Heparin-induced thrombocytopenia: a historical perspective

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Heparin was discovered 90 years ago, and within 2 decades it was being widely used as an anticoagulant. The numerous advantages of heparin lend to its broad use including its immediate onset of action, relatively short half-life (~60 minutes), simple laboratory monitoring (aPTT), ability to be reversed (using protamine), and low cost. Despite a long experience of using heparin, the counterintuitive notion that an anticoagulant could be intensely prothrombotic took almost 4 decades to become recognized.

Our understanding of heparin-induced thrombocytopenia (HIT) has increased considerably and to a large measure exemplifies the best of translational research. Sometimes, basic studies investigating the pathophysiology of HIT lead to clinical insights. In other instances, clinical observations prompted basic studies. Together, these basic and applied investigations have dramatically enhanced our understanding of the pathogenesis and treatment of HIT.

Heparin-induced arterial embolism

On June 1, 1957, at the Fifth Scientific Meeting of the International Society of Angiology in New York, Rodger E. Weismann, an Assistant Professor of Clinical Surgery at the Dartmouth Medical School, and his Resident in Surgery, Dr Richard W. Tobin, described 10 patients who developed arterial embolism during systemic heparin therapy. The first reported embolic event was a femoral artery embolic occlusion, which occurred in a 62-year-old woman who was receiving heparin because of a deep-vein thrombosis (DVT). Three days after successful femoral embolectomy, she developed sudden occlusion of the distal aorta requiring distal aortic and bilateral iliac embolectomies.

Multiple thromboemboli were observed in 9 of the 10 patients reported. Six patients died as a result of the thromboembolism, and 2 survivors underwent above-knee amputation. The clots were described as “pale, soft, salmon-colored” and were composed mostly of fibrin, platelets, and leukocytes. The arterial emboli began on average 10 days after commencing heparin treatment.

An additional 11 patients were described 5 years later by Roberts and colleagues. These vascular surgeons noted the paradox of “unexplained arterial embolization [occurring] for the first time while being treated with heparin for some condition that could not of itself reasonably be expected to cause arterial emboli. All patients had been receiving heparin for 10 days or more when the initial embolus occurred.” Thus, both groups noted the temporal hallmark of HIT, a delay of approximately 1 week from initiation of heparin to onset of its thrombotic manifestations.

Heparin-induced thrombocytopenia

Routine platelet count measurements were not routinely performed until the 1970s. This may explain why thrombocytopenia was not reported in the first 24 patients with heparin-induced arterial emboli. In 1969, the term “heparin-induced thrombocytopenia” was used by Natelson to describe a 78-year-old man with pulmonary embolism who developed severe thrombocytopenia after heparin. Over the ensuing days, 2 separate periods of heparin readministration were each characterized by abrupt platelet count declines and corresponding increases in fibrinogen. The addition of heparin to the patient’s citrated platelet-rich plasma caused platelet aggregation. The striking dichotomy of a heparin-induced platelet count decrease, but rise in the level of fibrinogen, captures the essence of HIT: heparin simultaneously promotes and treats the thrombosis.

The syndrome of heparin-induced thrombocytopenia and thrombosis

The first to identify the central features of the HIT syndrome—thrombocytopenia, thrombosis, and its immune pathogenesis—were Drs Silver, Rhodes, and Dixon. In their 1973 paper, they described 2 patients with severe thrombocytopenia, myocardial infarction, and heparin resistance, with platelet count recovery on discontinuing heparin treatment. Both patients developed rapid recurrence of thrombocytopenia when heparin rechallenges were given.

An immune basis for this syndrome was suggested by increased numbers of bone marrow megakaryocytes and a rapid recurrence of the thrombocytopenia upon heparin reexposure. A circulating heparin-dependent, platelet-activating substance (subsequently identified as IgG) was found in the patients’ blood, which caused aggregation of donor platelets in the presence of heparin.

A subsequent report by Rhodes and coinvestigators helped establish HIT as a distinct syndrome. Eight patients were described with thrombocytopenia (platelet count nadir, 25 × 10^9/L) that occurred during heparin administration. Thrombotic, rather than hemorrhagic, complications predominated: 7 patients had new or recurrent thromboembolic events, and one patient had a hemorrhagic stroke. Complement-fixing, heparin-dependent antibodies were found in blood from 5 patients.

Platelet activation in HIT

During the latter half of the 1970s, at least 7 groups of investigators reported patients who resembled those of Rhodes and colleagues. Together, these studies provided further evidence of an
immunologic basis for HIT. A common feature of these reports was evidence of platelet activation induced by patient serum, plasma, or purified immunoglobulin.11-17

HIT: an immune disorder or a consumptive coagulopathy?

Doubts persisted regarding the immune basis of HIT. After all, Rhodes and colleagues had also noted that when their patients were deliberately rechallenged with heparin several months after their episode of HIT, thrombocytopenia failed to recur.5,6 Moreover, HIT patients typically did not exhibit severe thrombocytopenia and purpura—feature characteristic of established drug-induced immune-mediated thrombocytopenia reported with quinine, among other drugs. Also arguing against the model of typical immune-mediated drug-induced thrombocytopenia were our observations that thrombocytopenia could resolve while the patient continued on heparin therapy.18

But other evidence supported an immune pathogenesis: for example, Cines and associates19 documented heparin-dependent binding of complement to platelets. Another observation that suggested a complex antigen was provided by Green and coworkers.12 These investigators demonstrated that the antibodies did not bind to heparin per se, but required heparin plus a cofactor found in platelet lysates.

The uncertainty regarding etiopathogenesis was also reflected in the name of the condition: HIT was often termed heparin-associated thrombocytopenia to reflect the assumption that the thrombocytopenia might not be directly related to the heparin.20 Some investigators21-23 raised the possibility that a procoagulant contaminant within the heparin preparation could be causing the reaction, perhaps by triggering disseminated intravascular coagulation. Further support for this hypothesis was provided by the demonstration that different heparin preparations carried different risks for thrombocytopenia.18,24 In addition, consistent with a "contaminant" possibility was the fact that heparin is unique among almost all medications: it consists of polydispersed and heterogeneous polysaccharide chains that have been extracted and partially purified from either beef lung or pork intestinal mucosa.

Heparin itself can directly interact with platelets and cause variable platelet aggregation when added to platelets in vitro. In addition, some investigators have reported that when heparin is injected into patients, there can be an early, transient drop in platelet count.25,26 At a platelet immunobiology workshop held in Milwaukee, it was proposed that the early, nonimmune disorder would be termed "HIT, Type 1" and the later onset immune disorder would be called "HIT, Type 2." Today these designations are not commonly used and most physicians diagnose the immune disorder simply as heparin-induced thrombocytopenia (HIT).

Our research group became interested in developing a laboratory test to diagnose HIT. Although platelet-associated IgG levels were elevated in HIT patients, we found that it was not a diagnostically useful assay. Subsequent investigations have documented that the various assays for PAIgG have minimal diagnostic usefulness in any thrombocytopenia.10,28,29 We next prospectively evaluated the widely used assay of heparin-dependent platelet aggregation.30 The results indicated that heparin-dependent platelet aggregation was only a moderately useful test for HIT and although it had a high specificity, its sensitivity was low. We also made an observation that subsequently proved informative, namely that platelet aggregation was maximal at pharmacologic concentrations of heparin (0.1 U/mL), but that higher heparin concentrations (above 5 U/mL final) often produced a negative result.

Our next aim was to improve the diagnostic usefulness of the functional (platelet activation) assay for HIT.31 The sensitivity was increased by optimizing the reactivity of the test platelets and by using the release of radiolabeled 14C-serotonin as the end point. The specificity was increased by observing that the platelet-activating effects of HIT antibodies were inhibited at high heparin concentrations (Figure 1). The serotonin release assay (SRA) was prospectively evaluated against a group of 600 patient and control samples, and proved both sensitive and specific. Subsequent modifications have further enhanced the assay’s diagnostic utility.32

A sensitive and specific test for a disorder can also be used to characterize the component reactions. For example, we were able to confirm the work of previous investigators that the reaction was mediated by IgG. Furthermore, the unimodal pattern of antigen-dependent progressive platelet activation followed by reduced platelet activation (at higher heparin concentrations) suggested to us that this was an immune complex type of reaction.33

In an attempt to identify the platelet target for the HIT antibodies, we tested platelets with congenital deficiencies of glycoprotein Ib/III (Glanzmann thrombasthenia) and platelets deficient in glycoprotein Ib/IX/V complex (Bernard-Soulier syndrome).34 The identical reaction to normal platelets indicated that these glycoproteins did not directly participate in the reaction. Next, IgG from patients with HIT was purified and digested. The requirement of F(ab')2 indicated that HIT was an immunologic disorder recognizing a specific, but as yet unidentified, epitope. Inhibition by human or animal Fc indicated that HIT was an immune complex disorder. Finally, the complete inhibition of platelet reactivity via a monoclonal antibody against the platelet Fc receptor confirmed that platelet activation in HIT was mediated through the platelet Fc receptor.35

We now know that HIT-mediated platelet activation is a dynamic process36 in which the Fab from the HIT-IgG binds to platelet-associated PF4. Subsequently the Fc region on the IgG molecule binds to the Fc receptor on the same or adjacent platelets, which in turn triggers platelet activation.35,36
Figure 2. Platelet-derived microparticles generated by heparin-induced thrombocytopenia serum. Platelets and microparticles were identified using fluorescence (FL1, FITC-antiGPIbα) and size (FSC, forward scatter) characteristics. The platelets had been incubated with heparin-induced thrombocytopenia serum in the presence of 0, 0.1, 0.3, or 100 U/mL heparin. The microparticles (inset box) were generated in the presence of 0.1 and 0.5 U/mL heparin, but not at 0 or 100 U/mL heparin. Results of the representative experiment are shown. Adapted from Warkentin et al45 with permission.

The platelet Fc receptor was identified by Karas et al37 with further characterization by Rosenfeld et al38 as well as by our group.39 Platelets carry the Fcγ receptor present at relatively low copy numbers (~1000 to 2000 copies per platelet).37-39 IgG immune complexes, which form in patients with HIT, produce receptor cross-linking, which strongly activates platelets. A common polymorphism of FcγIIa (arg131/ his131) have proven to be of minor relevance in HIT.

Microparticles: the platelet procoagulant response

It is rare for a prothrombotic disorder to cause both arterial and venous thrombosis. HIT is an exception. In many HIT patients there was evidence of hypercoagulability, but the pathway that could initiate both arterial as well as venous thrombosis remained unexplained. Three explanations were proposed: (1) HIT antibodies could bind to and injure endothelial cells, thereby initiating coagulation40,42; (2) HIT antibodies could bind to monocytes and release tissue factor43,44; and (3) HIT antibodies induce a platelet procoagulant response.

Our group focused on the platelet procoagulant explanation. Using flow cytometry, we found that HIT sera caused platelets to form microparticles (Figure 2).45 In contrast, quinine/quinidine-induced thrombocytopenia sera did not cause microparticles, even though there was a dramatic increase in drug-dependent antibody binding to platelets. The procoagulant nature of the HIT microparticles was evidenced by shortening of the Russell viper venom time.45 We also showed that in at least some patients, there were detectable circulating platelet-derived microparticles during the acute episode of HIT.45 In subsequent comparative studies, we found that the magnitude of this platelet procoagulant response induced by HIT antibodies exceeded that of other physiologic agonists, including thrombin and collagen.46 Microparticle formation induced by HIT sera was sufficiently reliable to be used as a diagnostic test for HIT.47

To better understand these microparticles, we examined their morphology using a variety of microscopic techniques (Figure 3).48 Using confocal microscopy, HIT antibodies plus heparin could be shown to produce platelet particles. Scanning and transmission electron microscopy showed that these microparticles ranged in size from 0.1 to 1.0 μm in diameter. These studies demonstrated that platelet activation resulted in the formation of localized points of swelling on the platelet body with the formation of well-defined buds. These platelet buds are released from the platelets to form the microparticles.48

PF4/heparin complexes are the major antigen of HIT

In 1992, in a significant advance for HIT-related research, Amiral et al49 identified the elusive platelet component of the HIT antigen when he demonstrated that platelet factor 4 (PF4), a tetrameric member of the C-X-C subfamily of chemokines, formed complexes with heparin that bound HIT antibodies. This seminal observation was confirmed and extended by other groups.50,51 The antigen was shown to be present on multimolecular complexes of PF4 and heparin that required an optimal stoichiometric ratio of PF4:heparin of 1:1 to 2:1. In addition, it was shown that endothelial cells could bind PF4 and also produce the antigen. The identification of PF4 as the target antigen allowed the development of enzyme-immunoassay (EIA) techniques.52

The amino acid composition of PF4 had already been identified in 1987 by Poncz and colleagues.53 The small size of the PF4 monomer (70 amino acids) allowed Horsewood to synthesize a series of overlapping peptides that spanned the entire length of the PF4 molecule.54 We found that a minimal length of PF4 (19 amino acids encompassing the carboxy-terminal peptide including the
lysine-rich moiety that binds heparin) was required for reactivity with certain HIT antibodies. But, it was not possible to identify a linear epitope on PF4 that served as a target antigen. These results suggested that heparin molecules bundle the PF4, resulting in conformational changes to the molecule, which in turn, become the binding sites for the HIT-IgG. Studies by the groups in Milwaukee and Philadelphia have identified several regions on PF4 that are binding sites for HIT antibodies. More recent studies suggest that the antigen sites are located at apposition points where PF4 tetramers are brought into proximity through charge neutralization by heparin. Figure 4 presents a schematic of the pathogenesis of HIT.

Amiral et al have also documented several other potential heparin-dependent antigens, including interleukin-8 and neutrophil-activating peptide-2, but antibodies against these chemokines probably explain only a tiny minority of cases of HIT.

**Characterization of the immune response in HIT**

The demonstration that HIT was caused by PF4/heparin-containing immune complexes that activated platelets through their Fcγ receptors suggests a central role of the IgG immunoglobulin class in the pathophysiology of HIT. The HIT-IgG is polyclonal and IgG1 predominates with smaller amounts of IgG2. Although PF4/heparin-reactive IgM and IgA antibodies are also formed in heparin-treated patients, their role in HIT remains uncertain.

Certain aspects about the immunobiology of HIT remain unexplained. The high frequency of heparin-induced autoantibodies against the self protein PF4 is perplexing. As well, the brief persistence of this antibody in patients with HIT (Figure 5) also remains unexplained, as does the lack of an anamnestic immune response upon reexposure.

**Structural requirements of heparin to form the antigen**

The chemical and structural determinants allowing heparin to induce antigenic changes in the PF4 molecule have been studied by a number of investigators. The impetus was both scientific and commercial: one goal was the identification of a nonheparin polyanion that could be useful for in vitro testing. Visentin and coworkers identified such a substance (polyvinyl sulfonate) that is currently used in a commercial EIA. Another focus of research has been to identify a heparin species that would neither initiate nor propagate HIT. In vitro studies indicated that a variety of sulfated polysaccharides could substitute for heparin to inducing the
antigenic changes in PF4. However, there were 2 key determinants that were required for antigenicity. First, a certain chain length (ie, approximately 1000 Da); and second, a minimal amount of sulfation per saccharide unit were required.50,66 These results suggested that progressively smaller heparin preparations carry a progressively lower risk of HIT. Clinical validation of this potential has been provided by the demonstration that low-molecular-weight heparin (enoxaparin) carries a lower risk of HIT of inducing antibodies and of causing clinical HIT, compared with UFH.68

Recently, there has been interest in whether fondaparinux, a pentasaccharide modeled after the antithrombin-binding region of heparin, will be even less likely to cause or to potentiate HIT. To date, only 2 patient cases of HIT possibly caused by fondaparinux have been reported.69 Whether the presence of anti-PF4/heparin antibodies confers adverse prognosis in certain clinical situations—even in the absence of clinical HIT—is an emerging topic of debate.78-81

Animal models of HIT

The development of an animal (murine) model of HIT has been difficult. The problem reflects the lack of FcyRIIA receptors on murine platelets. Furthermore, murine platelets do not express a PF4 immunologically similar to human PF4. Nonetheless progress is being made in this area. Using a double-transgenic mouse expressing both FcyRIIA and human PF4, Reilly and coinvestigators82 injected the mice with KKO,83 a mouse monoclonal antibody raised against human PF4/heparin. The mice were then injected with heparin, developing thrombocytopenia, including some with thrombosis. This model was used to demonstrate the importance of platelet-bound PF4 in the development of thrombocytopenia. The investigators further evolved the murine model using the same transgenic mice, but with a murine PF4 knockout. This model demonstrated the importance of host factors such as hypercholesterolemia in thrombocytopenia and thrombosis.84 A murine model was used to investigate the immunogenic potential of various ratios of PF4 (murine) to unfractionated heparin.85 These investigators determined that high ratios of murine PF4 to heparin were more immunogenic than the more equimolar ratio that serves as the optimum target for antibody binding.

Evolving concepts in HIT

The thrombocytopenia of HIT is typically moderate (median platelet count nadir, ~60 × 10^9/L), which is different from classic drug-induced immune thrombocytopenic purpura (median nadir, 10 × 10^9/L).86 Some patients with HIT will have a
More recently, agents that inhibit the generation of thrombin, or that inhibit thrombin itself, such as danaparoid, lepirudin, and argatroban, have been used.

HIT was first described as an arterial prothrombotic disorder, perhaps because of its dramatic onset and its recognition by vascular surgeons. For a number of years physicians did not recognize venous thrombi as part of the syndrome. It is now appreciated that VTE predominates over arterial thrombosis in HIT, in a ratio of approximately 4:1. It is also apparent that patient-dependent risk factors play a role in the site of the thrombosis. For example, recent arterial surgery or severe atherosclerosis is associated with arterial thrombosis in HIT, while a central venous catheter predisposes to development of upper limb DVT in patients with HIT. Inherited prothrombotic risk disorders such as factor V Leiden have not been shown to play a major role in explaining HIT-associated thrombosis, although a contributory role in specific circumstances remains plausible.

Venous limb gangrene is another manifestation of HIT, which usually occurs as a result of warfarin-induced microthrombosis due to an altered procoagulant-anticoagulant balance. In this disorder, HIT-associated hypercoagulability interacts with warfarin-induced protein C depletion. Other venous thrombotic events in HIT include unilateral or bilateral adrenal hemorrhagic necrosis (resulting from adrenal vein thrombosis) and cerebral venous (dural sinus) thrombosis.

These concepts help explain the oftentimes severe clinical course of patients with delayed-onset HIT. In this disorder, thrombocytopenia and thrombosis begin days to weeks after heparin has been stopped. Antibodies from these patients can cause platelet activation, in vitro, in the absence of heparin. It is possible that delayed-onset HIT is caused by binding of HIT-IgG to a complex of platelet-bound PF4 and chondroitin sulfate.

By 1998, there was sufficient agreement regarding the pathophysiologic, clinical, and laboratory diagnostic features of HIT that a consensus statement was prepared by representatives of 3 research groups. HIT was conceptualized as a clinicopathologic syndrome with one or more clinical events (thrombocytopenia with or without thrombosis) temporally related to heparin administration and caused by HIT antibodies.

**Treatment strategies for HIT**

The treatment of HIT has paralleled an understanding of its pathophysiology. Initial strategies did not treat the hypercoagulability of HIT, and consisted of heparin cessation alone, warfarin, anecrod, and antiplatelet agents such as aspirin. More recently, agents that inhibit the generation of thrombin, or that inhibit thrombin itself, such as danaparoid, lepirudin, and argatroban have been used.

An important first step after diagnosing HIT is to stop the heparin. Ironically, for some patients, continuation of heparin does not result in clinical worsening, and even resolution of thrombocytopenia has been observed. In other patients, the thrombotic events would begin or worsen when the heparin was discontinued. In 1996, we described a group of patients with HIT and isolated thrombocytopenia. When these patients were managed conservatively by cessation of heparin (with or without initiation or continuation of warfarin) approximately 50% developed a thrombosis within the next days to weeks (Figure 7). Similar observations were made by Wallis and colleagues who also reported that heparin cessation often failed to prevent thrombotic events. The precise risk of thrombosis after discontinuation of heparin in a patient with HIT and isolated thrombocytopenia remains uncertain with risk estimates range from 20% to 50%. The duration of anticoagulation for a patient with HIT and isolated thrombocytopenia is not known, but we typically continue anticoagulation for 6 to 8 weeks. This is anecdotal and in part reflecting the ongoing prothrombotic risk we observed in our retrospective study (Figure 7).

In the 1990s, many physicians would diagnose HIT and immediately discontinue the heparin and anticoagulate with warfarin. But one patient who was managed this way, but dramatically worsened, led us to question this approach. In a case control study, we found that warfarin therapy in patients with HIT was often complicated by a dramatic progression of the DVT to distal extremity necrosis (venous gangrene), even when pulses were palpable. Some of these patients ultimately required limb amputation. Plasma samples from several patients demonstrated that warfarin therapy was associated with a severe reduction in the natural anticoagulant protein C, while at the same time the warfarin failed to inhibit the increased thrombin generation. One of the hallmarks of this syndrome was a dramatic increase in the INR to supratherapeutic levels (typically, greater than 4.0), which was explained by parallel reductions in factor VII. This syndrome, which has also been observed by other investigators, has led to the treatment principle that warfarin should be avoided during the acute (thrombocytopenic) phase of HIT.

Our current approach is to postpone warfarin therapy in a patient with acute HIT until there has been substantial resolution of the thrombocytopenia (platelet count rise to at least 150 × 10^9/L). Furthermore, careful overlap of the direct thrombin inhibitor (DTI) and warfarin, or of danaparoid/warfarin therapy, should occur, that...
is, starting with low (maintenance) doses of warfarin, ensuring at least a 5-day DTI/warfarin or danaparoid/warfarin overlap, and maintaining the DTI or danaparoid until the platelet count has reached a stable plateau within the normal range.65

Two distinctly different direct thrombin inhibitors (DTIs) have been evaluated in prospective studies using historical controls.108-114 Lepirudin is a recombinant hirudin derivative and argatroban is a small, synthetic molecule. The strengths and weaknesses of these trials have been recently reviewed.115 The lepirudin studies108-113 had the diagnosis confirmed serologically in the success rate is high even when the drug is given without prior testing. Advantages include potential for cross-reactivity of HIT antibodies; however, for many patients, the manufacturer’s recommended starting doses are too high.65 In addition, antithrombin antibodies have also been associated with acute anaphylaxis after lepirudin bolus.116

In many countries (although not in the United States), danaparoid, a mixture of anticoagulant glycosaminoglycans, predominantly heparan, dermatan, and chondroitin sulfate, is available.65 Danaparoid has been shown to be more effect than dextran-70, anecrod, or coumadin 102,106 Advantages of danaparoid include its long half-life, ability to monitor drug levels directly (via anti-Xa levels), and the theoretical disruption of thromboembolic events among patients with HIT-associated thrombosis (poled analyses vs historical controls, relative risk [RR] of 0.28 and 0.45 for lepirudin and argatroban, respectively). Advantages of DTIs include their ability to inhibit thrombin rapidly, simple monitoring with the aPTT, and short half-life (in situations of bleeding or need for surgery). Potential drawbacks include difficulty judging adequacy of anticoagulation by aPTT in some circumstances, potential for rebound hypercoagulability if stopped prematurely, and drug accumulation in renal (lepirudin) or hepato-biliary (argatroban) dysfunction. Moreover, it is now recognized that for many patients, the manufacturer’s recommended starting doses are too high.65 In addition, antithrombin antibodies have also been associated with acute anaphylaxis after lepirudin bolus.116

References


Ted Warkentin (left) and John G. Kelton

John G. Kelton: My current responsibilities include Dean for the Faculty of Health Sciences, including the Michael G. DeGroote School of Medicine, and Vice President at McMaster University. I completed my MD training at the University of Western Ontario and then did internal medicine and hematology training at Duke University. The intense training experience, perhaps best described as a Stockholm Syndrome, led to lifelong friendships that continue today, including friendships with Drs Russel Kaufman, Farrell Collins, Wendell Rosse, Wayne Rundels (now deceased), and E. Holmes, among many others. Returning to McMaster University, I learned the true joy of translational research and developed friendships and collaborations (Drs Ted Warkentin, Cedric Carter, Jack Hirsh, D. Sheridan, L. Boshkov, D. Arnold, P. Horsewood, I. Nazi, C. Hayward, I. Walker, P. Wasi, N. Heddle, and M. Blajchman, among many others). Much of my laboratory’s success reflects the extraordinary dedication of my research technologists. Recently, anordinate amount of time has been spent worrying about whether long-term friends who haven’t seen me for years will look at my picture and feel that I’ve gained weight and aged poorly.

Ted Warkentin: How did a teenager growing up in the Canadian prairies end up in the Great Lakes region (McMaster University) so focused on a drug reaction, HIT? In medical school (University of Manitoba), I was amazed how hematologic diagnoses could be made simply by viewing a blood film. In Toronto, a 1-month rotation with the late Dr Michael F. X. Glynn convinced me that hemostasis was really interesting; this endearing hematologist also pointed me westward alongside Lake Ontario to Hamilton. But why HIT? During a hematology elective and subsequent research fellowship, I was introduced to this topic by my supervisor, Dr Kelton. At that time, the very existence of HIT was debated, and my own first forays into detecting HIT antibodies gave mixed results. I became discouraged, but then everything changed (“Eureka!” moment): a single experiment showed that the inconsistency of experimental data had resulted from widely variable—but hierarchically ordered—reactivities of HIT sera and target platelets. This insight improved detection of HIT antibodies and made me an HIT “believer.” Dr Kelton also engineered my subsequent appointment at the Hamilton General Hospital, with both clinical and laboratory responsibilities. I realized there that HIT was perplexingly counterintuitive, and something worth spending time on. Soon after, I met an HIT aficionado, Andreas Greinacher, who was roughly at the same stage of his research and clinical career (though in Germany), and who shared similar perspectives on HIT. And so I had a mentor near, and a soulmate far, with whom to pursue my fascination with HIT.

Looking back, there are 5 reasons why McMaster University provided an ideal environment to study HIT. First, my research fellowship supervisor—and ongoing career mentor—Dr John Kelton developed a superior test for identifying HIT antibodies; this tool distinguishes the (few) patients with HIT from those (many) without. Second, the “British” system of hematology practiced at McMaster, which emphasizes dual clinical-laboratory appointments, facilitates study of a clinical-pathological disorder such as HIT. Third, the tradition of methodologic rigor exemplified by McMaster’s research leaders, particularly Dr Jack Hirsh, demands that observational research be performed as meticulously as possible. Fourth, McMaster fosters an entrepreneurial spirit, and collaborations with industry have led to remarkable research opportunities. And fifth, my primary research assistant, Jo-Ann Sheppard, demonstrates an affability and efficiency of output that never ceases to amaze me.
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