This treatment is quite the most effective and is the least disturbing to the patient.

We would like to thank Professor D. W. Smithers, of the Radiotherapy Department, and Professor W. V. Mayneord, of the Physics Department, and members of their staffs, for making this work possible. We are also grateful to numerous colleagues in this and other hospitals for referring cases to us, and in particular to Dr. P. E. T. Hancock. The earlier cases in the series were treated by Dr. R. J. Walton, to whom we acknowledge our debt.

REFERENCES

Abbatt, J. D., Chaplin, H., Darte, J. M. M., and Pitney, W. R. (1954). *Quart. J. Med.*, **23**, 91.
Lawrence, J. H., Berlin, N. I., and Huff, R. L. (1953). *Medicine (Baltimore)*, **32**, 323.
Mollison, P. L. (1951). *Blood Transfusion in Clinical Medicine*. Blackwell Scientific Publ., Oxford.
Scott, R. Bodley (1953). *British Medical Journal*, **1**, 1128.
Stroebel, C. F. (1954). *Proc. Mayo Clin.*, **29**, 1.

PROTHROMBIN AND THE ONE-STAGE PROTHROMBIN TIME*

BY

ARMAND J. QUICK, Ph.D., M.D.

AND

CLARA V. HUSSEY, M.S.

(From the Department of Biochemistry, Marquette University School of Medicine, Milwaukee, Wisconsin)

The discovery that the prolonged prothrombin time of stored human plasma was caused by the disappearance of a clotting factor, hitherto unrecognized (Quick, 1943), made it clear that prothrombin activity depended on more than prothrombin itself and that the one-stage procedure could no longer be regarded unequivocally as a specific test for this constituent. When it was subsequently established that the plasma contained a second prothrombin accessory factor (Alexander *et al.*, 1952), the need for a reinterpretation of the test was further emphasized. It is the purpose of this paper to present pertinent experimental and clinical observations that should be helpful for the re-evaluation of the test, and for furnishing at least a partial answer to several basic questions concerning the prothrombin time.

Methods and Materials

Since the purpose of this study is a critical evaluation of the one-stage prothrombin time, it is necessary to limit discussion to results obtained by the original rigidly standardized method (Quick, 1938). Of particular importance is the source and preparation of the thromboplastic reagent. Rabbit brain carefully cleared of blood and blood vessels and dehydrated with acetone not only has a high and constant activity but is devoid of both stable and labile factors.

In this study blood was collected with a silicone-coated syringe and needle and kept in test-tubes similarly coated. All clotting tests were carried out in uncoated glass test-tubes at 37° C. unless otherwise stated.

Tricalcium-phosphate-treated Plasma.—By means of this adsorbent, prothrombin and stable factor are quantitatively removed, while labile factor and fibrinogen remain unaltered. Since rabbit plasma is exceedingly high in labile factor, it serves as a good source for this agent as well as for fibrinogen. The preparation of the tricalcium phosphate reagent and the procedure for deprothrombinizing plasma have been described in detail (Quick, 1951). Plasma treated with tricalcium phosphate is designated as "$Ca_3(PO_4)_2$ plasma." Stable factor was prepared by the method of Duckert, Koller, and Matter (1953). In many experiments aged serum from normal blood served as the supply of this factor.

Serum Prothrombin Time.—The blood or plasma was clotted in a glass test-tube at 37° C., centrifuged 15 minutes after a solid clot had formed, and reincubated for an additional 45 minutes. The prothrombin time was carried out as follows : 0.1 ml. of fresh rabbit plasma deprothrombinized with $Ca_3(PO_4)_2$ was mixed with 0.1 ml. of 0.02 M $CaCl_2$ and 0.1 ml. of thromboplastin reagent (from rabbit brain). To this mixture 0.1 ml. of the serum was blown in and the clotting-time determined. In this procedure the deprothrombinized rabbit plasma supplies both fibrinogen and stable factor.

Three patients with true congenital hypoprothrombinaemia were available for this study. Two are brothers whose prothrombin times have remained 19 to 26 seconds for the past seven years. The third is a girl whose prothrombin time is 37 seconds. The patients have a normal concentration of labile factor and their prothrombin time is not shortened by stable factor. A patient with pure stable-factor deficiency was also utilized in this investigation. Her prothrombin time varies from 26 to 55 seconds, but is usually about 27 seconds. The addition of stable factor prepared according to Koller completely corrects the prothrombin time. A detailed study of these patients has recently been presented (Quick, Pisciotta, and Hussey, 1955).

For the sake of simplicity the terms " labile " and " stable " (factors) are employed. Labile factor may be considered to be synonymous with factor V or proaccelerin of Owren and ac-globulin of Seegers, while stable factor is probably the same as factor VII of Koller, proconvertin of Owren, S.P.C.A. of Alexander, stable prothrombin conversion factor of Owen, and co-thromboplastin of Mann.

Why is the Prothrombin Time Constant in Fresh Normal Plasma ?

Few values of blood are as constant as the prothrombin time. It is consistently 12 seconds in normal subjects, in contrast to the wide variations of prothrombin concentration as measured by the two-stage method, which, according to Mann and his associates (1948), may vary from 244 to 452 units. While it is established that three agents—namely, prothrombin, and stable and labile factors—affect the prothrombin time, it remains to be determined which of these is specifically responsible for the 12-second value of normal blood. A rather convincing answer can be found from the results of Table I. It is to be noted that an excess of neither

TABLE I.—*Effect on Prothrombin Time of Adding Excess Labile and Stable Factors to Normal Plasma and Plasma Deficient in These Accessory Agents*

	Prothrombin Time (Seconds)		
	Original	With Excess	
		Labile Factor*	Stable Factor†
Normal plasma	12	12	11½
Stored plasma (labile factor deficient)‡	16	12	16
Plasma deficient in prothrombin	21	21	21
Plasma deficient in stable factor	39	40	12

* To 0.1 ml. of plasma, 0.01 ml. of rabbit plasma deprothrombinized with $Ca_3(PO_4)_2$ was added.
† To 0.1 ml. of plasma, 0.01 ml. of aged serum prepared from normal blood was added.
‡ Stored in a silicone-coated test-tube for 24 hours at 4° C.

labile nor stable factor significantly shortens the prothrombin time of fresh normal plasma. After storage in a silicone-treated container for 24 hours, the prothrombin time is increased to 16 seconds. The addition of excess

*This work was supported by a grant from the National Heart Institute, National Institutes of Health, United States Public Health Service.

labile factor in the form of deprothrombinized rabbit plasma corrects the prothrombin time to 12 seconds, whereas stable factor has no effect. The addition of labile factor does not correct the prolonged prothrombin time of plasma from a patient with congenital deficiency of stable factor, but a small quantity of aged serum, which has an excess of this factor, brings the value to exactly 12 seconds. Plasma with a prolonged prothrombin time due to a true deficiency of prothrombin is not corrected by an excess of either labile or stable factor.

These results clearly suggest that the concentration of prothrombin fixes the value of the prothrombin time, provided adequate amounts of labile and stable factors are present. Since excess of these accessory factors exerts a corrective effect only on those plasmas which lack the specific factor, it seems clear that a deficiency of any one is not compensated by an excess of the other two. The determinant of the prothrombin time is the component which decreases below a minimal critical level. In normal blood, labile and stable factors are in excess while prothrombin is the limited factor and, therefore, is the agent responsible for the prothrombin time. The constancy of the prothrombin time of fresh normal plasma can therefore be explained by assuming a fixed level of prothrombin.

Why Does the Prothrombin Time Change During Storage?

It is generally accepted that the increase of prothrombin time during storage is caused by a decrease of labile factor. Apparently, the rate of disappearance is related to the calcium-ion concentration, for it is much more when blood is mixed with one-ninth its volume of 0.1 M sodium oxalate or 0.2 M sodium citrate than with 0.1 M sodium citrate. The latter does not completely depress the concentration of ionized calcium and, as seen from the results recorded in Table II, no demonstrable amount of labile factor is lost in

TABLE II.—*Changes in Prothrombin Activity of Normal, Prothrombin-deficient, and Stable-factor-deficient Blood During Storage*

	Immediate	After 24 Hours' Storage	
		In Glass	In Silicone
Normal blood (9 volumes) and sodium oxalate 0·1 M (1 volume)	12	15	16
After adding labile factor ..	12	8	12
,, ,, stable ,, ..	11½	15	16
Normal blood (9 volumes) and sodium citrate 0·1 M (1 volume)	12	9	12
After adding labile factor ..	12	8	12
,, ,, stable ,, ..	11½	9	12
Prothrombin-deficient blood (9 volumes) and sodium oxalate 0·1 M (1 volume)	23	37	39
After adding labile factor ..	23	17	23
,, ,, stable ,, ..	23	37	39
Stable-factor-deficient blood (9 volumes) and sodium oxalate 0·1 M (1 volume)	39	30	33
After adding labile factor ..	40	25	30
,, ,, stable ,, ..	12	18	18
,, ,, labile and stable factor	11½	9	12

24 hours. Significantly, with this anticoagulant no change in the prothrombin time occurs if the plasma is stored in a silicone-coated tube, but a marked decrease is observed when stored in glass. This rise in prothrombin activity can be explained either by an actual increase in prothrombin or by the generation of an accelerator. Irrespective of which explanation is correct, it is obvious that storage in glass increases prothrombin activity as measured by the one-stage test. Owing to the simultaneous decrease in labile factor, the increase in activity is usually masked. Thus the prothrombin time of oxalated plasma after 24 hours' storage in glass is 15 seconds, but when labile factor is added it decreases to 8 seconds. The plasma in the silicone-coated test-tube has nearly the same prolonged prothrombin time, but labile factor reduces it only to 12 seconds. This suggests that the generation of prothrombin activity is slower in silicone than in glass.

When oxalated plasma deficient in stable factor is stored the prothrombin time is further increased in both glass and silicone. If labile factor is added, a partial correction occurs, whereas the addition of stable factor caused no shortening. When both labile and stable factors are added the prothrombin time is reduced to 8 or 9 seconds. Plasma from a patient with true hypoprothrombinaemia likewise, when stored, exhibits a further prolongation of the prothrombin time which is partly corrected by the addition of labile factor. Stable factor has no corrective action.

From these results one may conclude that if the increase in the prothrombin activity of stored plasma is caused by the generation of an accelerator, it is produced independently of either labile or stable factors. It is significant that plasma which lacks prothrombin shows only a small increase in activity on storage and that neither stable nor labile factors bring the prothrombin time to normal. Two basic causes account for changes in the prothrombin time of stored plasma: the first is a loss of labile factor, the second is either an actual increase of prothrombin or the generation of an accelerator independent of either labile or stable factors. In the absence of labile factor the increase of this prothrombin activity is masked.

Why is the Prothrombin Time of Serum from Haemophilic or Thrombocytopenic Blood Shorter Than That of Plasma?

When plasma deprived of platelets by means of high centrifugation or obtained from subjects having thrombocytopenia or haemophilia is clotted in glass, the serum has a prothrombin time of 8 seconds provided the plasma is normal —that is, gives a value of 12 seconds (Table III). It is certain that the poor consumption of prothrombin explains in

TABLE III.—*Prothrombin Time of Plasma and Its Corresponding Serum in Haemophilia and Thrombocytopenia*

Type of Plasma	Platelet Count	Prothrombin Time		
		Of Plasma	Of Serum	Of Stored Plasma with Labile Factor Added
		Sec.	Sec.	Sec.
Haemophilic	300,000	12	8	8
Thrombocytopenic	65,000	12	9½	8
Normal (highly centrifuged) ..	3,000	12	8	8
Hypoprothrombinaemic (congenital)	270,000	20	180+	16
Congenital hypoprothrombinaemia (highly centrifuged) ..	3,500	20	20	16
Stable factor deficient ..	250,000	27½	73	18½
,, ,, ,, (highly centrifuged)	3,000	27½	19	18½

part the short prothrombin time, but does not account for a value of 4 seconds less than that of the fresh plasma. Since the same decrease occurs in plasma stored in glass to which excess labile factor is added, one may conclude that a common mechanism is responsible for the increased prothrombin activity. As already stated, the most obvious explanation is either an actual increase in prothrombin or the generation of an accelerator.

When one compares the prothrombin time of the serum obtained from normal blood with that of blood from a patient with true hypoprothrombinaemia, one finds that the serum prothrombin becomes extremely prolonged in the latter and only to 20 seconds in the particular normal blood used in this experiment. When blood from the hypoprothrombinaemic patient is highly centrifuged and the resulting plasma clotted, the serum has about the same prothrombin time as the serum, thus suggesting that either little new prothrombin is formed or little accelerator is generated.

The results obtained on blood lacking stable factor are particularly interesting. With an adequate supply of platelets the consumption of prothrombin as measured by the serum prothrombin time is fairly high, indicating that

deficiency of stable factor does not prevent normal utilization of prothrombin. When stable factor is added in determining the prothrombin time of the serum a value lowered to normal is obtained, thus showing that the serum does not contain adequate amounts of the factor to assure an accurate prothrombin time. Even more striking are the results when the stable-factor-deficient and platelet-poor plasma is clotted. The serum shows a prothrombin time less than that of the plasma but still markedly prolonged. The addition of stable factor brings the prothrombin time to 9 seconds. Since the addition of a fixed amount of stable factor corrects the prothrombin time of the fresh plasma from the patient with pure stable-factor deficiency to 12 seconds and the serum from the platelet-poor plasma to 9 seconds, it is obvious that these two values are not fixed by the stable factor. The results obtained on the serum from true hypoprothrombinaemic plasma suggest that the serum prothrombin time is closely related to the prothrombin concentration.

The answer to the question heading this discussion is : The prothrombin time of serum from haemophilic or thrombocytopenic blood is shorter than that of the corresponding plasma because almost no prothrombin is consumed and, in addition, there is formed either additional prothrombin or an accelerator independent of labile or stable factors.

Why is the Prothrombin Time of Blood of Newborn Babies Normal When Measured by the One-stage Method and Low by the Two-stage Procedure?

If it is possible to answer this question satisfactorily a real advance should be made in clearing the confusion concerning the interrelationship of prothrombin and accelerators. The original study of Brinkhous, Smith, and Warner (1937) established that the prothrombin is only about 30% as high in newborn as in adult blood. Equally as incontrovertible is the fact that the prothrombin time is 12 seconds in almost all newborn infants whose mothers had adequate amounts of vitamin K (Quick, Murat, Hussey, and Burgess, 1952). Warner, Brinkhous, and Smith (1939) explained this difference by postulating a change in convertibility of prothrombin. Later, the discovery of the labile and stable factors made it appear probable that these accessory factors might in some way be accountable for this striking discrepancy. The finding that the labile factor is normal in newborn blood (Quick, Flood, and Hussey, 1953; Owen and Hurn, 1953) eliminates this agent from consideration. The report of Loeliger and Koller (1952) that the stable factor is reduced in newborn blood clearly shows that it cannot be the agent that compensated for the lack of prothrombin and thereby normalizes the prothrombin time.

The results of a few simple experiments recorded in Table IV offer pertinent information. While the prothrombin time of newborn plasma is 12 seconds, which is the same as that of adult plasma, it fails to show the characteristic shortening of the latter on storage. Likewise, the prothrombin time of serum prepared from platelet-poor newborn plasma is not 8 seconds, as is the serum from platelet-poor adult plasma, but is 12 seconds, which is the same as the original plasma.

TABLE IV.—*Comparison of Prothrombin Activity in Adult and in Newborn Blood*

	Prothrombin Time	
	Adult	Newborn
1. Fresh plasma	12 sec.	12 sec.
2. Stored plasma*	9 ,,	12 ,,
3. Serum from platelet-poor plasma	8 ,,	12 ,,
4. Plasma diluted with equal volume of saline	15 ,,	15 ,,
5. Plasma diluted with equal volume of $Ca_3(PO_4)_2$-treated plasma	12 ,,	15 ,,

* In glass at 4° C. for 24 hours with 0·1 M sodium citrate.

Earlier it was pointed out that the increase in prothrombin activity of adult plasma on storage or in serum from platelet-poor plasma could be explained by postulating either an actual increase in prothrombin or by the evolution of an accelerator. From the results obtained on newborn plasma it is clear why the first is the more likely explanation. According to the two-stage test, the prothrombin of newborn blood is only about one-third of that in adult blood. Since no evidence of an accelerator in newborn blood has been demonstrated, it seems quite plausible that the augmented prothrombin activity in adult blood is caused by an actual increase in prothrombin derived from an inactive precursor that may be designated as prothrombinogen. According to this hypothesis, newborn blood lacks this precursor, and this accounts for the low prothrombin obtained with the two-stage method. The one-stage method specifically measures active prothrombin and is unaffected by prothrombinogen.

Further support for the concept is obtained from the results of experiments 4 and 5 of Table IV. If either newborn or adult oxalated plasma is diluted with an equal volume of saline the prothrombin time is increased to 15 seconds. If, however, plasma treated with $Ca_3(PO_4)_2$ is used as the diluent, the prothrombin time of adult plasma remains 12 seconds, whereas that of the diluted newborn plasma is 15 seconds. Apparently, $Ca_3(PO_4)_2$-treated plasma contains a factor which can convert inactive prothrombin to the active state. Since newborn plasma is devoid of prothrombinogen, the addition of the deprothrombinized plasma cannot increase the active prothrombin, and therefore the prothrombin time becomes prolonged to 15 seconds, the same as is obtained by dilution with saline.

To present the hypothesis in an easily comprehensible form one may visualize prothrombinogen as prothrombin kept inactive by an inhibitor, "X." On storage the inhibitor deteriorates, thus liberating prothrombin, which accounts for the increased prothrombin activity. Plasma treated with $Ca_3(PO_4)_2$ contains an agent which can activate prothrombinogen presumably by removing the inhibitor. If the factor be designated "Y" one can postulate an equilibrium according to the following equation :

$$\underset{\text{(prothrombinogen)}}{\text{Prothrombin X}} + \text{Y} \rightleftharpoons \text{Prothrombin} + \text{XY}$$

This is undoubtedly an oversimplification, but the essential idea offers a logical answer to the four basic questions presented. It appears to be the Y factor which fixes the level of free prothrombin in human blood, and therefore it is the basic determinant of the prothrombin time. There is evidence that the concentration of this agent is determined by heredity. A family has been reported in which a mother and two of her children have a prothrombin time of 16 minutes, due presumably to a lower-fixed concentration of factor Y (Quick, Flood, and Hussey, 1953).

According to the present findings, the answer to this fourth question is : The newborn plasma has a normal prothrombin time because it has a normal concentration of free prothrombin, but it has a lower prothrombin as measured by the two-stage method because it is devoid of prothrombinogen. Its total prothrombin content which the latter test measures is much lower than in adult blood.

Relation of Haemorrhage to Prothrombin Time

In the early study of poisoning from spoiled sweet clover hay it was observed that a heart puncture caused fatal haemopericardium whenever the rabbit's prothrombin time was markedly prolonged (Quick, 1937). Later it was shown that a puncture caused fatal bleeding when the prothrombin time was 24 seconds or longer (Quick, Honorato, and Stefanini, 1948). Interestingly enough, these findings correspond remarkably well with human findings. Two boys who have a prothrombin time varying from 19 to 26 seconds due to congenital true hypoprothrombinaemia have a rather mild but distinct bleeding tendency. A girl of another family who has a more severe deficiency of prothrombin, with a prothrombin time of 35 seconds, has a much more severe bleeding condition. A woman aged 50 who has a prothrombin time which varies from 27 to 51 seconds due to a pure deficiency of stable factor has a rather mild bleeding history.

The exact relation of the prothrombin time to haemorrhage in the human is difficult to determine. In most types

of coagulation defect bleeding does not occur unless induced by trauma. Even a severe haemophiliac with a clotting-time over one hour may have no bleeding episodes for long periods. Since the newborn infant with a normal prothrombin time but a low prothrombin as measured by the two-stage method can undergo surgery with impunity, one can conclude that the one-stage method is the more reliable in that it measures the fraction of prothrombin that apparently participates directly in haemostasis.

Discussion

A hypothesis has been offered to help answer four basic questions concerning the prothrombin time. The central idea is that the prothrombin in adult blood is present partly in the active form and partly as prothrombinogen. The one-stage method measures only the active prothrombin, while the two-stage test determines total prothrombin—that is, both the active and the inactive fractions. The early studies of Bordet (1919) already indicated the possibility of inactive prothrombin. He concluded that all of the prothrombin was in the precursor state, to which he gave the name proserozyme. The concept of Warner *et al.* (1939) of an altered convertibility of prothrombin is in accord with the basic concept provided one reinterprets convertibility. It is unlikely that the prothrombin molecule can have gradations of convertibility. There is a much greater probability that the convertibility follows the all-or-none law. It is either entirely non-convertible—that is, in an inactive state—or fully convertible, and the apparent convertibility actually is the ratio of free to total prothrombin. The higher the percentage of free prothrombin, the greater will appear to be the convertibility.

Whether the hypothesis is accepted or not, it must be recognized that the prothrombin time of plasma is easily altered by relatively simple factors such as contact with glass. Any modification of the original procedure is apt to measure something different from what is present in the plasma immediately after removal from the vein. Modifications designed to measure prothrombin specifically deserve particular scrutiny. Contrary to the claims that the prothrombin time is not a measure of prothrombin, it can be argued from the evidence presented in this paper that it is actually the only method which determines active prothrombin. It is to be emphasized that the one-stage and two-stage methods do not measure the same thing in human blood, and therefore there is no justification to use the two-stage procedure as the criterion to evaluate the one-stage test. Since deficiency of stable and labile factor can easily be detected and the test corrected accordingly, the one-stage method continues to remain the simplest and probably the most reliable means to determine prothrombin.

Summary

In this study evidence is offered to show that the constancy of the prothrombin time of fresh normal human plasma is due to the fixed concentration of active prothrombin. The increase of prothrombin activity during storage and during the clotting of haemophilic or platelet-poor plasma can be explained simply by the assumption that adult blood contains in addition to active prothrombin a high concentration of inactive prothrombin (prothrombinogen) which does not influence the one-stage method but is measured by the two-stage test. During storage or clotting the precursor is converted to active prothrombin, which in the hypothromboplastic states is not consumed and therefore accumulates. Newborn blood contains a normal concentration of active prothrombin but is devoid of prothrombinogen, which accounts for the normal prothrombin time but the low prothrombin as measured by the two-stage test.

References

Alexander, B., Flynn, J. E., Mann, F. D., Owren, P. A., and Seegers, W. H. (1952). *Blood Clotting and Allied Problems*, edited by J. E. Flynn. Trans. Fifth Conf. New York, Josiah Macy, Jr., Foundation.
Bordet, J. (1919). *C.R. Soc. Biol. (Paris)*, **82**, 896.
Brinkhous, K. M., Smith, H. P., and Warner, E. D. (1937). *Amer. J. med. Sci.*, **193**, 475.
Duckert, F., Koller, F., and Matter, M. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **82**, 259.
Loeliger, A., and Koller, F. (1952). *Acta Haemat. (Basel)*, **7**, 157.
Mann, F. D., Butt, H. R., and Hurn, M. (1948). *Gastroenterology*, **11**, 221.
Owen, C. A., and Hurn, M. M. (1953). *J. Pediat.*, **42**, 424.
Quick, A. J. (1937). *Amer. J. Physiol.*, **118**, 260.
—— (1938). *J. Amer. med. Ass.*, **110**, 1658.
—— (1943). *Amer. J. Physiol.*, **140**, 212.
—— (1951). *The Physiology and Pathology of Hemostasis*. Lea and Febiger, Philadelphia.
—— Flood, F. T., and Hussey, C. V. (1953). *Amer. J. clin. Path.*, **23**, 951.
—— Honorato, R., and Stefanini, M (1948). *Blood*, **3**, 1120.
—— Murat, L. G., Hussey, C. V., and Burgess, G. F. (1952). *Surg. Gynec. Obstet.*, **95**, 671.
—— Pisciotta, A. V., and Hussey, C. V. (1955). *Arch. intern. med.*, **95**, 2.
Warner, E. D., Brinkhous, K. M., and Smith, H. P. (1939). *Amer. J. Physiol.*, **125**, 296.

CARDIAC GLYCOSIDES IN THE TREATMENT OF CARDIOGENIC SHOCK

BY

RICHARD GORLIN, M.D.
Chief Medical Resident, Peter Bent Brigham Hospital, 1953–4

AND

EUGENE D. ROBIN, M.D.
Chief Medical Resident, Peter Bent Brigham Hospital, 1954–5

From the Medical Clinics, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School

Myocardial infarction complicated by severe shock is usually attended by a mortality estimated as high as 93% (Rosenbaum and Levine, 1941). Numerous forms of therapy have been advocated for this serious complication, including vasopressor agents, transfusions, and cardiac glycosides (Hellerstein and Brofman, 1951). The use of the first two agents has been fairly well clarified in the past five years, but the role of cardiac glycosides, in the absence of overt or predominant congestive failure, is as yet unsettled.

Four cases are presented to illustrate the specific use of the cardiac glycosides in the treatment of cardiogenic shock, and in so doing to demonstrate survival from the usually lethal combination of pulmonary oedema and shock.

Case 1

A 60-year-old undigitalized hypertensive man entered hospital in shock. He had had a previous myocardial infarction four years prior to admission. He collapsed on the morning before admission and was found to be cold, sweaty, cyanotic, and unresponsive. No blood pressure was obtainable. There were bilateral moist rales up to the scapulae. An electrocardiogram showed an acute posterior myocardial infarction with bizarre arrhythmias, including ventricular tachycardia, ventricular bigeminy, and auricular flutter. He was given 50 mg. of procaine amide hydrochloride ("pronestyl") intravenously, with conversion to a normal sinus mechanism. Treatment with intravenous noradrenaline raised the blood pressure to 100/80, but he remained unresponsive and in clinical shock. Slowing of the infusion resulted in an immediate fall in blood pressure. He was then given 0.4 mg. of lanatoside C intravenously. Thirty minutes later the heart sounds became more distinct, and he was able to speak and recognize his family. Blood pressure was maintained without vasopressors. Signs of congestion virtually