ORAL THROMBIN IN THE TREATMENT OF HAEMATEMESIS

BY

VINCENT EDMUNDS, M.D., M.R.C.P.

*Assistant Physician to Charing Cross Hospital Unit,
Mount Vernon Hospital; Medical Registrar,
Central Middlesex Hospital*

*(From the Department of Gastro-enterology, Central
Middlesex Hospital)*

The clinician is always interested in new methods of producing local haemostasis in cases of internal bleeding where the surgical principle of local treatment by pressure or suture is unfortunately not applicable. Various thromboplastins for enteral or parenteral use have been produced, but none have been convincingly successful in practice. The example of intravenous Congo-red solution in haemoptysis can be instanced, as also may the oral administration of adrenaline for haematemesis.

Thrombin is a substance which for many years has been much used in all branches of surgery, and particularly in neurosurgery, for the production of local haemostasis, and there is a sound scientific basis for this in that it is capable of clotting fibrinogen directly to fibrin in a few seconds. Needless to say, it is effective only when the bleeding is in the nature of a capillary ooze, and cannot be expected to work in the presence of severed vessels of any size.

Daly (1947) has recommended the use of thrombin orally in cases of gastric haemorrhage. Certain technical difficulties are involved in that the thrombin must be present in sufficient concentration in the stomach to produce clotting of fibrinogen; also the pH of the medium is important, since its action is impeded at pH 6.5 and the substance itself is completely destroyed at pH 4.3. Daly obviated this difficulty by administering orally an M/7 phosphate buffer solution five minutes before and again with the thrombin. Using this method, he was able to show that in a normal individual adequate raising of the pH and adequate thrombin activity were present for at least 15 minutes after the oral administration of 10,000 units of thrombin in 30 ml. of buffer.

Subsequently, Daly *et al.* (1949) published a series of 100 cases of upper gastro-intestinal bleeding treated with oral thrombin. The series was uncontrolled, though their impression, gathered from their previous experiences, was that "the method is a valuable adjunct in the treatment of upper gastro-intestinal haemorrhage."

Rogers (1948) reported dramatic improvement in two cases of severe continued haematemesis following the administration of thrombin in saline and without buffer solution. Unpublished favourable results in this country have been brought to our notice, and as a mode of treatment it would seem to have become an accepted practice, at least in some American centres (Wechsler and Odle, 1950).

In a review of the treatment of haemorrhage from peptic ulcer Crohn and Janowitz (1951) use these words: "... the use of 'gelfoam' and of buffered thrombin has been advocated. ... The administration of these substances by mouth during haemorrhage is very simple and is often followed by a cessation of haemorrhage;

this was the case in a few cases, and whether this was merely the result of coincidence remains to be established."

In view of the absence of any controlled investigation into the value of oral thrombin in the treatment of gastro-duodenal haemorrhage it was felt that such a survey should be attempted. Dr. Savage, of Messrs. S. Maw Son & Sons Ltd., kindly supplied us with thrombin and also an inert substance conveniently made up in doses of 1 g. (10,000 units) in separate bottles and ready for solution in phosphate buffer. These bottles were labelled with code letters and their identity was not revealed until the end of each stage of the investigation.

Method

The method adopted was based on that evolved by Daly, who had found that valuable information could be learned about the patients' progress if periodic gastric aspirations were made and the presence or absence of fresh blood was noted. Accordingly a Ryle tube was passed whenever possible on patients admitted with a history of recent haematemesis, and periodic (usually hourly) aspirations were made. This had the added advantage that we were able to make regular pH readings and thus ensure that the buffering was adequate.

At the beginning of the investigation the stomach was aspirated and emptied hourly from the time of admission. If the stomach contents proved to contain fresh blood 50 ml. of phosphate buffer was administered down the tube followed after five minutes by 2 g. of powder—A (thrombin) or B (inert control substance)—dissolved in a further 30 ml. of buffer. In cases of fresh blood-staining this procedure was to be repeated at half-hourly intervals until either no further evidence of fresh blood appeared or it became obvious that successive doses of powder were not arresting the haemorrhage. Cases in which recent blood could not be aspirated from the stomach were not included in the series.

This method was later modified, using a fresh batch of powders—K (thrombin) and N (inert substance). On this occasion all cases with a history of haematemesis within the past six hours were given a dose of buffer followed by test substance on admission. A Ryle tube was then passed. Three hours were then allowed to elapse before a further aspiration. If on aspiration three hours after admission there was still evidence of fresh gastric haemorrhage, the method was proceeded with as previously.

Experience over some years at this hospital has shown that about 25% of cases of gastro-intestinal haemorrhage have episodes of recurrent bleeding after hospital admission, and it was felt that if we could reduce this percentage in our cases it would be a point in favour of thrombin therapy.

Cases on admission were allotted to alternate groups without any selection whatsoever.

Results

In spite of using a controlled series treated with an inert substance it was often found very difficult in assessing the results to decide whether or not a patient had benefited from the therapy. This is discussed later, but in any case in which there was the slightest suspicion that the subject might have gained even temporary benefit from the treatment then this was recorded as a success. The Table

Summary of Results

Substance	Success	Failure	Doubtful	Total
Thrombin A ..	2	4	0	6
" K ..	1	3	1	5
Control B ..	0	5	0	5
" N ..	4	1	1	6
Total ..	7	13	2	22

summarizes the results obtained, first using A and B and then K and N. When assessing these results both gastric aspirations and clinical impression were taken into account.

In the investigation a total of 22 cases of gastro-duodenal bleeding were treated—11 with thrombin and 11 with an inert control substance. Our results do not show that thrombin had any influence on the course of the condition in these cases.

It is perhaps of some significance to note that of the seven successes, four were regarded clinically as mild, and would, in our experience, have done well on any treatment. Of the 13 failures, 3 were shown either at operation or at necropsy to have vessels so eroded that an arrest of the haemorrhage was scarcely to have been expected short of major surgery.

Discussion

Thus far the experiences with thrombin in the treatment of acute gastro-duodenal bleeding have been disappointing, and in a short controlled series it has not been possible to establish that it has any convincing value. The series is admittedly a small one, but the cases have all been followed with good care and the trial has been done without knowing what preparation was being used on any individual case.

It may be that our technique was inadequate in various ways, and that greater persistence should have been shown and the doses of thrombin more often repeated. However, a therapeutic agent such as thrombin should be effective after one or two doses, and if evidence of continued bleeding is then still obtainable the treatment has failed to accomplish what was expected of it. Admittedly it was often very difficult to be absolutely certain that bleeding had ceased even when repeated gastric aspirations were being made. Daly *et al.* (1949) emphasize that loose blood clots will be aspirated from the stomach when bleeding is continuing, whereas if bleeding has ceased the material aspirated will contain fine brown granules of different colour and texture. This may sometimes be the case, but we were not always convinced. The techniques that were being followed were rather tedious (especially when performed during the night) and time-consuming if the results were to be of any value, and it was felt that these findings did not justify continuing the investigation. Rather our results confirm the impression that many patients with haemorrhage have no further bleeding after their admission to hospital, and therefore do well on any therapy. Of those who have further episodes of bleeding, some will eventually come to operation or post-mortem examination, when the size of the vessel opened up by the ulcer explains the persistence of the haemorrhage and the failure of all conservative measures, including thrombin.

Avery Jones (1952) has suggested the use of thrombin solution in the treatment of bleeding from oesophageal varices, 10,000 units of thrombin in solution being sipped slowly by the patient over a period of half an hour. It would seem possible that treatment would have more chance of succeeding here, as the bleeding is venous and the thrombin can have direct contact with the affected varices without the diluting effect of acid gastric juice in the stomach. Even in these cases, however, there are, as yet, no figures to substantiate its value.

Summary

An attempt has been made to assess the value of oral thrombin in the treatment of gastro-duodenal bleeding. A controlled series of 22 patients have been treated with thrombin and an inert substance in phosphate buffer. Haemorrhage appeared to be arrested in three of the thrombin group and in four of the control group, while six of the control and seven of the thrombin group showed evidence of continued bleeding.

It is concluded that, with the use of the method described, thrombin has no value in the treatment of gastro-duodenal bleeding. It is possible that it might have some value in the control of oesophageal bleeding.

My thanks are due to Dr. Avery Jones for his encouragement and helpful criticism; to the doctors, sisters, and nurses who co-operated during the investigation; to S. Maw Son and Sons Ltd., and particularly their chief chemist, Dr. Savage, who arranged the supply of the unknown thrombin and control powders.

REFERENCES

- Crohn, B. B., and Janowitz, H. D. (1951). *Gastroenterology*, 19, 608.
 Daly, B. M. (1947). *Arch. Surg., Chicago*, 55, 208.
 ——— Johnston, C. G., and Penberthy, G. C. (1949). *Ann. Surg.*, 129, 832.
 Jones, F. Avery (1952). In C. A. Birch's *Emergencies in Medical Practice*, p. 75. Livingstone.
 Rogers, T. M. (1948). *J. Amer. med. Ass.*, 137, 1035.
 Wechsler, L., and Odle, S. G. (1950). *Amer. J. dig. Dis.*, 17, 276.

THE PROGNOSIS OF ACUTE PORPHYRIA

BY

CEDRIC HIRSON, M.R.C.P.

Over 300 cases of acute porphyria have been reported, but the previous diagnostic history of many of the recorded cases and the increasing frequency of clinical reports make it probable that the lesser manifestations of the disease have often been overlooked. In consequence, an undue gravity of prognosis has been accepted. In the two cases described below complete symptomatic resolution followed severe episodes of acute porphyria with peripheral neuritis. The striking uniformity of the clinical picture of the disease is emphasized by the close similarity of these cases to previous reported cases.

Case 1

A woman of 23 was admitted to hospital with a history of abdominal pain and vomiting for two weeks. The pain had radiated from the bladder region to the epigastrium. There was no abnormality of the bowel action, but micturition was frequent and difficult. She had been employed in making lead plates and three weeks previously had taken phenobarbitone for one week.

On admission she appeared to be in pain and was over-breathing. The abdomen was soft and not distended. Her blood pressure was 160/130 mm. Hg. She was tender over the bladder. Apart from some quadriceps wasting, full neurological examination was negative. The clinical picture was thought to be partly hysterical. The blood count showed a polymorph leucocytosis; haemoglobin 106%; no punctate basophilia. Urine: no abnormal deposit; porphyrins demonstrated. E.C.G. showed sinus tachycardia with P-T summation. Spasms of severe pain failed to respond to a full range of sedatives and antispasmodics, but the blood pressure returned to normal. One month after the initial onset of the illness the patient complained of tenderness of the upper arms and thighs, but the tendon reflexes and power were normal. She was severely constipated and failed to respond to daily enemata for a week.

Clinical improvement for the next two months was followed by further abdominal pain and vomiting. She was restless, agitated, and distraught. General and neurological examinations were still normal. There was marked increase in the gas shadows seen on abdominal x-ray films. At times she was uncontrollable and was still thought to be hysterical. For two weeks no objective evidence could be found to support her claim of weakness of the wrists. Then bilateral wrist-drop developed, and progressed rapidly. One month later further urgent vomiting occurred and her legs were tender. Her knee-jerks were greatly diminished. The neurological status deteriorated and she developed pareses of the quadriceps femoris muscles and the dorsiflexors of the ankles, with abolition of all tendon reflexes except the ankle-jerks. Sensation was normal. She became emaciated and had episodes of urinary retention.