Studies on Fletcher trait and Fitzgerald trait

A rare chance to disclose body's defense reactions against injury

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Summary
The way by which contact of blood with foreign surface accelerates clotting has been elucidated from the discovery of four rare disorders of blood coagulation; Hageman trait, plasma thromboplastin antecedent (PTA) deficiency, Fletcher trait, and Fitzgerald trait. Interestingly, it was unexpectedly found that Fletcher factor is plasma prekallikrein and Fitzgerald factor is high-molecular-weight kininogen; components of the kinin-generating system, thus disclosing intimate relationships among clotting, fibrinolysis and kinin generation which may be viewed as body's defense reactions against injury. This review mainly reflects our research on Fletcher trait and Fitzgerald trait during the 1970s in Cleveland.

Keywords
Contact factor, kinin system, fibrinolysis, Fletcher trait, Fitzgerald trait

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Received: January 22, 2010
Accepted after minor revision: April 6, 2010
Prepublished online: September 13, 2010
doi:10.1160/TH10-01-0058
Thromb Haemost 2010; 104: 867–874

Introduction

I joined Dr. Oscar Ratnoff's laboratory at the University Hospitals of Cleveland as a research fellow of the American Heart Association in the fall of 1971. Before my start, Oscar suggested several projects that were going on. At that time Oscar had another fellow, Dr. Bruce Bennett from Scotland, who was performing clinical studies on von Willebrand disease and classic haemophilia. The immunological method to measure AHF-like antigen (Factor VIII-von Willebrand factor complex), developed by Drs. Ted Zimmerman and Ratnoff, had been instrumental in our understanding of classic haemophilia and von Willebrand disease and was being successfully applied for the detection of female carriers of classic haemophilia. I was more interested in contact system studies than in haemophilia. Oscar had the view that blood clotting is considered as one of the host defense mechanisms against injury through the contact activation. So, I picked a project on contact phase of blood coagulation which was Oscar's long-standing interest. My specific project was to examine whether or not antigen-antibody reaction initiates blood clotting. Looking back now, I think that the 1970s were the golden era when several competitive investigators, such as Drs. Charles Cochrane, Robert Colman, Virginia Donaldson, John Griffin, Allen Kaplan, and Sandra Schiffman, and Kirk Wuepper were also actively doing research in this field.

Historical background

It has been known for many years that the exposure of blood to a glass surface greatly accelerates blood coagulation. The clot-promoting property of blood was ascribed to the platelet-poor plasma. But the agent in plasma upon which glass exerts its clot-promoting effect remained elusive. Pioneering works by Margolis (1) and Shafrir and de Vries (2) showed in 1956 that an agent deficient in haemophilic, Christmas disease or Dindivan (phenylindanedione) plasma had no role in contact activation. It was specu-

Figure 1: Dr. Oscar Ratnoff drawing blood from Mr. John Hageman. Courtesy of Dr. Ratnoff.

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lated that a plasma clotting factor other than those listed above may be activated by contact with glass. Discovery of Mr. Hageman in 1955 by Ratnoff (▶Fig. 1) (3) filled a gap, as Hageman factor (factor XII) seemed to be an agent that mediated the effect of glass contact on clotting (4).

Around the same time, in the course of investigation of pain-producing substance, Armstrong and her colleagues found that when human blood plasma comes in contact with a glass surface a pain-producing substance (PPS) is released (5). PPS also caused contraction of the isolated rat uterus. It appeared that it is a polypeptide and most closely resembles bradykinin. Margolis was ingenious in developing an original concept that the initiation of clotting and kinin release by glass contact may share a common trigger: Component A (Hageman factor) (4). In his scheme he also speculated the existence of Component B that is a precursor of PPS. There was no naturally occurring condition known at that time in which Component B was missing.

▶Figure 2 illustrates what we understood about surface contact- induced plasma reactions in the early 1970s. Contact of blood with foreign surface generates, under certain *in vitro* conditions, thrombin, bradykinin, and plasmin, thereby leading to clotting, increased vascular permeability, pain, muscle contraction and clot lysis. Studies of blood from subjects with Hageman trait firmly established that Hageman factor plays a central role in initiating these reactions. It is, however, important to note that although all these reactions seem to require Hageman factor it was not clear in the early 1970s if any additional factor participated in these reactions.

Another factor that was suspected to participate in contact activation was Fletcher factor described by Dr. William Hathaway at the University of Colorado in 1965 (▶Fig. 3) (6). An 11-year-old girl, Bonnie Fletcher, was incidentally found to have a prolonged whole blood clotting time performed prior to tonsillectomy (7). She had a prolonged activated partial thromboplastin time (APTT) with a normal prothrombin time, but had no bleeding history. Three siblings were also found to have a similar coagulation defect. Attempts to demonstrate a deficiency of any then recognised clotting factor failed. The defect was thought to be due to a deficiency of a hitherto unknown clotting factor and was named Fletcher factor deficiency after the surname of the index family. Interestingly, prolonged APTT of Fletcher factor-deficient plasma became normal when it was incubated with glass for a long time. This is a puzzling phenomenon that is not observed in either Hageman factor or factor XI deficient plasma. The nature and location of Fletcher factor in the clotting sequence were unknown, although Hathaway assumed it may participate before Hageman factor (8).

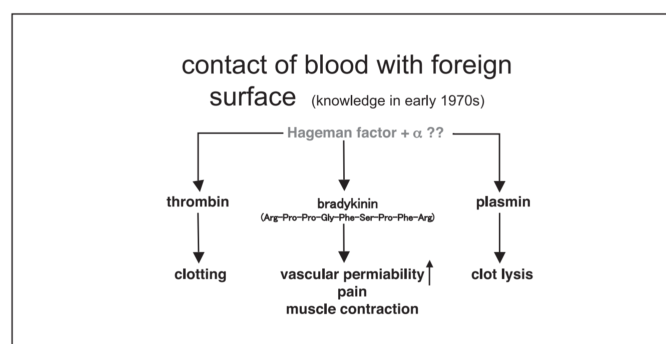

Figure 2: Surface contact-induced plasma reactions (knowledge in the early 1970s).

Figure 3: The Fletcher family near their home, circa 1963. Courtesy of Dr. William Hathaway (7).

Most coagulation factors were initially discovered as agents functionally deficient in the plasmas of rare patients with hereditary coagulation disorders. Clotting factors were only recognised and measured by their clot-promoting activities. In the 1970s it became possible to obtain highly purified preparations of most proteins involved in blood coagulation and to study their interactions in reconstituted system. Antibodies were raised against many clotting factors and it became feasible to estimate clotting factors as immunoreactive proteins. These advances helped promote our understanding of blood clotting mechanism and the nature of hereditary coagulation disorders. The first Gordon Research Conference on haemostasis was organised by Drs. Ratnoff and Davie in 1973 in New Hampshire (▶Fig. 4). I had a chance to attend the meeting. The conference attracted many active people in the field and many topics, including contact factors, factor VIII, von Willebrand factor, and fibrinogen, were discussed.

Studies on Fletcher trait plasma

My first job in Oscar's laboratory was to purify Hageman factor and factor XI (plasma thromboplastin antecedent, PTA) from normal human plasma. When I arrived in Cleveland, Oscar had stocked 500 ml of Hageman factor-deficient plasma and 1 l of PTA-deficient cow plasma, so that I could perform hundreds and thousands of assays of Hageman factor activity and PTA activity during purification. We showed the activation of partially purified factor XI by trypsin (9).

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We had a chance to study plasma of Fletcher trait and found that the addition of partially purified activated Hageman factor or activated factor XI corrected the clotting defect of Fletcher factor-deficient plasma (10). We also observed a strange phenomenon that Fletcher factor-deficient plasma had the property of inhibiting the clot-promoting effect of glass, just like Hageman factor-deficient plasma (11).

The nature of Fletcher factor became clear by the results of studies by Wuepper. In the course of investigation of components of plasma kinin-forming system he identified Fletcher factor with plasma prekallikrein (12). Thus, Fletcher trait turned out to be a naturally occurring condition in which 'Component B' of Margolis (4) is missing. About the same time we and Kaplan's group also found that Fletcher trait plasma has not only defective clotting, but also defective fibrinolysis, kinin generation, and vascular permeability enhancing activity (13–15). Interestingly, a defect in surface-mediated fibrinolysis as tested by kaolin-induced fibrinolytic activity was normalised by a prolonged incubation with surface, just like a clotting defect. The importance of prekallikrein in normal blood clotting was also confirmed by the observation that the addition of an antiserum raised against plasma kallikrein to normal plasma inhibited blood coagulation (16).

Studies on Fitzgerald trait plasma

In August of 1974, Mr. Fitzgerald, a 71-year-old man, came to the Emergency Room of Henry Ford Hospital in Detroit for the care of a gunshot wound. He had no known history of abnormal bleeding following trauma or surgery, but was incidentally found to have a prolonged APTT. Dr. Robert Waldmann of Henry Ford Hospital brought a small ice box containing the patient's plasma to Oscar's laboratory for further studies. Within one hour we found that the prolonged APTT of Mr. Fitzgerald was corrected to normal by the addition of plasma from every known clotting factor deficiency, including Fletcher factor deficiency. We then hypothesised that his plasma was missing a new clotting factor. All of us were very exited. The clotting defect was corrected with activated factor XI, while it was not corrected with activated Hageman factor or activated Fletcher factor. Thus, we assume that Fitzgerald factor operates in the clotting cascade after activation of Hageman factor and Fletcher factor. We named the new factor Fitzgerald factor after the index patient (▶Fig. 5) (17, 18).

Figure 4: The first Gordon Research Conference on haemostasis (August 1973), New Hampshire.

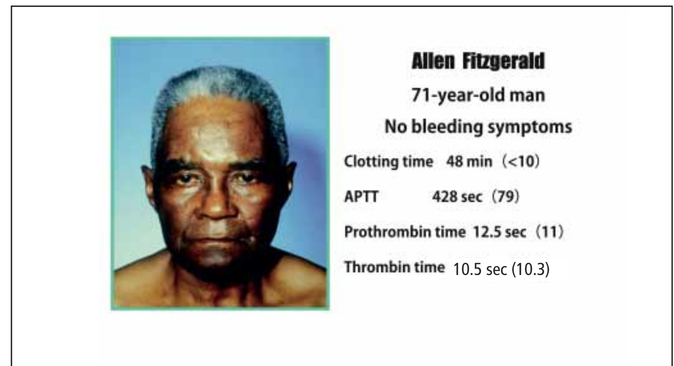

Figure 5: Mr. Fitzgerald. Courtesy of Dr. Robert Waldmann. The numbers in brackets indicate normal control plasma.

As we already knew that surface-mediated fibrinolysis, kinin generation and vascular permeability-enhancing activity were defective in both Hageman trait and Fletcher trait plasma, we immediately tested these reactions in Mr. Fitzgerald's plasma. The clot lysis time of normal plasma in a test of kaolin-induced fibrinolysis was 7 minutes (min), whereas that of Fitzgerald plasma was

Table 1: Effect of addition of ellagic acid, HF fragments, and kallikrein upon kinin generation. Test plasmas were incubated with either ellagic acid, HF fragments (activated HF), or kallikrein at 37°C. Portions were tested on a uterus muscle for kinin activity in comparison with a bradykinin standard, expressing the results as nanogram bradykinin equivalent. Reprinted with permission from Saito et al. (18).

Sample	Kinin activity
	nanogram bradykinin equivalent per 0.1 ml sample
Normal + ellagic acid	11.6
HF deficient + ellagic acid	0
Fletcher trait + ellagic acid	0
Fitzgerald trait + ellagic acid	0
Fitzgerald trait + HF deficient + ellagic acid	6.0
Fitzgerald trait + Fletcher trait + ellagic acid	2.3
Fletcher trait + HF fragments	0
Fitzgerald trait + HF fragments	0
Fletcher trait + Fitzgerald trait + HF fragments	5.0
Fletcher trait + kallikrein	3.6
Fitzgerald trait + kallikrein	0
Fitzgerald trait + Fletcher trait + kallikrein	2.8
Fitzgerald trait + buffer + kallikrein	0

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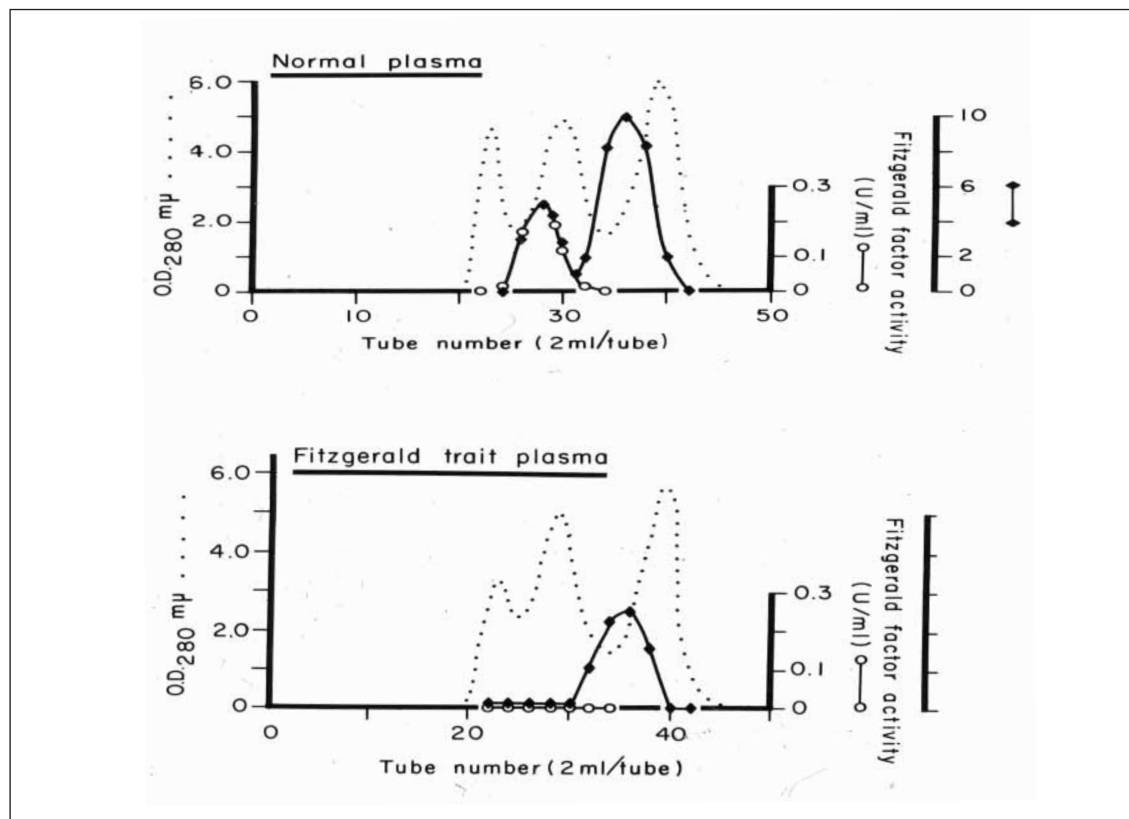

Figure 6: Gel filtration of normal and Fitzgerald plasma. Normal plasma (upper panel) or Fitzgerald plasma (lower panel) was filtered on Sephadex G-150 column and aliquots were tested for OD280mμ (dotted line), kininogen (solid circle) and Fitzgerald factor activity (open circle).

more than 120 min, just like Hageman- or Fletcher factor-deficient plasma. Prolonged clot lysis times were mutually corrected, suggesting that the plasmas lacked different agents (18).

Kinin generation was assayed by applying the test substance to an isolated rat uterus suspended in oxygenated Tyrode's solution at 37°C. When normal plasma was incubated with ellagic acid, an agent to contract muscles was formed with time. In contrast, incubation of Fitzgerald plasma induced no contraction (▶Table 1). The addition of plasma kallikrein or Hageman factor fragments (that is activated Hageman factor) to Fitzgerald plasma did not generate kinin activity. However, the addition of trypsin to Fitzgerald plasma did induce muscle contraction. These data suggested to us that Fitzgerald plasma contained no kininogen cleaved by plasma kallikrein, but some kininogen which is cleaved by trypsin.

PF/dil (permeability factor of dilution) was measured by using the depilated backs of albino guinea pigs that had been injected i.v. with pontamine sky blue dye. At 15 min after the injection, the size of the blue spots was estimated. We used four guinea pigs in each experiment, because this assay gives variable results. Oscar participated in the measurement of PF/dil and he enjoyed using a table of random numbers to minimise the influence of the location of the spots on the results. Normal plasma diluted in ellagic acid gave a bigger size of blue spot in 12 min, indicating enhanced vascular permeability. In contrast, Fitzgerald plasma incubated with ellagic acid showed no change in the size of spot in 12 min, similar to Hageman trait or Fletcher trait plasma. Defective permeablity was mutually corrected by mixing these plasmas.

We reported at the annual meeting of the American Society of Hematology in December 1974 that the missing agent in Mr. Fitzgerald's plasma was a new clotting factor and was required for surface-mediated fibrinolysis, kinin generation and PF/dil. At about the same time Schiffman presented evidence that an unrecognised plasma activity, named contact activation co-factor, seems to participate in the interaction of factors XI and XII (19). Soon it was found to be identical with Fitzgerald factor (20).

Two types of plasma kininogen were known to exist: high-molecular-weight (HMW) and low-molecular-weight (LMW) (21). Gel filtration of normal plasma disclosed two peaks of kininogen of which only high molecular weight species has Fitzgerald factor clotting activity. In contrast, Fitzgerald plasma has only one peak of kininogen and is missing in HMW kininogen (▶Fig.6).

About the same time several other patients that had an identical clotting defect with Fitzgerald trait were described by other investigators. These include Williams, Flaujeac, Reid trait (22–26). Wuepper first identified Flaujeac factor with HMW kininogen (23). Almost simultaneously other investigators came to the same conclusion (18, 24, 25).

This disorder appears to be inherited in an autosomal recessive manner. Although a common feature in all cases was the functional deficiency of HMW kininogen (less than 1% of HMW kininogen coagulant activity), the plasma concentrations of prekallikrein and LMW kininogen were quite variable in different cases. Fitzgerald plasma is deficient only in HMW kininogen, whereas some plasma such as Flaujeac, Williams and Dr. Donaldson's patient was defi-

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cient in total (both HMW and LMW) kininogen (23–25). The concentrations of prekallikrein (Fletcher factor) were found to be variable among patients.

Role of Fitzgerald factor and Fletcher factor in contact activation

The addition of purified HMW kininogen completely corrected the prolonged APTT of Mr. Fitzgerald. In contrast, the addition of purified prekallikrein normalised prolonged APTT of Fletcher factor-deficient plasma. The roles of purified contact factors were examined for their ability to support the activation of factor XI. Kinetic studies showed that the yield of activated factor XI depended not only on the concentration of factor XI, but also on the concentration of Fitzgerald factor (▶Fig. 7) and Hageman factor (27). These and other experiments suggest that they might form a complex in the presence of ellagic acid.

How does Fitzgerald factor (HMW-kininogen) function in the clotting cascade? ▶Figure 8 shows the concept we had in the late 1970s. Exposure of blood to negatively charged surfaces leads to rapid binding of contact factors to surface. Hageman factor and HMW kininogen bind directly, but prekallikrein and factor XI are bound through HMW kininogen. Surface binding is assumed to serve to bring Hageman factor, factor XI, prekallikrein and HMW kininogen in close proximity and to increase their chance of interacting. Binding of Hageman factor to surfaces was also proposed to make the molecule more susceptible to proteolysis (28). Once surface-bound Hageman factor is activated, activated Hageman factor (aHF) converts surface-bound prekallikrein (PK) to kallikrein. Kallikrein, in turn, activates Hageman factor. This reciprocal activation is a positive loop that serves to amplify the rapid mutual activation of Hageman factor and prekallikrein (29). HMW kininogen (HMW-K) functions as a co-factor in contact activation. It exists as a complex with prekallikrein (PK·HMW-K) or factor XI (XI·HMW-K) in plasma (30, 31), and augments the activation of factor XI and prekallikrein with surface-bound activated Hageman factor by linking both proteins to surface (32, 33).

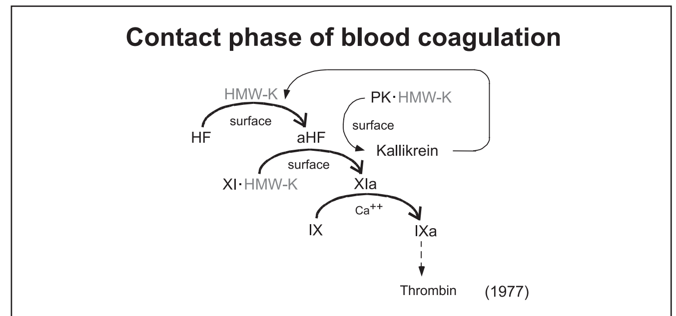

Figure 8: Contact phase of blood coagulation. Abbreviations used: HF; Hageman factor, aHF; activated Hageman factor, HMW-K; high-molecular-weight kininogen, PK; prekallikrein, XI; factor XI, PK· EHMW-K; prekallikrein-high-molecular-weight kininogen complex, XI· EHMW-K; factor XI-high-molecular-weight kininogen complex.

The leading question was how the *first* Hageman factor or prekallikrein is activated on negatively charged surface. Several hypotheses have been proposed, including autoactivation of Hageman factor or prekallikrein (34). The origin and nature of the initial enzymatic activity were unknown. It seemed like the "chicken or egg" issue. The molecular basis of autoactivation was not fully understood, although a conformational change of Hageman factor upon binding negatively charged surfaces was demonstrated by various techniques, including circular dichroism, fluorescence spectroscopy, and ultraviolet difference spectroscopy (35–37).

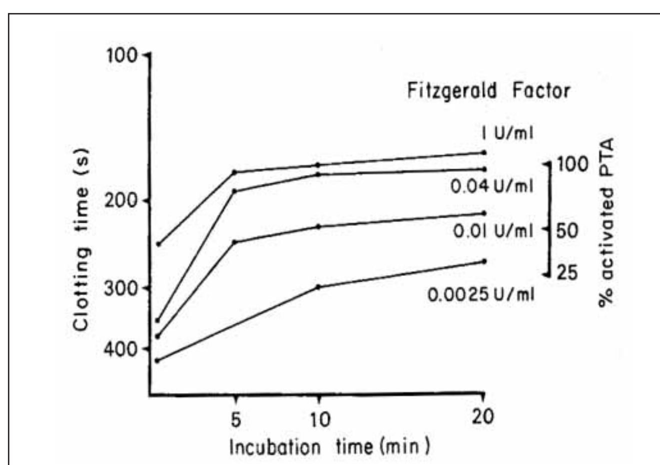

Figure 7: The effect of varying concentration of HMW kininogen upon PTA activation. In a 10×75-mm polystyrene tube, 0.075 ml PTA (0.2 U/ml) was incubated at 37°C with 0.025 ml HF (1.8 U/ml), 0.025 ml HMW kininogen (1, 0.04, 0.01, or 0.0025 U/ml), 0,025 ml BSA, and 0.075 ml ellagic acid (0.1 mM). At time intervals, 0.05-ml aliquots were tested for activated PTA activity. Reprinted with permission from Saito (27).

In vivo studies on Fletcher trait and Fitzgerald trait

All experiments that I have referred to so far concerned *in vitro* abnormalities in Fletcher trait and Fitzgerald trait plasma. However, a few *in vivo* studies have been reported. With Dr. Rebuck at Henry Ford Hospital in Detroit we studied the *in vivo* inflammatory response using skin window technique. Mr. Fitzgerald showed greatly enhanced leukocytes migration to both trauma and antigen stimulation (17). In contrast to Fitzgerald trait, both subjects with Hageman trait and Fletcher trait showed reduced or normal response to trauma or antigen stimulation (38). The clinical significance of prekallikrein deficiency was extensively studied by Hathaway et al. in two siblings of the original family (39). Both immediate and delayed sensitivity skin test reactions were within normal limits. Migration of leukocytes in skin windows and in Boyden chambers was the same as in normal subjects. Poon et al. (40) found reduced leukocytes migration to trauma, but normal migration to antigen stimulation in one subject with Fletcher trait. The reason for non-consistent results is not clear.

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Interrelationship among host defense mechanisms

From the study of Mr. Hageman, Oscar expanded a concept that blood coagulation, fibrinolysis, kinin generation, and complement activation are intimately related via surface contact, which he called "a seamless web of host defense reactions" (41). The discoveries and studies of Fletcher factor and Fitzgerald factor deficiencies have unexpectedly disclosed that prekallikrein and HMW kininogen, components of the plasma kinin system, also participate in blood coagulation. The intimate interrelationship among clotting, fibrinolysis, and kinin generation through contact activation may be viewed as 'intermeshed gears' (▶Fig. 9). Without such very rare individuals with a prolonged clotting time the role of prekallikrein and HMW kininogen in blood coagulation would not yet have been elucidated.

More evidence that clotting and kinin generation are inseparable came from amino acid sequence comparison of factor XI and prekallikrein: they are so similar that they seem to be evolved from the same ancestral protein (42). Thus, Oscar's insight was proven to be right. However, this concept applied only to *in vitro* plasma reactions and what initiates contact system *in vivo* was not well understood in the 1970s, and we have to wait until the 21st century before we know some *in vivo* relevance.

It is interesting to note that blood coagulation also interacts via tissue factor with other systems of host response to injury such as inflammation. Tissue factor not only initiates clotting, but also modulates inflammation. Inflammation in turn up-regulates tissue factor expression on monocytes or vascular endothelial cells by the actions of cytokines and chemokines (43). Thus, blood coagulation system seems to interplay with other host defense reactions through both intrinsic and extrinsic pathways.

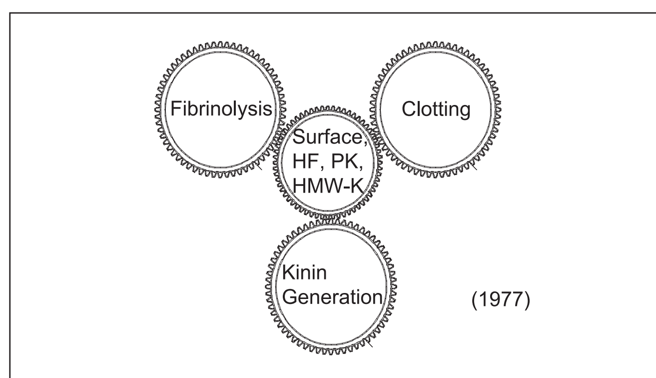

Figure 9: Interrelationship among clotting, fibrinolysis, and kinin generation viewed as "intermeshed gears".

Hageman factor, Fletcher factor and Fitzgerald factor in health and disease

The contact factors seem to have no significant role in normal haemostasis, but they may have important roles in the pathophysiology of human diseases. Hageman factor was shown to participate in human pathology. In 1978 hypotension following administration of some plasma fraction was reported to be caused by contaminated HF-fragments (activated Hageman factor) (44). Similar adverse reactions were just reported last year in patients following haemodialysis with contaminated heparin (45).

Plasma concentrations of Fitzgerald factor and Fletcher factor were measured by the clot-promoting activity in a variety of physiologic and pathologic conditions (46, 47). Both factors were reduced in the neonate, probably reflecting immature liver function. No alterations in both factors occur during pregnancy, but they decreased significantly in the immediate postpartum period. Both factors were decreased in plasmas of the patients with disseminated intravascular coagulation (DIC), liver cirrhosis or shock, implicating their possible roles in the pathophysiology of these disorders. There is, however, no direct evidence for this hypothesis. It was also reported that the clotting activities of Fletcher factor and Fitzgerald factor were significantly decreased during acute attacks of hereditary angioedema, suggesting that some of the clinical manifestations may be mediated through kinins (48).

Some recent developments

Several developments shed a new light on our understanding of contact system (49). Proteolytic activation of prekallikrein by an endothelial cell activator (50) has been found, implicating *in vivo* kallikrein formation independent of factor XII. Autoactivation of Hageman factor by polyphosphate (51), RNA (52), and misfolded proteins (53) have been discovered. These findings suggest that polyphosphates secreted from activated platelets and RNA released by necrotic cells may play a role in thrombus formation *in vivo*. Interestingly, the activation by misfolded protein aggregates is considered to lead to activation of the kallikrein-kinin system without affecting the coagulation cascade. How this occurs *in vivo* remains to be studied.

Studies of knock-out mouse of the contact factors revealed that Hageman factor and HMW kininogen play some role in the formation and maintenance of arterial thrombosis. Hageman factor-deficient mice were shown to have a defect in occlusive thrombus formation in response to ferric chloride-injury (54). It was shown by Keith McCrae and Alvin Schmaier that mice deficient in plasma kininogen are also protected from arterial thrombosis induced by vascular injury (55). These findings are intriguing in the light of the fact that mice deficient in either Hageman factor or kininogen do not display a prolonged bleeding time, suggesting that haemostasis at the site of vascular injury appears to be normal. It remains to be studied if this is true in humans.

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Abbreviations

HF, Hageman factor; aHF, activated Hageman factor; HMW-K, high-molecular-weight kininogen; HMW kininogen, high-molecular-weight kininogen;, LMW kininogen, low-molecular-weight kininogen; PF/dil, permeability factor of dilution; PTA, plasma thromboplastin antecedent; PK, prekallikrein; XI, factor XI.

Conclusion

Looking back on the 1970s when I spent time with Oscar Ratnoff, it was not only a great chance to learn from him, but also a delight and fun to work with him. He was a keen observer, an incisive thinker, and an imaginative investigator. Above all he was a warm hearted, charming person. Oscar served as President of the American Society of Hematology during 1974–1975, but he was still working at bench, doing his experiments by his own hands. He was very kind and thoughtful to patients and hated doing any invasive procedures on them for research purpose. I was fortunate to enjoy his insightful, penetrating, and stimulating inquiries and comments. I can only say that I was in the right place at the right time. After I returned to Japan, I switched my research focus from contact factor to other areas in haemostasis and thrombosis. But what Oscar taught me helped me a lot. As I reflect on my old Cleveland days, I still hear Oscar's voice "Hide, nothing new under the sun".

Acknowledgements

I am grateful to Drs. Oscar Ratnoff, William Hathaway and Robert Waldmann for the photographs of Mr. Hageman, Fletcher family and Mr. Fitzgerald.

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