*J Clin Pathol.* 33, Suppl (R oy Coll Path), **14**, 35-40

## *Therapeutic considerations*

# Basis of antifibrinolytic therapy

CRM PRENTICE

*From the University Department of Medicine, Royal Infirmary, Glasgow*

The coagulation and fibrinolytic enzyme systems oppose each other in the haemostatic process. Coagulation occurs, of necessity, rapidly and explosively so that a site of vessel damage causing blood loss can be rapidly sealed. The fibrinolytic process, on the other hand, serves as a repair system to remove fibrin deposits which might otherwise cause permanent vascular occlusion. This must occur slowly so that vascular repair and re-endothelialisation can take place before the fibrin is removed. Therefore there is an elaborate system of inhibitors of plasminogen activator and plasmin in the circulation to prevent hyperplasminaemia and the indiscriminate digestion of fibrinogen. Additionally, thrombolysis is determined by the binding and spatial relationship between fibrin, Lys-plasminogen, and activator. In this way selective fibrin digestion can occur without systemic proteolytic activity. The structure of fibrin is also important in determining the rate of fibrinolysis. In cross-linked fibrin the normally susceptible alpha-chain has become polymerised to alpha-polymer, which is inaccessible and resistant to plasmin action.[1] In this situation the beta-chain is digested first and the polymerised fibrin is much more robust than the non-crosslinked material.[2]

There are two major situations where the healthy physiological balance between coagulation and fibrinolysis may be lost, leading to a need for antifibrinolytic therapy. Firstly, unopposed fibrinolytic activity may be excessive so that forming or formed fibrin is digested by plasmin before a firm haemostatic plug is produced. Secondly, in the presence of a coagulation defect such as haemophilia the fibrin may be so inadequate in amount that physiological fibrinolytic activity may be sufficient to start haemorrhage. Several causes, however, may operate together to cause haemorrhage. For instance, in the presence of defective small vessel constriction or low-grade disseminated intravascular coagulation the action of the normal fibrinolytic response may be sufficient to initiate haemorrhage.

In this review I outline the mechanism of action of the antifibrinolytic drugs and then consider the clinical situations in which they might be expected to be beneficial. Others will discuss the pharmacology and detailed clinical indications for the drug.

### Mode of action of fibrinolytic inhibitors

The main inhibitors in current use comprise epsilon-aminocaproic acid, tranexamic acid, and aprotinin. The chemical formulae for these compounds are shown in the Figure.

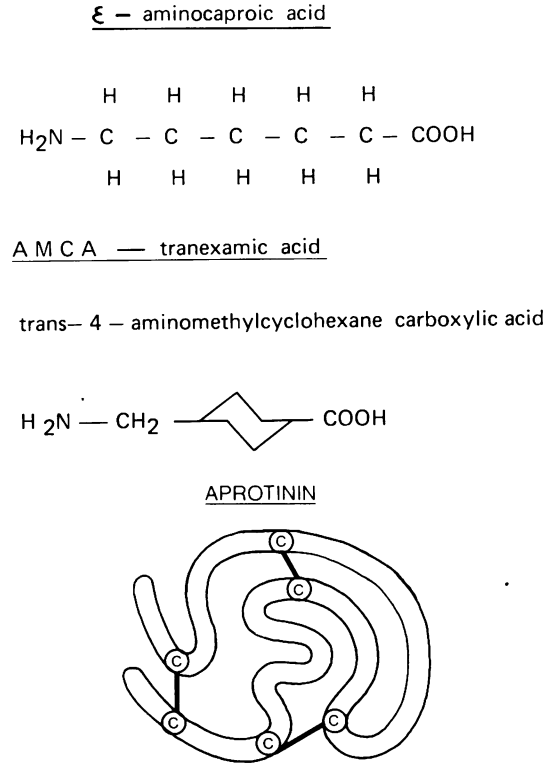


Fig. *Chemical formulae of ε-aminocaproic acid, tranexamic acid, and aprotinin.*

EPSILON-AMINOCAPROIC ACID (EACA, 6-AMINOHEXANOIC ACID)

The approved name, *British Pharmacopeia*, of this compound is aminocaproic acid. It was introduced by Okamoto and colleagues.[3] The relation between its chemical structure and its antifibrinolytic activity is well established, based on its action as a lysine substitute. The 5 carbon chain is important for its optimum action. Molecules with a longer or shorter aliphatic chain have lesser activity. Similarly, the amino- and carboxylic-acid radicles are both important for inhibitory activity.[4]

CYCLIC AMINOCARBOXYLIC ACIDS (TRANEXAMIC ACID, *BP*)

A series of cyclic compounds were found to have more potent fibrinolytic activity than EACA. One of the most suitable was AMCHA (4-aminomethyl-cyclohexanecarboxylic acid). The potency of this compound, which is a mixture of stereoisomers, is due to the residues in the trans-isomer, known as tranexamic acid, which forms about 20-25% of the parent mixture.[5 6] Tranexamic acid is some 7-10 times more potent than EACA.[7 8] It is interesting that the potency of the compound depends on a critical distance of 7Å between the essential amino- and carboxylic-acid groups.

APROTININ

Aprotinin (Trasylol) is a protease inhibitor derived from bovine pancreas, parotid gland, and lung. It is a basic protein, MW 6500, with strong inhibitory action against kallikrein and is also an inhibitor of proteases such as plasmin.

## Mode of action of aminocarboxylic acids

The main action of the aminocaproic acid compounds is to compete with lysine binding sites on plasminogen and plasmin. They inhibit the activation of plasminogen by streptokinase, urokinase, and tissue activator. The binding of the heavy chain of plasmin to fibrin monomer is achieved by lysine binding sites. The blocking of these sites by aminocaproic acid causes stoichiometric inhibition of plasmin, with the formation of an inactive complex between plasmin and aminocaproic acid.[9] It will be noted from the excellent review by D Collen (see page 24) that the rate of binding of alpha 2-antiplasmin to plasmin is dependent on the availability of free lysine residues in plasmin. In the presence of free residues plasmin is rapidly inactivated by alpha 2-antiplasmin. Conversely, when the lysine residues are blocked, either by fibrin monomer or by aminocaproic acid, inactivation by alpha 2-antiplasmin is reduced. This potent action of aminocaproic acid as an inhibitor of plasmin in physiological fibrinolysis on a substrate of fibrinogen or fibrin has been recognised only fairly recently since much of the earlier work was carried out using casein as a substrate for plasmin.[8 10] Similarly, aminocaproic acid is relatively inactive against the hydrolytic action of plasmin on synthetic esters. Thus the striking action of aminocaproic acid is to block the action of plasmin on fibrin.

The interaction between plasminogen, plasmin, activator, and fibrin is complex.[9] Tissue activators adsorb on to fibrin[11] and in the presence of plasminogen mediate proteolytic cleavage of the terminal part of plasminogen, changing 'native' Glu-plasminogen into Lys-plasminogen. The latter has a higher affinity for fibrin than native plasminogen[12–14] and promotes the preferential resolution of fibrin within a thrombus rather than causing the digestion of circulating fibrinogen during the fibrinolytic process. Plasmin is formed from plasminogen by further cleavage of an internal Arg-Lys peptide bond in plasminogen.[15] Plasmin also has high affinity for fibrin. Thus consideration of fibrinolytic inhibitors must include not only their effect at the active enzyme site but also their ability to interfere with the binding of the various components. The problem is further complicated by the type of activator studied, for tissue activator has much greater affinity for fibrin than urokinase.[11]

## Effect of EACA on caseinolysis

6-Aminohexanoic acid forms reversible complexes with plasminogen causing conformational changes in the plasminogen molecule. At concentrations of between $10^{-4}$ and $3{\cdot}3 \times 10^{-3}$ M 6-aminohexanoic acid the amount of plasmin generated by urokinase from plasminogen increases owing to the conformational change in plasminogen. Inhibition of preformed plasmin is noted only at a high concentration of 0·1 M 6-aminohexanoic acid. 6-Aminohexanoic acid increases the rate at which proteolytic degradation of Glu-plasminogen to Lys-plasminogen occurs.[16 17] The inhibitor also increases the rate at which the internal peptide bond in plasminogen is split to form plasmin and it may be this effect which leads to the paradoxical acceleration of Glu- to Lys- plasminogen conversion in the presence of inhibitor. At concentrations greater than $3{\cdot}3 \times 10^{-3}$ M 6-aminohexanoic acid the rate of plasminogen activation by both urokinase and tissue activator decreases. This is due to the direct effect of 6-aminohexanoic acid as a competitive inhibitor of activator.

**Effect of EACA on fibrinolysis: role of fibrin**

When fibrin rather than casein is used as the substrate for plasmin the situation alters considerably. Here inhibition starts with concentrations of 6-aminohexanoic acid as low as $10^{-5}$ M when tissue activator is used and $10^{-3}$ M in the presence of urokinase.

The greater effect of inhibition by 6-aminohexanoic against plasmin when fibrin rather than casein is used as substrate is due to the fact that the heavy chain of plasmin possesses special binding sites for fibrin.[18 19] These sites are not utilised when the substrate for plasmin is fibrinogen, lysed fibrin, casein, or synthetic esters.[18 20] 6-Aminohexanoic acid inhibits fibrin digestion by complex formation with the heavy chain of plasmin preventing interaction between the active centre in the plasmin light chain and fibrin.[21] Plasminogen as well as plasmin has these binding sites which are blocked by the amino-acid inhibitors.

6-Aminohexanoic acid can cause dissociation of the preformed fibrin-plasminogen complex. This causes separation of plasminogen from tissue activator which is also bound to fibrin. As plasminogen bound to fibrin is activated more rapidly than free plasminogen it follows that dissociation by 6-aminohexanoic acid of plasminogen and fibrin causes a reduction in the activation rate of plasminogen.[9 22] The situation with regard to the effect of 6-aminohexanoic acid against urokinase is different since, in contrast to tissue activator, urokinase does not preferentially activate plasminogen complexed to fibrin rather than free plasminogen.

The inhibitory action of 6-aminohexanoic acid is increased in the presence of plasminogen-depleted plasma, which contains the natural inhibitors of fibrinolysis. This is because the dissociation of plasmin from fibrin by the inhibitor releases plasmin which is subsequently inhibited by the natural plasmin inhibitors. Probably this potentiating effect of 6-aminohexanoic acid on plasma inhibitors is the main reason for the therapeutic effect of these drugs in inhibiting fibrinolysis.

**Mode of action of aprotinin**

The antifibrinolytic effect of aprotinin is due to its action as a non-competitive inhibitor of plasmin. Aprotinin forms complexes with several of the serine protease enzymes[23–25] and is a potent kallikrein inhibitor, reducing shock in experimental animals. The reaction is reversible and proceeds rapidly. Dissociation of these complexes occurs at low pH values of 3-4. The reaction of the inhibitor with trypsin is reduced in the presence of enzyme substrates, but the inhibitor-kallikrein reaction is not impaired by substrate.

The activity of aprotinin as an inhibitor depends on the lysine residue at position 15, which participates in complex binding.[23] Acetylation and methylation of the inhibitor lead to loss of its activity, indicating the importance of carboxyl and amino groups. The inhibition of plasmin by aprotinin is stoichiometric. The inhibitor blocks an equivalent amount of enzyme to form an inactive complex.

There is some, but inconclusive, evidence to suggest that aprotinin may have an inhibitory action against plasminogen activator. The kinetics of the reaction are complicated by the antiplasmin action of aprotinin, and at present there is no protein-like inhibitor able to inhibit a plasminogen-activating enzyme under well-defined biological conditions. For instance, the inhibitors from bovine organs do not impair the action of urokinase.[26 27]

Aprotinin is standardised in terms of kallikrein inhibitor units (KIU) which are based on an inexact biological procedure in dogs. For this reason the inhibitory action of aprotinin against enzymes is often measured on synthetic substrates. This can only lead to problems since the action of an inhibitor using synthetic substrates is often different from that on the natural biological substrates. In practice the activities of a pure inhibitor standard can be compared with commercial preparations.[28]

In experimental animals the *in-vivo* activity of aprotinin may easily be demonstrated. Fibrinolysis can be induced in rabbits by the intravenous injection of 2500 U streptokinase/kg. If 1 mg aprotinin/kg is injected 10 minutes before streptokinase fibrinolysis is completely prevented. Similarly, aprotinin can inhibit an established hyperplasminaemic state in rabbits.[29] If fibrinolysis is established by an infusion of streptokinase causing a reduction in fibrinogen level and increase in thrombin clotting time the process can be reversed by intravenous injection of 5 mg aprotinin/kg.

It must be remembered that in man treatment with aprotinin entails injecting an animal protein and allergic reactions may occur. In general, tranexamic acid is the inhibitor of choice in clinical treatment, since it is effective and relatively free from unpleasant or toxic reactions.

**Classification of haemorrhage due to unopposed or excessive fibrinolytic activity**

From the clinical aspect there are four main groups of disorders in which excessive or unopposed fibrinolysis might play a role in causing haemorrhage and in which antifibrinolytic therapy might be

indicated.[4 30] They are (1) hyperplasminaemia: (*a*) primary fibrinolysis or hyperplasminaemia, (*b*) secondary fibrinolysis as a consequence of disseminated intravascular coagulation (DIC); (2) local fibrinolysis within organs or tissues; (3) coagulation defects associated with normal fibrinolysis.

## HYPERPLASMINAEMIA

*Primary fibrinolysis or primary hyperplasminaemia*

In this condition excessive circulating concentrations of plasminogen activator convert sufficient plasminogen to plasmin to overcome plasma inhibitors. Free plasmin is then able to cause digestion of haemostatic factors such as fibrin, fibrinogen, factor V, and factor VIII. The combined effect of removal of fibrin plugs at the site of vascular damage together with depletion of coagulation factors is sufficient to cause bleeding. If proteolysis is pronounced there may be total fibrinogen depletion together with a rise of fibrin degradation products (FDP), which have an anticoagulant action.

It is notoriously difficult to distinguish clinically and in the laboratory between primary fibrinolysis and intravascular coagulation with a secondary fibrinolytic response. I agree with Merskey *et al.*[31] that primary fibrinolysis is a rare event and that most cases of defibrination are due to DIC. In DIC the first priority is to treat the underlying cause of the disorder such as sepsis or shock.[32] In DIC associated with malignancy the prognosis is often grave. In obstetric accidents the main goal is to evacuate the uterus. After that defibrination will rapidly cure itself with the aid of blood transfusion and clotting factor concentrates if necessary. Basu[33] has recommended antifibrinolytic drugs in the treatment of obstetric defibrination on the basis that high FDP levels interfere with uterine contractibility. However, there is the theoretical danger that continuing intravascular coagulation in this situation may provoke generalised thrombosis.

The clinician should be aware of conditions causing a primary fibrinolytic state, which occur particularly when tissues rich in plasminogen activator have been handled during surgery. Operations on the prostate gland, uterus, pelvic colon, and surgery for malignancy are liable to primary fibrinolytic haemorrhage. If prolonged or excessive bleeding occurs after this type of operation laboratory tests should be carried out to exclude primary hyperplasminaemia. Such tests would include a platelet count, prothrombin time, partial thromboplastin time, thrombin clotting time, and rapid tests for fibrinogen and FDP levels. A simple whole blood clotting time test can be carried out in the operating theatre by putting some of the patient's blood, without anticoagulants, into a plain glass clotting tube. The hand grasped firmly around this makes an admirable improvised incubator at 37°C. The presence of non-clotting blood or a defective blood clot indicates that a haemostatic abnormality is present. A test for accelerated lysis should then be carried out. If, as often occurs, the blood is incoagulable or the clot defective fibrinogen must be added.

In the presence of unequivocally accelerated clot lysis a presumptive diagnosis of hyperplasminaemia may be made and treatment with antifibrinolytic drugs started plus replacement blood, fibrinogen, and coagulation factors or platelets as necessary. The use of antifibrinolytic agents in these conditions can lead to dramatic clinical improvement. For example, we saw a patient who developed generalised bleeding with hypofibrinogenaemia after excision of the rectum for malignancy. As the whole clot lysis time was under 30 minutes epsilon-aminocaproic acid was given with gratifying reversal of haemorrhage.

Exceptionally, life threatening haemostatic breakdown may occur with such rapidity that time does not allow laboratory investigation. In this situation initial treatment with whole blood and plasma components such as fibrinogen, which may be conveniently given as cryoprecipitate, is given. If these measures fail intravenous tranexamic acid may be given empirically in view of the possibility of systemic hyperplasminaemia being present. Antifibrinolytic agents often provide benefits in these patients that outweigh the risk of widespread unlysable clot formation. However, this hazard has been noted—for instance, in the case reported by McNicol[34] where EACA was given for hyperplasminaemia after cardiac surgery. Although control of bleeding was achieved the patient died 36 hours later with a clotted haemopericardium and haemothorax.

Hyperplasminaemia may occasionally be associated with tumours producing excess plasminogen activator[35] or with acute leukaemia.[36] These patients respond to tranexamic acid. However, they are rare in comparison with patients who have underlying DIC. Similarly, prostatic carcinoma either with or without surgery may cause hyperplasminaemia or local fibrinolytic excess leading to haematuria.[37] These situations have been dealt with successfully by antifibrinolytic agents.

*Excess fibrinolysis secondary to DIC*

Bleeding in DIC is unlikely to be due to an excessive or inappropriate fibrinolytic response and antifibrinolytic agents are not advised. Activation of

fibrinolysis in this situation is a secondary protective mechanism which should not be inhibited.

### LOCAL FIBRINOLYSIS WITHIN ORGANS

The individual clinical conditions where local excess fibrinolysis within organs may cause haemorrhage will be dealt with separately by others.

Excess local fibrinolysis is seen mainly in diseases of the following organs: (1) uterus, causing menorrhagia; (2) stomach and duodenum, causing gastrointestinal bleeding; (3) prostate gland, causing haematuria; (4) in the cerebrospinal fluid, after subarachnoid haemorrhage.

The reason for localised haemorrhage in these organs is that the relevant tissues are rich in plasminogen activators (tissue activators). The response of tissues damaged by trauma is to release tissue activator. The equilibrium between coagulation and fibrinolysis within these tissues is disturbed with local production of free plasmin causing digestion of haemostatic plugs.

When tissue activator production by an organ such as the prostate is sufficiently high there may be release of plasmin in the circulation leading to hyperplasminaemia. Thus the distinction between local and general fibrinolytic excess is not absolute. Fortunately, the penetration of fibrinolytic inhibitors such as tranexamic acid is good, so that systemic administration of these agents can inhibit plasmin produced at sites of organ damage without the hazard of widespread thrombosis. It is notable that the thrombotic complications of antifibrinolytic agents are not often seen when the drugs are being used for local indications such as menorrhagia, although a few cases of thrombosis in these circumstances have been reported, but rather when a systemic disorder of coagulation or fibrinolysis is present. The exception to this is in the treatment of haematuria, when obstruction in the ureters or urethra may occur due to clot formation.

### HEREDITARY COAGULATION DISORDERS

Coagulation defects causing haemorrhage, but with a normal fibrinolytic response, are seen in haemophilia and other hereditary bleeding disorders. In these circumstances any clot formed is friable and can be disrupted by plasmin produced by normal fibrinolytic activity. There is now good evidence that blood loss from dental extraction and the amount of factor VIII transfused in haemophilia may be reduced by routine use of antifibrinolytic agents before and after the operation.[38 39] However, there is insufficient evidence to justify the routine use of antifibrinolytic drugs in haemophilia.[40] The hazards of ureteric obstruction by clot after haematuria in haemophilia have been reviewed.[41]

## References


[1] Schwartz ML, Pizzo SV, Hill RL, McKee PA. The effect of fibrin-stabilizing factor on the subunit structure of human fibrin. *J Clin Invest* 1971;**50**:1506-13.

[2] Gaffney PJ, Brasher M. Subunit structure of the plasmin-induced degradation products of cross-linked fibrin. *Biochim Biophys Acta* 1973;**295**:308-13.

[3] Okamoto S, Nakajima T, Okamoto U, *et al.* A surprising effect of ϵ-amino-n-caproic acid on the bleeding of dogs, produced with the activation of plasmin in the circulating blood. *Keio J Med* 1959;**8**:247-66.

[4] Markwardt F. Synthetic inhibitors of fibrinolysis. In: Markwardt F, ed. *Fibrinolytics and anti-fibrinolytics* (*Handbuch der experimentellen Pharmakologie*, vol 46). Berlin: Springer, 1978:511-77.

[5] Okamoto S, Okamoto U. Amino-methyl-cyclohexane-carboxylic acid: AMCHA. A new potent inhibitor of the fibrinolysis. *Keio J Med* 1962;**11**:105-15.

[6] Melander B, Gliniecki G, Granstrand B, Hanshoff G. Biochemistry and toxicology of amikapron: the antifibrinolytically active isomer of AMCHA (a comparative study with ϵ-aminocaproic acid). *Acta Pharmacol* (*Kbh*) 1965;**22**:340-52.

[7] Dubber AHC, McNicol GP, Douglas AS, Melander B. Some properties of the antifibrinolytically active isomer of amino-methylcyclohexane carboxylic acid. *Lancet* 1964;**2**:1317-9.

[8] Dubber AHC, McNicol GP, Douglas AS. Amino-methyl cyclohexane carboxylic acid (AMCHA), a new synthetic fibrinolytic inhibitor. *Br J Haematol* 1965;**11**:237-45.

[9] Thorsen S. Influence of fibrin on the effect of 6-aminohexanoic acid on fibrinolysis caused by tissue plasminogen activator or urokinase. In: Davidson JF, Rowan RM, Samama MM, Desnoyers PC, eds. *Progress in chemical fibrinolysis and thrombolysis*, vol 3. New York: Raven Press, 1978:269-83.

[10] Alkjaersig N, Fletcher AP, Sherry S. ϵ-Aminocaproic acid: an inhibitor of plasminogen activation. *J Biol Chem* 1959;**234**:832-7.

[11] Thorsen S, Glas-Greenwalt P, Astrup T. Differences in the binding to fibrin of urokinase and tissue plasminogen activator. *Thrombos Diathes Haemorrh* 1972;**28**:65-74.

[12] Rickli EE, Otavsky WI. Release of an N-terminal peptide from human plasminogen during activation with urokinase. *Biochim Biophys Acta* 1973;**295**:381-4.

[13] Wiman B, Wallên P. Activation of human plasminogen by an insoluble derivative of urokinase: structural changes of plasminogen in the course of activation to plasmin and demonstration of a possible intermediate compound. *Eur J Biochem* 1973;**36**:25-31.

[14] Thorsen S. Differences in the binding to fibrin of native plasminogen and plasminogen modified by proteolytic degradation: influence of ω-aminocarboxylic acids. *Biochim Biophys Acta* 1975;**393**:55-65.

[15] Robbins KL, Summaria L, Hsieh B, Shah RJ. The peptide chains of human plasmin: mechanism of

activation of human plasminogen to plasmin. *J Biol Chem* 1967;**242**:2333-42.

[16] Claeys H, Vermylen J. Physio-chemical and pro-enzyme properties of $NH_2$-terminal glutamic acid and $NH_2$-terminal lysine human plasminogen: influence of 6-aminohexanoic acid. *Biochim Biophys Acta* 1974;**342**:351-9.

[17] Walther PJ, Hill RL, McKee PA. The importance of the preactivation peptide in the two-stage mechanism of human plasminogen activation. *J Biol Chem* 1975;**250**:5926-33.

[18] Landmann H. Studies on the mechanism of action of synthetic antifibrinolytics. A comparison with the action of derivatives of benzamidine on the fibrinolytic process. *Thrombos Diathes Haemorrh* 1973;**29**: 253-75.

[19] Thorsen S, Kok P, Astrup T. Reversible and irreversible alterations of human plasminogen indicated by changes in susceptibility to plasminogen activators and in response to ϵ-aminocaproic acid. *Thrombos Diathes Haemorrh* 1974;**32**:325-40.

[20] Skoza L, Tse AO, Semar M, Johnson AJ. Comparative activities of amino acid and polypeptide inhibitors on natural and synthetic substrates. *Ann NY Acad Sci* 1968;**146**:659-72.

[21] Rickli EE, Otavsky WI. A new method of isolation and some properties of the heavy chain of human plasmin. *Eur J Biochem* 1975;**59**:441-7.

[22] Wallén P. Chemistry of plasminogen and plasminogen activation. In: Davidson JF, Rowan RM, Samama MM, Desnoyers PC, eds. *Progress in chemical fibrinolysis and thrombolysis*, vol 3. New York: Raven Press, 1978:167-81.

[23] Chauvet J, Acher R. The reactive site of basic trypsin inhibitor of pancreas. Role of lysine 15. *J Biol Chem* 1967;**242**:4274-5.

[24] Dubber AHC, McNicol GP, Uttley D, Douglas AS. *In vitro* and *in vivo* studies with Trasylol, an anticoagulant and a fibrinolytic inhibitor. *Br J Haematol* 1968;**14**:31-49.

[25] Markwardt F. Naturally occurring inhibitors of fibrinolysis. In: Markwardt F, ed. *Fibrinolytics and anti-fibrinolytics* (*Handbuch der experimentellen Pharmakologie*, vol 46). Berlin: Springer, 1978: 487-509.

[26] Lorand L, Condit EV. Ester hydrolysis by urokinase. *Biochemistry* 1965;**4**:265-70.

[27] Walton PL. The hydrolysis of alpha-N-acetylgycyl-L-lysine methyl ester by urokinase. *Biochim Biophys Acta* 1967;**132**:104-14.

[28] Markwardt F, Richter M. Zur Standardisierung des Proteaseninhibitors aus Rinderorganen. *Pharmazie* 1969;**24**:620-2.

[29] Klöcking HP, Markwardt F. Tierexperimendelle Verfahren zur Testung von Fibrinolytika und Antifibrinolytika. *Folia Haematol* 1969;**92**:84-9.

[30] Prentice CRM. Indications for antifibrinolytic therapy. *Thrombos Diathes Haemorrh* 1975;**34**:634-43.

[31] Merskey C, Johnson AJ, Kleiner GJ, Wohl H. The defibrination syndrome: clinical features and laboratory diagnosis. *Br J Haematol* 1967;**13**:528-49.

[32] Naeye RL. Thrombotic state after a hemorrhagic diathesis, a possible complication of therapy with epsilon-aminocaproic acid. *Blood* 1962;**19**:694-701.

[33] Basu HK. Fibrinolysis and abruptio placentae. *J Obstet Gynaec Brit Cmwlth* 1969;**76**:481-96.

[34] McNicol GP. Disordered fibrinolytic activity and its control. *Scot Med J* 1962;**7**:266-76.

[35] Davidson JF, McNicol GP, Frank GL, Anderson TJ, Douglas AS. Plasminogen-activator-producing tumour. *Br Med J* 1969;**i**:88-91.

[36] Nilsson IM, Björkman SE, Andersson L. Clinical experiences with ϵ-aminocaproic acid (ϵ-ACA) as an antifibrinolytic agent. *Acta Med Scand* 1961;**170**: 487-509.

[37] Andersson L, Nilsson IM. Effect of ϵ-amino-n-caproic acid (ϵ-ACA) on fibrinolysis and bleeding conditions in prostatic disease. *Acta Chir Scand* 1961;**121**:291-8.

[38] Walsh PN, Rizza CR, Matthews JM, *et al.* Epsilon-aminocaproic acid therapy for dental extractions in haemophilia and Christmas disease: a double blind controlled trial. *Br J Haematol* 1971;**20**:463-75.

[39] Forbes CD, Barr RD, Reid G, *et al.* Tranexamic acid in control of haemorrhage after dental extractions in haemophilia and Christmas disease. *Br Med J* 1972;**ii**:311-3.

[40] Gordon AM, McNicol GP, Dubber AHC, McDonald GA, Douglas AS. Clinical trial of epsilon-aminocaproic acid in severe haemophilia. *Br Med J* 1965; **i**:1632-5.

[41] Prentice CRM, Lindsay RM, Barr RD, *et al.* Renal complications in haemophilia and Christmas disease. *Q J Med* 1971;**40**:47-61.