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A further face of the partial thromboplastin time APTT

C. H. TOH
Roald Dahl Haemostasis and Thrombosis Centre, Royal Liverpool University Hospital, Liverpool, UK

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The value of the activated partial thromboplastin time (APTT) has been well described by the Forum authors in relation to its clot–endpoint determination [1–6]. Its performance also has added value and enabled our group to unravel the existence of a calcium-dependent complex between C-reactive protein (CRP) and very low-density lipoprotein (VLDL) [7]. Although Rowe *et al.* [8] have shown that this complex can be induced by incubating acute-phase serum containing elevated CRP levels with serum from type III hyperlipidemic patients, our investigations have clearly demonstrated its existence *in vivo* in critically ill patients [7]. In addition, we have also provided pathophysiological insight into the role of this complex which might outwardly be more relevant to cardiovascular disease, but is actually pertinent to critical care biology. All this stemmed from initial serendipitous observations of an atypical, biphasic light transmittance profile of clot formation in the performance of the APTT on samples from patients with disseminated intravascular coagulation (DIC) [9]. Further work by ourselves and others have shown that its detection has prognostic significance and can be useful in the monitoring of critically ill patients [10–12]. The close correlation between changes in the biphasic waveform and clinical events led us to hypothesize that there was an underlying biological mechanism and to this end, the great skills of Mike Nesheim enabled us to unravel its molecular composition and further demonstrate that the extent of CRP–VLDL complex formation correlated with the degree of the biphasic waveform abnormality. Although it is still early days in understanding the full pathophysiological consequence of this complex, it appears to link to DIC in that the VLDL component can enhance thrombin generation and procoagulant activity by at least 2.5-fold [13]. Indeed, a shortened APTT clot-time is often noted with the biphasic waveform. This highlights the relevance of performing the APTT beyond the traditional significance of clot-time prolongation to the pathophysiological significance of faster endpoint determinations. Shorter APTT clot-times have been demonstrated to predict adverse outcome in terms of general mortality in a general hospital setting [14] and more recently, associated with venous thromboembolic risk [15]. As with its importance in the development of the activated protein C resistance assay [5], the APTT promises to evolve beyond its well-archived role [16] to present a further, fresh dimension to the coagulationist in a new era of diagnostic importance, mechanistic understanding and research development.

Correspondence: Cheng Hock Toh, Roald Dahl Haemostasis and Thrombosis Centre, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK.
Tel.: +44 151 706 4322; fax: +44 151 706 5810; e-mail: toh@liverpool.ac.uk

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Is citrate deficiency universal?

E. SHANBROM
Santa Ana, CA, USA

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Recently, my grandson Corey, a math major at the University of California Santa Cruz, was attempting to explain some exotic mathematics and showed me the opening sentences of Chapter 2 in his text book: 'We have an intuitive concept of the real number system used by mathematicians since at least the period of ancient Greek mathematics.' That gave me the courage in this age of 'evidence-based medicine' [1] to intuitively conclude that much of our research in blood is either wrong or needs to be reevaluated. We discovered this during our work on 'cascade iodination', a method to inactivate pathogens in plasma proteins [2] which led to the concept of 'supercryoprecipitate' [3]. The original amount of anticoagulant used in transfusion was limited by the fact that higher amounts of citrate would damage the cellular portion of blood at a time when plasma elements were relatively unimportant. We now believe that blood should be collected in at least 1% (w/v) citrate content to stabilize and prevent protein 'activation'. Citrate also disinfects at higher concentrations. We hope to publish our findings in the future, but it seems wise to prevent further misinformation by printing this brief communication for plasma protein researchers. Factor VIII products might even become less antigenic if 'activation' is prevented.

I have just celebrated my 80th birthday and am reminded that I heard Armand Quick, at a similar age, present his ideas that aspirin increased bleeding. I do not remember exactly where and when, but I do remember some smiles and smirks in an audience of lesser age. I expect that my observations might elicit a similar response, but I hope a few of you will try to confirm this concept that more citrate means more preservation – at least of plasma components. Until recently, the main problem from decreased citrate concentration seems to be cellular damage resulting from cation imbalances, but now it appears that using organic counterions allows us to increase citrate concentration while actually improving cellular preservation.

Correspondence: E. Shanbrom, 2252 Liane Lane, Santa Ana, CA 92705, USA.
E-mail: wjowens@msx.ndc.mc.uci.edu

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