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 hypothermoplastastic 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.

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CARDIAC GLYCOSIDES IN THE TREATMENT OF CARDIOGENIC SHOCK

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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 ("pro-nestyl") 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

disappeared. He was given another 0.4 mg. of lanatoside C and appeared to be doing well. Approximately one hour after this dose he suddenly died. A pre-terminal electrocardiogram showed ventricular fibrillation. Post-mortem examination showed a fresh posterior myocardial infarction and pulmonary congestion.

Comment.—Shock and coma responded specifically to lanatoside C. Blood pressure was maintained without vasopressors. Death may have been related to a digitalis-induced arrhythmia.

Case 2

A 49-year-old white woman with disseminated lupus erythematosus had been on cortisone, 75 mg. daily, and had had severe hypertension, congestive heart failure, and angina pectoris. She was maintained on digitalis, 0.1 g. daily, but this had been omitted two days before admission. Five hours before admission she developed left anterior chest pain followed by acute dyspnoea and cyanosis. On admission to hospital she was found to have rales to the apices and gurgling respirations. The blood pressure was 250/138, pulse 152, respirations 40. An electrocardiogram showed left ventricular hypertrophy and a possible antero-septal myocardial infarction.

The patient was treated initially with morphine, 10 mg., atropine, tourniquets, and a 250-ml. venesection, with a fall in blood pressure to 110 systolic. Pressure was maintained at this minimum level with phenylephrine hydrochloride ("neosynephrine") intravenously in 5–15-mg. doses. When the blood pressure was at its peak of 110 systolic the pulmonary oedema became worse; however, when the blood pressure became less than 90 the pulmonary oedema lessened, but the patient became unresponsive. As the hours wore on she remained in coma and pulmonary oedema at all blood-pressure levels. The pulse rate was 135 and the blood pressure could not be maintained above 100 mm. Hg. At this time ouabain was given intravenously in divided doses of 0.05 mg., to a total of 0.15 mg. Forty-five minutes after initiation of this therapy three things occurred: the patient awakened and became alert, the blood pressure was easily maintained at any level on phenylephrine, and despite the blood pressure being maintained at about 120 to 130 mm. pulmonary oedema cleared.

Comment.—In this patient shock and coma were successfully treated with ouabain. Vasopressor action was aided and supported by digitalization.

Case 3

A 65-year-old widowed white woman had had a known hypertension of 160/100, angina pectoris, and probably myocardial infarctions for fourteen months before admission. Twenty-four hours before admission she developed severe substernal pain with radiation down the left arm and sweating. These disappeared only to recur four hours before admission, and were associated with progressively severe dyspnoea and later with orthopnoea and cyanosis. The patient entered the emergency ward, where her blood pressure was 190/110, pulse 150, and respirations 40. She was cyanotic, foaming at the mouth, the veins were full, and rales were heard to the apices. A diastolic gallop and pulsus alternans were present.

Oxygen, 15 mg. of morphine sulphate intravenously, and a 300-ml. phlebotomy was given. On this treatment respirations were noted to be less laboured. However, about half an hour later the blood pressure fell to 100/80 with disappearance of peripheral pulses and she lapsed into coma. She appeared to be in clinical shock at this time. Thereupon 0.2 mg. of ouabain was given intravenously. The pulse rate dropped from 150 to 120 in 15 minutes and the pulse became strong. The blood pressure rose to 125/80 and she awakened. Half an hour after the administration of ouabain she had transient multi-focal ventricular premature beats, treated successfully with 250 mg. of procaine amide hydrochloride intramuscularly. She gradually recovered. An electrocardiogram showed left ventricular hypertrophy and

an antero-septal infarct of uncertain duration. The sedimentation rate, white blood count, and blood sugar rose early with a fall in all three after the first two weeks, substantiating the clinical impression of myocardial infarction.

Comment.—This patient with shock and pulmonary oedema responded dramatically to digitalization. The dramatic clinical improvement probably cannot be attributed to the fall in heart rate from 150 to 120 because in the absence of mitral stenosis such a rate is seldom critical. The equivocal electrocardiogram is probably caused by the two prior infarctions.

Case 4

A 68-year-old white woman had been having exertional dyspnoea, chest pain, and paroxysmal nocturnal dyspnoea for two months. She was brought to hospital unconscious and slightly cyanotic. The skin was clammy and cool; blood pressure 280/140; pulse rate 130; respiratory rate 32. She had not been digitalized. There were rales to the apices and the veins were full. An electrocardiogram showed an antero-septal infarct and auricular flutter. She was treated with oxygen, 10 mg. of morphine sulphate, and venesection without effect. The blood pressure fell to 120/70 and the typical picture of shock developed. Then 0.125 mg. of ouabain was given intravenously; in 20 minutes she was awake, with clearing of her chest and stabilization of blood pressure at 160/80 and a heart rate of 110. She was discharged four weeks later.

Comment

Herrick (1912), in his classic article on the subject, recommended the routine use of digitalis in myocardial infarction. Within the last 25 years, however, clinicians have been hesitant to use digitalis in myocardial infarction because (1) the tolerance of the experimentally infarcted heart to digitalis is decreased (Travell *et al.*, 1938), and (2) both digitalis and myocardial infarction increase the likelihood of ventricular irritability and arrhythmia, and their effects may be additive in the same patient (Goodman and Gilman, 1941). In 1951 Askey gave digitalis to half of a group of 100 patients with proved myocardial infarction. He failed to show any increased incidence of arrhythmia or sudden death in the digitalis-treated group. In fact, Gilson and Schemm (1950) administered digitalis for its classical contraindication—namely, ventricular tachycardia—with salutary results in four patients.

There appears to be general agreement regarding the use of cardiac glycosides for frank congestive failure complicating cardiac infarction, but whether these agents have any role in treating the shock of cardiac origin is less certain. Goodman and Gilman (1941) take a strong position in opposing its use as follows: "Digitalis is contraindicated during the first few days following an acute coronary thrombosis. The clinical picture is usually one of shock rather than congestive heart failure, and digitalis, by further decreasing cardiac output, may make the patient worse."

Recent haemodynamic studies have contributed much to an understanding of this problem. Clinical shock implies that the blood pressure in the arterial tree is much less than normal. The level of the blood pressure depends on the height of systemic resistance—that is, vasoconstriction or dilatation—and the level of the cardiac output. Either the resistance or the cardiac output is low when there is shock. It is only in a small group of patients that a low systemic resistance is seen. G. Lee (personal communication) has demonstrated in some patients with the severe pain of an infarction that there may occur a marked muscle vasodilatation with a concomitant normal cardiac output and resulting fall in blood pressure. Most patients, however, show vasoconstriction with an increased systemic resistance and a decreased cardiac output (Freis *et al.*, 1952).

The lowered blood pressure indicates either inadequate, although increased, constriction or a greatly depressed cardiac output, out of proportion to homeostatic compensation. This decrease in output is related either directly to the myocardium itself or to poor venous return consequent

upon decreased venomotor and muscle pump activity. This latter is seen in nitrite syncope and spinal anaesthesia. However, this possibility seems less likely because shock often exists in the presence of an elevated venous pressure, and the simple restoration of venous pressure by either position in bed or intravenous infusion is not usually effective. The decreased output, then, is probably the direct result of a decreased myocardial contractility (Corday *et al.*, 1949) with the consequent immediately limited ability of the heart to do work following myocardial infarction. The ultimate response of the heart will, of course, depend on the size of the area of infarction and ischaemia, although small infarcts may in and of themselves initiate shock. The whole pattern is a vicious cycle in that the low perfusion pressure occasioned by the myocardium results in poor coronary inflow, with further myocardial ischaemia and hypodynamic myocardial contraction (Wiggers, 1923).

Why the systemic resistance is not maximally increased is not clearly understood. Whether there is a vasomotor paralysis with poor cerebral flow is not known, but in this regard cardiogenic shock is similar to traumatic shock. The first line of defence, then, is to further increase this systemic resistance and decrease the vascular bed to be perfused. The second line of defence is to increase the stroke work of the heart and hence perfusion pressure and minute output. Here has rested the controversy.

Harrison (1939) was among the first to call the shock of coronary thrombosis forward failure and thus semantically implicate the myocardium itself. Stead and Ebert (1942) reported six cases of myocardial infarction resulting in shock. One patient received ouabain and there was an increase in the blood pressure, although the patient subsequently died. Boyer (1944) stated that the shock and the pulmonary oedema syndromes were simply different stages of the same myocardial insult, and perhaps digitalis should be used in both conditions. Fink *et al.* (1953) described the cases of 10 patients in varying degrees of shock who had received lanatoside C. Their criterion for the use of this agent was an elevated venous pressure, suggesting that in such cases shock was myocardial in origin. In every case, despite the ultimate outcome, the blood pressure rose following digitalis administration while the venous pressure was variably affected. It is noteworthy that three of their patients had nearly normal venous pressure and still showed improvement in arterial blood pressure.

Lee (personal communication) demonstrated the fallacy of accepting normal venous pressure as an index of minimal right ventricular failure in patients with myocardial infarction. Although the venous pressure was normal, the gradient between veins and right atrium had disappeared and the right atrial pressure was higher than normal. Finally, studies by Sarnoff *et al.* (1954) have shown that the production of simple haemorrhagic shock in normal dogs results in elevation of left atrial pressure, while right atrial pressure is normal. These experimental observations fit well with the clinical fact that many patients with myocardial infarction have normal venous pressures, yet show pulmonary congestion first by x-ray examination and finally at necropsy (Friedberg, 1950).

Our own clinical reports support the above-presented evidence. The effect of the cardiac glycosides is not only to improve the stroke output of the heart but to increase its ability to deliver the blood against the increased peripheral resistance. The first patient demonstrated clearly that a normal arterial pressure could be maintained solely by digitalis. The second patient demonstrated that increased blood pressure could be delivered by the heart when digitalized optimally, and that this could be done without the production of pulmonary oedema. Similarly, shock was averted solely by the use of ouabain in two patients who had the combination of shock and pulmonary oedema. It is particularly noteworthy that all four patients had been in coma as well as shock; two received vasopressors without effect, yet came out of coma without change in blood pressure following cardiac glycoside, and one patient no longer

had pulmonary oedema yet maintained an increased arterial pressure. This suggested that cerebral and coronary blood flows were probably increased.

This is not to propose the standard use of the cardiac glycosides in myocardial infarction, but rather to re-emphasize that so-called cardiogenic shock is a manifestation of forward failure. Clinical methods of defining failure of the left ventricle are poor, and the right ventricle seldom manifests gross failure early in acute myocardial infarction. Finally, patients not previously in failure and with normal blood volumes may not develop massive right-sided congestion. Because overt evidence of failure is frequently absent, therapy in this type of shock is seldom aimed at the heart itself.

It is recommended that an orderly therapeutic problem might include the following: (1) morphine sulphate for pain; (2) position in bed for its effect on blood pressure and venous return; (3) phlebotomy for elevated venous pressure; (4) vasoconstrictor agents for increasing systemic resistance and arterial pressure; and (5) cardiac glycosides for increasing stroke work and with it cardiac output and arterial pressure. Each should be tried in additive succession—realizing the physiological contribution of each agent—that is, how digitalis may support the pressor response to phenylephrine hydrochloride as in Case 2. Digitalis is still a potentially dangerous drug and should be used only when the indications are clear cut. The dose is important in avoiding acute toxicity. We achieved therapeutic responses with 25–50% of the generally accepted effective dose of ouabain (Friedberg, 1950). The first patient may have died in a fashion temporally related to digitalis intoxication, and the third patient developed premature bigeminal beats thirty minutes after a remarkable therapeutic effect had been achieved. We recommend small doses of intravenous glycoside. Ouabain has not been a dangerous agent in our hands because we have used 0.05, 0.1, or 0.2 mg. as initial doses instead of the recommended 0.5 mg., and similar aliquots of other intravenous preparations.

Conclusions

Four patients, one in clinical shock and three with shock and pulmonary oedema, were treated primarily with a cardiac glycoside intravenously in small doses. All four patients showed remarkable clinical response, with a rise in blood pressure, decrease in pulmonary oedema, and dramatic clearing of coma. Three of the four ultimately survived. It is re-emphasized that the shock of myocardial infarction represents true myocardial failure and that the use of digitalis may be highly efficacious. When given, digitalis should be administered in doses fractionally 25–50% of the initial dose given to the average cardiac patient. In so doing many of the toxic complications may be avoided.

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