Cirrhosis and its end-stage complications have been well-known by medical practitioners for many centuries and were frequently described in historical writings and medical literature as far back as Hippocrates in 400 BCE.\(^1\) The ancient Greeks believed the liver to be the center of the circulation and the site of blood production, perhaps because of its propensity to bleed when injured in battle or accidents. Indeed, the liver was referred to by Galen\(^2\) as the “blood sac” because of its abundant blood flow, which comes from its almost unique dual blood supply, namely, the hepatic artery and the portal vein (almost because there is also a portal venous system between the pituitary and the hypothalamus\(^3\)) (Fig. 1). In 200 CE, Galen wrote of the liver as the \textit{fons venarum}, the source of the major veins of the body and the \textit{sanguificationis officina} or the “factory of the blood,” the site of sanguification.\(^2\) In modern times, even after the gross anatomy of the liver was clearly elucidated, poor understanding of liver disease resulted in a diagnosis of cirrhosis...
only when decompensation occurred. In many cases, decompensation was manifest as hematemesis, which we now know usually comes from ruptured esophageal and, less often, gastric varices. In 1719, a little more than 200 years after Vesalius had mapped the portal venous system,4 Morgagni5 reported apparent portal hypertensive bleeding. In the mid-19th century, gastrointestinal bleeding in patients with cirrhosis was strongly suspected to come from esophageal varices that Sappey6 was to describe in 1859, yet such a complication was considered to be distinctly rare7,8 even by the likes of Osler.9 At the turn of the 20th century, Prebble10 in Chicago lifted the veil, when he reported from an autopsy series that esophageal varices occurred in 64 of 80 (80%) cases of fatal gastrointestinal hemorrhage. This association was later corroborated by Enderlen and Magnus-Alsleben,11 who contended that bleeding caused by portal occlusion was more immediate and dramatic than that from portal hypertension per se, but they also thought, incidentally, that epistaxis was a feature of portal hypertension. Another rare source of gastrointestinal hemorrhage, namely, hemobilia,12 was identified in the late 18th century by the renowned anatomist, physician, and historian of French medicine, Baron Antoine Portal (1742-1832), Knight of the Empire (Fig. 2), whose name incidentally and ironically was unfortunately not eponymous, even though he later did describe the veins of
the esophagus. Resulting from his close relationship with Emperor Louis XVIII, not only was Portal named le premier médecin du roi, but additionally l’Académie Nationale de Médecine was created, of which he was the lifelong president.

The modern practitioner nowadays most closely identifies decompensation of cirrhosis with bleeding, jaundice, fluid retention in the form of ascites and edema, the altered mentation of hepatic encephalopathy, and changes in liver synthetic function, all expertly reviewed elsewhere in this series, and the routine blood test results that highlight protracted plasma coagulation, measured as prolonged prothrombin times (PT), as discussed later, and low blood platelet counts, which collectively constitute “the coagulopathy of cirrhosis.” Unfortunately, many who use this term do not appreciate or understand its true consequences in terms of bleeding and defective clotting that actually occur in patients with cirrhosis. But is there truly in vivo coagulopathy, that is, clinically significant defective clotting, present in cirrhosis, to justify correction with plasma or other blood products prior to surgery or other invasive procedures? Our modern understanding of coagulation in patients with cirrhosis, the

FIG 2 Baron Antoine Portal, depicted in a line engraving by J.P. Dupin, Jr., 1782, after A. Pujo, 1781. Copyrighted work is available under Creative Commons Attribution International license CC BY 4.0, at https://wellcomecollection.org/works/k8a2pckg. Credit: Wellcome Library, London.
fruit of many years of research, has led us to a concept that is termed *rebalanced hemostasis*, which means that the hemostatic imbalance due to a decrease in the hepatic synthesis of procoagulants that might imply a risk for bleeding is “rebalanced,” by a concomitant decrease in the hepatic synthesis of anticoagulant proteins.

**FIG 3** Transition from normal hemostatic balance to the “rebalanced” hemostasis of cirrhosis. Reproduced with permission from *Scientific American Medicine*. Copyright 2018, Decker Intellectual Properties.
Of course, this paradigm is predicated on the knowledge that the liver is the source of the great majority of the proteins involved in coagulation. Figure 3 shows the balance between the normal activity and/or concentrations of procoagulants and anticoagulants in health, which will be described later, so that neither abnormal bleeding nor inappropriate clotting occur (Fig. 3A). The new balance that occurs in liver disease between equally reduced levels of clotting protagonists, so that neither abnormal bleeding nor excessive clotting occur unless there is some additional derangement of that process by comorbidities, is depicted in Fig. 3B as well as the opposing elements in primary, secondary, and tertiary hemostasis that lead to rebalancing (Fig. 3C).16

This rebalanced hemostatic state of cirrhosis is somewhat tenuous, however, because it comes about as a result of a global reduction in the normal healthy concentrations of clotting factors (Fig. 4A), which results in a fragile new state (Fig. 4B) that is easily perturbed.

The rebalanced state describes well the influence of the diseased liver on the propensity both to bleed and to clot, sometimes and counterintuitively even simultaneously in the same patient. The bipolar clinical outcome of the rebalanced coagulation status in patients with liver disease is graphically illustrated in the announcements for the biannual International Symposia on Coagulation in Liver Disease (Fig. 5), the 8th Meeting of which was held on September 27 and 28, 2019, in Groningen, the Netherlands.

In this essay, therefore, we discuss some key aspects of the history of coagulation that are unique to liver disease, and explain how we arrived at our modern understanding of deranged hemostasis in cirrhosis.

The medical term coagulopathy implies an inability of the blood to congeal and seal defects in blood vessels at times of injury, but this designation is commonly (mis)used interchangeably to describe a presumed liability for spontaneous bleeding in patients with cirrhosis.

Due to consanguineous marriage in the European royalty that persisted late into the 19th century, with consequences resonating early in the 20th century (arguably, for example, in contributing to the cause of the Bolshevik Revolution17), the bleeding that resulted from defects in the coagulation system became known to court physicians and even the general public as the “royal disease,”18,19 which should not be confused with the other royal malady, porphyria. There was little to no understanding of the actual bleeding disease itself, or of its mode of genetic transmission. This disease was not simply confined to European royalty20 but had been encountered as far back as the 2nd century CE.21 Eventually, medical knowledge began to catch up with the clinical manifestations of these diseases. The royal disease is now recognized as being a severe form of hemophilia B, or Christmas disease, which is associated with sex-linked factor IX (Christmas factor) deficiency and was named after the first patient in whom the disorder was
recognized.22 This deficiency is thought to be due to a mutation of the eight-exon $F_9$ gene, causing incorrect RNA splicing that produces a truncated, nonfunctional factor IX protein.23,24 Deficiency of anti-hemophilic factor/globulin (i.e., factor VIII) that is responsible for hemophilia A19 is due to a mutation in the 26-exon $F_8$ gene that, like $F_9$, is located on the X chromosome.

There is no doubt that the royal disease, hemophilia, was prevalent in the oft-intramarried European royalty. It is controversial,25 however, whether the autosomal dominant disorder, acute variegate porphyria, was indeed carried in the British Royal Houses of Stuart, Hanover, and Windsor (as shown in Fig. 6), for which some protagonists argue strongly.26 Acute porphyrias are autosomal traits that show highly variable clinical expression, and thus might not appear in every generation, as is the case with manifestations that some authorities think are compatible with porphyria and were seen in British royal lines that passed through Queen Victoria (Fig. 6). Close examination of the pedigrees of European royal families in which hemophilia was prevalent (Fig. 7) shows that their inheritance was from Queen Victoria, through whom the inheritance of porphyria also passed.26

An individual’s hemophilia can usually be traced in their ancestry, but in about 30% of cases there is no family history of the disorder, and the condition is speculated to be the result of spontaneous mutation in the first sufferer. An acquired mutation seems to have been the case with Mrs. Brown (as the Empress of India, aka Victoria, was referred to in the gutter press and satirical magazines, in which she was lampooned because of her close liaison with her Scottish servant John Brown). Victoria, who was also nicknamed “Grandmama of Europe”27 because of her bountiful fecundity having given birth to nine children, all of whom survived, is usually considered to be the source of hemophilia that devastated many of her descendants among the royal families of Europe.

Largely through the study of the hemophilias and other inborn defects leading to bleeding diatheses, the existence of “factors” in the blood that promoted clotting was implied through deduction and comparison of various families of patients with inborn bleeding disorders. The absence of one or more of these “factors” would lead to defective clot formation, that is, coagulopathy, and a bleeding disorder. As each of the unknown factors was discovered, they were often named after the patients in whom the respective bleeding disorders were first recognized, and later were given Roman numeral designations, typically in the order of discovery,28 according to the International Committee on the Nomenclature of Blood Coagulation Factors, which was established in 1954.29

Once there was some understanding of the coagulation proteins and blood components, the traditional Waterfall/Cascade of Blood Coagulation (Fig. 8) eventually became elucidated over many decades.30 This clotting cascade is readily recognized by students of medicine and biochemistry by its intimidating pathways and seemingly out of
order Roman numerals and recursive arrows, and is generally feared during examinations by those same students. Some devotees of the history of coagulation have suggested that the term coagulation conflict would be more fitting because of the rivalries and mutual criticisms among researchers in the early days.

The modern era of coagulation understanding was heralded in by Morawitz's 1905 proposal of a “classic theory of blood coagulation” in which only four factors were involved, namely, thrombokinase (i.e., thromboplastin) from damaged tissue, prothrombin, fibrinogen, and calcium. Yet the fascination with blood clotting predated Morawitz, as far back as the ancient Greeks. Plato believed that fibers in the blood, which Aristotle thought were solid and made of earth, aided clotting as the blood cooled. Malpighi in the late 1600s washed clotted blood and “enjoyed the pretty white fibers” of fibrin, a term that Chaptal coined much later in 1797, for the fibers that had been converted from fibrinogen (so named by Virchow as

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**FIG 6** Simplified royal pedigree including the Houses of Stuart, Hanover, and Windsor. Individuals who had manifestations compatible with porphyria are marked with a green symbol; those who also reported red or discolored urine are marked in red. Reprinted with permission from *Lancet*. Copyright 2005, Elsevier.
a precursor of fibrin or its product under the action of oxygen), catalyzed by fibrin ferment, later called thrombin, for which a precursor, prothrombin, had to exist.

In the frenetic and crowded timeline of discovery in the field of blood coagulation (Fig. 9), the invention of the disarmingly simple PT test by Armand Quick (1894-1978) ranks high among so many landmarks, alongside the activated partial thromboplastin time (aPTT), which is the origin of the invention of the PT or Quick time (Fig. 9), alongside the aPTT, which are two of the most commonly requested and commonly misunderstood blood tests in medicine today. Armand Quick’s initiation into the nascent science of blood coagulation is somewhat theatrical and worthy of a novella. Quick, a young physician with a cervical tuberculous gibbus (Fig. 10), who lost his research position at Cornell...
during the Depression when funds ran out, responded to an invitation by two surgeons (one of whom was the granddaughter of US President Garfield) at Fifth Avenue Hospital in New York City to investigate the cause of postoperative deep venous thrombosis.

Based on an expanded two-phase concept of blood clotting,

I. Prothrombin + thromboplastin + calcium = thrombin

II. Fibrinogen + thrombin = fibrin,

Quick used the one-step plasma PT coagulation test that he devised and that bears his name, and found no coagulation abnormality in blood from patients suffering from the royal disease, nor could he detect accelerated clotting in surgical patients, which was his original assignment. In contrast, the PT was prolonged in patients with bleeding states (termed cholemic hemorrhage) associated with obstructive jaundice.  

The international normalized ratio (INR) was developed in the 1980s by the World Health Organization (WHO) as a means of standardizing highly variable PT results and was intended to aid in the dose adjustment of the vitamin K antagonist, warfarin, used in therapeutic anticoagulation. The dangerously variable PT results from various laboratories around the world came about because reagents were used with differing levels of thromboplastic activity. An international calibration method for thromboplastins was introduced by the WHO, which created an international sensitivity index (ISI) for a given thromboplastin based on its coagulation performance with normal plasma and

FIG 8 (A) Coagulation cascade and fibrin formation. (B) Current concept of the clotting cascade. Factor VII is critical in setting off a cascade characterized by priming and amplification phases. Clot formation begins with a breach in the vascular endothelium, which exposes tissue factor to circulating factor Vlla. A small amount of thrombin is formed in this priming step. An amplification phase follows, during which activated coagulation factors and platelets help to produce a thrombin burst, leading to fibrin and clot formation. (A) Reprinted with permission from Journal of Biological Chemistry. Copyright 2003, American Society for Biochemistry and Molecular Biology; (B) reprinted with permission from Hepatology. Copyright 2004, American Association for the Study of Liver Diseases.
plasma from warfarin-treated patients, compared with the performance of the WHO reference standard under the same experimental conditions. An INR is derived for the ratio of the PT of a given patient’s plasma compared with the PT of pooled normal “control” plasma, normalized according to the derived ISI of the thromboplastin in the local reagents[^37][^38] by the simple arithmetic calculation: \[ \text{INR} = \left( \frac{\text{PT}_{\text{patient}}}{\text{PT}_{\text{control}}} \right)^{\text{ISI}} \]. The INR of the plasma of a given patient with liver disease, which is derived using plasma from warfarin-treated individuals and not from patients with liver disease, was never intended for use as a liver disease severity index in cirrhosis and has been shown in many scenarios not to be predictive of bleeding in patients with cirrhosis despite its frequent (mis)use in that capacity[^39].

For decades, the anatomic source of clotting factors that we now know is the liver was elusive to scientists and physicians. However, it was well-known that undefined substances in the liver were involved with bleeding tendencies. The original isolation of a substance known to inhibit clot formation was from a preparation of canine liver and was termed *heparin* because of its anatomic source[^40]. As the study of liver disease advanced into the 20th century, it was determined that the majority of these clotting factors were synthesized in liver, and a hallmark of advanced liver disease was prolongation of the PT due to acquired factor deficiency. Despite this discovery, laboratory testing lagged behind the understanding of liver disease, and the PT and bleeding time were the only measurements that were available for most practitioners. This reinforced the now-debunked myth that patients with liver disease had an innate “coagulopathy” and thus were very prone to bleeding. Much of this fear was spurious because it reflected the combination of a delay in diagnosis of most patients with cirrhosis until they presented with decompensating symptoms and the early surgical reports of disastrous complications and mortality during surgery in patients with cirrhosis.
who suffered massive blood loss that did not respond to transfusion with fresh frozen plasma (FFP) in the same way that trauma patients with massive blood loss responded, notwithstanding similar defects in PT and platelet counts. One archaic report discusses bleeding in liver resection:

Control of Hemorrhage . . . This is by far the most important problem in liver resection. Oozing is apt to be profuse and persistent with ordinary cutting methods. The liver tissue is friable and frequently does not hold ligatures or sutures particularly well . . .

Clearly an informed understanding of hemostasis in cirrhosis was still years away.

Hemostasis in cirrhosis began to be explored in earnest in the 1960s with descriptions of defects in plasma clotting factors, fibrinolysis, platelet function, “consumption coagulopathy,” and circulating anticoagulants. Detailed descriptions of whole blood hemostasis assays are shown in Fig. 11 (viscoelastic hemostasis assays [VHAs], either as thromboelastography [TEG] or rotational thromboelastometry [ROTEM]), which were introduced in the early years of liver transplantation, as shown in an early TEG example from 1985 (Fig. 12).

Calcium and test-specific factors are added to citrated plasma to initiate clotting. VHAs measure the change in shear elastic modulus as activated blood goes from a liquid state to a clot in a low shear environment. Both devices measure the changes in the clot’s physical properties by monitoring movement of a pin (torsion wire) suspended in the activated blood. In TEG, the chamber rotates, whereas in ROTEM, the pin rotates; in either case, rotation is progressively impaired by clotting. As the clot starts to form, its viscoelastic strength increases and more rotation is transmitted to the torsion wire. The fibrin strands start to couple progressively slow the motion of the cup to the pin (TEG; Fig. 11, left diagram) or resist rotation of the pin (ROTEM; Fig. 11, right diagram). In TEG, the decreasing rotation of the pin is detected by an electromagnetic transducer; in ROTEM, impeded pin rotation is detected optically from laser light reflected from the pin.

**FIG 10** (A) Armand Quick at age 5 years with his widowed mother, when he was thought to be dying of spinal tuberculosis. (B) In his laboratory at Marquette University in Milwaukee, WI, performing the one-stage PT test that bears his name. Courtesy The Roche Historical Collection and Archive, Basel, Switzerland.
As long as the blood is in a liquid state, the pin remains stationary and a straight line is displayed on the tracing. Thus, the physical properties of the clot (shear modulus and elasticity) are transmitted to the pin, the motion of which is detected either electromechanically or optically, respectively. Via a coupled computer, the resulting tracing is displayed as a deviation from a straight line. The magnitude of the pin rotation is directly related to the mechanical properties of the developing clot (i.e., clot strength) and displayed as amplitude on the $y$ axis of the VHA profile (Fig. 11, middle diagram). Reprinted with permission from Dr. R.T. Stravitz (Virginia Commonwealth University, Richmond, VA).

Reaction time (lag to onset of trace), maximum amplitude (height of trace), and clot formation rate (slope of trace) improved after sequential transfusion of FFP, platelets, and cryoprecipitate during the first stage of surgery. Rapid whole blood clot lysis (abrupt collapse of trace) was demonstrated during the second stage and the early part of the third stage of surgery. Transfusion of platelets and cryoprecipitate normalized the TEG pattern at the end of the operation.

These whole blood hemostasis assays were used intraoperatively by liver transplant and cardiac surgical teams, but their clinical utility was not understood by medical teams caring for patients with liver disease until much more recently. It was clear from the transplantation experience that curing the liver disease with successful transplantation reversed the hemostasis defects of cirrhosis—further proof of the hepatic origin of the clotting proteins. The development of factor concentrates allowed manipulation of clotting factor levels in humans, resulting in normalization of PTs and other measures of coagulation. This was demonstrated most strikingly with recombinant factor VII in the early 2000s in the setting of acute liver failure. Despite these breakthroughs with correction of clotting factor deficiencies, patients with liver disease still had bleeding events, usually from esophageal varices, that seemed not to improve with correction of PTs, even with large volumes of FFP transfusion. Even more startling was the clinical finding that despite abnormal clotting factors and thrombocytopenia, patients with liver disease actually had clinical thrombotic events, such as portal vein thrombosis, deep vein thrombosis, and pulmonary embolism. In 2005, Tripodi et al. showed, using an in vitro assay not previously used...
FIG 12 Representative TEGs from patients with cirrhosis, with associated standard hemostatic laboratory values measured at the same time point. (A) A normal TEG from a patient with well-compensated (Child-Pugh class A) alcoholic cirrhosis. (B) An abnormal TEG with low maximum amplitude due to thrombocytopenia in a patient with stable but mildly decompensated (Child-Pugh class B) cirrhosis due to hepatitis C virus infection. (C) An abnormal TEG with a high kinetic time, a low α angle, and low maximum amplitude due to thrombocytopenia and hypofibrinogenemia in a patient with severely decompensated (Child-Pugh class C) alcoholic cirrhosis. (D) An abnormal TEG with unmeasurably high (NA) kinetic time, a very low α angle, and very low maximum amplitude due to sepsis; this TEG is from the same patient shown in B but was taken 3 weeks later, during presentation for a fatal acute infection. Normal ranges for TEG parameters and standard laboratory tests are noted in the table in C (R.T. Stravitz, personal observations). Reproduced with permission from Gastroenterology Hepatology. Copyright 2018, Millennium Medical Publishing, Inc.
in patients with cirrhosis, that patients with advanced cirrhosis can produce clots of similar thrombin content compared with the general healthy population. This involved adding to the assay other components of the hemostasis system not reflected in the classic measurement of the PT, notably, the membrane-bound endothelial factor, thrombomodulin. The results of the investigations described in this landmark publication gave a feasible physiological explanation for the clinically evident increased thrombosis risk in some patients with cirrhosis.

This discovery triggered an upsurge in publications related to clotting and bleeding in cirrhosis (Fig. 13). The ensuing renewed interest in the area of coagulation in liver disease stimulated collaboration among researchers across the world in this narrow field and resulted in an international symposium to bring researchers in the field together for the first time in 2005. The International Symposium on Coagulopathy in Liver Disease (Fig. 5) continues as a biannual meeting focused on the topic of bleeding and clotting complications in acute and chronic liver disease, and stimulates collaboration, experimentation, and clinical investigation in the topic.

In light of the aforementioned discoveries about the true clinical impact of coagulopathy in patients with liver disease, it is disappointing but perhaps understandable that some surgeons and interventionists still demand correction of a prolonged PT/elevated INR as a measure to avoid severe bleeding preemptively due to the proposed procedure and their ensuing liability. In this charged atmosphere, urban legends and myths are often hard to ignore, despite their lack of factual basis. There is little to no evidence that cirrhosis patients with an elevated INR bleed excessively with invasive procedures, or that plasma, within reasonable limits of volumes of infusion, will more than transiently reverse an elevated INR and reduce bleeding. Moreover, there are a slew of specific adverse effects from plasma that are best avoided if its administration is not essential, not forgetting provoked variceal bleeding by circulating volume expansion and as yet poorly worked out effects on procoagulants and thrombin generation by the coagulation factors in the FFP. Yet, there is now hope that the tide may be turning at last against the wanton use of FFP; if a recent editorial proves to be the bellwether of clinical practice in this field.

Today, ongoing research into bleeding and clotting, and their relation to progression of liver disease, continues in no small part due to the history outlined earlier. New pharmacological interventions in all aspects of hemostasis, including platelet function and number, coagulation factors and anticoagulants, and fibrin supplementation, offer exciting areas of intervention. Future discoveries related to intrahepatic thrombosis, treatment of portal vein thrombosis, and perhaps even liver fibrogenesis as it relates to the hemostasis system in chronic liver disease stand to change the standard of care in hepatology and may be critical in altering the natural history of liver disease itself. We stand at the threshold of a new era of liver disease therapy, and
future articles on the history of coagulation will undoubtedly look back on this time as momentous in the annals of the hepatology therapy.

**SERIES EDITOR’S POSTSCRIPT**

From Aristotle and the Ancient Greeks to the Bolshevik Revolution, from Queen Victoria to the invention of arguably the most widespread yet misunderstood blood test in hepatology, it is all here in Patrick Northup’s lucid cinematic history of coagulopathy in liver disease. This is a dramatic tale of legends and myths, which even now is still unfolding, as clinical misconceptions and prejudices are being dispelled under the scrutiny of scientific rigor and clinical trial. I wager that you will be enlightened and enthralled by this arcane stepwise revelation of the intricacies of normal and deranged blood coagulation in patients with liver disease. More important and practical, after completing this review you should be able to work out whether a bleeding risk is likely to complicate surgery or another invasive procedure in a given patient with liver disease. If so, you will understand how to evaluate that likelihood further with additional functional testing of the coagulation process, using whole blood viscoelastic assays and other hemostatic tools. This informed approach should replace a traditional knee-jerk response to an elevated PT/INR.

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