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Based on a Dissertation read before the Royal Medical Society on Friday. 20th January, 1961.

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FIBRINOLYSIS AND OCCLUSIVE VASCULAR DISEASE

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The magnitude of the problem of occlusive vascular disease needs no introduction; we should therefore be acquaint with any new therapeutic developments, particularly if these have reached the stage of clinical trials. I apologise for any bias and simplification in this article. The purpose of the original Dissertation was to arouse curiosity; this article attempts to do no more.

The System

The end-product of the complicated clotting mechanism is a fibrin clot. Fibrinolysis appears to be an equally complicated mechanism, the end-product of which is an enzyme, Plasmin, which can lyse the fibrin clot. Less detail is known of the various stages in Fibrinolysis than is known of the clotting mechanism. Astrup (1956), however, has produced a rough scheme which represents current thought fairly well. His scheme (Fig. 1) is based on the work of Christiensen & McLeod (1945).

Space does not permit discussion of known details in the fibrinolytic process. Suffice to say that circulating in the blood of all mammals so far studied is the precursor of the enzyme, Plasminogen. In the presence of an activator, which in turn is the end-product of a complicated process, Plasminogen is converted to Plasmin, the active fibrinolytic enzyme.

Inhibition of this mechanism appears to occur. So far the inhibitors appear to attack specifically at two sites. There are specific inhibitors of Plasmin and of Plasmin activators. One circulating Plasmin inhibitor is known to be an a-globulin. Synthetic inhibitors have been produced, the most recent being D-amino caproic acid.

Physiology

Fearnley (1953, 1955), pioneered the concept of a basal level of spontaneous fibrinolysis in normal people. He was able to show a diurnal variation, and a measurably higher level of activity in venous blood, particularly in that from the muscles. Buckell and Elliot (1959) using different assay methods have confirmed this, and agree with Mullertz (1956) that the cause of the raised activity in venous blood was a raised level of activator. Sherry (1960) has also confirmed a raised level of activator following periods of fear, parenteral adrenaline, anoxia and after intravenous acetyl choline.

The mechanisms behind the release of Plasminogen activator are still for the most part obscure. Two significant observations, however, deserve mention. Albrechtsen (1957) has shown that certain organs store a high concentration

of activator ; the uterus, prostate, adrenal gland, thyroid, lungs and ovaries are such organs. The kidneys, all muscle, testes and spleen have very little, while the liver has none. It is possible that those sources of activator listed above may be used to raise the level of circulating activator.

Many workers have found a high level of fibrinolytic activity in venous blood draining muscles, despite Albrechtsen's finding of a low yield of activator from muscle tissue. Kwaan & McFadyean (1957, 1958) in some brilliant experiments on this problem concluded that there exists in the walls of arteries, veins and of some capillaries, cholinergic effector mechanisms which can react locally and reflexly to release Plasminogen activator. They have very tentatively suggested that constriction of the vasa vasorum producing relative ischaemia may trigger off this mechanism. Confirmation of these observations is urgently required.

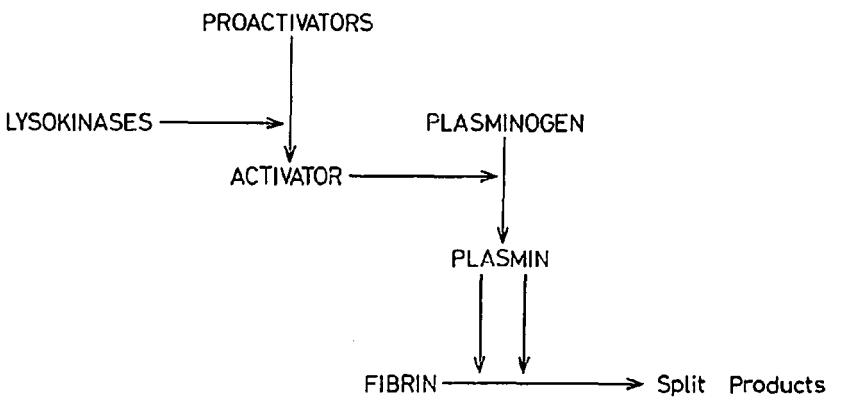

FIG. I.

Pathology

Thus we see so far that Fibrinolysis is a complicated yet delicately controlled mechanism. It is now necessary to look for any disturbance in the mechanism in association with occlusive vascular disease.

Over 100 years ago Rokitansky postulated that arteriosclerosis was the result of organisation of mural fibrin thrombi. Duguid (1946, 1948) has recently revived this hypothesis as giving a part explanation for the origin of arteriosclerosis. Duguid's work has been confirmed by many other workers, but he has shown great restraint in explaining why focal deposits of fibrin occur. Mole (1948) and Astrup (1956) have concluded that the cause is an upset in the fibrinolytic mechanism. Gillman (1958) believes that a decreased level of fibrinolysis plays at least some part in thrombosis.

Work has only just begun in measuring the fibrinolytic activity of circulating blood in patients with occlusive vascular disease. There is as yet no convincing evidence of reduced fibrinolysis after myocardial infarction, but Nestel (1959) has shown convincingly a 2/3 reduction in fibrinolytic activity in patients suffering from intermittent claudication.

The work of Kwaan & McFadyean (1957) and Buckell & Elliott (1959) has shown that fats, specifically saturated fatty acids, inhibit fibrinolysis. It is perhaps all to easy and fashionable to relate the association of fats with occlusive vascular disease through fibrinolysis. Measurements of the fibrinolytic

activity in diabetics on simple reducing diets are urgently required. In them, Beckett & al. (1960) observed an incidence 20% higher than expected of occlusive vascular catastrophes, and Southwood & al. (1959) had previously shown a profound lipaemia at such times, and that the fats were saturated.

The evidence supporting the hypothesis that a disturbance of the fibrinolytic system plays an important role in the pathology of occlusive vascular disease is still fragmentary and controversial. Nevertheless, armed with this evidence, American workers **have** proceeded into the exciting field of therapeutics.

Therapeutics

The possibility of unblocking blood vessels using fibrinolytic techniques is an exciting one. It is perhaps necessary to set apart atherosclerosis in which epithelization has taken place as compared with the more sudden process of thrombosis or embolism. The evidence suggesting that fibrinolytic therapy is useful in atherosclerosis is slight and the more interesting results have come from treatment of thrombosis and embolism.

At the moment the only effective method involves the use of human Plasmin intravenously. An American company now produces a preparation known as "Thrombolysin." Local infusions are necessary to be really effective, as the circulating Plasmin inhibitors soon nullify a raised systemic fibrinolysis.

Ruegsegger & al. (1960) have obtained some important results from radiographic studies, in the dog, of occluded coronary vessels infused with "Thrombolysin." Their work merits close study. Frieman & al. (1960) have also given successful local infusions in dogs' peripheral vessels.

The amount of work performed on patients is still very limited. The problem of assessing the results is particularly difficult in such fields as coronary thrombosis and cerebral thrombosis. Nevertheless, Richter & al. (1960) and Boucek & al. (1960) have both reported promising results. The latter have successfully perfused the coronary vessels with "Thrombolysin."

The treatment of peripheral thromboembolic disease has involved more straightforward techniques and the results therefore are of more definite significance. Anylan & al. (1960) and in particular Clifton (1960) have produced some most encouraging results, from patients with femoral embolism and femoral thrombosis.

The possibility of preventing occlusive vascular disease becomes very real, particularly when a patient has been enabled to survive a first acute attack. Since the limitations of long-term anticoagulant therapy are daily more apparent, it must be considered whether a raised level of spontaneous fibrinolysis would not be a safer and more effective prophylaxis. Certainly, at least, Frieman & al. (1960) were unable to produce artificial thrombi in their dogs, once these had been thoroughly "thrombolysed."

Intravenous "Thrombolysin" for the rest of one's life is obviously inconceivable but attempts have been made to find compounds which when taken orally will produce a raised level of spontaneous fibrinolysis.

Finding a powerful hypolipaemic agent is an obvious start in the solving of this problem. Constantintides & al. (1960) have reported that a sulphated polymannuronide, "Paritol C" is a powerful hypolipaemic agent with no side effects. One oral dose is effective for 24 hours. Fearnley (1960) and Singh & al. (1960) have produced some remarkable improvements in patients with intermittent claudication by giving them oral sulphonylureas, Tolbutamide and Chlorpropamide. Fearnley has demonstrated a raised level of spontaneous fibrinolysis in patients taking these drugs.

These advances in the study of Fibrinolysis promise an important breakthrough in the management of occlusive vascular disease. The foregoing

has been a brief, biased account ; lest we become wildly enthusiastic it should be pointed out that no " double blind " trials have yet been reported. There is a great need for more effective fibrinolytic agents and for careful, critically-reported trials. Despite the many problems, the clinical and anatomical restitution of occluded vessels and prophylactic measures against such catastrophes by medical means, is an exciting goal.

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