Thrombosis and haemostasis

from Robert W. Colman, Gwen Stewart, Andre Budzynski, T. Roy Ittyerah, Stephanie Olexa, Edward Kirby, Miriam Fukami and Jeanette Piperno.

FOR over a century investigators have been fascinated by the mechanisms by which blood remains in a fluid state while circulating *in vivo* but forms a fibrin-platelet thrombus *in vitro* or in disease states. Current research directed at solving this problem was presented at the VIIth International Congress on Thrombosis and Hemostasis held in London earlier this year*. The presentations were notable for the wide range of approaches and disciplines applied to the study of haemorrhage and thrombosis. The hypothesis was presented by J. Vane and S. Moncada (Wellcome Research Laboratories, Beckenham, UK) that PGI_2 (prostacyclin) synthesised by endothelium cells lining vessels is responsible for preventing thrombosis in the normal vessel. This prostaglandin derivative increases platelet intracellular cyclic AMP levels, thus inhibiting platelet aggregation. This attractive concept was criticised by several groups at the meeting. J.B. Smith and his colleagues (Jefferson Medical College, Philadelphia) found that an antibody which could neutralise the platelet inhibitory action of PGI_2 failed to alter the *in vivo* bleeding time. Moreover, G. deGaetano and his colleague (Instituto di Richerche Farmacologide, Milan) demonstrated that PGI_2 failed to protect rats against venous thrombosis. Thus, PGI_2 may represent one but not the only endogenous substance responsible for the nonthrombogenicity of the blood vessel wall.

Haemophilia is one of the most common congenital haemorrhagic disorders. Yet the protein which is missing or abnormal, anti-haemophilic factor, has never been purified to a homogenous state. For this reason assays for detection of carriers for prenatal diagnosis in fetal blood have been limited to coagulant assays or immunoassays of the related protein, von Willebrand's factor. L. Hoyer and his group (University of Connecticut Health Center, Farmington) reported on the use of an immunoradiometric assay based on human inhibitors but these naturally occurring antibodies are limited in availability. G.A. Vehar and E.W. Davie, (University of Washington, Seattle) however, reported a 500,000-fold purification of coagulant factor VIII which may pave the way to simpler assays based on heterologous antibodies.

The role of phospholipid micelles in blood coagulation has been appreciated for many years but the anatomical localisation in the organism has not been clear. R.F.A. Zwaal and his associates (States University of Limburg, Maastrich) presented data indicating that the phospholipids may be on the internal plasma membrane of the platelet and exposure may occur by translocation of these phospholipids to the external platelet membrane. Further reactions at the platelet surface involve the binding of an accelerator of blood coagulation activated factor V (K. Mann *et al.* Mayo Clinic Foundation, Rochester) followed by the attachment of the serine protease factor Xa which then converts prothrombin to thrombin (J. Miletich & P. Majerus, Washington University, St Louis). The source of the factor V may be the alpha granules of platelets according to T. R. Ittyerah, R. Rawala and R. Colman (Temple University, Philadelphia). These investigators found that bovine platelet factor V is a single chain of molecular weight 270,000 which is released by collagen from platelets and in the process is proteolytically converted to an activated form. Thus, the entire middle phase of blood coagulation occurs on the platelet surface and requires activation of the platelet. P. Walsh (Temple University, Philadelphia) and J. Griffin (Scripps Clinic, La Jolla) reported that platelets may accelerate the early contact phase of blood coagulation, further emphasising the functional interdependence of coagulation and platelet activation. This theme was further emphasised by the findings of D. Phillips *et al.* (St Jude Children's Research Hospital, Memphis). These investigators found that thrombin aggregates platelets forming a filamentous complex which contains glycoproteins II_B and III of the platelet membrane. Yet another example of the critical interactions between coagulant proteins and platelets is the well known requirement of fibrinogen for platelet aggregation by ADP. J.S. Bennett (University of Pennsylvania) T.S. Edgington *et al.* (Scripps Clinic, La Jolla) and M. Zucker *et al.* (New York University Medical Center) have all demonstrated that ADP stimulation of platelets makes available fibrinogen binding sites on the platelet sticking one to another in the fibrin thrombus.

The fibrin thrombus once formed will occlude the vessel until lysed by the enzyme plasmin. Collen (University of Leuven) presented an integrated theory explaining lysis of the clot in the gel phase but not fibrinogen in the fluid state. Fibrin binds both plasminogen activators and plasminogen. Plasmin formed remains bound and is protected from the potent, naturally occurring proteolytic inhibitor α_2-antiplasmin. Determination of components of the fibrinolytic system may thus allow better control of thrombolytic therapy.

As a whole, the meeting emphasised that to elucidate the mechanisms of haemostasis and the pathophysiology of thrombosis, a knowledge of cell biology, biochemistry and immunology must be applied to study vessel wall cells, plasma coagulation factors and platelets. □

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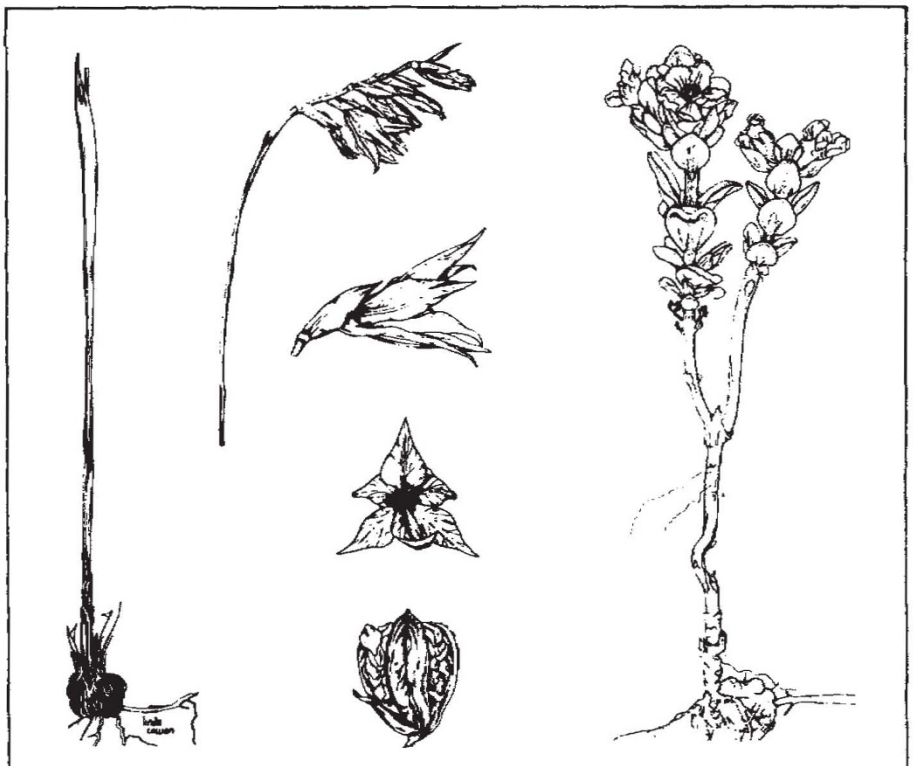

Two new species from Natal: *Alectra dunensis* (right) and *Gladiolus pugioniformis* (from Hilliard & Burtt, *Notes from the Royal Botanic Garden Edinburgh*, 37, 285; 1979).

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