Coagulation disorders
Recent lessons from clinical conditions

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For clinicians, who are not experienced in hemostasis and thrombosis, coagulation and coagulation disorders remain a ‘book of seven seals’ (1). This may be due, at least in part, to the complexity of the hemostatic apparatus and its interaction with inflammatory processes and immune mechanisms, all of which require detailed theoretical knowledge, practical experience, and continuous medical education (CME). More recently, the use of direct oral anticoagulants, which have specific pharmacological targets and pharmacodynamics distinct from those of vitamin K antagonists, heparins, or the pentasaccharide fondaparinux, has created insecurities and concerns among clinicians. Some of these concerns result from the fact that these novel agents with their superior safety profile impact on standard coagulation screening tests (such as prothrombin time and activated partial thromboplastin time) in a way that is different from conventional anticoagulants.

This theme issue of Hämostaseologie should facilitate the readers’ access to several acquired coagulation disorders and assist to overcome fundamental problems of understanding hemostasis or, metaphorically spoken, to ‘break some of the seals’ of hemostasis and thrombosis textbooks. As third part in a series of reviews, the current edition also reflects several highlights of the GTH Congress 2015 (2, 3, 4).

In his article, Medcalf provides an up-to-date view on fibrinolysis, demonstrating that tissue-type plasminogen activator (t-PA)-mediated conversion of plasminogen into plasmin is not solely designed to remove fibrin deposits and blood clots in a self-regulated proteolytic process (5). Importantly, it is shown that t-PA and plasmin have pleotrophic effects and other substrates than fibrin such as prion proteins, amyloid-β, and misfolded or aggregated proteins. Thus, t-PA can act in a non-fibrinolytic (i.e., plasmin-independent) manner and have multiple effects on cerebral functions (e.g., synaptic plasticity, neurotransmission, visual processing, learning and memory). The author therefore concludes that the “original concept for the fibrinolytic system, being focused on fibrin, is a massive understatement” (5). Tiede et al. report on recent advances in the management of acquired hemophilia A (AHA) (6). At an incidence of about 1.3 cases per million people (7), AHA is a rare but challenging bleeding disorder caused by inhibitory autoantibodies against coagulation factor (F) VIII. Apart from hemostatic management to control active bleeding, immunosuppressive treatment is mandatory in AHA to achieve remission. However, the outcome of AHA remains highly variable. Therefore, clinically valid prognostic factors for remission are urgently required. Recently, the GTH-AH (01/2010) study, a multicenter trial conducted under the leadership of Andreas Tiede, has demonstrated for the first time that residual FVIII activity and inhibitor
concentration at baseline are potentially useful predictors for remission of and survival in AHA (8).

Cancer and thrombosis remains a hot topic (9) and has been subject of a recent CME article by Langer in this Journal (10). As documented in large, population-based studies, cancer patients have a 4- to 7-fold increased risk of venous thromboembolism (VTE) compared with the general population (11). The crucial issue in patients with solid tumors is: “who needs pharmacological thromboprophylaxis and who does not?” This question is addressed by Ay and Pabinger, reviewing the risk assessment of VTE with regard to cancer-, treatment- and patient-related determinants (12). Recent scoring models for stratification of cancer patients into risk categories and corresponding thromboprophylaxis with low-molecular weight heparins in distinct clinical settings are discussed. The phenomenon of cancer-associated thrombosis is much more complex since multiple interactions between tumor cells and hemostatic components can occur. Numerous experimental findings show that platelets promote tumor growth, induce tumor angiogenesis and support metastatic dissemination. The pivotal role of platelets in cancer is reviewed by Mammadova-Bach et al., covering the broad area from basic research to therapeutic consequences (13). Indeed, several observations suggest that antiplatelet drugs (such as aspirin, clopidogrel, or alloβ3 antagonists) may also have anticancer effects. However, randomized controlled trials are needed before these drugs can be introduced into cancer care. As discussed by the authors, a novel pharmacological strategy is seen in targeting and disrupting specific platelet-tumor cell interactions (13).

Drug-induced bleeding upon treatment with currently used anticoagulants and antiplatelet agents remains a serious concern. Ideally, novel agents should be antithrombotic but not antihemostatic. Labberton et al. demonstrate that targeting FXII, FXIIa, or polyphosphate, an inorganic polymer (polyP), can implement such a pharmacological strategy (14). Indeed, inhibitors of FXII/XIIa and polyP have anticoagulant and anti-inflammatory activities, which are not compromised by bleeding complications. Specifically, the authors report that an antibody, blocking the enzymatic pocket of FXIIa and thus neutralizing its activity, provides thromboprotection in a rabbit model of extracorporeal circulation. The promising experimental data require further examination in other clinically useful settings. While suchlike strategies and tools may become relevant in the future, the use of currently available antithrombotic agents is associated with fear of bleeding. This persistent burden is discussed in detail by Bosch and Eikelboom for stroke prevention in patients with atrial fibrillation (AF), using vitamin K antagonists (VKA) or non-vitamin K antagonist oral anticoagulants (NOAC) (15). Despite the superior safety profile of NOAC in comparison with VKA, the lack of specific antidotes is a concern among physicians regarding the inability to promptly reverse the anticoagulant effect of NOAC in patients with major bleeding. Several agents are being tested for reversal of FIIa or FXa inhibitors. By end of September 2015, the European Medicine Agency has recommended granting a marketing authorization for idarucizumab (Praxbind®) as a specific antidote to dabigatran etexilate (Pradaxa®). Approval of specific antidotes for reversal of FXa inhibitors is underway.

Apart from these highlights of the GTH Congress 2015, original papers on thromboprophylaxis after arthroplasty (Heckmann et al.) (16), turoctocog alfa, a novel recombinant FVIII (Tiede et al.) (17), and heparin-induced thrombocytopenia (Sanidas et al.) (18) complete this edition.

As Editor-in-Chief, I am grateful to all authors for their contributions and trust that this issue of Hämostaseologie will help to unseal the hemostasis and thrombosis ‘book of seven seals’.

References