1. Axelrod, A. E., Pruzansky, J., *Vitamins and Hormones,* 1955, v13, 1.

2. Kolmer, J. A., in *Modern Nutrition in Health and Disease,* 1st ed., Lea & Febiger, 1955, p498.

3. Axelrod, A. E., *ibid.,* 2nd ed., Lea & Febiger, 1960, p550.

4. Axelrod, A. E., Hopper, S. J., *J. Nutrition,* 1960, v72, 325.

5. Axelrod, A. E., Hopper, S. J., Long, D. A., *ibid.,* 1961, v74, 61.

6. National Research Council, Nutrient Requirements of Poultry, 1960.

7. Stoerk, H. C., Eisen, H. N., PROC. SOC. EXP. BIOL. AND MED., 1946, v62, 88.

8. Stoerk, H. C., Eisen, H. N., John, H. M., *J. Exp. Med.,* 1947, v85, 365.

9. Merchant, I. A., Packer, R. A., Brown, L. N., *Laboratory Manual for Veterinary Bacteriology,* 1961, Burgess Pub. Co., p59.

10. Underdahl, N. R., Young, G. A., *Virology,* 1956, v2, 415.

11. Lassen, H. C. A., *J. Hyg.,* 1930, v30, 300.

12. Osborn, T. W., *Biochem. J.,* 1932, v25, 2137.

13. Ludovici, P. P., Axelrod, A. E., PROC. SOC. EXP. BIOL. AND MED., 1951, v77, 526.

14. Harmon, B. G., Miller, E. R., Ullery, D. E., Hoefer, J. A., *J. Animal Sci.,* 1960, v19, 1265.

15. Hodges, R. E., Bean, W. B., *Am. J. Clin. Nutrition,* 1961, v9, 244.

16. Wayne, L., Will, J. J., Friedman, B. I., Becker, L. S., Vilter, R. W., *Arch. Int. Med.,* 1958, v101, 143.

17. Ludovici, P. P., Axelrod, A. E., Carter, B. B., Pannel, J., PROC. SOC. EXP. BIOL. AND MED., 1949, v72, 81.

18. Wretman, K., Crisley, F. D., Sarandria, J. L., *ibid.,* 1952, v80, 404.

19. Beaver, D. L., *Am. J. Pathol.,* 1961, v38, 335.

20. Sadler, C. R., Glick, B., *Poultry Sci.,* 1961, v40, 508.

21. Muller, A. P., Wolfe, H. R., Meyer, R. K., *J. Immunol.,* 1960, v85, 172.

22. Papermaster, B. W., Friedman, D. F., Good, R. A., PROC. SOC. EXP. BIOL. AND MED., 1962, v110, 62.

23. Burnet, M., *Scientific Am.,* Nov., 1962, 50.

Received March 20, 1963. P.S.E.B.M., 1963, v113.

Time Factor in Reversibility of Myocardial Metabolic Changes in Hemorrhagic Shock.* (28419)

DONALD B. HACKEL and RUDIGER BREITENECKER
(With the technical assistance of Eileen Mikat)
Department of Pathology, Duke University Medical Center, Durham, N. C.

Myocardial failure may play an important role in the terminal cardiovascular collapse that occurs in hemorrhagic shock(1). This could be partly due to the lowered coronary perfusion pressure, which limits coronary flow response. It has also been shown that there is an abnormal pattern of myocardial metabolism in shock(2,3). Although previous studies have shown that transfusion may partly reverse this abnormal metabolic position of the heart(3,4), no attempts have been made to identify the relation of this reversibility to the duration of experimental shock. The present studies were designed with this problem in mind, and the response of the heart to transfusion was tested in dogs subjected to shock of varying durations.

Methods. The studies were carried out on 18 normal mongrel dogs. They were given morphine sulfate (3 mg/kg subcutaneously) followed by a 50/50 mixture of Nembutal, and dial-urethane† (0.25 cc/kg intravenously). Intravenous heparin was given (5 mg/kg) as well as an intramuscular injection of 100,000 units of penicillin and 0.25 g of streptomycin. A catheter was inserted through the jugular vein and maneuvered into the coronary sinus with fluoroscopic visualization, and a polyethylene tube was inserted into the thoracic aorta by way of a femoral artery. Blood samples were drawn simultaneously from each catheter, and analyzed for oxygen, carbon dioxide, lactate, and pyruvate by methods previously described(2).

* This work was supported by a research grant from U. S. Public Health Service.

† The dial-urethane was generously supplied by Ciba Pharmaceutical Co., Summit, N. J.

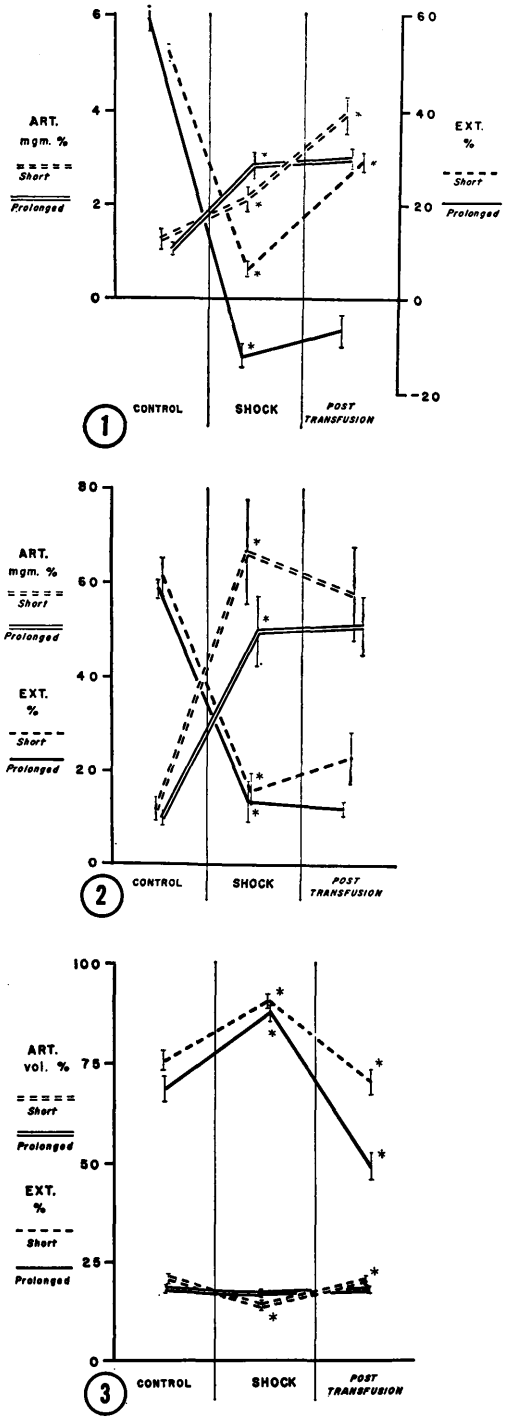

FIG. 1. Arterial level and % extraction (A-V/A) by the myocardium of *pyruvate*; mean values, with standard error of mean represented by vertical bars. * Indicates a statistically significant change ($p < .01$) from the immediately preceding experimental period, means being compared by Student "t" test. For example, the mean % extraction of pyruvate in shock of both short and long duration is significantly decreased from control period; when post-transfusion values are compared with shock values, there is seen a significant increase in short duration shock, but not in prolonged shock.

FIG. 2. Arterial level and % extraction (A-V/A) by the myocardium of *lactate*; markings same as in Fig. 1.

FIG. 3. Arterial level and % extraction (A-V/A) by the myocardium of *oxygen*; markings same as in Fig. 1.

Measurements were made and blood samples drawn in each dog during an initial control period. The animal was then bled from a femoral artery into a reservoir which was arranged so that the mean arterial blood presture fell to approximately 32 mm of mercury within 15 minutes. This pressure level was maintained constant by permitting free interchange of blood between the reservoir and the dog. Seven of the dogs were kept at this level of shock for 1 or 1¼ hours (Group A) and the other eleven dogs were kept in shock for 3 to 3¼ hours (Group B). At the end of the prescribed period blood samples were again drawn, and the reservoir blood was returned to the animal. Five minutes after the end of the blood infusion, the third set of blood samples was drawn.

Results. In the Group A dogs (shock of short duration) the mean systemic blood pressure fell from an initial control value of 111.9±3.4 (standard error of mean), to 31.0±0.8 during shock, and increased to 96.4±4.3 mm of mercury after transfusion. Corresponding values in the Group B animals (prolonged shock) were 106.0±4.2, 33.9±0.4, and 75.5±4.5 mm of mercury.

Fig. 1 through 3 indicate the metabolic findings in the 2 groups at the different experimental periods. As has been previously observed(2) there was a markedly decreased coronary arteriovenous difference of pyruvate during shock, so that the % extraction of pyruvate (arteriovenous difference/arterial level) was close to 0 in the Group A dogs, and was actually a negative mean value in the Group B dogs (Fig. 1). Infusion of the shed blood in Group A resulted in a significant increase in the % extraction of pyruvate, bringing it back toward normal. When blood was returned to the Group B dogs,

TABLE I. Statistical Analysis of Mean Change from One Experimental Period to Another, Comparing Shock of Short Duration (Group A) with Prolonged Shock (Group B).

			Change from: Control–Shock	Shock–Transf.	Control–Transf.
Pyruvate	Art. mg %	Short duration	.87	1.66	2.53
		Prolonged	1.79	.36	2.15
		p	<.01	N.S.	N.S.
	% ext.	Short duration	−45.9	24.9	−21.0
		Prolonged	−72.3	6.0	−66.4
		p	<.01	<.05	<.01
Lactate	Art. mg %	Short duration	52.8	−7.4	45.4
		Prolonged	41.8	1.2	43.0
		p	N.S.	<.05	N.S.
	% ext.	Short duration	−35.5	10.0	−25.5
		Prolonged	−36.8	−1.6	−38.4
		p	N.S.	<.05	<.05
Oxygen	Art. vol %	Short duration	−3.7	3.7	0
		Prolonged	− .2	1.5	1.3
		p	<.01	<.02	N.S.
	% ext.	Short duration	15.2	−19.8	− 4.6
		Prolonged	16.5	−37.1	−20.0
		p	N.S.	<.01	<.02

Abbreviations: Art. = systemic arterial level; p = the probability that the observed differences between group with shock of short duration and group with prolonged shock could be due to chance; N.S. = difference not significant. Student "t" test used to determine the significance of the difference between the two groups.

however, there was no significant change in the % extraction of pyruvate, and the concentration of pyruvate remained higher in the coronary sinus than in the arterial blood. These findings are presented in a somewhat different manner in Table I, in which the changes from one period to the next in Group A are compared to the changes in Group B. It is seen that the Group B dogs had a significantly greater decrease in percent extraction of pyruvate between control and shock periods than did the Group A dogs. When the change from the shock period to that following transfusion is analyzed, it is further seen that the mean increase in % extraction of pyruvate in Group A was significantly greater than that of Group B.

The alterations in lactate (Fig. 2) were similar in general to those for pyruvate. Despite markedly increased arterial blood lactate levels, the % extraction of lactate was markedly decreased in shock. The mean level for the % extraction of lactate after transfusion was 25.6±5.3% in Group A which was not significantly different from the shock level of 15.6±3.4%. However, when the figures for the change between the shock and post-transfusion periods are compared (Table I) a significant difference (p less than .05) is seen to exist between the two groups.

The % extraction of oxygen was significantly increased during the period of shock in both groups of dogs (Fig. 3). Reinfusion of the reservoir blood resulted in a return of this factor to the control range in Group A. In contrast, infusion of blood in the dogs after prolonged shock (Group B) resulted in a marked decrease in the % extraction of oxygen to a level significantly below the control group. The decrease in % extraction of oxygen following blood transfusion was significantly greater in Group B than in Group A in either the shock-transfusion or control-transfusion periods (Table I).

Discussion. There is a striking difference in the manner in which the Group A dogs (shock of short duration) respond to transfusion as compared to Group B (prolonged shock). This is best seen in the ability of the Group A dogs to develop a significant increase after transfusion in the % extraction of pyruvate and lactate, so that the low values that exist in shock are raised toward normal. In the Group B dogs, however, there

is no significant change in the % extraction of pyruvate and lactate following transfusion and the pyruvate values actually remain negative.

It has been previously suggested that the abnormal myocardial metabolic findings in hemorrhagic shock may be the result of a block or decrease in myocardial enzymes (2,3). The present studies can be interpreted to mean that if shock is prolonged beyond a certain limit, this enzyme abnormality becomes irreversible. This corresponds well with the observation that if hemorrhagic shock is maintained at about 30 mm mercury for over 1½ hours, the dogs stop bleeding into the reservoir and there is a gradual return of reservoir blood to the experimental animals. It has been shown that beyond this point at which blood begins to return to the animal, there is a shift from a high to a low % survival(1,5).

The marked increase in the % extraction of oxygen during shock in both experimental groups (Fig. 3) confirms previous observations from this(2) and other(6) laboratories. It indicates that, despite decreased coronary vascular resistance and decreased cardiac work in shock, there is a relative inadequacy in the supply of blood to the heart. The return of the % extraction of oxygen to the normal range in the Group A dogs fits with the similar reversal toward normal in lactate and pyruvate metabolism, and suggests that a normal metabolic pattern has been restored. In the Group B dogs, however, infusion of the shed blood results in a marked decrease in the % extraction of oxygen to a level significantly below the control level. This may be a reflection of the same abnormal enzyme systems that have resulted in the irreversible changes in pyruvate and lactate extraction in these dogs. An explanation of this effect may be derived by considering the hemodynamic conditions during this period of normovolemic shock. Cardiac output and blood pressure are elevated following the blood infusion; at the same time coronary blood flow is increased out of proportion to this increased work load(7). Previous studies of dogs in acute thiamin deficiency(8) revealed a similar dependency of % O_2 extraction on rate of coronary blood flow, so that in dogs with acute thiamin deficiency there was an indirect relation between flow and % O_2 extraction, with low % extractions at high rates of flow. In contrast, in a series of normal control dogs the % O_2 extraction bore no relation to coronary blood flow within a normal range of variation in flow.

Summary. 1. The abnormal changes that occur in the % extraction of pyruvate and lactate by the heart in shock are returned to normal if a blood transfusion is given within 1 to 1¼ hours of onset of shock. If the shock period is prolonged to 3 or more hours, the changes are irreversible to transfusion. 2. The % extraction of O_2 by the heart, which is markedly elevated in hemorrhagic shock, is returned to normal after an infusion of blood given following 1 to 1¼ hours of shock. In contrast, if transfusion is given after more prolonged shock, the myocardial % extraction of O_2 is depressed to abnormally low levels. It is suggested that this may be a reflection of depleted or abnormal myocardial enzyme systems after prolonged shock. 3. These findings support other biochemical, physiological, and pathological observations which point to irreversible myocardial damage as an important factor in the irreversibility of prolonged shock.

1. Crowell, J. W., Guyton, A. C., *Am. J. Physiol.*, 1961, v201, 893.

2. Hackel, D. B., Goodale, W. T., *Circulation,* 1955, v11, 628.

3. Edwards, W. S., Siegal, A., Bing, R. J., *J. Clin. Invest.*, 1954, v33, 1646.

4. Hackel, D. B., PROC. SOC. EXP. BIOL. AND MED., 1960, v103, 780.

5. Frank, H., Seligman, A., Fine, J., *J. Clin. Invest.*, 1945, v24, 435.

6. Horvath, S. M., Farrand, E. A., Hutt, B. K., *Am. J. Cardiol.*, 1958, v2, 357.

7. Opdyke, D. F., Foreman, R. C., *Am. J. Physiol.*, 1947, v148, 726.

8. Hackel, D. B., Goodale, W. T., Kleinerman, J., *Am. Heart J.*, 1953, v46, 883.

Received March 27, 1963. P.S.E.B.M., 1963, v113.