References and Notes

1. M. M. Elkind and H. Sutton, *Nature* **184**, 1293 (1959); ———, *Radiation Res.* **13**, 556 (1960).
2. R. Z. Lockart, M. M. Elkind, W. B. Moses, *J. Natl. Cancer Inst.* **27**, 1393 (1961); G. W. Barendsen, *Nature* **193**, 1153 (1962).
3. S. Hornsey and G. Silini, *Radiation Res.* **16**, 712 (1962); J. E. Till and E. A. McCulloch, *ibid.* **18**, 96 (1963).
4. M. M. Elkind, *Brookhaven Symp. Biol.* **14** (**1961**), 220 (1961); E. J. Hall and L. G. Lajtha, *Radiation Res.* **20**, 187 (1963).
5. Our temperature studies were first reported at the 11th annual meeting of the Radiation Research Society; M. M. Elkind and T. Alescio, *Radiation Res.* **19**, 216 (1963).
6. M. M. Elkind, A. Han, K. W. Volz, *J. Natl. Cancer Inst.* **30**, 705 (1963).
7. M. M. Elkind, H. Sutton, W. B. Moses, *J. Cell. Comp. Physiol.*, Suppl. 1, **58**, 113 (1961).
8. T. Alper, N. E. Gillies, M. M. Elkind, *Nature* **186**, 1062 (1960). We denote the extrapolation number by $\bar{n}$ instead of n to avoid implying the target number in multi-target, single-hit inactivation. See also W. C. Mohler and M. M. Elkind, *Exptl. Cell Res.* **30**, 481 (1963).
9. T. Alper, J. F. Fowler, D. D. Vonberg, F. Ellis, R. Oliver, *Brit. J. Radiol.* **35**, 722 (1962).
10. W. K. Sinclair and R. Morton, *Nature* **199**, 1158 (1963); T. Terasima and L. J. Tolmach, *Biophys. J.* **3**, 11 (1963).
11. E. Reich, R. M. Franklin, A. J. Shatkin, E. L. Tatum, *Proc. Natl. Acad. Sci. U.S.* **48**, 1238 (1962); J. Hurwitz, J. J. Furth, M. Malamy, M. Alexander, *ibid.*, p. 1222; C. Levinthal, A. Keyman, A. Higa, *ibid.*, p. 1631; I. H. Goldberg, M. Rabinowitz, E. Reich, *ibid.*, p. 2094; B. Mach and E. L. Tatum, *Science* **139**, 1051 (1963); I. H. Goldberg and M. Rabinowitz, *ibid.* **136**, 315 (1962).
12. R. E. Bases, *Cancer Res.* **19**, 1223 (1959).
13. M. M. Elkind, *Radiology* **74**, 529 (1960).

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Excess Lactate: An Index of Reversibility of Shock in Human Patients

Abstract. *"Excess lactate," an indicator of oxygen debt, has been studied as a metabolic index of severity of the shock state in human patients. The levels of excess lactate correspond to severity of circulatory failure, and an excess of more than 4 millimoles per liter prognosticates a fatal outcome. The validity of this index was confirmed by studies on experimental hemorrhagic shock in dogs. It provides a parameter for measurement of "reversibility" and serves as an objective clinical guide.*

The fundamental defect in shock is failure of effective blood flow, and hence defective transport of vital nutrients (*1*). Functional impairment of cellular metabolism is followed by permanent cellular damage. Since the availability and delivery of oxygen are critical, the severity of oxygen deprivation and differential sensitivity of tissues to this lack are immediate determinants of survival.

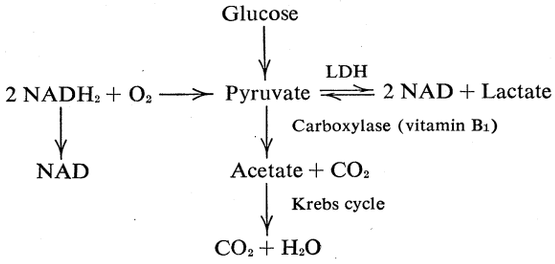

Fig. 1.

During periods in which metabolism is sustained by anoxic energy exchange, the metabolic fate of pyruvic acid is temporarily altered. Aerobic oxidation in the tricarboxylic acid cycle is blocked and pyruvic acid is converted to lactic acid. Nicotinamide-adenine dinucleotide ($NADH_2$) provides for this electron exchange. The transformation of $NADH_2$ to NAD during the conversion of pyruvic to lactic acid allows glycolysis to proceed without obligatory rejuvenation of $NADH_2$ by oxygen, according to the process shown in Fig. 1, where LDH is lactic dehydrogenase. The oxidation of $NADH_2$ may be blocked by cyanide or anoxia, for example. The accumulation of lactic acid accounts, in part, for the progressive acidosis of shock.

Increase in blood lactic acid concentrations is a feature not only of circulatory anoxia but also of ventilatory anoxia. Sometimes a profound lack of circulating hemoglobin or an enzymatic block (as in cyanide intoxication) reflect a defect in chemical transfer of oxygen but do not, in themselves, reflect hypoxia. During hyperventilation, infusion of glucose, or adrenal medullary stimulation, there is an increase in both blood lactate and pyruvate but no selective increase in lactic acid content. A series of studies on the relationship of blood lactic acid concentrations and oxygen deficiency have been made by Huckabee (*2*). He relates oxygen debt to an excess of lactate (XL), defined as

$$XL = (L_T - Lo) - (P_T - Po)\frac{Lo}{Po}$$

where L_T is lactate at time T, Lo is the "normal" lactate during the basal state, P_T is pyruvate at time T, and Po is the "normal" pyruvate during the basal state. Inherent in this assumption is a predictable increase in lactate with increase in pyruvate. Huckabee has provided theoretical and empirical justification for this formulation.

Several workers have recently provided theoretical objections to the derivation of the excess lactate measurement and empirical objections to excess lactate as a precise measure of oxygen debt (*3*). In our own work we have not measured oxygen debt because of the technical difficulties inherent in making such measurements in patients who are in shock. Thus we neither support nor refute the concept that excess lactate is a valuable index of oxygen debt. However, the empirical observations which are the subject of this report indicate the potential prognostic value of this index for patients who are in shock.

The role of oxygen debt as a limiting factor to survival in dogs has been defined by Guyton and Crowell (*4*), based on measurements of oxygen consumption prior to, during, and after hemorrhagic shock. They found a very close relationship between oxygen debt and severity of shock as reflected in mortality. We have made similar observations in dogs shocked with endotoxin (*5*). Techniques available for measuring oxygen debt in human patients are not sufficiently sensitive. However, the availability of a metabolic index for estimating oxygen debt has four advantages: (i) It has high sensitivity; (ii) it provides a guide to the cumulative oxygen debt; (iii) the laboratory determination has satisfactory chemical precision; and (iv) the test is easily adapted for routine use with the facilities available in general hospital laboratories.

In the study reported here, the excess lactate was measured serially in 56 patients with clinical signs of circulatory failure. Measurements were made at approximately 8-hour intervals during observation, which continued from admission to recovery or death. Only patients who survived 4 hours or more were included. Patients were observed for an average period of 36 hours, but occasionally for as long as 5 days. The highest value obtained is reported here since it is regarded as most descriptive of the largest oxygen debt measured. The patients were studied in the Shock

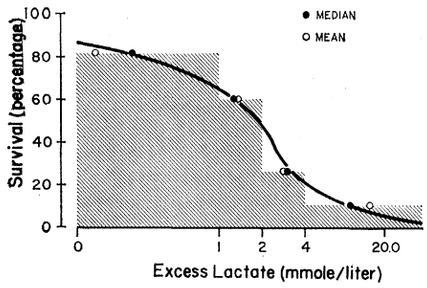

Fig. 2. The relation between excess lactate and survival of patients in shock.

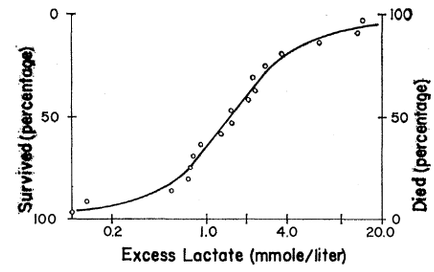

Fig. 3. Excess lactate related to the probability of survival of patients in shock.

Research Unit of the Los Angeles County Hospital where arterial pressure, superior vena cava or right arterial pressure, cardiac output, *p*H, pCO_2, pO_2, blood volume, and other physiological parameters were continuously monitored while intensive therapy was administered.

The causes for shock were classified as follows: hypovolemia, 17 patients; septicemia, 9; cardiac failure, 7; neural dysfunction and endocrine deficiencies, 4; vascular obstruction to flow, 2; mixed causes, 9; and unclassified, 8. Included in the unclassified group were three patients who had significantly reduced oxygen saturation of arterial blood, ranging from 73 to 90 percent, because of complicating pulmonary disease; in the remaining patients arterial oxygen saturation exceeded 90 percent. Arterial blood samples were obtained from the brachial artery into which a catheter had been inserted (*6*). The blood sample was collected and immediately deproteinized in chilled, previously weighed test tubes containing 10 percent trichloroacetic acid. Blood lactate was measured by the method of Barker and Summerson (*7*), and blood pyruvate by the method of Friedemann and Haugen (*8*). A Beckman DU spectrophotometer or a Bausch and Lomb model H spectrophotometer was used. Normal values for arterial blood lactate and pyruvate were established in 11 hospitalized convalescent patients free of anemia, cardio-respiratory pathology, or metabolic disorders. The values in these normal subjects were 0.732 mmole/lit. (S.E. ± 0.356 S.E.M. ± 0.107) for lactate, and 0.180 mmole/lit. (S.E. ± 0.061 S.E.M. ± 0.019) for pyruvate.

Eighty-two percent of the patients in whom excess lactate was 1 mmole/lit. or less survived (Fig. 2). Death in each of the patients was due to late sequelae of the primary disease and not due to shock. In patients in whom the amount of excess lactate was elevated to 2 mmole/lit. survival decreased to 60 percent. When the excess lactate ranged between 2 and 4 mmole/lit., only 26 percent survived. Three of 27 patients who were in shock and in whom excess lactate exceeded 4 mmole/lit. survived. Each of the three patients in the unclassified group with arterial hypoxemia died. The expected mortality was calculated according to standard probid techniques. It was based on 18 survivors in the transition group between patients with excess lactate of over 14 mmole/lit. (all of whom died), and the group of patients with excess lactate less than 0.2 mmole/lit. (all of whom lived). When excess lactate was plotted as an exponential function, a typical S-shaped distribution was observed (Fig. 3) which demonstrated the value of excess lactate as an index of prognosis in patients during shock.

The direction of change in excess lactate was of limited prognostic value. The prompt reduction of excess lactate after mild or moderate elevation prognosticated a favorable outcome. However, if at any time excess lactate was above 4 mmole/lit., the usually fatal outcome was not altered even by promptly reducing it.

The presence of excess lactate during controlled conditions in which shock was experimentally induced by hemorrhage was also studied. Raw data on blood lactate and blood pyruvate were abstracted from published investigations on hemorrhagic shock in dogs and related to mortality (Table 1). In studies by Hackel and Goodale on reversible hemorrhagic shock (*9*), the highest excess lactate obtained was 2.02 mmole/lit., but in shock refractory to transfusion the excess lactate was increased to 5.40 mmole/lit. In two dogs studied by Seligman and his coworkers, after standardized "irreversible" hemorrhagic shock, one had an excess lactate of 6.1 mmole/lit. and the other 3.6 mmole/lit. (*10*). In studies by Beatty (*11*) the animals that recovered had an average excess lactate of 1.55 mmole/lit., but when shock was fatal the excess lactate averaged 8.83 mmole/lit.

The only studies of excess lactate in human patients with circulatory failure have been those in which heart and lung by-pass has been used in cardiac surgery, sometimes in combination with hypothermia (*12*). In two studies with a total of 13 patients, Ballinger *et al.* (*12*, *13*) found that when the maximum arterial excess lactate was below 3 mmole/lit., as was the case in eight of the patients, there were no fatalities. When the excess lactate level was above 3 mmole/lit. three patients died and two survived. Hypothermia was used in a majority of the patients and the possibility that this was an important complicating condition is not excluded.

The relationship of the lactacidemia found in circulatory failure (*14*) to an idiopathic condition not accompanied by hypotension (*15*) and clinical signs of shock is now under intensive study.

Table 1. Calculations from published data on the lactic acid (L), pyruvic acid (P), and excess lactate (XL) content of blood (millimoles per liter) of dogs in hemorrhagic shock.

Controls				Survived				Died			
No. of dogs	L	P	XL	No. of dogs	L	P	XL	No. of dogs	L	P	XL
				Hackel and Goodale (9)							
12	1.24	0.182	0	3	4.22	0.322	2.02	9	8.36	0.434	5.40
				Seligman et al. (10)							
1	1.59	1.48	0					1	12.1	0.558	6.1
1	2.11	0.204	0					1	8.33	.455	3.62
				Beatty (11)							
2	1.30	0.193	0	2	1.70	0.273	0				
5	1.17	.17	0	5	4.68	.454	1.55				
20	1.45	.216	0					5	12.95	0.534	8.83

Severe acidosis is the rule in primary lactacidemia, but we have observed milder, compensated acidosis in patients with hypotension. Attempts to improve the supply of oxygen by increasing the dissolved oxygen content of blood by use of hyperbaric chambers has been studied experimentally and clinically. In one report (*16*) this form of treatment seems to have had a favorable effect on mortality in experimental hemorrhagic shock in dogs. Methylene blue has had favorable effects in primary lactacidemia (*17*), but no reduction in excess lactate has been shown during shock.

In the work reported here arterial blood was sampled because of the possibility that local influences more directly affecting venous blood might alter the excess lactate as a reflection of oxygen debt. This would be particularly so in patients in shock and in whom peripheral blood flow is selectively impaired. However, the possibility clearly exists that venous blood might be satisfactory. Because of the particular advantage of venous blood for simple clinical tests, the adequacy of the venous sample will be more thoroughly investigated. The applicability of these findings to treatment will be of interest. Oxygen lack is most likely the primary injurious factor in shock, and effective treatment involves prevention of, or prompt repayment of, the oxygen debt. Based on our studies, excess lactate of 1 mmole/lit. or below is a safe level. When excess lactate is increased to 2 to 4 mmole/lit. it is in a twilight zone with regard to survival. If the excess lactate during shock is above 4 mmole/lit., prognosis is grave and circulatory anoxia will probably lead to irreversible change.

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References and Notes

1. J. E. Rhoads, *Federation Proc.* **20**, Suppl. 9, 235 (1961).
2. W. E. Huckabee, *J. Clin. Invest.* **37**, 244 (1958); *ibid.*, pp. 255, 264.
3. P. Harris, M. Bateman, J. Gloster, *Clin. Sci.* **23**, 531 (1962); H. G. Knutkin, *J. Appl. Physiol.* **17**, 639 (1962); R. E. Olson, *Ann. Internal Med.* **59**, 960 (1963).
4. A. C. Guyton and J. W. Crowell, *Federation Proc.* **20**, Suppl. 9, 51 (1961).
5. M. H. Weil, in preparation.
6. V. N. Udhoji, M. H. Weil, M. P. Sambhi, L. Rosoff, *Am. J. Med.* **34**, 461 (1963).
7. S. B. Barker and W. H. Summerson, *J. Biol. Chem.* **138**, 535 (1941).
8. T. E. Friedemann and G. E. Haugen, *ibid.* **147**, 415 (1943).
9. D. B. Hackel and W. T. Goodale, *Circulation* **11**, 628 (1955).
10. A. M. Seligman, H. A. Frank, B. Alexander, J. Fine, *J. Clin. Invest.* **26**, 535 (1947).
11. C. H. Beatty, *Am. J. Physiol.* **143**, 579 (1945).
12. W. F. Ballinger, II, H. Vollenweider, L. Pierucci, Jr., J. Y. Templeton, III, *Surgery* **51**, 738 (1962).
13. ———, *Ann. Surg.* **153**, 499 (1961).
14. M. H. Weil and G. Broder, in preparation.
15. W. E. Huckabee, *Am. J. Med.* **30**, 840 (1961).
16. S. Attar, W. G. Esmond, R. A. Cowley, *J. Thorac. Cardiovasc. Surg.* **44**, 759 (1962).
17. R. E. Tranquada, S. Bernstein, W. J. Grant, *Clin. Res.* **11**, 230 (1963).
18. Supported by U.S. Public Health Service research grant H-5570 from the National Heart Institute and by the John A. Hartford Foundation, Inc., New York. We gratefully acknowledge the statistical collaboration of Frank B. Cramer.

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Defense of Mate and Mating Chamber in a Wood Roach

Abstract. *Studies of the eastern wood roach,* Cryptocercus punctulatus, *reveal that, under laboratory conditions, the mating chambers in rotten wood are inhabited by mated pairs, the male of which will usually defend the chamber successfully against intruding males by a form of fighting. In every staged contest in which the intruder won the fight, it also won the resident female. Females, as well as unmated males singly inhabiting a chamber, could not be induced to defend against an intruder of either sex.*

Living individuals of the eastern wood roach (*Cryptocercus punctulatus*), which are maintained for study of the well-known mutualistic protozoa that inhabit their hind-gut, have incidentally shown an interesting pattern of combative "territorial" behavior. This behavior, as seen under laboratory conditions simulating the natural rotten-log habitat, takes place in narrow "mating chambers" and the adjacent connecting galleries constructed by the roaches in the rotten wood. Each of the chambers normally contains a single mated pair of roaches, and unmated males placed in their vicinity may or may not attempt to enter a chamber. An invading male is usually engaged in combat by the resident male, which attempts to eject its rival from the chamber and its approaches.

Initial contests were watched rather casually, without checking sexes by definitive examination, but a comparison with later experiments in which marked individuals of determined sex were used makes it reasonably clear that the males do all the fighting. A common type of encounter is exemplified by the following account of an early observation, the sexes being assumed from the context: An unpaired male entered one of the occupied mating chambers. Almost immediately this individual and the resident pair evacuated the chamber by the opposite gallery opening. The female then quickly returned to the mating chamber, but the resident and intruding males began a contest lasting about 10 minutes. Head-on butting by pronotum contact became vigorous as each individual blocked advance of the other attempting to gain side access. Butting continued within the limited space just outside the mating chamber as both individuals turned first one way and then the other. Later, one of the two roaches gained advantage by quick approach to the side of the other which was then deftly pushed over onto its back. The overturned roach righted itself after considerable struggle, during which it received numerous leg bites from the other roach. These events were repeated twice with the balance of force favoring the same individual in each attack. The scramble continued until the "weaker" roach was forced into a position of retreat, which happened to be one end of the mating chamber. There it held forth facing its opponent for approximately 5 minutes. The opponent was blocked from entrance in spite of persistent butting and pushing. The blocker finally gave way in further retreat, forcing the female out of the opposite end of the mating chamber. The blocker exited in reverse, and the opponent followed. Pushing continued until both roaches ended the struggle behind a piece of wood adjacent to the mating chamber. There the roach which had fared badly all along remained. It was seen several hours later grooming its appendages. The "victor" returned to the mating chamber to join the unchallenged occupant which had moved back in as before when the opening was clear of the battling pair.

To obtain more systematic results, I used freshly collected mating pairs from Mountain Lake, Virginia. Insects were transported to the laboratory, each in its original mating chamber cut whole out of the rotten log during collection, and placed in a special plastic chamber filled with rotten bits of wood. An alternate mating chamber constructed by another pair not to be involved in the experiment was included. Each