Is prostacyclin a circulating anti-coagulant?

from C. T. Dollery and C. N. Hensby

LUNG tissue from numerous animal species, including man, has been shown to be capable of synthesising and releasing a variety of prostaglandins (Piper & Vane *Ann. N.Y. Acad. Sci.* **180,** 363; 1971). Furthermore, metabolic transformation in the lung rapidly inactivates these prostaglandins (Ferreira & Vane *Nature* **216,** 868; 1973). It seemed unlikely, therefore, that the naturally occurring prostaglandins would be released from the lung in sufficient quantities to act as 'circulating hormones'. One exception to which the term 'circulating hormone' could be applied was the evidence in many animal species (but not man) that prostaglandin $F_{2\alpha}$ was the uterine leuteolytic hormone (for references see Horton & Poyser *Physiol. Rev.* **56,** 959; 1976). In this instance, however, prostaglandin $F_{2\alpha}$ cannot be considered as a genuine circulating hormone, as a complicated transfer mechanism has evolved, enabling $PGF_{2\alpha}$ to pass directly from the uterine vein into the ovarian artery, thereby bypassing the lung inactivation process. With the discovery that prostacyclin, the major product of arachidonic acid metabolism produced by arteries and veins (Moncada, Higgs & Vane *Lancet* **i,** 18; 1977) could pass through the lung circulation unchanged (Armstrong *et al. Brit. J. Pharmac.* **62,** 125; 1978) the possibility that prostacyclin could function as a circulating hormone had to be given serious consideration. In this issue of *Nature,* two independent groups, Gryglewski's from Poland (page 765) and Vane's from England (page 767) present evidence to suggest that lung vascular tissue continuously produces and releases prostacyclin *in vivo* and that this substance acts as a circulating anti-thrombotic agent especially on the arterial side of the circulation. Other evidence has been presented to support this theory (Moncada & Korbutt *Lancet* **i,** 1286; 1978). These authors suggest that prostacyclin increases platelet cyclic AMP thereby decreasing platelet aggregability. Whether the prostacyclin liberated from the pulmonary circulation is a 'spill over' phenomenon rather than a fully functioning anticoagulant mechanism has still to be determined. However, the results obtained by Moncada and Korbutt suggest that this is the case—at least in the rabbit. Recently Boot and his colleagues (*Int. Arch. appl. Immun.* **57,** 159; 1978) have confirmed that prostacyclin is the major product of arachidonic acid formed in the pulmonary vascular bed. The extent to which prostacyclin has a local role in the lung in regulating the resistance of the pulmonary vascular bed also remains to be established but it is an aspect which ought not to be forgotten. These workers have also shown that the lung can metabolise prostacyclin after it has been hydrated to 6-keto $PGF_{1\alpha}$ so the lung can both form and inactivate prostacyclin.

Factors that modify prostacyclin production in the lung may be of some importance in relation to lung pathology and intravascular thrombosis. Gryglewski and his colleagues suggest that noxious stimuli such as cigarette smoking may reduce formation of prostacyclin and increase the risk of thrombosis. Interestingly, Boot and his colleagues found that successive immunological challenge decreased the production of prostacyclin whereas formation of thromboxane A_2 was increased. This too may have implications for pathology.

The implications of recent research on circulating prostacyclin for clinical medicine may be substantial. Formation of blood clots in veins seems to be a much more common event than in arteries. There may be several reasons for this; a lower velocity of flow in veins must be one, but the presence of higher concentrations of prostacyclin in arterial blood may turn out to be more important. Extension of blood clots on the venous side of the circulation also seems to be more common than on the arterial and a possible explanation may again lie in the higher levels of prostacyclin. Ever since the discovery of the highly potent platelet-aggregating activity of thromboxane A_2 released from platelets, what limits the chain reaction of intravascular thrombosis has been a puzzle. In theory it seemed that aggregation of more platelets to a thrombus would release yet more thromboxane and aggregate more platelets until either all the platelets had been sequestered or the whole circulation had thrombosed. The presence of prostacyclin in the blood would act as a negative feedback mechanism limiting the spread of the clotting process back into the flowing blood.

Interest is bound to shift towards pharmacological means of manipulating the balance between formation of thromboxanes and prostacyclin as a more physiological means of controlling intravascular coagulation. It also seems possible that either synthetic prostacyclins with greater stability than the natural compound or drugs which selectively inhibit thromboxane synthetase may be useful as anti-coagulant drugs, for example in extracorporeal circulation through artificial kidneys or oxygenators. For long it seemed that prostaglandin research might remain as an exciting biological discovery which had very limited applications to human disease. With the discovery of the thromboxanes and prostacyclins it seems destined to return to the centre of the stage. □

C. T. Dollery is Head of the Department of Clinical Pharmacology and C. N. Hensby is a member of the research staff of the Department of Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London.

A new interaction for leptons?

from F. E. Close

SOME recent data from Gargamelle (*News and Views* **273,** 98; 1978) have raised a question mark over the Weinberg-Salam model which is the simplest candidate for unifying the weak and electromagnetic interactions. An experimental study was made of the elastic scattering of muon neutrinos on atomic electrons. Twelve events were found where only two had been expected according to the model.

Any player of roulette will know that it is not uncommon for one to win a small amount when 4 or 5 successive reds emerge. A run of 50 successives would be a clear indication that some external agent was at work. The immediate concern in the Gargamelle data is to have more of it to see if the present result is just a statistical fluctuation or whether it heralds a genuine effect. It does seem that statistics may turn out to be the culprit. A recent seminar at Fermilab has been reported as showing that in an analogous experiment there, six events were seen where six were expected. These data are still being analysed.

The interesting theoretical question therefore remains for the moment: what must we do to the Weinberg-Salam model if the effect is genuine?

Clearly, many ideas will be put

F. E. Close works at the Rutherford Laboratory.