

THE EFFECTS ON THE RESPIRATION AND PERFORMANCE  
DURING EXERCISE OF ADDING OXYGEN  
TO THE INSPIRED AIR

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There have been several reports in the literature of the effects of oxygen on the respiration and performance during heavy work. The most extensive of these was by Asmussen & Nielsen (1946) who showed, among other things, that during moderately severe exercise on the bicycle ergometer the addition of oxygen to the inspired air resulted in a marked and sudden depression of the respiration. To explain their findings they postulated that muscle working under partially anaerobic conditions liberated into the blood stream an unknown substance which stimulated the respiration and which was rapidly destroyed by high concentrations of oxygen. This was in addition to any effects which might be ascribed to the production of excess lactate. More recently, Miller (1952) has reported that he could detect no effect on any of the quantities which he measured when oxygen was added to the inspired air of athletic and non-athletic subjects performing moderate and severe exercise on a treadmill.

It therefore seemed worth while to see whether the effects described by Asmussen & Nielsen (1946) could be produced during hard exercise on the treadmill and to consider the possibility that these effects, if present, might be explained without invoking the intervention of an unknown hypothetical substance.

METHODS

The methods used and the four subjects employed have been described in a previous paper (Bannister, Cunningham & Douglas, 1954).

RESULTS

*Exercise to exhaustion while breathing air enriched with oxygen*

Four experiments were carried out on each subject. An intensity of exercise was chosen for each subject such that the breaking point was reached in 6-9 min when breathing atmospheric air. The subjects then ran to exhaustion in three further experiments during which they breathed 33, 66 and 100 %

oxygen respectively. The  $\text{CO}_2$  output when breathing higher concentrations of oxygen was about the same as when breathing air. The oxygen consumptions were recorded, but were obviously unreliable for the reasons discussed by Hill, Long & Lupton (1924*a*). The results of twenty such runs by four subjects are shown in Fig. 1 *a-e*, and the duration of the exercise and breaking points in Table 1.

TABLE 1. Duration of exercise during the inhalation of different air-oxygen mixtures. Speed in all experiments  $6\frac{1}{2}$  m.p.h.

Subject	Gradient	Duration of exercise when breathing			
		21% $\text{O}_2$ min sec	33% $\text{O}_2$ min sec	66% $\text{O}_2$ min sec	100% $\text{O}_2$ min sec
R.G.B. (1)	1 in 7	8 45	8 45	*17 15	*16 32
R.G.B. (2)	1 in 7	8 26	15 17	23 40	20 40
D.J.C.C.	1 in 10	8 58	11 20	*24 48	20 45
N.D.McW.	1 in 8	6 35	13 25	*23 0	17 18
P.J.P.	1 in 16	6 25	10 15	13 50	11 55

\* Denotes breaking point not reached.

The addition of oxygen to the inspired air always improved performance considerably and often resulted in the establishment of a steady state during exercise which would normally produce rapid exhaustion (Table 1).

Substitution of 66% or 100% oxygen for air reduced the pulmonary ventilation by 5–25 l./min in all subjects. In the air-breathing experiments on P.J.P. and N.D.McW. the breaking points occurred so early that only one or two measurements of ventilation were possible. These were almost certainly not steady state values, and the ventilation was probably still rising rapidly. It is likely that had the maximum ventilation been recorded with these two subjects the differences between the air and oxygen experiments would have been greater than is indicated in Fig. 1 *d* and *e*. The blood lactate response was reduced by one-third to a half in three subjects and by one-seventh in the other by the inhalation of the higher concentrations of oxygen. The magnitude of the differences in blood lactate in three subjects is masked by the fact that they were completely exhausted before the blood lactate reached its highest level when breathing air, whereas the lower concentrations recorded during oxygen inhalation were steady state or near-steady state values. When inspiring 66% or 100% oxygen the alveolar  $\text{pCO}_2$  was from 4 to 9 mm higher than when air was breathed; in the two athletes figures as high as 54 and 55 mm were recorded, 14 and 15 mm above the preliminary resting values. The alveolar  $\text{pCO}_2$  showed a tendency to fall slightly as the exercise continued.

The effects of 33% oxygen were intermediate between those of air and of the higher concentrations of oxygen.

66 and 100% oxygen. The experiments showed that the inhalation of 100% oxygen during severe exercise at sea level resulted in complete exhaustion

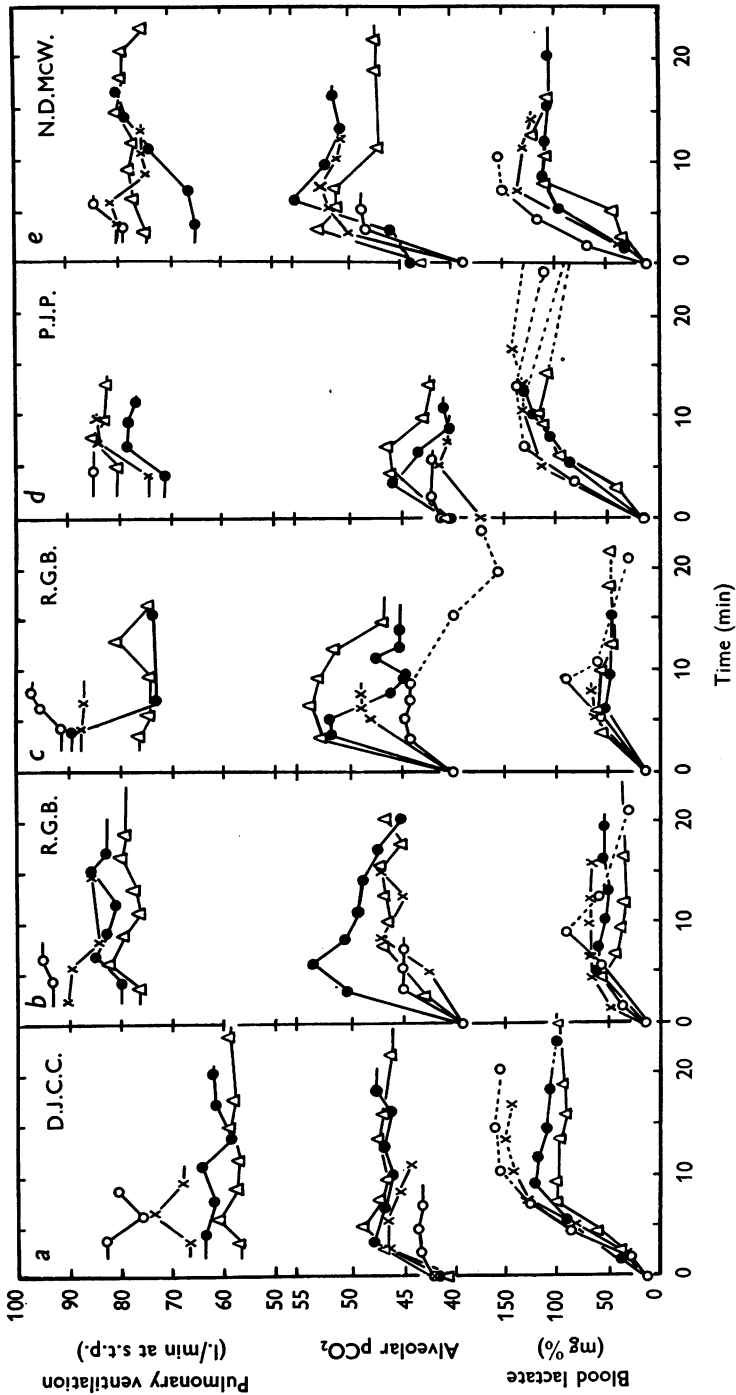


Fig. 1. *a-e*: Effect of different concentrations of oxygen in the inspired air on respiration and blood lactate during very heavy standardized exercise. Speed in all experiments,  $6\frac{1}{2}$  m.p.h.  $\circ$ — $\circ$ , breathing atmospheric air;  $\times$ — $\times$ , breathing 33% O<sub>2</sub>;  $\triangle$ — $\triangle$ , breathing 66% O<sub>2</sub>;  $\bullet$ — $\bullet$ , breathing 100% O<sub>2</sub>. Points obtained during exercise joined by full lines; points obtained during recovery at rest joined by broken lines. *a*, subject D.J.C.C., gradient, 1 in 10; *b*, *c*, subject R.G.B., gradient 1 in 16; *d*, subject P.J.P., gradient, 1 in 16; *e*, subject N.D.McW., gradient, 1 in 8.

within 12–21 min, whereas three of the subjects, when they breathed 66% oxygen, had not reached their breaking points when they stopped running after 23 min; the fourth reached his breaking point 2 min later than in the experiment when he breathed 100% oxygen. There were no clear-cut differences between the pulmonary ventilations or the blood lactate and alveolar  $p\text{CO}_2$  levels with 100% and 66% oxygen. A small difference in one direction with one subject was usually offset by a difference in the opposite direction with another.

The subjective effects were impressive. Three of the four subjects found the exercise much easier when breathing 66% oxygen. R.G.B. noticed with surprise that he felt mentally elated when breathing 66%, but not when breathing pure oxygen. The exercise was incomparably easier than in any of the previous runs at this intensity; breathing was effortless and he stopped running more from boredom than from exhaustion. In the second series of experiments when he ran for 24 min on 66% oxygen he again noticed these effects, although he had completed a run to exhaustion on the previous day. D.J.C.C. felt breathless when breathing 100% oxygen, although the pulmonary ventilation was 19 l./min less than when breathing air. With 66% oxygen his breathing was comfortable and he felt that he could continue to run indefinitely. The other subjects did not know the composition of the inspired air. P.J.P. ran on 66% oxygen on the day after his run to exhaustion on pure oxygen, and although he made no comments he lasted for 2 min longer than on the previous day. N.D.McW. ran on 66% oxygen one morning having completed a run to exhaustion on 100% oxygen the evening before. As he stopped running he said, 'You don't have to tell me that there was more oxygen that time!' His breathing seemed easier than during other runs. He thought that there was a definite elation which he distinguished from the mere absence of discomfort. He would have been prepared to run indefinitely had he not had to catch a train.

*Sudden changes in the oxygen content of the inspired air during less severe exercise*

In these experiments the subjects R.G.B. and D.J.C.C. exercised at slightly lower intensities. Running at  $6\frac{1}{4}$  m.p.h. up a gradient of 1 in 12 (R.G.B.) and on the level (D.J.C.C.), intensities at which their oxygen consumptions were 3390 and 1970 c.c./min respectively, no perceptible change in pulmonary ventilation or alveolar  $p\text{CO}_2$  occurred when the inspired gas was suddenly changed from air to 66% oxygen. The subjects were presumably free from oxygen lack during these runs. When they ran at the same speed up gradients of 1 in 10 and 1 in 16 respectively (oxygen consumptions, 3860 and 2500 c.c./min) definite effects were observed on raising the concentration of oxygen in the inspired air. The subjects breathed atmospheric air for the first

20 min, then 66% oxygen for 10 min, then air for another 10 min. After this R.G.B. stopped running, but D.J.C.C. was switched to 33% oxygen for a further 10 min and finally back to air for 5 min. Blood samples for the estimation of lactate were withdrawn at intervals, the alveolar  $p\text{CO}_2$  was measured very frequently with the carbon dioxide meter and the pulmonary ventilation was determined immediately before and after the changes. The results are shown in Fig. 2*a* and *b*. In the case of R.G.B. the pulmonary ventilation changed extremely quickly after the switches from 74 to 64 and from 72 to 80 l./min. The collection of expired air was started after only a few seconds and by that time the changes must have been almost complete. Had there been a significant delay the first bag determination would have given a value intermediate between those for the steady states before and after the switch. However, it showed a change in ventilation greater than that finally established. The  $\text{CO}_2$  meter recorded changes of alveolar  $p\text{CO}_2$  from 41.5 to 43 and from 44 to 38 mm. They started about 20 sec after the switch, and there was a large overshoot before a steady value was achieved, particularly after the change from 66% oxygen back to air. The latency of the response of the alveolar  $p\text{CO}_2$  to the altered alveolar  $p\text{O}_2$  must have been extremely short in view of the length of tubing from the alveolar air sampler to the meter (about 6 ft.), the time taken for the alveolar  $p\text{O}_2$  to change and for the alveolar  $p\text{CO}_2$  to alter following a change in pulmonary ventilation. The experiment on D.J.C.C. was carried out before the rapidity of the changes was appreciated and measurements were not made sufficiently quickly, but the latency in his case was also small and the changes similar in magnitude. Alterations of ventilation and alveolar  $p\text{CO}_2$  in the same directions occurred later in the same experiment on D.J.C.C. when he was switched to 33% oxygen and back to air, but the effects were not so great. Trotter (personal communication) has provided some evidence that there may be fluctuations in the  $\text{CO}_2$  meter reading following large changes in the nitrogen and oxygen contents of the mixture analysed. This may have contributed to the effects reported here, but the magnitude of the changes in alveolar  $p\text{CO}_2$  reflected the changes in ventilation. In five out of six subjects investigated in another connexion these rapid changes have been observed following sudden changes in the inspired oxygen concentration.

The blood lactate changed comparatively slowly after each switch and could not have been responsible for the rapid alterations in ventilation and alveolar  $p\text{CO}_2$ .

Marked subjective effects were also present. The slight pain in D.J.C.C.'s legs which was present when he breathed air disappeared when 66% oxygen was inspired. When the switch back to air occurred 10 min later he became much more aware of his breathing. After a further 10 min he was getting very tired, but 20 sec after the switch to 33% oxygen his breathing became easier

and his vision became suddenly brighter. He was reminded of the change which occurs when normal atmospheric air is suddenly inspired after a period

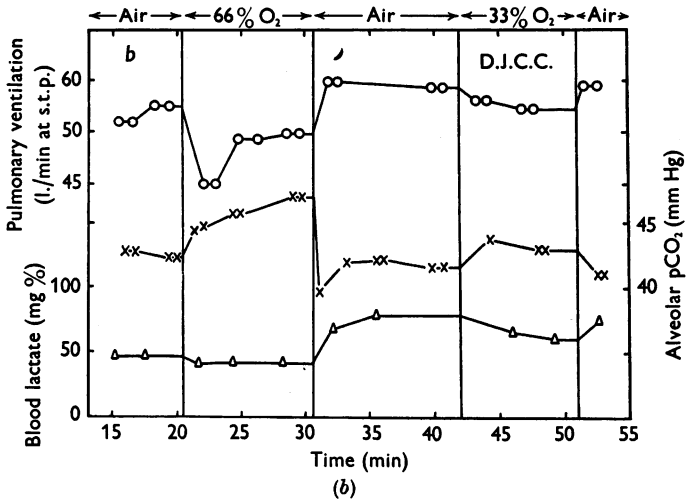
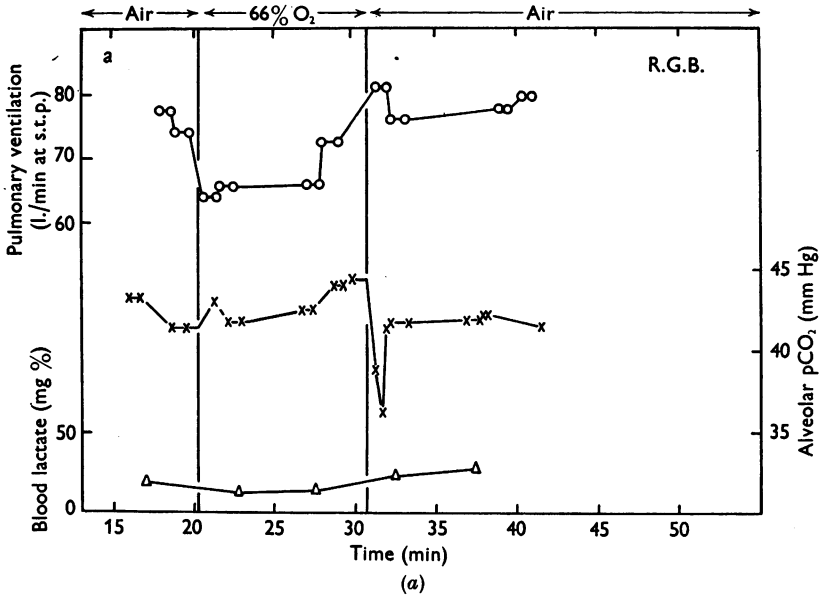


Fig. 2. *a, b*: effects of rapid changes of oxygen content of inspired air during severe exercise. *a*, subject R.G.B., speed 6½ m.p.h., gradient, 1 in 10; *b*, subject, D.J.C.C., speed 6½ m.p.h., gradient, 1 in 16. Inspired gas mixtures are indicated at the top of the figure.

of breathing air deficient in oxygen at rest. Ten minutes later, when he started breathing air instead of 33% oxygen, he became dyspnoeic and was forced to change his respiratory rate from 30 to 45 breaths per minute.

## DISCUSSION

*Respiratory effects of adding oxygen to the inspired air*

The difference in the concentrations of lactate in the blood which were observed when gas mixtures enriched with oxygen were breathed during work are in general agreement with the findings of Asmussen & Nielsen (1946) and of Lundin & Ström (1947).

The significance of the changes in alveolar  $p\text{CO}_2$  produced by oxygen are discussed elsewhere (Bannister *et al.* 1954). The mode of action of oxygen in producing the results reported here requires further consideration.

The effects of adding oxygen to the inspired air during exercise was studied by Hill, Long & Lupton (1924*b*). During heavy work of approximately constant severity they found that the pulmonary ventilation was not always reduced. However, the capacity for maximal exertion was considerably increased when 50% oxygen was inspired. The oxygen consumptions were about 20% greater than when air was breathed and higher concentrations of lactate in the blood could be tolerated. They thought that the differences were too great to be explained in terms of the increased oxygen content of the arterial blood alone, and postulated that during maximal work breathing air there might be a fall in the oxygen tension of the arterial blood which might affect the heart and brain. The abolition of the anoxaemia by the addition of oxygen to the inspired air would result in an increase in cardiac output and possibly in the tolerance of the brain for acid metabolites.

Haldane & Priestley (1935*a*) reported that during moderate exercise in untrained subjects the alveolar  $p\text{CO}_2$  rose to higher levels and the work seemed easier when oxygen was inhaled. They did not detect this difference during moderate exercise in a subject who led a more active life. Briggs (1920) made similar observations on the pulmonary ventilation and  $\text{CO}_2$  content of the expired air. In 1934, Christensen, Krogh & Lindhard summarized their studies on heavy work. In particular they found that when the exercise was so severe that it could not be maintained for 2 min the addition of oxygen to the inspired air had no effect on the performance. With work of slightly lower intensity oxygen increased the endurance and the capacity for work. When, breathing oxygen, the subject started with moderate exercise and the intensity was subsequently increased by stages, he was able to maintain rates of work which had previously exhausted him within 2 min. Evidently time was required for the adjustment of the respiratory and circulatory systems to the new conditions if the extra oxygen was to produce its effect. There are no contradictions between any of these findings and our own.

Asmussen & Nielsen (1946, 1950) and Asmussen (1950) were the first to show conclusively that during prolonged heavy work on a bicycle ergometer the addition of oxygen to the inspired air produced a considerable reduction in

the pulmonary ventilation, an increase in the alveolar  $p\text{CO}_2$  and a reduction in the blood lactate. They could not detect such an effect with light or moderate work and concluded that it was present only above certain intensities. They showed that the effect was graded in that the reduction in ventilation was small with 30 %, large with 60 % and maximal with 100 % oxygen. They also found that if a sudden switch was made from atmospheric air to oxygen during the work, the change in ventilation occurred much more rapidly than the alterations in the concentration of lactate or pyruvate in the blood. All our findings are, generally speaking, in agreement with theirs, except that in two of our four subjects the depression of ventilation was greater with 66 % than with 100 % oxygen and that the differences at these levels were probably insignificant. However, our main experiments were different in that the work resulted in exhaustion within 6–9 min when breathing air. We did not investigate the relative values of 66 % and pure oxygen during prolonged exercise at the slightly lower intensity used by Asmussen & Nielsen.

Hickam, Pryor, Page & Atwell (1951) have shown that the substitution of pure oxygen for air reduces markedly and suddenly the ventilation during heavy exercise in untrained subjects. This is accompanied by the abolition of a previously existing slight arterial desaturation with oxygen. Unlike Asmussen & Nielsen, they conclude that the effect is due to the removal of an anoxic stimulation of the carotid chemoreceptors. It is a pity that such short experimental periods were used. The subjects could hardly have been in a steady state in any part of these experiments, and so the large numbers of measurements made cannot be compared quantitatively with our own or others in the literature. However, their results are in qualitative agreement with many of ours.

Miller (1952) was unable to record any important subjective or objective differences either in untrained subjects or in athletes running to exhaustion when 100 % oxygen was substituted for air. No respiratory measurements were made. This is in complete contradiction to our findings and to those of the earlier workers. He reports that when subjects were told that they were to run on oxygen their performance improved. We can scarcely believe that the differences which we and many others have observed were entirely subjective. In particular, the inspired air mixtures were unknown to two of our subjects, and we were still able to detect effects which varied in magnitude with the amount of oxygen added to the inspired air.

Asmussen & Nielsen (1946, 1950) did not think that a reduction of the arterial  $p\text{O}_2$  during heavy exercise when breathing air was responsible for the effects they observed on the grounds that if it occurred at all it was too small to stimulate the chemoreceptors. They also pointed out that the further depression in ventilation which occurred when pure oxygen was substituted for 60 % could not be explained on the basis of an abolition of arterial



anoxaemia. They excluded changes in blood lactate, which were too slow to be responsible. Subsequent experiments in which they trapped blood in the legs with pneumatic cuffs during work and observed the effects produced when the circulation was re-established during the subsequent rest led to the postulation of a substance closely related to the 'hyperpnoein' of Yandell Henderson (1938). This substance was supposedly produced by ischaemic muscle; it stimulated the chemoreceptors and was rapidly destroyed in the presence of oxygen. Further evidence for their view was provided by the observation that during heavy work with the arms alone, similar effects were obtained from the substitution of oxygen for air. This occurred at relatively low metabolic rates, when the cardiovascular and respiratory systems were not working to capacity.

However, our data and those of Asmussen & Nielsen are not incompatible with a more orthodox explanation in terms of arterial anoxaemia. If the arterial  $pO_2$  is depressed during heavy exercise, the addition of oxygen to the inspired air would be expected to raise the arterial  $pO_2$  to values in excess of the threshold of the carotid and aortic chemoreceptors and to lower the ventilation. In addition, a lowered arterial  $pO_2$  might result in cardiac embarrassment, which would be relieved by breathing oxygen. This is another possible means by which arterial anoxaemia might affect the pulmonary ventilation, and is briefly considered later in this paper. For the theory that the effects were due to arterial anoxaemia acting by way of the chemoreceptors to be satisfactory by itself, certain requirements must be met: (1) The part of the hyperpnoea in heavy exercise which may be ascribed to anoxic stimulation of the chemoreceptors (i.e. the increase which is recorded when air is substituted for 66% or 100%  $O_2$ ) should be comparable to the increase in ventilation when the subject is exposed to a similar degree of anoxia at rest. (2) The arterial  $pO_2$  in heavy exercise should be depressed to levels which would stimulate the chemoreceptors. (3) If possible, satisfactory explanations for the depression of the arterial  $pO_2$  should be available. It might be the result of limitations in the rate of diffusion of oxygen across the pulmonary epithelium or of fairly gross irregularities of distribution of blood flow and air flow in different parts of the lungs, or of both. (4) If these requirements are met, it has to be decided whether the graded effect of 33 and 66%  $O_2$  on the ventilation may be explained in similar terms; in other words, is it possible that the inhalation of 33% oxygen is insufficient to abolish completely the arterial anoxaemia which exists when air is breathed? The theory must also account for the effect of oxygen on the ventilation during work with the arms alone. We have no data on this point. These requirements must now be considered in some detail.

*Response to oxygen lack at rest*

Recent accounts of the causes of hyperpnoea during strenuous exercise have rejected the suggestion that a lowering of the arterial  $pO_2$  may be a factor in normal subjects (Comroe, 1944; Pitts, 1949; Gray, 1950; Grodins, 1950). This is presumably due to the widespread belief that the ventilatory response of normal subjects to anoxia of short duration at rest is relatively small (e.g. Dripps & Comroe, 1947). Such data, though correct in themselves, do not take account of the inhibitory effect of the accompanying acapnia. When this acapnia is reduced to a minimum by the process of acclimatization, the effectiveness of quite small reductions in the arterial  $pO_2$  in stimulating the ventilation becomes apparent (FitzGerald, 1914; Boothby, 1945). Haldane, Meakins & Priestley (1918*a*) showed that when oxygen lack is added to the effects of an excess of carbon dioxide, as occurs when a subject rebreathes air from a confined space at rest, the effects of the anoxia appear earlier and more powerfully than when the subject rebreathes air and the  $pO_2$  falls at a similar rate, but the  $CO_2$  is not allowed to accumulate. Nielsen & Smith (1951) and Gee (1949) have produced evidence to show that the effects of the two stimuli combined need not necessarily be strictly additive, as has been assumed by Gray (1950). Gee's results agreed with those of Haldane *et al.* (1918*a*) in suggesting that in the presence of an excess of  $CO_2$  stimulation of the breathing by anoxia may occur with only slight depressions of the alveolar oxygen tension. Hill & Flack (1908), Douglas & Haldane (1909) and DuBois (1952) in breath-holding experiments showed that the breaking point was reached later and at a higher alveolar  $pCO_2$  when oxygen was added to the inspired air. It appeared that anoxia played some part in advancing the breaking point even when the alveolar  $pO_2$  was well above 100 mm. Recent experiments in this laboratory (Cormack, Cunningham & Gee, unpublished) on rebreathing at rest from a 6 l. spirometer containing either air or oxygen indicated the same thing, namely, that in the presence of a large excess of  $CO_2$  a very powerful stimulation of respiration from 'oxygen lack' may occur when the alveolar  $pO_2$  is still well above 100 mm. In contrast, when the same rebreathing experiments are carried out following a period of acapnia induced by the inhalation of 10% oxygen for 30 min, no effect from oxygen lack alone may be detected until the alveolar  $pO_2$  falls to 60 or 55 mm. It will be seen from Fig. 1 that in our exercising subjects there was a considerable rise in alveolar  $pCO_2$  and blood lactate, and hence in the arterial hydrogen-ion concentration. It is therefore possible that a considerable anoxic stimulus existed even though the arterial  $pO_2$  may not have fallen very much. The mechanism of this response is obscure since Åström (1952) and Metz & Bernthal (1953) have shown that acapnia potentiates and  $CO_2$  excess reduces the stimulant effects of anoxia on the respiration of anaesthetized animals. At present there is no obvious explanation for

these contradictory findings but for our purposes the experiments of Nielsen & Smith (1951), of Gee (1949) and of Cormack *et al.* (unpublished) on unanaesthetized man are more directly applicable. We may therefore conclude that the ventilatory response to simple oxygen lack may be quantitatively adequate for the present purpose.

*The arterial oxygen tension in severe exercise*

It has been known for a long time that at high altitudes the performance of very severe exercise results in a reduction in the saturation with oxygen of the arterial blood (Douglas, Haldane, Henderson & Schneider, 1912). At sea level the position is not so clear. Several workers reported a fall in the arterial oxygen percentage saturation during severe exercise (e.g. Harrop, 1919; Himwich & Barr, 1923). Most of these observations were based on determinations of saturation with the Van Slyke apparatus, which, as used in those days, gave rise to a small systematic error (Roughton, Darling & Root, 1944). The data are unsuitable for the present purpose since changes in oxygen tension rather than saturation are responsible for chemoreceptor stimulation (Comroe & Schmidt, 1938), and only large changes of tension can be detected by measuring saturation at sea level. This criticism applies to determinations with the oximeter and also to those reported by Asmussen & Nielsen (1946). The only direct measurements of arterial oxygen tension during heavy exercise at sea level of which we are aware are those of Lilienthal, Riley, Proemmel & Franke (1946). They found that it fell from 94 mm at rest to 73 mm during three experiments on one subject who exercised at an intensity which was rather less than that reported in this paper. Hickam *et al.* (1951) found a fall of about 2% saturation during fairly heavy exercise in eleven untrained subjects. This would correspond to a fall in tension of about 20 mm if the oxygen dissociation curve remained unchanged. However, there was also a considerable alteration of serum pH which may account for part of the change in saturation.

*The causes of anoxaemia in heavy exercise*

(a) *Limitations in the rate of diffusion of oxygen across the pulmonary epithelium.* Little can be said on this subject since we have no relevant data and the figures given for the diffusion coefficient of the lung ( $DO_2$ ) are conflicting. It is agreed that the  $DO_2$  is increased during exercise, but the absolute values are not known for certain. Marie Krogh (1914) gave figures of about 25 at rest and 50 to 60 in moderate exercise. Bøje (1933), using the same method, got slightly higher values at rest and figures of up to 57 in very severe exercise. Lilienthal *et al.* (1946) obtained similar figures at rest and during moderate exercise, but recorded a value of 75 in one subject who performed severe exercise of a slightly lower relative intensity than we used. On the

other hand, Hartridge & Roughton (1927) suggested that the CO method might give low values, and Roughton (1944) pointed out that a  $\text{DO}_2$  of 200 would be required to explain the data from a single experiment of Asmussen & Chiodi (1941) on exercise at high altitude. The comments on this work by Lilienthal *et al.* (1946) assumed a large error in the measurement of the arterial percentage saturation with  $\text{O}_2$  by Asmussen & Chiodi. Schmidt, Lambertsen, Aviado, Pontius, Barker & Moyer (1950) found that the  $\text{DO}_2$  at rest was in excess of 60, which is more in keeping with Roughton's calculations. Making reasonable assumptions for the cardiac outputs of our two subjects R.G.B. and D.J.C.C., almost complete equilibrium between the oxygen of the alveolar air and the pulmonary capillary blood would be reached if their  $\text{DO}_2$ 's exceeded 100 and 75 respectively. In the circumstances the question must be left open, but in either case we think that the major part of the arterial anoxaemia was produced by the factors considered in the next subsection.

(b) *Imperfect distribution of blood and air within the lungs.* Imperfect distribution of the blood and air was first suggested by Haldane, Meakins & Priestley (1918*b*) as a cause of arterial anoxaemia. Their views were summarized by Haldane & Priestley (1935*b*). The effects of such local inequalities of air supply and blood flow have recently been worked out quantitatively by Riley & Courmand (1949, 1951). They express in terms of a complete 'venous shunt' the combined effects of local underventilation and overperfusion in parts of the lung proper, together with the addition of true venous blood to the blood in the left side of the heart, such as probably occurs through the bronchial and Thebesian veins. Their data suggest that this 'shunt' probably amounts to about 3% of the total blood flow in normal subjects at rest. So far there are no data relating to rapidly exhausting exercise. The nature of the extremely efficient mechanism which probably regulates the distribution of air and blood to various parts of the lungs during rest is incompletely understood. It would not be surprising if it were to become less effective during the severe strain of maximal physical work. It is possible to calculate the limits within which such an 'effective venous shunt' must lie in order to produce a low arterial  $\text{pO}_2$  with 33%, but a normal or raised arterial  $\text{pO}_2$  with 66% oxygen. Certain numerical assumptions are made in the calculation. For the subject R.G.B., with an oxygen consumption of 4.4 l./min it is assumed that the mixed venous blood was 40% saturated with oxygen and that the oxygen capacity of his blood was 20 vol. %. These figures would give a cardiac output of about 37.5 l./min, a figure which seems reasonable in view of the work of Christensen (1931). The blood which passed through adequately ventilated alveoli probably came very near to equilibrium with the alveolar oxygen. During the experiments in which 33 and 66% oxygen were breathed, it would take up oxygen in excess of that required to raise its  $\text{pO}_2$  to 100 mm, and the surplus would be available to oxygenate the blood from the 'effective venous shunt'. The relative

magnitude of a shunt which could be oxygenated to a  $pO_2$  of 100 mm may be found from the equation:

$$\frac{\text{Surplus } O_2 \text{ (vol. \%)}}{\text{Arteriovenous difference (vol. \%)}} = \frac{\text{effective venous shunt (\% of cardiac output)}}{100 - \text{effective venous shunt (\% of cardiac output)}}$$

The calculation is shown in Table 2. The dissociation curve of Courtice & Douglas (1947), extrapolated to high values of  $pO_2$ , and the Bohr coefficients of solubility have been used.

TABLE 2. Calculation of the magnitude of the 'effective venous shunt' which would produce an arterial  $pO_2$  of 100 mm Hg when gas mixtures other than air are breathed

	Inspired oxygen		
	21 %	33 %	66 %
Alveolar $pO_2$	100	193	428
$O_2$ content of blood from normally ventilated alveoli:			
Combined, $HbO_2$ %	97.5	99.69	100
Combined, vol. %	19.5	19.95	20.0
Dissolved, vol. %	0.29	0.56	1.24
Total, vol. %	19.79	20.51	21.24
Mixed arterial $O_2$ , vol. %	19.79	19.79	19.79
'Surplus' $O_2$ , vol. %	0	0.72	1.45
$O_2$ content of mixed venous blood:			
Combined, $HbO_2$ %	40	40	40
Combined vol. %	8	8	8
Dissolved, vol. %	0.07	0.07	0.07
Total, vol. %	8.07	8.07	8.07
Arteriovenous difference, vol. %	11.72	11.72	11.72
'Effective shunt', % of total flow	0	5.8	11.0

If the cardiac output was lower and the arteriovenous difference greater, a smaller shunt would suffice. Under the conditions specified, a shunt of 6% when air was breathed would have resulted in an arterial  $pO_2$  of 67 mm which is a little lower than the figure found by Lilienthal *et al.* (1946). It is therefore quite possible that occurrences of this type were responsible for a depression of the arterial  $pO_2$  to levels which would produce a strong stimulation of the chemoreceptors. We would like to emphasize once more that this 6% 'effective venous shunt' does not mean that 6% of the cardiac output bypasses the lungs altogether. The Thebesian vein component of the true shunt may well increase considerably, but a large part of the 'effective venous shunt' would probably be made up of blood which passes through regions of the lungs where the air supply is relatively deficient, but not completely absent. Such an effect might result from a cessation of pulmonary vasoconstrictor activity in the interests of the maximum possible blood flow. In this case, active regulation of blood distribution would cease.

*The graded effect of 33 and 66 % oxygen on the ventilation*

The full effect of oxygen in reducing the ventilation was achieved with 66 % but not with 33 % oxygen. In order to explain these findings in terms of arterial anoxaemia alone, the arterial  $pO_2$  would have to be less than 100 mm even when 33 % oxygen was breathed. This would occur if the 'effective venous shunt' were between 6 and 11 % of the total blood flow, which seems rather large. It may be that the depression of the arterial  $pO_2$ , if present at all, was insufficient to account for the whole of the difference between results with 33 and 66 % oxygen. However, the difference between the blood lactate levels may have been sufficient to increase the ventilation considerably. To be certain that this was not the cause, it would be necessary to show that the ventilation changed *abruptly*, from, for example, 85 to 75 l./min in the case of R.G.B. if he were switched suddenly from 33 to 66 % oxygen. No such experiment is on record. The same considerations apply to the differences between 60 and 100 % oxygen which were found by Asmussen & Nielsen (1946) but which we failed to confirm, and also to the difference between work with the arms alone on air and pure oxygen. It seems, therefore, that the effects observed may be explained tentatively in terms of known factors, namely arterial anoxaemia and acidosis resulting from the accumulation of lactate. Further experiments of the type suggested should provide an answer to some of the problems, and direct measurement of the arterial  $pO_2$  would settle them all. It seems likely that a fall in the arterial  $pO_2$  would affect the breathing by way of the carotid and aortic chemoreceptors. In addition, it is possible that cardiac function might be limited by anoxia, as was suggested by Hill *et al.* (1924*b*) and this might influence the breathing. Little is known about the way in which such a relatively cardiac insufficiency would produce dyspnoea, but it would probably allow the pressures on the right side of the heart to rise, and this in turn might initiate reflexes from the great veins, right heart, or pulmonary vessels. Such respiratory reflexes have been demonstrated in cats by Harrison, Harrison & Marsh (1932) and by Megibow, Katz & Feinstein (1943), and in man by Mills (1944).

It has been mentioned elsewhere (Bannister *et al.* 1954) that when the oxygen want of severe exertion is abolished, the pulmonary ventilation is not much greater than that produced by the application of an equivalent  $CO_2$  stimulus at rest. We think that the greater part of the hyperpnoea of severe exercise can be explained in terms of oxygen lack, lactate accumulation and  $CO_2$  excess. The thresholds for these are probably lowered by the rise of body temperature. We do not discard altogether the effects of nervous stimuli from the working limbs, but we think they contribute comparatively little to the ventilation in the steady state, though they are probably of importance in producing the rapid adjustments to the changing conditions which occur at the beginning of exercise.

*The difference between the effects of 66 and 100 % oxygen*

These experiments differ from others reported in the literature in showing that there is an optimum level for the alveolar oxygen tension in heavy exercise and that if this is exceeded performance suffers. The limits between which this optimum value lie have not been determined. It may be that the inhalation of about 50 % would be sufficient to produce the benefit which resulted from 66 % oxygen, and that the disadvantages which result from an excess do not become apparent until considerably more oxygen is added to the inspired air.

The reasons for this optimum value are obscure. At rest adverse effects do not occur until pure oxygen has been breathed for many hours, unless the pressure is greatly increased. With 100 % oxygen the symptoms experienced by our subjects were generalized rather than local. This, together with the fact that a small excess of lactate accumulated in the blood, suggests that the working muscles were not responsible. There is no reason to think that the heart was adversely affected when pure oxygen was substituted for 66 %. The load on the heart was reduced since there was probably no increase in the oxygen consumption and the arterial blood was carrying nearly an extra volume per cent of dissolved oxygen. The situation differs from that described by Hill *et al.* (1924*b*) when they postulated a considerable increase in the cardiac output to explain the large increases in oxygen consumption of which their subjects were capable when 50 % oxygen was breathed. In their experiments the intensity of the work was increased when oxygen was inhaled, while in ours it was kept constant. On our hypothesis oxygen lack was slight or absent in the two cases and the stimuli from pH and pCO<sub>2</sub> were similar. The chemoreceptors could scarcely have been responsible for the difference. Irritation of the respiratory tract by the oxygen or from the dryness of the gas, inhaled as it was straight from storage cylinders, cannot be excluded. However, when 66 % oxygen in nitrogen was supplied direct from cylinders it did not have this effect, and in any case not all the subjects complained of respiratory distress. The comments of three of the subjects suggested that the effect was nervous. When breathing 66 % oxygen they felt an elation which was strikingly absent when breathing pure oxygen. It may have been due partly to the absence of the expected unpleasant sensations which normally accompany exercise of this severity and partly to the unexpected feeling of enhanced physical capability. However, the known factors which produce distress were not increased when pure oxygen was inspired, yet the subjects felt depressed rather than elated. Dautrebande & Haldane (1921) noticed that the respiration was increased when oxygen at slightly increased pressure was breathed at rest and explained this in terms of a slowing of the cerebral circulation. Dripps & Comroe (1947) and Asmussen & Nielsen (1946) have reported similar findings, though Dripps & Comroe attributed them to irrita-

tion of the respiratory tract. Kety & Schmidt (1948) found that the inhalation of pure oxygen reduced the cerebral blood flow by about 13%. Lambertsen, Kough, Cooper, Emmel, Loeschcke & Schmidt (1953) have shown that when pure oxygen at a pressure of 3.5 atm is inspired by subjects at rest the slowing is sufficient to result in an almost normal  $pO_2$  in the jugular venous blood, in spite of the heavy load of extra oxygen carried in solution by the arterial blood. As a result by no means the whole of the brain is exposed to high pressures of oxygen. Under these circumstances the subject usually experiences the convulsions of oxygen poisoning after an exposure of 1 hr. When the subject inspires  $CO_2$  at a pressure of about 52 mm (Kough, Lambertsen, Stroud, Gould & Ewing, 1951), or takes mild exercise (Lambertsen, personal communication), the convulsions occur much earlier.  $CO_2$  probably acts by increasing the cerebral blood flow, and thereby reducing the protection from high tensions of oxygen afforded to the brain by circulatory changes; Lambertsen was unable to show a similar increase in blood flow during mild exercise (oxygen consumption, 1200 c.c./min), but Kleinerman & Sokoloff (1953) found an increase which was almost significant when their subjects performed mild exercise breathing air. In our subjects breathing 100%  $O_2$  at atmospheric pressure during very severe exercise the alveolar and probably also the arterial  $CO_2$  tensions were considerably elevated. We would suggest tentatively that the adverse effects which we experienced were caused by the exposure of large parts of the central nervous system to abnormally high tensions of oxygen. If the 'effective venous shunt' in the pulmonary circulation, which was mentioned earlier, was of the magnitude suggested, the inhalation of 66% oxygen would not have resulted in substantial increases of arterial  $pO_2$  so an increased circulation to the brain would have produced no ill effects. If, as a result of the very high arterial  $pO_2$  when 100% oxygen was breathed the haemoglobin passing through the brain were not reduced, the buffering capacity of the blood for  $CO_2$  would be impaired. The data of Lambertsen *et al.* (1953) are contrary to the view that oxygen poisoning results from the failure of the blood to transport  $CO_2$ , but a modest rise in the tissue  $CO_2$  pressure might contribute to the other adverse effects of oxygen at high pressure. There is, however, no positive evidence for these views; the absence of an increase of cerebral blood flow during Lambertsen's experiments on exercise does not support them, though it must be borne in mind that the exercise was not comparable to that performed by our subjects.

These considerations bring us back to the respiratory effects of 66 and 100%  $O_2$ . It might be thought from the data of Lambertsen and his colleagues that the increased  $pO_2$  in the blood vessels of the brain when 100%  $O_2$  is breathed would produce a small further rise in the  $pCO_2$  of the respiratory centre and hence a small increase in pulmonary ventilation, compared with the experiments using 66%  $O_2$ . We did, in fact, record a small difference in



two subjects, but, as already mentioned, the other two subjects showed small changes in the opposite direction. It may be that this effect was sometimes masked by slight differences in other variables, e.g. the blood lactate. It is clear from Fig. 1 that there was no systematic difference between the respiratory effects of 66 and 100 % O<sub>2</sub>.

#### SUMMARY

1. Two athletes and two non-athletic subjects ran on a motor-driven treadmill up various gradients. The intensity of the work was adjusted so as to ensure that each individual reached his breaking point between the 7th and the 10th minute when he breathed atmospheric air. In other experiments he performed the same exercise whilst breathing 33, 66, or 100 % O<sub>2</sub>.

2. Pulmonary ventilation, alveolar pCO<sub>2</sub> and pO<sub>2</sub> and blood lactate were measured frequently during each run. The time taken to reach a breaking point was also recorded.

3. In all instances, addition of oxygen to the inspired air increased the time required to reach a breaking point. The performance was improved more by 66 % and 100 % than by 33 % O<sub>2</sub>.

4. With 66 % O<sub>2</sub> three of the subjects did not reach a breaking point within 23 min. The discomfort which they had experienced when breathing air was replaced by a feeling of positive well-being. In contrast, when breathing 100 % O<sub>2</sub> they never felt elated, and all reached breaking points within 21 min.

5. Oxygen reduced the pulmonary ventilation and the blood lactate response, and allowed the alveolar pCO<sub>2</sub> to rise to higher levels. 33 % O<sub>2</sub> had a smaller effect than 66 % or 100 % O<sub>2</sub>. No systematic difference could be detected between the effects of 66 % and 100 % O<sub>2</sub> on respiration.

6. Two subjects exercised at a slightly lower intensity of work. Sudden changes were made in the inspired gas mixtures, from air to 66 % or 33 % O<sub>2</sub> in the course of the runs. These changes were followed extremely rapidly by reductions in the pulmonary ventilation and increases in the alveolar pCO<sub>2</sub>. Subjective improvement occurred over the space of a few breaths. On switching back to air, the reverse changes in the pulmonary ventilation and the alveolar pCO<sub>2</sub> followed very rapidly. These effects were not observed during moderate exercise.

7. Reasons were presented for regarding the respiratory effects of inhaling high concentrations of O<sub>2</sub> as being due to the abolition of an arterial anoxaemia which was thought to be present when air was breathed during exercise of more than a critical intensity. Relief of the anoxaemia might exert its effects through the carotid and aortic chemoreceptors, or by improving cardiac function, or both.

8. It was thought unnecessary to postulate the existence of an unknown respiratory stimulant liberated by muscles working under partially anaerobic conditions, though the possibility was not excluded.

9. The depressant action of 100% when compared with 66% O<sub>2</sub> was discussed. It was tentatively suggested that it might be due to increases in the cerebral circulation resulting from the excess of circulating CO<sub>2</sub> and lactate. Such an increase would nullify the protection from the deleterious effects of high-pressure oxygen afforded to the brain by the cerebral vasoconstriction which occurs at rest when pure oxygen is breathed.

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