

# RELATIONSHIPS OF PYRUVATE AND LACTATE DURING ANAEROBIC METABOLISM. III. EFFECT OF BREATHING LOW-OXYGEN GASES<sup>1</sup>

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When the oxygen supply to tissues is impaired progressively, as in continuous reduction of the oxygen content of alveolar air, oxygen tensions in various other parts of the gas transport system proceed to fall progressively also. At some stage in the course of this unbroken continuum a state of "hypoxia" presumably may be said to exist. It is, in any event, a useful concept to suppose that it does, inasmuch as symptoms and dysfunction of organs may appear in the course of diseases of the oxygen transport systems which might be accounted for by hypoxia.

If hypoxia is induced by all diminutions of alveolar  $P_{O_2}$ , then this condition may exist with arterial blood saturations reduced by an unmeasurable amount and arterial oxygen contents which are normal or above normal. It seems unprofitable to apply the term in this way because there is no reason to believe that the body suffers in any sense from deprivation of needed oxygen in this situation. It is also true that hypoxia is not necessarily present even at the stage of this continuum in which arterial oxygen content has become significantly decreased (*i.e.*, hypoxemia), since an increase in blood flow may act to prevent any real diminution in  $P_{O_2}$  in the tissues or venous blood. Finally, even if the term hypoxia be reserved for situations in which tissue  $P_{O_2}$  falls, the implication that the tissues are deprived of oxygen under these circumstances is not consistent with the fact that the rate of oxygen consumption may remain unchanged, *i.e.*, the amount of oxygen delivered to and taken up by the tissues per minute is normal.

In the previous papers of this series (1, 2) it has been proposed that the occurrence of anaerobic metabolism in tissues indicates that the rate of supply of oxygen to the interior of tissue cells has fallen below the rate of energy utilization, *i.e.*, has

fallen below the rate of oxygen requirement. It seemed possible that if this discrepancy between rates of supply and demand in tissues were taken as the proper indication of physiologic hypoxia, a distinct starting point of hypoxia could be identified in the course of progressive pulmonary or circulatory impairment. In the present study, experimental subjects and animals were given various low oxygen gas mixtures to breathe while anaerobic metabolism, as previously defined (1), was estimated at various blood oxygen tensions.

## METHODS

The human subjects were fasting and lay quietly for one to two hour control periods after insertion of a brachial arterial needle. During control determinations of oxygen consumption with air breathing, and during 15 to 30 minute periods breathing prepared gas mixtures, the subjects respired through a rubber mouthpiece and low resistance valve, inhaling from a spirometer or tank demand valve and exhaling into a Douglas bag. All gas mixtures were prepared in pressure tanks and analyzed to determine their exact composition. Oxygen consumption (pulmonary oxygen absorption,  $V_{O_2}$ ), pulmonary ventilation, and arterial blood pH, lactate, pyruvate and oxygen determinations were carried out as previously described (2). Experimental animals were dogs lightly anesthetized with chloralose; the same determinations were carried out as in the human subjects, and, in addition,  $O_2$ -debts were calculated from the curves of continuously measured oxygen consumption.

Gas mixtures employed contained only oxygen and nitrogen. Oxygen contents were 15.05 per cent (15 per cent  $O_2$ ), 12.91 per cent (13 per cent  $O_2$ ), 10.09 per cent (10 per cent  $O_2$ ), and, in dogs, also 7.12 per cent (7 per cent  $O_2$ ), or 7.89 per cent (8 per cent  $O_2$ ), and 5.18 per cent (5 per cent  $O_2$ ).

The quantity of anaerobic metabolism was determined as "excess lactate" (XL) accumulation, calculated as follows (1):

$$XL = (L_n - L_o) - (P_n - P_o) (L_o/P_o)$$

$L_o$  and  $P_o$  are the control arterial blood lactate and pyruvate concentrations in mM per L. of blood water, during air breathing;  $L_n$  and  $P_n$  are the concentrations at

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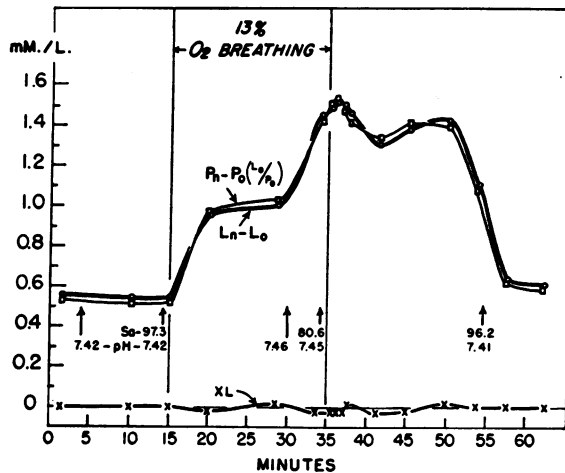


FIG. 1. CHANGES IN ARTERIAL BLOOD LACTATE ( $L_n - L_o$ ) AND PYRUVATE [ $(P_n - P_o) (L_o/P_o)$ ] CONCENTRATIONS, pH AND OXYGEN SATURATION ( $S_a$ ) IN A NORMAL HUMAN SUBJECT (38 YEAR OLD, MALE, 70.4 KG.) DURING THE BREATHING OF 13 PER CENT OXYGEN IN NITROGEN

Calculated "excess lactate" (XL) remained essentially zero.

any other time  $t_n$ , i.e., during the breathing of a low oxygen gas mixture.

#### RESULTS

Figures 1 and 2 illustrate typical experiments in a human subject breathing 13 per cent  $O_2$  and 10 per cent  $O_2$ , respectively, for 20 minute periods. In both experiments arterial blood oxygen saturation ( $S_a$ ) fell, pH rose and blood lactate ( $L_n - L_o$ ) and pyruvate [ $(P_n - P_o) (L_o/P_o)$ ] concentrations rose. During the breathing of 13 per cent  $O_2$ , however, the lactate accumulation was accounted for totally by the rise in pyruvate which occurred during the "hypoxia" since no "excess lactate" (XL) was produced. As shown in Table I this finding was noted in all subjects breathing 15 per cent  $O_2$  and 13 per cent  $O_2$  which, in fact, are very slight reductions of  $F_{IO_2}$  (inspired oxygen concentration). Figure 2, however, with more severe reduction of  $F_{IO_2}$ , illustrates (curve XL) an increasing discrepancy or excess of lactate production over that to be expected from the observed pyruvate change; this excess lactate accumulation or anaerobic metabolism of tissues during 10 per cent  $O_2$  breathing occurred in 10 of 13 experiments as shown in Table I. Arterial oxygen saturations,  $S_a$ , vary in all three groups, pre-

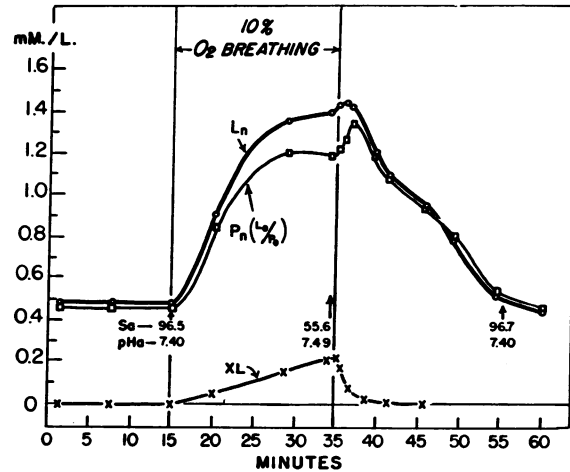


FIG. 2. TYPICAL CHANGES IN ARTERIAL BLOOD LACTATE, PYRUVATE, pH AND OXYGEN SATURATION IN A HUMAN SUBJECT (42 YEAR OLD, MALE, 56.2 KG.) DURING THE BREATHING OF 10 PER CENT OXYGEN IN NITROGEN

The rise in "excess lactate" (XL) distinguishes these results from those obtained with 15 per cent and 13 per cent oxygen.

sumably from the different ventilatory responses to low oxygen. One of the three subjects who failed to show anaerobiosis during 10 per cent  $O_2$  breathing had a relatively small depression of blood oxygen which might account for the lack of anaerobiosis; the other two, however, did not appear to differ significantly from the remainder of the group as regards arterial oxygen. Two of this group, Nos. 6 and 8, were reexamined on another occasion with the same result. Similarly, Subjects 1, 4, 11, and 13 were restudied once or twice and invariably exhibited XL accumulation with 10 per cent  $O_2$ .

The study of graded respiratory hypoxia could be carried much further in animals, as shown in Table II. Dogs showed the same "pseudo-hypoxia" as human subjects when breathing 15 per cent  $O_2$  and 13 per cent  $O_2$ , in that blood oxygen values fell and lactic acidemia appeared. Again, however, no excess lactate was present. On the other hand, the breathing of 7 or 8 per cent  $O_2$  and 5 per cent  $O_2$  uniformly resulted in excess lactate accumulation.

The transition appeared to occur at an inspired oxygen content of 10 per cent; part of the experiments in this group showed XL production and part did not. As in the human subjects, measure-

TABLE I

*Effects in human subjects of breathing gas mixtures of various oxygen concentrations ( $FI_{O_2}$ ) on arterial blood oxygen saturation, blood lactate, pyruvate and calculated "excess lactate" (XL) concentrations, pulmonary minute ventilation ( $\Delta\dot{V}$ ), and arterial blood pH*

$FI_{O_2}$	Sa	$\Delta$ Lactate	$\Delta$ Pyruvate	XL	( $\Delta\dot{V}$ )	pH
%	%	mM/L.	mM/L.	mM/L.	%	
15% 1	86.5	0.265	0.053	0	16.7	+0.03
2	88.9	0.640	0.162	0	20.1	+0.04
3	89.2	0.449	0.082	0	50.1	+0.06
Mean $\pm$ range/2	88.2 $\pm$ 1.4	0.451 $\pm$ 0.188	0.099 $\pm$ 0.040	0	29.0 $\pm$ 16.7	0.04 $\pm$ 0.02
13% 1	83.1	0.340	0.080	0	45.0	+0.05
2	78.4	0.242	0.063	0	32.4	
3	86.7	0.560	0.108	0	25.6	+0.04
4	82.0	0.423	0.085	0	22.1	+0.06
5	80.6	0.964	0.179	0	40.9	+0.03
Mean $\pm\sigma$	82.2 $\pm$ 3.2	0.506 $\pm$ 0.283	0.103 $\pm$ 0.090	0	33.2 $\pm$ 9.76	0.04
10% 1	63.5	0.542	0.118	0.077	67.6	+0.08
2	69.6	2.650	0.405	0.142	56.2	+0.05
3	66.4	1.165	0.220	0	30.6	+0.10
4	67.0	1.264	0.209	0.073	92.9	+0.11
5	55.6	0.964	0.172	0.204	28.6	+0.09
6	80.1	1.433	0.293	0	105.0	
7	50.1	2.681	0.375	0.109	30.2	+0.08
8	70.7	0.967	0.236	0	56.2	+0.10
9	70.4	0.984	0.248	0.064	65.9	
10	72.6	0.699	0.129	0.089	23.4	+0.05
11	65.4	1.070	0.215	0.050	64.5	+0.07
12	71.0	1.223	0.223	0.177	70.8	+0.07
13	65.4	1.571	0.249	0.200	65.0	+0.06
Mean $\pm\sigma$	66.7 $\pm$ 7.6	1.324 $\pm$ 0.656	0.238 $\pm$ 0.083	0.091 $\pm$ 0.072*	58.2 $\pm$ 24.9	0.08 $\pm$ 0.02

\* Physiologically this group of figures probably must be regarded as inhomogeneous, containing at least two, and probably n unrelated populations, so that it is not actually susceptible to description by a mean $\pm\sigma$ .

ments of molecular oxygen did not show any distinguishing features between the two.

Animals under light chloralose anesthesia have usually exhibited about the same ventilatory response to low oxygen gases as unanesthetized animals, although such figures are very variable for any group. Pulmonary ventilation per minute increased by an average of 22 per cent for  $FI_{O_2}$  of 15 per cent and 13 per cent  $O_2$ , 38 per cent for 10 per cent  $O_2$ , and 76 per cent for 8 and 7 per cent  $O_2$ . Average control ventilation was 2,050 ml. per minute per 10 Kg., and recovered to 1,930 ml. per minute per 10 Kg. on returning to air breathing.

Respiratory  $O_2$ -debts were measured in the animals for comparison with XL production as an estimate of the adequacy of oxygen supply rate. Previous comparisons have been made and a close qualitative (1) and quantitative (2) correlation has been found. Figure 3 illustrates the method used for measuring  $O_2$ -debt during respiratory

hypoxia. The heavy line shows the actual curve of continuously measured oxygen uptake, during an experiment with 10 per cent  $O_2$  breathing and no  $O_2$ -debt, and illustrates the desaturation period at the onset of low oxygen breathing (ABC) when an apparent reduction of oxygen utilization occurs until the blood and body fluids reach a new oxygen tension. This dip in the curve is the mirror image of that which occurs on the return to air breathing (DEF). For the calculation of  $O_2$ -debt, therefore, the area ABC is subtracted from such an area as DGH, when it is present, and the true  $O_2$ -debt is indicated by the upper portion. Figure 4 illustrates results obtained in an anesthetized intact dog with spontaneous respiratory control during the breathing of 8 per cent  $O_2$ . The respiratory  $O_2$ -debt curve is included in this figure and shows the marked divergence between blood lactate changes and  $O_2$ -debt, but a close correspondence between XL and the respiratory measurement.

TABLE II  
Effect, in anesthetized dogs, of breathing gases of various oxygen concentrations ( $F_{I_{O_2}}$ )

$F_{I_{O_2}}$		Oxygen debt* ml. $O_2$			Sa	$\Delta pH$
		From $\dot{V}_{O_2}$	From Lactate	From XL		
15%	1	12	25.0	0	74.6	+0.11
	2	0	182.7	0	82.7	+0.08
	3	8	196.1	6.7	76.1	+0.04
	4	0	109.3	4.2	70.4	+0.06
	5	0	299.4	0	85.6	+0.05
	6	14	82.0	0	78.4	+0.04
Mean $\pm\sigma$		5.7 $\pm$ 6.5	149.1 $\pm$ 95	1.8 $\pm$ 5.2	78.0 $\pm$ 5.5	+0.06 $\pm$ 0.03
13%	1	0	388.0	0	73.2	+0.03
	2	0	92.6	0	70.1	+0.09
	3	10	169.8	14.6	69.8	+0.05
	4	11	34.6	8.2	79.0	+0.11
	5	5	494.1	0	78.6	+0.10
Mean $\pm\sigma$		5.2 $\pm$ 5.3	235.8 $\pm$ 219	4.6 $\pm$ 4.4	74.1 $\pm$ 4.5	+0.07 $\pm$ 0.03
10%	1	209	668.4	194.6	64.2	+0.05
	2	186	491.0	159.4	63.4	+0.03
	3	298	740.8	299.9	68.7	+0.06
	4	0	498.4	0	72.5	+0.15
	5	0	299.4	0	79.6	+0.12
	6	99	325.0	58.8	65.4	+0.10
	7	84	347.7	104.2	62.1	+0.11
	8	0	194.6	9.4	69.7	+0.09
	9	110	544.0	112.4	64.6	+0.10
	10	0	262.7	4.1	72.4	+0.08
Mean $\pm\sigma$		98.6†	437.2 $\pm$ 180.4	94.3†	68.3 $\pm$ 5.4	0.09 $\pm$ 0.04
8%	1	255	649.7	240.5	55.6	+0.15
	2	309	674.0	310.6	58.9	+0.12
	3	274	590.3	295.7	57.8	+0.10
	4	426	588.4	410.7	51.4	+0.12
	5	330	620.6	355.0	52.9	+0.13
7%	6	198	349.0	209.4	48.9	+0.09
	7	569	785.0	558.9	53.4	+0.10
	8	504	626.0	505.0	55.0	+0.11
	9	486	594.3	490.7	50.6	+0.09
	10	394	399.4	392.7	48.4	+0.10
Mean $\pm\sigma$		375.5 $\pm$ 121‡	587.7 $\pm$ 127.1	375.9 $\pm$ 116.8‡	53.3 $\pm$ 3.6	0.11 $\pm$ 0.02
5%	1	644	704.9	632.4	47.4	+0.05
	2	695	799.4	680.7	48.9	+0.03
	3	704	857.6	710.8	46.2	+0.09
	4	394	670.4	410.0	47.0	+0.10
Mean $\pm$ range/2		609.2 $\pm$ 155	758.0 $\pm$ 93.6	608.4 $\pm$ 150.4	47.4 $\pm$ 1.4	+0.07 $\pm$ 0.04

\* Total  $O_2$ -debts contracted in the periods studied (30 to 40 minutes) are calculated from the recovery oxygen consumption ratio ( $\dot{V}_{O_2}$ ), from blood lactate changes and from both lactate and pyruvate (XL) for comparison.

† This mean serves only to denote the relative order of magnitude. On physiologic grounds it seems likely that this group is not a single population of figures which can be described by a mean $\pm\sigma$ , but is at least two and probably n unrelated populations. The values of  $\sigma$  are 105 and 100.9, respectively, for  $\dot{V}_{O_2}$  and XL.

‡ Again, as in (†), this variance does not describe the reliability of the value in one individual, which is about 10 per cent for  $O_2$ -debt and less than 5 per cent for XL, but the variability of response between animals.

The same correlation between XL and  $O_2$ -debt found in exercise (2) may also be noted in the 35 experiments in Table II. No  $O_2$ -debt was contracted during 15 per cent or 13 per cent  $O_2$  breathing in any experiment, or in those animals

breathing 10 per cent  $O_2$  in which no XL accumulation was found. In the remainder the respiratory  $O_2$ -debt was of the same order of magnitude as the XL accumulation. As in exercise (2), total blood lactate showed no such correlation with

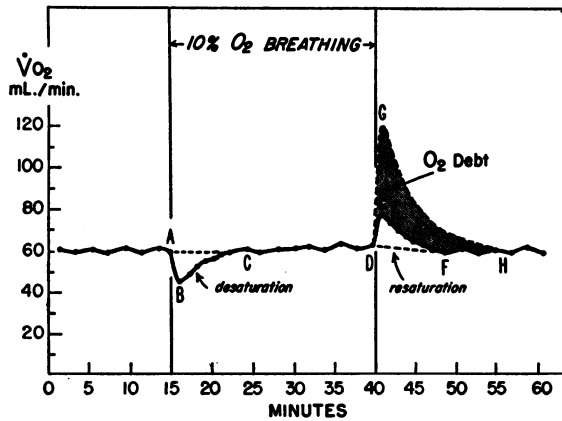


FIG. 3. TYPICAL CHANGES IN CONTINUOUSLY MEASURED OXYGEN CONSUMPTION RATE ( $\dot{V}_{O_2}$ ) IN A DOG BREATHING 10 PER CENT OXYGEN IN NITROGEN WHEN NO MEASURABLE RESPIRATORY  $O_2$ -DEBT WAS CONTRACTED (A TO F), SHOWING THE ESSENTIALLY IDENTICAL "DESATURATION" AND "RESATURATION" CURVES

Curve DGH is taken from another experiment in which an  $O_2$ -debt was contracted and is superimposed to illustrate the method of deriving  $O_2$ -debt.

$O_2$ -debt. The mean errors of estimating 210  $O_2$ -debts were: a) for total lactate, 276.4 ml. oxygen ( $\sigma = 178.2$ ) or 172.1 per cent ( $\sigma = 115.2$  per cent); b) for XL, 17.2 ml. oxygen ( $\sigma = 17.9$ ) or 11.4 per cent ( $\sigma = 12.1$  per cent). The difference between the two sets of errors is highly significant ( $p < 0.001$ ). The errors of lactate were all positive; those of XL were both positive and negative (algebraic mean = +3.2 ml.). The lactate error showed a rough tendency to follow the pH effects of the different gases, averaging 270.5 ml. for the groups breathing 13 to 15 per cent  $O_2$ , 322.9 ml. for 10 per cent  $O_2$ , 284.3 ml. for 7 to 8 per cent  $O_2$ , and 178.9 ml. for 5 per cent  $O_2$ .

#### DISCUSSION

An increase in blood lactate occurs in human subjects as a result of breathing almost any gas mixture with an oxygen content less than that of air. If previous results (1) are considered along with the present ones, it may be inferred that this lactic acidemia occurs whenever hyperventilation with respect to carbon dioxide occurs. As shown in the present data, the mean rise in lactate becomes greater with each further reduction in the oxygen tension of inspired air. Similarly, arterial blood and tissue  $P_{O_2}$  change gradually (with con-

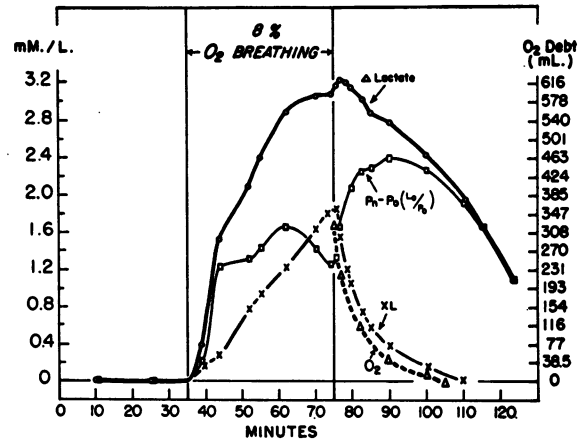


FIG. 4. EFFECT OF BREATHING 8 PER CENT OXYGEN ON THE RELATIONSHIPS OF LACTATE, XL AND  $O_2$ -DEBT IN A DOG

siderable variation) as the impediment to oxygenation becomes more severe. From these measurements one cannot identify a transition from adequate oxygenation to hypoxia, if it occurs, and in spite of these changes the rate of oxygen supply continues unaltered. None of the subjects or animals showed decrease of the total rate of metabolic uptake of oxygen from the breathing of low oxygen gases, except terminally in some of the animals breathing 5 per cent  $O_2$ . From the  $\dot{V}_{O_2}$  alone, it might be concluded that no deficiency of oxygen occurred in any of the experiments. An objection might be raised, however, that this measurement is relatively imprecise, and the  $\dot{V}_{O_2}$  itself somewhat variable from moment to moment, so that a reduction of a few ml. per minute for a prolonged period would not be recognizable, especially in view of the small increases in  $\dot{V}_{O_2}$  resulting from the increased work of breathing.

Excess lactate production differed from the other observations in this spectrum of changes. At all oxygen concentrations above approximately 10 per cent (equivalent to 18,000 feet altitude) no XL accumulation occurred in human subjects or animals. This encompassed in the present observations arterial oxygen saturations of  $88.2 \pm 1.4$  per cent and  $82.2 \pm 3.2$  per cent for the human subjects and for the animals  $78.0 \pm 5.5$  per cent and  $74.1 \pm 4.5$  per cent. But with all concentrations below 10 per cent  $O_2$ , XL accumulation uniformly occurred; values of  $S_a$  were  $53.3 \pm 3.6$  per cent and  $47.4 \pm 1.4$  per cent. Inspired gas of

about 10 per cent oxygen content appeared to be the transition zone in both species, with  $S_a$  figures of  $66.7 \pm 7.6$  per cent and  $68.3 \pm 5.4$  per cent at this apparently critical level. At this level, the cardiopulmonary responses in some individuals seem to have been able to prevent a fall in oxygen supply below the critical needs of the tissues, while in others they were unable to compensate, and the tissues had to resort to anaerobic metabolism and contraction of  $O_2$ -debt. It may be inferred that the "efficiency" of the individual oxygen transport system became critical to the peripheral body tissues at arterial oxygen saturations between 60 and 74 per cent or  $P_{O_2}$  of 26 to 32 mm. of mercury; this inference has been confirmed in studies of patients with cardiovascular or pulmonary disease which will be reported separately.

Previous investigations of respiratory hypoxia are difficult to compare with the present study for several technological reasons which have been discussed previously (1): *a*) pyruvate and lactate in arm venous blood may change very little, or fail to change altogether, during stimuli which lead to considerable alterations in concentrations in mixed venous and arterial blood; *b*) delay in collection and denaturation of blood samples may produce *in vitro* errors of such magnitude as to mask small *in vivo* changes; *c*) older methods of analysis appear to give systematically different and more variable results; and *d*) failure to start from absolutely basal levels seriously obscures fairly large changes and may even give changes in an opposite direction.

Jervell (3) found normal lactate values during the breathing of low oxygen gases of more than 7.5 per cent; below this an increase was detected with his methods. Marked increases, however, had been reported (4) at high altitudes.

Resting blood lactates appear to have been about normal at rest at an altitude of 14,000 feet (equivalent to about 12 per cent oxygen) in studies by Dill and co-workers (5), but rose excessively on exercise; pulmonary ventilation also rose excessively, however, and this phenomenon may itself account for relatively large rises of lactate (1).

Myerson, Loman, Edwards, and Dill (6) found a slight and variable increase in arterial blood lactate during the breathing of 9 per cent oxygen for 10 minutes, but the magnitude of increase was un-

related to degree of anoxemia, and oxygen supply was concluded to be unaffected in the experiments. An insignificant rise in venous blood lactate during 9 per cent oxygen breathing has also been found (7). Edwards (8) noted a slight increase during rapid ascent to 9,000 feet (14.6 per cent oxygen), but normal values after reaching 20,000 feet (9 per cent oxygen), when arterial oxygen was much lower. Friedemann, Haugen, and Kmiecik (9), studying one subject, observed some increase in both lactate and pyruvate of venous blood at all altitudes (10,000 to 22,000 feet, 14 to 8 per cent oxygen) while the lactate-pyruvate ratio either showed no significant change, or else rose or fell slightly. Bay and co-workers (10) found no difference between sea level and 10,000 or 15,000 feet (14 per cent and 11 per cent oxygen) in resting blood lactate, pyruvate or the ratio. Both lactate and pyruvate rose more with exercise during respiratory "hypoxia," but the changes in lactate-pyruvate ratio were unrelated to the presence of hypoxia. Other workers (11) have likewise found that lactate-pyruvate ratio bears no relation to hypoxia during exercise, although a systematic increase in absolute lactate response occurs with increasing anoxemia. Presumably this may be attributable to the increasing degree of hyperventilation which occurs with exercise at low oxygen tensions (5, 12). Herber (13) found no increase in arterial blood lactate of asphyxiated dogs until arterial oxygen content had fallen below 5.0 volumes per cent (perhaps 30 per cent saturation); but this hypoxia was associated with marked carbon dioxide retention, by contrast with the alkalosis seen with unimpaired respiration. In another investigation (14) venous blood lactate was slightly elevated and the lactate-pyruvate ratio was apparently not consistently or significantly altered at 19,000 and 23,000 feet (9.5 and 7.8 per cent oxygen) except when a high carbohydrate diet had been eaten, but no control values for the latter are given, although fasting seemed to have a similar effect. These results, taken as a whole, do not provide any generalization regarding adequacy of oxygen supply at any inspired oxygen tension.

The interrelationships of total lactate, XL, and  $O_2$ -debt previously reported under various conditions (1, 2) are confirmed for respiratory hypoxia in the present experiments. The conditions de-

scribed here differed significantly from exercise in that they produced no change in tissue oxygen requirements, and led to a primary reduction in blood oxygen content rather than a normal value. Tissue carbon dioxide was reduced rather than increased, and all the organs, rather than primarily the muscles, were affected. The common denominator was a *relative* oxygen lack. As before, total lactate failed to be related to  $O_2$ -debt. It seems likely that there is no necessary relationship at all between tissue lactate production *per se* and oxygen deficiency or anaerobic metabolism, whether in exercise, glucose infusion or respiratory hypoxia. When a more complete view of the status of all the components of the lactic dehydrogenase system is taken, however, as has been attempted in the calculation of "excess lactate," a satisfactory qualitative and quantitative reconciliation is achieved between the independent estimate of respiratory  $O_2$ -debt and tissue metabolic processes estimated in body fluids.

The body fluids in question here require some comment, inasmuch as the measurements of relative pyruvate and lactate increments are carried out on blood. It should be emphasized that the blood draining all body tissues, mixed in the central circulation, and sampled as it leaves the heart, provides determinations which we regard as representing the conceptual mean of the entire body at a particular moment prior to the sampling. Such a concept does not require that the body be a homogeneous medium. At the same time, of course, such a sample provides no information about events in any functional subdivisions which may be present, but only the net results of all these events. Studies of many individual organs during respiratory hypoxia, for instance, clearly indicate that certain sites may predominate in XL production at a given time and others, notably skeletal muscle, may at the same time be active in removing XL from the blood; and the location of these respective sites may change from moment to moment. This variation in different organs involves new aspects of the subject that will be presented at a later time, but the time-scale of these shifts has not been found to be rapid, being of the order of five or more complete circulation times, so that the concept of the integrated blood drainage of the "mean body" is not impaired in the results presented in this and the preceding papers.

The further question of local blood-tissue concentration equilibrium is discussed elsewhere (1, 2).

It will be recognized that estimates of respiratory  $O_2$ -debt by the present method probably are somewhat more variable than in exercise (2) because of the necessity of measuring the "desaturation area" of the  $Vo_2$  curve illustrated in Figure 3. This diminution in pulmonary oxygen absorption occurs during the initial fall in blood oxygen and disappears as the blood oxygen content levels off at a new value after about 10 minutes, and is presumably due to the supply of oxygen coming from this desaturation of blood and body fluids since its magnitude is related to  $FI_{O_2}$ . Reduction of myoglobin, cytochrome oxidase, cytochromes and flavoproteins might also conceivably have taken part in this process if  $PO_2$  in some tissue cells fell to extremely low levels, although these substances are unaffected by oxygen tensions of the order of those in the blood (15, 16). The absence of any detectable notch in the XL curve suggests that DPN did not take part in the "desaturation," and presumably the DPN-coupled metabolic systems were unaffected. The question arises, however, whether a reduction in the high energy phosphate pool accompanied the desaturation phase (17).

In that event an actual decrease in metabolic oxygen consumption would have occurred, so that part of the "desaturation area" would be actual  $O_2$ -debt and should not have been subtracted from the excess oxygen uptake of recovery. An approximate computation of the change in oxygen pool size can be made, however, from *a*) the known change in arterial and mixed venous blood  $PO_2$  and the total circulating hemoglobin mass (assuming 70 per cent of the blood to be venous), plus small additional portions from *b*) change in alveolar  $PO_2$ , *c*) the change in plasma  $PO_2$ , assuming this change to be uniform in extracellular fluid, and *d*) the desaturation of the intracellular fluid, assumed to have a mean  $PO_2$  of 15 to 20 mm. Hg and to undergo a similar percentage change. These calculated changes approximately accounted for the desaturation area; the errors of the approximation were both positive and negative and had an arithmetic mean of 15 per cent. The entire desaturation area is small by comparison with the  $O_2$ -debt area in experiments with 5 to 8 per cent oxygen breathing, and 15 per cent of this area represents a negligible variance. The

absence of any large or consistent error in this approximation suggests that if reductions of the creatine phosphate-adenosine triphosphate pool of the whole body occurred they were of insignificant magnitude.

#### SUMMARY AND CONCLUSIONS

1. Blood total lactate concentration bears no relationship to severity of respiratory hypoxia, but calculated "excess lactate" corresponds closely to the magnitude of the  $O_2$ -debt developed in this as in other types of hypoxia.

2. Progressive reduction of oxygen content of inspired air in human subjects and anesthetized animals leads to gradual alteration in blood oxygen, pH, lactate and pyruvate; but excess lactate is absent until  $FI_{O_2}$  is reduced to a critical value of about half (arterial blood oxygen saturation reduced to 60 to 74 per cent,  $PO_2$  to 26 to 32 mm. Hg) and thereafter is produced in increasing amounts as oxygen supply diminishes.

3. It is suggested that a wide range of hypoxemia, including the range of visible cyanosis in many subjects, is not associated with hypoxia or deficiency of oxygen in body tissues, and that caution should be exercised in ascribing symptoms or signs to this particular aspect of pulmonary or circulatory disease.

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