Use of Human Thrombin in Some Cases of Pulmonary Hemorrhage

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Thrombin is the most "active clotter of blood or plasma known at the present time." Since its isolation more than 10 years ago, bovine thrombin has been used in a great variety of surgical procedures, including ophthalmic surgery, rhinological operations, and in major surgical procedures including neurosurgery. Its more recent application to the control of gastric hemorrhage by ingestion, suggested that this substance might conceivably be used in the treatment of certain cases of pulmonary bleeding. It was administered by inhalation for this purpose by Puder, whose report, however, had not yet appeared when these investigations were undertaken.

There are, however, a few objections, both theoretical and practical, to thrombin aerosol. In cases of massive hemorrhage, rapid clotting of the blood in the airways might induce asphyxia. Massive hemorrhage of the exsanguinating type such as occurs from the rupture of a large vein in a tuberculous cavity might, therefore, be a contraindication to the use of aerosol thrombin. Bovine thrombin is objectionable because it may prove sensitizing and provoke allergic reactions. Bovine thrombin should not be used by aerosol in the human subject. According to Bratton, "Bovine thrombin, from antigenicity studies in guinea pigs, will be classified as a weak to moderately active antigen. Assuming that the antibody response in man is comparable to that in guinea pigs, there is little doubt in our mind that antibodies would be formed, perhaps even attached to pulmonary tissues, after administration of bovine thrombin by the aerosol technique. Since pulmonary bleeding is frequently a recurrent event, and treatment might possibly be repeated on several occasions, we feel there is grave danger of sensitization of the patient at the time of the initial use of the drug, and perhaps death would result from its second administration."

For aerosol purposes, therefore, the source of the thrombin must be human and not bovine. Fortunately, human thrombin is readily available. Indications for the use of human thrombin aerosol might extend not only to patients with pulmonary tuberculosis who are persistently or repeatedly bleeding but also to cases of hemorrhage from bronchiectasis or pulmonary neoplasms. In those
cases where bleeding obscures bronchoscopic inspection of a suspicious lesion, thrombin aerosol (or direct instillation through the bronchoscope) might be of particular value. The cases reported in this paper, however, are limited only to those of active pulmonary tuberculosis in all of whom active bleeding was present. As yet, it is too early to determine precisely the effect of the thrombin treatment on the underlying disease although no harm seems to have been done.

Preliminary Trials

Human thrombin in vials of 2500 units each was made available through the courtesy of Cutter Laboratories. Physiological saline is supplied as the diluent and the solution was freshly prepared in the strength of 500 to 1000 units per cc. at the time of administration. Experiments with these solutions were first begun on August 6, 1948 on two patients at the Boston State Hospital (M.D. and M.F.) with bilateral active tuberculosis who were streaking persistently. When it was demonstrated that the aerosol delivered through a hand nebulizer was easily tolerated, additional tests were conducted, using oxygen at a 6 to 10 liter flow per minute. One or two cc. of solution, containing from 500 to 2000 units, were aerosolized at each treatment. Such treatments were easily tolerated.

In order to observe any possible sensitizing action, these tests were repeated at weekly intervals for two weeks and then at bi-weekly intervals for two weeks. No further hemoptysis was noted after the first tests and no clinical evidence of sensitization was observed. During the same period of clinical observation three additional patients (W.C., T.G. and C.K.) were also given aerosol treatment with immediate effectiveness. In all of the cases studied, one course of treatment appeared to provide the patient with relief lasting for as long as two weeks or longer. It did not preclude the resumption of bleeding at a later date.

Case Report

Case Report: M. DeL., a 61 year old male, had his first hemoptysis 20 years ago and was treated by bed rest for six months in a sanatorium. He had another hemorrhage in 1935 for which he was again hospitalized and a left phrenic crush was done. He was discharged a year later as "arrested." During March 1948, he had severe hemorrhages but these quieted down with bed rest at home. Two months later bleeding recurred. At this time x-ray inspection of the chest revealed bilateral upper lobe disease, some elevation of the left diaphragm, and a suggestion of cavitation in the left lung.

He was treated conservatively at home with rest, sedation and the administration of menadione tablets. Sputum was negative on concen-
trate but positive by culture. One month later, however, he again expectedorate a mouthful of blood and sputum concentrate at this time it was positive. He was again treated conservatively and the streaking gradually cleared. For the following year he had no active bleeding.

On July 11, 1949 he awoke with a sudden and massive hemoptysis. He resorted to codeine and menadione but this failed to control the bleeding. For the next five days bleeding persisted, both streaking and active hemorrhage that failed to respond to the usual conservative measures. He was hospitalized at a general hospital and pneumoperitoneum was immediately induced. Bleeding however persisted the remainder of that day and the next in spite of a large air refill. At about 2:00 a.m. on July 18 he had another massive hemoptysis in spite of a seemingly adequate pneumoperitoneum. The patient was given human thrombin aerosol, 1,000 units in 2 cc. of saline with prompt inhibition of his bleeding and remarkable control of his cough.

For the next few days only slight streaking was evident. Pneumoperitoneum refills have been maintained. The patient was discharged home on July 26 since repeated sputum tests were negative for acid-fast organisms. He has had no bleeding or streaking. His cough is diminished and his dyspnea is less.

SUMMARY AND CONCLUSIONS

The use of human thrombin by aerosol administration appears to be effective in the control of certain cases of pulmonary hemorrhage and is worthy of more extended clinical trial.

RESUMEN Y CONCLUSIONES

El uso de la trombina humana administrada por aerosol parece ser efectiva en el dominio de ciertos casos de hemorragia pulmonar y vale la pena hacer ensayos clínicos más extensos con ella.

REFERENCES

7 Bratton, A. C. Jr.: Personal communication.