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Letters to the Editor should not exceed 500 words.

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Thrombolytic Therapy

SIR,-We have read your leading article on thrombolytic therapy with some concern (21 December, p. 721); the present status of this therapy is much less clearly defined than the tone of your leader might imply. Your leader writer points out that thrombolytic therapy has been slow to develop for three reasons: lack of a pure agent that could be given safely by the intravenous route; the initial lack of adequate tests of fibrinolytic activity, and when these were subsequently evolved to the shortage of skilled personnel to perform them frequently during the night; and the absence of properly performed and controlled clinical trials. The leader continues, "Though the first two of these problems have now been solved, the third is still being worked out.'

In regard to the first issue, at the present time the only thrombolytic enzyme commercially available in this country is streptokinase, which still may cause pyrexial reactions and which is a streptococcal antigen; inherent in its property as an indirect activator of plasminogen is the risk of causing a severe haemorrhagic state. Your second point, "initial (our italics) lack of adequate tests of fibrinolytic activity" still obtains; indeed, all the test systems at present in common use to control streptokinase therapy have been available for many years, and no adequate very simple tests have yet been evolved. Of the two most commonly used tests to show fibrinolytic activity in plasma, both have major deficiencies. The fibrin plate test takes 18 hours to perform, and so is unsuitable for concurrent control of therapy. The euglobulin lysis time depends not only on the plasminogen activator content of the sample under test but also on its plasminogen content; hence, when giving high-dosage streptokinase therapy with plasminogen depletion infinite euglobulin lysis times can be found in samples with a high free streptokinase content. One might perhaps make a plea for a central effort to standardize laboratory methods, perhaps under the auspices of the W.H.O. International Laboratory for Biological Standards. As an initial step it would be valuable to have available from a central source ¹²³I labelled fibrinogen for use as a substrate in thrombolytic assays.

Despite the statement made in your leader. adequate large-scale controlled clinical trials of streptokinase are virtually non-existent; there is an extensive clinical literature which, though valuable, is virtually all of an anecdotal character. Based on the article by Dr. J. Hirsh and others (21 December, p. 729) your leader states the view that "streptokinase is a valuable and effective method of treating pulmonary embolism." It should be noted that this is going considerably beyond the conclusion reached by Dr. Hirsh and his colleagues themselves, who state in their interesting and valuable article: "The results of this study suggest (our italics) that streptokinase accelerates resolution of pulmonary emboli ; however, further investigations comparing the effects of heparin and streptokinase on the early . . . course of major pulmonary embolism are required. It would be premature to define the role of thrombolytic therapy in the management of major pulmonary embolism until such studies are performed." It must, of course, be pointed out that the investigation of Dr. Hirsh and colleagues was in no way a controlled study; unfortunately, although 18 patients

were given streptokinase only three were treated with heparin alone.

Your leader suggests that if laboratory tests to control dosage are not available "a loading dose of 0.6 mega units in 30 minutes followed by 0.1 mega units per hour for two or three days will be effective." Effective in doing what? Streptokinase dosage schedules depend on complex theoretical considerations, and there is no general agreement as to the best approach to dosage ; indeed, the findings of Johnson and McCarty,¹ a paper quoted in your leader, suggest that the dosage scheme mentioned in your leader may well not be the most effective in promoting thrombolysis, and there are considerable theoretical arguments against it.

The treatment recommended in your leader for streptokinase-induced bleeding is epsilonaminocaproic acid and fresh fibrinogen." Aminocaproic acid (E.A.C.A.) is seldom indicated in this situation. Its main action is to inhibit plasminogen activation, and, in view of the short half-life of streptokinase-induced plasminogen activator in the circulation, the best way to stop activation is to stop the infusion. Perhaps the most important factor in the streptokinase-induced coagulation defect is impaired fibrin polymerization due to circulation of products of fibrinogen proteolysis. This is not directly affected by aminocaproic acid, which may carry a serious risk if further thrombosis occurs; such new thrombus may well be unlysable even by physiological fibrinolysis, as plasminogen levels are much depleted by the streptokinase and as E.A.C.A. is incorporated in the thrombus. Apart from stopping the infusion, the main emphasis in treatment of haemorrhage during streptokinase therapy should be administration of whole blood, fresh if possible, the use of which your leader does not mention, unless by "fresh fibrinogen" whole blood is intended. Your leader goes on to state of streptokinase : "Browse and his co-workers and others have recently demonstrated its superiority over