On October 16, 1968, a nationwide cooperative study was officially begun to assess the therapeutic efficacy of urokinase in acute pulmonary thromboembolism. The beginning of the “Urokinase-Pulmonary Embolism Trial” was the culmination of the efforts of many individuals* during the course of several years. The fact that the study is now in progress is in large part a result of extensive cooperation between the academic medical community, the pharmaceutical industry,† and the National Heart Institute, the sponsoring agency.

Following the first observation of the in vitro fibrinolytic activity of human urine by MacFarlane and Pilling in 1947, this activity was identified as due to urokinase, a plasminogen (profibrinolysin) activator with a molecular weight of 53,000. In addition to its availability, human urokinase possesses certain properties which made it a promising thrombolytic agent; for unlike the streptococcal plasminogen activator, streptokinase, urokinase is nonantigenic in man and less likely to be toxic. Early clinical experience indicated that intravenous administration into humans was both safe‡ and effective in dissolving experimental intravascular clots.§ The identification of certain problems relative to the orderly development of urokinase as a therapeutic agent prompted the establishment of the Committee on Thrombolytic Agents of the National Heart Institute in February 1963. Sufficient quantities of the material for clinical trials then became available under contract to the National Heart Institute according to rigid specifications; for example, it was free from thromboplastic contamination, possessed high specific activity, was heat treated at 60°C for 10 hours for virus inactivation, and was shown to be nontoxic and nonpyrogenic in animals. A CTA (Committee on Thrombolytic Agents) unit was established and reproducible assay methods were developed. Finally, the material was demonstrated to be effective in lysing de novo intravascular human thrombi and for inducing and sustaining a predictable and reproducible thrombolytic state in man without the necessity of rigid laboratory monitoring.¶

For several reasons, acute pulmonary embolism was chosen as the most suitable clinical entity and experimental model for the initial evaluation of urokinase: First, pulmonary embolism is a relatively common and important disease and restoration of blood flow could provide a significant clinical benefit. Second, lung scanning, pulmonary angiography, and assessment of hemodynamic data provide objective methods for diagnosing and following the course of pulmonary embolism. Third, a relatively fresh
clot, composed primarily of fibrin, is generally lodged in an otherwise normal pulmonary vessel which is perfused rapidly by a large volume of blood under high pressure. Fourth, since pulmonary emboli tend to resolve spontaneously, an effective agent would be expected to have a striking influence on this process. Finally, the information to be derived from a study of this lesion, where the direct effects of urokinase on the embolism can be measured, could prove invaluable in the planning of subsequent studies in other thromboembolic disorders, when the direct effects of the agent cannot be quantitated. Since early 1966, therefore, a number of investigators have been making preliminary observations on patients with pulmonary embolism treated with urokinase. The results of these studies in approximately 50 patients, some of which have been published,\textsuperscript{5-8} established that urokinase, when administered in amounts sufficient to produce levels of activity currently considered therapeutic, is adequately tolerated even by critically ill patients. In addition, present evidence suggests that thrombolytic therapy is capable, sometimes dramatically, of removing thromboemboli from the pulmonary circulation and restoring normal hemodynamics. Based upon this experience, the decision was made in October 1966 to initiate a cooperative, controlled clinical trial designed to establish the extent to which thrombolytic therapy accelerates the resolution rate of pulmonary thromboemboli as compared with conventional therapy.

The justification for conduct of a collaborative study and the organizational structure of the Urokinase-Pulmonary Embolism Trial were based upon principles outlined in a report from the Heart Special Project Committee to the National Advisory Heart Council, "Organization, Review and Administration of Cooperative Studies," in May of 1967. It was felt (1) that the investigative problem had extensive therapeutic implications of major public health importance; (2) that a multi-institutional collaborative effort was the only means of answering the question at issue within a reasonable period of time; (3) that the experience of the pilot phase suggested that the study was not only feasible but likely to yield positive and significant results; and (4) that the vital interest and performance of individuals associated with the development of the trial promised adequate leadership for the duration of the study. Therefore, a group of senior investigators with special talents and interests in the fields of biometrics, collaborative research, cardiovascular disease, and fibrinolysis was assembled as a Policy Board to serve as an advisory committee to the trial. A Steering Committee, composed of investigators who had participated in pilot-phase clinical studies, was established for the primary purpose of generating a study protocol. Members of the National Heart Institute staff comprised a Coordinating Center, charged with the responsibility of the operational conduct of the trial. Various subcommittees were appointed to make recommendations concerning standardization of methodology and means for analysis of data. Potentially interested and qualified investigators were sought to participate in the study.

The "Urokinase-Pulmonary Embolism Trial Manual of Operations," now completed after seven revisions, contains the study protocol, detailed specifications for standard methods, information concerning organizational structure and policy matters, data analysis information, data forms, and so forth. The stated objective of the study is to determine whether abnormalities evidenced in pulmonary photoscanning, pulmonary angiography, and hemodynamic measurements, and reflecting the presence of thrombus in the pulmonary circulation, resolve more rapidly after thrombolytic plus anticoagulant therapy than after anticoagulant therapy alone. The potential for demonstrating decreased mortality is limited by the relatively low mortality in patients given conventional therapy.\textsuperscript{10} The rapidity with which death occurs\textsuperscript{10} will limit the number of potentially
fatal cases in which sufficient diagnostic information will be available to initiate enzymatic therapy. Nonetheless, provisions have been made for extending eligibility for admission to desperately ill patients with persistent shock, in whom performance of pretreatment lung scans will be optional; for all other patients, right heart catheterization, pulmonary arteriogram, and lung scan are prerequisites for inclusion into the trial.

Preliminary studies suggest that patients with recent embolism respond better to thrombolytic therapy than patients with symptoms of long duration; therefore, only patients with symptoms suggesting acute pulmonary embolism within 5 days of contemplated therapy are eligible for inclusion. The design of the trial is best described as “modified double blind,” since only the physician responsible for the therapeutic infusion will have knowledge of the treatment assignment. After obtaining a randomized treatment assignment by telephone from a Drug Assignment Center, investigators will administer either urokinase or heparin intravenously by a constant infusion pump for a period of 12 hours, following which all patients will be maintained on heparin. Follow-up studies will include right heart catheterization and pulmonary arteriograms within 18 hours after completion of the infusion of the test drug and serial lung scans for 2 weeks. Provisions have also been made for long-term follow-up at 3, 6, and 12 months.

Currently, the Urokinase-Pulmonary Embolism Trial is being conducted in 13 participating institutions. However, if the patient access rate is inadequate for completion of the study within a reasonable period of time, the National Heart Institute may seek additional qualified and interested investigators for participation.

The Urokinase-Pulmonary Embolism Trial represents the first coordinated American attempt to evaluate a thrombolytic agent. It is hoped that the time and effort which has gone into the development of clot-dissolving agents for the treatment of thromboembolic disorders will soon have a sound base for further and even more exciting advances.

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References


EDITORIAL

An Invitation For A Genetic Study
Milroy's Disease (Hereditary Lymphedema)

. . . In 1928 Milroy published a follow-up on the family with lymphedema . . . , which was first reported in 1892. The propositus was at that time still alive in his late 60's and was active as a missionary in Burma. Affected members of the family also included a clergyman in Florida (who had died before 1928), a congressman, a U. S. senator, and a Chicago physician (also deceased), who had served as a surgeon in the U. S. Navy in the Civil War.

Surely affected members of that family are still living. The account of the fortunes of the family with regard to the ailment might profitably be updated, now 40 years after Milroy's follow-up. My colleagues and I have found this sort of long-term, indeed multi-generation follow-up useful from the standpoint of both the genetics of the entity and its natural history. . . . I would urge that some physician, caring for present day bearers of the "original" Milroy, gene chart the odyssey of the gene during the last 40 years.—Victor A. McKusick: Letters to the Editor. JAMA 204: 832, 1968.
The Urokinase-Pulmonary Embolism Trial
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