of shock.

Fulminant meningococcemia, which is characterized by shock and bleeding, is of particular interest for two reasons. First, it is another example of the outcome of a septicemia that may or may not be complicated by shock and DIC. The detection of meningococcal antigen in meningococcemia [31] has provided a useful diagnostic and prognostic tool. The sera of all patients with fulminant meningococcemia contain antigen [32], and all sera containing antigen (which is pure capsular polysaccharide), also contain endotoxin as assayed by classical techniques in rabbits [33]. Second, bleeding is much more common than in other gram-negative septicemias. There is comparative evidence linking this syndrome with the generalized Shwartzman reaction. Renal and adrenal hemorrhage and fibrin deposition are common. Meningococcal endotoxin is eight times more potent in eliciting the Shwartzman reaction in rabbits than is Salmonella typhi endotoxin [34]. The fact that this property does not reside with a protein or polysaccharide contaminant of the lipopolysaccharide suggests that "endotoxins" from different organisms may also have other biological differences that will affect their clinical activities and may be reflected in different assay systems. Nevertheless, antigenemia in meningococcal disease correlates only roughly with septicemia, and the factors that turn septicemia into antigenemia are little understood.

Dengue shock syndrome is seen in children and young adults in Southeast Asia; these individuals develop severe shock, which is usually accompanied by bleeding, after four to 10 days of an otherwise simple viral illness [35, 36]. Death is due to shock, which, in turn, is probably due to massive release of vascular permeability factors from complement activation and platelet damage. Both the classical and alternate complement pathways are vigorously activated, in contrast to the situation in endotoxemia, in which activation is predominantly through the alternate pathway [37, 38]. Although there is much evidence of DIC in this syndrome, it is of interest that renal and adrenal lesions are very rare, and that bleeding is not the usual cause of death. DIC and vascular damage are clearly not synonymous. The trigger to this syndrome is a second dengue infection in the presence of preexisting antibodies; a pathogenetic role for immune complexes is suspected but not yet proven.

This superficial comparison should be sufficient to remind us of the separate identities of septicemia, antigenemia, and endotoxemia and of the complicated interactions of inflammation, shock, and bleeding. Each clinical situation must be dissected and its pathogenesis understood before we can help patients fully.

References


