# Molecular insight into thrombosis

*from E. W. Horton*

WHY don't platelets stick to the surface of healthy blood vessels whereas they will stick to foreign surfaces such as glass or to damaged or diseased blood vessels? The recent discoveries of two naturally occurring compounds have revealed much about the underlying chemical mechanisms and may provide an answer to this intriguing problem.

In 1975 Samuelsson and his group at the Karolinska Institute in Stockholm discovered that when platelets stick to each other (or aggregate) they release a substance called thromboxane $A_2$ (*Proc. natn. Acad. Sci. U.S.A.*, **72**, 2994). This highly unstable compound (half-life in water about 30 s) is formed from the same precursor as the prostaglandins (arachidonic acid through an unstable endoperoxide, prostaglandin $G_2$), but differs sufficiently in structure from the prostaglandins to justify the use of new nomenclature. Thromboxane $A_2$ (which is almost certainly identical to the rabbit aorta-contracting substance previously discovered by Piper and Vane) is a powerful stimulant of platelet aggregation. It is probable that the formation of this substance is responsible for the clumping of platelets which, if allowed to continue inside a blood vessel, may result in thrombus formation. If the blood vessel becomes completely occluded by such a thrombus, the consequent tissue damage, for example in the heart or brain, may prove rapidly fatal.

Oates and his colleagues at Vanderbilt University have reported (*Science*, **193**, 1135; 1976) that thromboxane $A_2$ released from human platelets can constrict coronary blood vessels of the pig. They postulate that platelet aggregation in areas of damaged endothelium can release thromboxane $A_2$ and thus cause constriction of large coronary arteries.

A more recent development is reported in this issue of *Nature* (page 663). It comes from Vane's group at the Wellcome Research Laboratories, Beckenham. In the microsomal fraction of homogenised blood vessels they have discovered an enzyme which converts the endoperoxide intermediary, prostaglandin $G_2$, not to the classical prostaglandins ($E_2$, $F_{2\alpha}$ and $D_2$) nor to thromboxane $A_2$ (as occurs in platelets) but to a new substance (PGX) which has not yet been identified. PGX has two important pharmacological properties both opposite to those of thromboxane $A_2$. It is the most powerful inhibitor of platelet aggregation yet discovered and it dilates blood vessels. Thus the endothelial lining of blood vessels possesses its own mechanism for generating a substance which will prevent platelets from adhering to its surface or to each other. Moreover, the substance will tend to maintain the flow of blood by dilating the vessel itself.

The following sequence of events can therefore be envisaged. When platelets come into contact with endothelium of the normal blood vessel wall they release a quantity of the prostaglandin endoperoxide, which is then used as a substrate by the blood vessel enzyme to form PGX. By its inhibitory properties this substance will, in turn, counteract any tendency of platelets to aggregate, or of the blood vessels to constrict. If, however, platelets come into contact with blood vessels whose endothelium has been disrupted or destroyed by pathological changes, there will be no enzyme for the formation of PGX and so the aggregating action of thromboxane $A_2$ formed by the platelets from prostaglandin endoperoxide, will go unopposed leading to thrombosis and local vasoconstriction.

Since PGX, like thromboxane $A_2$, is an unstable compound, its usefulness as a drug to treat or prevent thrombosis in man may be limited. Nonetheless, the elucidation of its structure is of paramount importance. Once the structure is known, analogues can be synthesised with the object of finding a compound which combines the pharmacological (PGX-like) activity with greater stability. Such a drug could be used in both the treatment and prevention of thrombosis.

Thrombosis is one of the most common causes of death in the western world. Young and middle-aged men, apparently fit and in the prime of life, are frequent victims. Few really effective remedies or preventative measures are available. Until now, in spite of much outstanding research, the sequence of events which leads to thrombosis at what is popularly called the 'molecular level' has been incompletely understood. The potential value to medicine of the discovery of PGX is therefore incalculable.

the relative importance of the climatic controls, which is an essential step towards climatic prediction, collaboration between people using often widely divergent methods to study climatic change is highly desirable.

The recent article by Colebrook (*Nature*, **263**, 576; 1976) highlights one area where such collaboration should prove fruitful. Colebrook analyses long series of oceanographic and climatic data in order to define changes in the North Atlantic current systems and ocean temperature during the past 100 yr and to suggest ways in which shifts in the ocean and atmospheric circulation are related. He concludes that, on time scales of decades, sea surface temperature changes are largely due to variations in advection associated with the changing intensity of the Gulf Stream and North Atlantic Drift currents. He states that these currents are responding to variations in the atmospheric circulation over the North Atlantic, although the atmospheric circulation index chosen (tropical cyclone frequency) is remarkably indirect.

Colebrook also shows, contrary to other widely publicised opinions, that recent changes in the oceanic climate are not unusual in the context of the past 100 yr. In addition, he presents further evidence of the approximately 10-yr periodicity in sea surface temperature in the North-East Atlantic that has been mentioned by other investigators. He links this periodicity to changes in atmosphere pressure associated with the sunspot cycle, as given by Parker (*Met. Mag.*, **105**, 33; 1976). It is interesting that the connection between variations in the strength of the East Atlantic meridional atmospheric flow and solar activity is also apparent in the 24-h change in atmospheric pressure distribution following a solar flare (see, for example, Schuurmans, *Meded Verh. K. ned. met. Inst.*, **92**; 1969). The effects on climate of solar variation are gradually being accepted as genuine but of secondary importance, tending to modify the nature of the meridional rather than the dominant zonal atmospheric air flow.

Increasing evidence of frequency-dependent relationships between climatic variables is coming to light. Sea surface temperature to the west of the United Kingdom seems to be controlled by the strength of the broad Atlantic westerly air flow on time scales of decades and longer. Yet, on the shorter time scale of the 10-yr periodicity, local changes in the meridional component of the atmospheric circulation are more important. This association between sea temperature and southerly air flow in the East Atlantic on short time scales has been demonstrated by Dickson (*Dt. hydrogr. Z.*, **24** (3), 97; 1971).

Investigations such as this are hampered by the lack of long climatic data series. As usual when limited data are