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Phenformin as a fibrinolytic drug

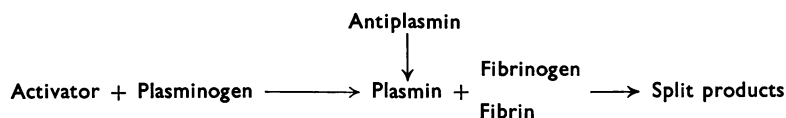
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DURING the past 20 years fibrinolysis, once an apparently rare and pathological phenomenon, has begun to emerge as the physiological anti-thesis of coagulation, a system whose function seems to be the removal of fibrin. Basically the system consists of plasminogen, an inactive enzyme precursor present in blood and other body fluids which can be converted to plasmin, an active proteolytic enzyme, by activators present in the blood, body fluids and the tissues. Anti-

plasmin is present in blood and neutralizes any plasmin liberated, so that in normal circumstance free plasmin is absent from circulating blood and the fibrinolytic system is in effect inert.

Since plasmin digests fibrinogen as well as fibrin, antiplasmin is a necessary safeguard against destruction of fibrinogen in fluid blood; but when fibrin is formed activator is adsorbed to it and converts the plasminogen incorporated with it to plasmin which in turn is adsorbed to fibrin



and hence protected from inactivation by antiplasmin. Thus protected, the plasmin is free to digest deposited fibrin.

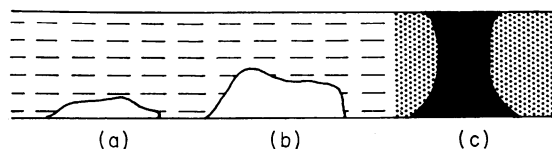


FIG. 1. In a mural thrombus (a) or a retracted thrombus (b), activator is available for adsorption and concentration from circulating blood. In occlusive thrombosis (c) the circulation ceases and activator is not available. (From Fearnley, G.R., 1961, *Lancet*, i, 992.)

This forms the basis of a concept of natural fibrinolysis shown in Fig. 1, whereby the fibrinolytic system functions as a fibrin-clearing and hence antithrombotic mechanism without impairing haemostasis (Fearnley, 1953, 1961). Normal blood contains an activator of plasminogen (Fearnley & Tweed, 1953; Flute, 1960) which varies between individuals, and appears to be deficient in 60% of patients with peripheral arteriosclerosis (Fearnley & Chakrabarti, 1964), and in 45% of male survivors of myocardial infarctions under the age of 60, as compared with 10% of age-matched controls (Chakrabarti *et al.*, 1966).

Natural fibrinolytic activity is conveniently measured by the dilute-blood-clot lysis-time (Fearnley, Balmforth & Fearnley, 1957) in which the time required for lysis of a 1 in 10 dilution of freshly obtained blood clotted with thrombin is measured at 37°C. Fibrinolytic activity is inversely proportional to the lysis-time. Normal lysis-times by this method range from 1½ to 7 hr.

Some years ago it occurred to me that it might be possible to enhance the fibrinolytic activity of blood pharmacologically with the object of developing a new approach to the prophylaxis of vascular occlusion in patients with ischaemic disease.

Background

At that time the only pharmacological substance, as distinct from the thrombolytic agent streptokinase, known to increase blood fibrinolytic activity was adrenaline, as was first shown by Biggs, Macfarlane & Pilling (1947), using a dilute-plasma-clot test-system. When Biggs *et al.* (1947) published their results spontaneous fibrinolytic activity had not been shown to be a normal property of blood, and the appearance of fibrinolytic activity in diluted plasma was be-

lieved to be a reaction of the body to stress. Following the observation that fibrinolytic activity induced by adrenaline is labile in fluid blood and plasma, but is stabilized by fibrin formation (Fearnley, Reville & Tweed, 1952), fibrinolytic activity was found to be a property of normal blood, as already mentioned. The problem therefore seemed to be one of enhancing something which is normally present, but there was no clue as to what kind of drug might do this or for that matter whether such a drug existed. Early pilot trials of sympathomimetic drugs given by mouth, ephedrine, dextroamphetamine and isoprenaline, gave disappointing results; and experiments with other commonly used therapeutic substances, including single doses of prednisone, were equally unproductive. In 1959 my colleagues and I decided to test insulin for any possible effect on fibrinolysis. The subcutaneous injection of insulin in diabetics was found to result in a biphasic fibrinolytic response, consisting of an initial reduction followed by an increase of blood fibrinolytic activity, as measured by the dilute-blood-clot lysis-time (Fearnley, Vincent & Chakrabarti, 1959). The increase of fibrinolytic activity coincided with low blood-glucose levels and was postulated to be due to release of adrenaline. This suggested that sulphonylurea compounds might increase blood fibrinolytic activity, and tolbutamide and chlorpropamide were found to do so in arteriosclerotic patients studied in the fasting, resting state (Fearnley, Chakrabarti & Vincent, 1960). Since increased fibrinolytic activity was not accompanied by reduction of blood glucose levels in our patients, hypoglycaemia was evidently not the cause of the fibrinolytic effect of these compounds. Although subsequent experience showed that many people become resistant to the fibrinolytic effect of the sulphonylureas (Fearnley & Chakrabarti, 1964), these were the first substances discovered to enhance fibrinolytic activity for several weeks when given by mouth.

It seemed possible that hormones might influence the fibrinolytic system, and testosterone given intramuscularly in large dosage daily or on alternate days was found to produce a sustained increase of fibrinolytic activity (Fearnley & Chakrabarti, 1962; Winther, 1967). As a result of this finding, the anabolic steroids, methenolone and ethyloestrenol, given by mouth were investigated for fibrinolytic effects. Both increased fibrinolytic activity, but as with the sulphonylureas resistance developed in many patients within a few weeks (Fearnley & Chakrabarti, 1964). In the meantime ACTH and corticosteroids were shown to increase fibrinolytic activity both in

patients with inflammatory and with non-inflammatory conditions, the latter indicating the effect of corticosteroids on fibrinolysis to be primary and specific, rather than a reflection of improvement of inflammation (Chakrabarti, Fearnley & Hocking, 1964).

The diguanides

The fibrinolytic effect of the sulphonylureas, though disappointingly temporary, suggested that other drugs which influence carbohydrate metabolism might also enhance fibrinolytic activity. Phenformin in tablet form, 100–150 mg daily, was found to increase fibrinolytic activity but caused too high an incidence of gastric intolerance; when timed-release capsules became available these in a dosage of 50 mg twice daily were well tolerated by most patients and produced an increase of fibrinolytic activity in the majority, which was sustained when the drug was evaluated for a period of 3 months (Fearnley & Chakrabarti, 1964). The allied substance metformin in a dosage of 500 mg thrice daily was found to have a comparable fibrinolytic effect in patients with coronary artery disease (Chakrabarti, Hocking & Fearnley, 1965). Subsequently resistance was found to develop to the fibrinolytic effects of both phenformin and metformin after 3–4 months' treatment (Hocking *et al.*, 1967).

Combined fibrinolytic drugs

The problem of resistance which seemed to develop sooner or later to the fibrinolytic effect of drugs given by mouth prompted us to investigate combined therapy.

In a trial lasting 21 months the effects on the dilute-blood-clot lysis-time, the euglobulin lysis-time, plasma fibrinogen and serum cholesterol levels of metformin 1.0 g daily plus ethyloestrenol 8 mg daily were studied in fifteen patients with occlusive vascular disease and of phenformin capsules 100 mg daily plus ethyloestrenol 8 mg daily in eighteen patients. Both combinations given over a period of 12 months produced a sustained increase of fibrinolytic activity in 80% and 89% of the patients respectively. The diguanides were then withdrawn for 3 months, the patients continuing to take ethyloestrenol alone, which failed to maintain the full fibrinolytic effect of combined treatment. When metformin and phenformin were restituted for the last 6 months of the trial, the full fibrinolytic effect was restored. Both combinations of drugs reduced plasma fibrinogen levels; serum cholesterol was reduced by phenformin but not by metformin (Fearnley, Chakrabarti & Hocking,

1967). The results obtained with phenformin plus ethyloestrenol are shown in Fig. 2.

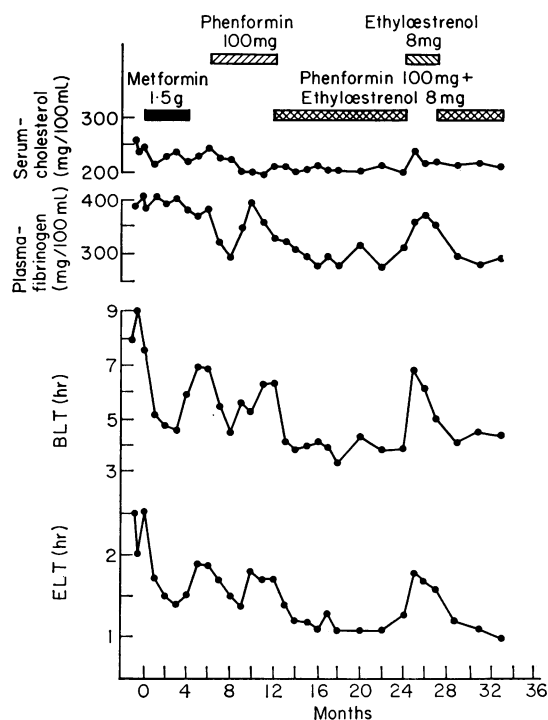


FIG. 2. Effect of phenformin plus ethyloestrenol on mean serum cholesterol, plasma fibrinogen, dilute blood clot lysis-time (BLT) and euglobulin lysis-time (ELT) compared with metformin, phenformin, and ethyloestrenol alone in eighteen patients with occlusive vascular disease. (From Fearnley, G.R., Chakrabarti, R. & Hocking, E.D., 1967, *Lancet*, ii, 1008.)

Phenformin combined with ethyloestrenol was also found to reduce platelet stickiness by about 50% in fifteen of twenty patients with occlusive vascular disease (Chakrabarti & Fearnley, 1967) as shown in Fig. 3. Metformin with ethyloestrenol does not have this effect (unpublished data).

Applications

Since phenformin with ethyloestrenol favourably influences four factors believed to be of importance in the genesis of vascular occlusions, i.e. fibrinolytic activity, plasma fibrinogen, serum cholesterol, and platelet stickiness, this combination of drugs would seem to be suitable for trial in the prophylaxis of arterial occlusions in patients with ischaemic disease, for example, survivors of myocardial infarction. Serious toxicity has not so far been encountered, and gastric intolerance to phenformin of sufficient severity

to cause cessation of treatment occurs in less than 5% of patients. The full effects of the drugs, and this applies especially to reduction of platelet stickiness, are not apparent, however, in many patients until they have been given for up to 3 months. It follows that should phenformin plus ethyloestrenol exercise a protective effect in arteriosclerotic patients over-all benefit could not be expected during the first 2-3 months of treatment. We are at present conducting a pilot trial of this combination of drugs in survivors of a first attack of myocardial infarction below the age of 60.

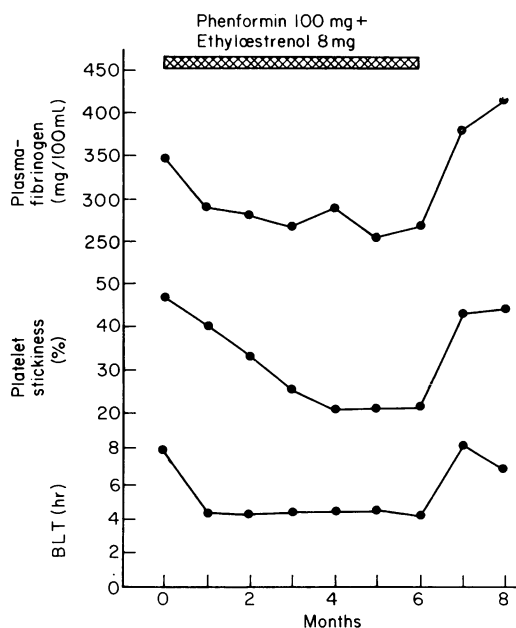


FIG. 3. Mean reduction of platelet stickiness by phenformin plus ethyloestrenol in ten patients. (From Chakrabarti, R. & Fearnley, G.R., 1967, *Lancet*, ii, 1012.)

An entirely different aspect of pharmacological fibrinolysis is its relevance to the treatment of chronic inflammatory conditions in which deposition and persistence of fibrin may be a causative factor in continuing inflammation. The finding that corticosteroids increase fibrinolytic activity suggested that this might be a component of their therapeutic action, and led to the trial of fibrinolytic drugs in rheumatoid arthritis. Phenformin plus ethyloestrenol were given to twenty patients with rheumatoid arthritis, twelve of whom improved clinically together with reduction of plasma fibrinogen level and blood sedimentation rate. When treatment was inter-

rupted in five patients they relapsed and regained improvement when phenformin plus ethyloestrenol were given again (Fearnley & Chakrabarti, 1966).

Pharmacological fibrinolysis is a new therapeutic concept, which now that the resistance which develops to fibrinolytic drugs given orally has been overcome by combined treatment seems suitable for trial in ischaemic and chronic inflammatory conditions.

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