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THE OXYGEN TENSION OF ARTERIAL BLOOD.

By JOHN HALDANE, M.A., M.D. AND J. LORRAIN SMITH, M.A., M.D. (One Figure in Text.)

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THE OXYGEN TENSION OF ARTERIAL BLOOD.

By
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THE chief interest of the present investigation centres round the question whether diffusion alone explains the transference of oxygen from the air of the pulmonary alveoli into the blood, or whether other important factors are concerned in this process. If the oxygen tension of the blood leaving the alveolar capillaries is always, or even occasionally, higher than that of the alveolar air, diffusion alone evidently cannot explain the transference.

The analogy presented by other organs of absorption or excretion would perhaps lead us to believe that absorption of oxygen by the lungs is probably not due to any simple physical process such as diffusion. On the other hand it does not seem at all clear that any physiological advantage would accrue from an active absorption of oxygen by the lungs. The red corpuscles of blood, saturated with air of alveolar oxygen tension (about $14\,^{\circ}/_{0}$ of an atmosphere in man), would contain very nearly as much oxygen as the hæmoglobin is capable of absorbing[1], so that any further increase in the oxygen tension of arterial blood would imply only a very trifling increase in the quantity of oxygen taken up by the blood. If, therefore, the exposure of the blood to the alveolar air is sufficiently prolonged under all ordinary circumstances for saturation to occur by diffusion alone, no appreciable advantage would apparently result from an active absorption of oxygen. On this point however we have no experimental data, so that there is thus not much

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[1] $99\,^{\circ}/_{0}$ of the total quantity capable of being taken up from air, according to Hüfner's determinations.

to be said on *a priori* grounds as to the probabilities in favour of the one or the other view as to the cause of absorption.

Before proceeding to give an account of our own experiments we must first refer to the chief investigations already made on the same subject.

Previous Investigations.

In 1868 Pflüger carried out by means of the blood pump careful determinations of the oxygen contained in arterial blood, and in a sample the same blood saturated with air. He found that the blood direct from the artery contained 24·7 % of oxygen (at 760 mm. and 0° C.), and that the same blood saturated with air contained 26·2 %[1]. If we accept this result, and interpret it in the light of Hüfner's more recent researches on the dissociation of oxyhæmoglobin[2] we are led to the conclusion that the oxygen tension of arterial blood is very low— about 5 % of an atmosphere. Pflüger's conclusion that the arterial blood is not normally saturated with air seemed to receive confirmation from further experiments by himself[3] and by Ewald[4], who found that in apnœa the percentage of oxygen in arterial blood was distinctly increased.

A further well-known series of experiments carried out in Pflüger's laboratory by Wolfberg[5], Strassburg[6], and Nussbaum[7] gave for result that the tension of carbonic acid and oxygen in venous blood as determined by the aerotonometer is on an average about the same as that of the air in a portion of the lung which has been blocked off by obstruction of its bronchus. From these experiments the conclusion was drawn that the passage of gas from the alveolar air to the blood and *vice versa* is due to diffusion alone. The oxygen tension of venous blood was found by this method to be about 3·5 % of an atmosphere. Such a result seems most difficult to understand in the light of Hüfner's work on the dissociation of oxyhæmoglobin. Venous blood is not more than about two-thirds saturated with oxygen; but with hæmoglobin two-thirds saturated the oxygen tension is only about 0·7 % of an atmosphere. This consideration seems to suggest the possibility of experimental errors or fallacies in connection with the aerotonometer and lung-

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[1] *Pflüger's Archiv*, I. p. 70. 1868.

[2] *Archiv f. (Anat. u.) Physiologie*, 1890, p. 1.

[3] *Loc. cit.* pp. 71–73.　　　　　　[4] *Pflüger's Archiv*, VII. p. 575. 1873.

[5] *Pflüger's Archiv*, IV. p. 465. 1871.　　　　[6] *Ibid.* VI. p. 65. 1872.

[7] *Ibid.* VII. p. 23.

catheter experiments. Such a possibility seems also to be suggested by some of the results obtained by Strassburg with lymph from the thoracic duct. Thus in one experiment[1] the quantity of lymph which passed through the aerotonometer was 29 c.c. The volume of oxygen contained in the aerotonometer at the beginning of the experiment was apparently about 0·54 c.c., and at the end 0·74 c.c. Thus 29 c.c. of lymph had apparently given off ·20 c.c. of oxygen to the apparatus. As the coefficient of absorption of lymph for oxygen cannot well be higher than that of water (·024 at 37°) this experiment would seem to indicate that the oxygen tension of the lymph was at least 30 % of an atmosphere. Such a high oxygen tension for lymph seems scarcely probable. Without entering into further criticisms we would venture to point out the need for further experimental control of these important investigations.

Direct determinations of the arterial oxygen tension were first made by Herter[2] with the aerotonometer. He obtained only minimal values, the highest being 10·44 % of an atmosphere.

The subject was again taken up some years ago by Bohr[3], who devised for the purpose a much more perfect apparatus (the "hæmataerometer") through which he was able to maintain during each experiment a constant and rapid stream of blood. He came to the unexpected conclusion that the oxygen tension may sometimes be slightly higher, and that the carbonic acid tension is often much lower in the arterial blood than in the alveolar air. From this he inferred that both absorption of oxygen and excretion of carbonic acid by the lungs are to a large extent active processes, and not due merely to diffusion.

In a still more recent series of experiments Fredericq[4] used an aerotonometer similar to Pflüger's original one, but so arranged that a continuous stream of blood trickled through the apparatus and back to the animal, as in Bohr's experiments. Fredericq found that the oxygen tension of arterial blood is about 12 to 14 % of an atmosphere, and is always a little lower in the arterial blood than in the alveolar air. He criticises Bohr's results on the ground that the latter did not present sufficient evidence that the gas tension in the blood and the air of the hæmataerometer had equalised themselves. This criticism does

[1] *Pflüger's Archiv*, VII. p. 88.
[2] *Zeitschrift für physiologische Chemie*, III. p. 98. 1879.
[3] *Skand. Archiv für Physiologie*, 1891, p. 236.
[4] *Centralblatt für Physiologie*, 1893, p. 33.

not explain away Bohr's main conclusions, since in several of his experiments the latter found that the carbonic acid tension in the air of the aerotonometer sank from a point higher than, to a point lower than, that of the expired air. In two experiments a corresponding, though slight, rise in the oxygen tension in the hæmataerometer over that in the expired air was also observed.

It appears to us that there are serious reasons for doubting the correctness of the values for oxygen tension obtained either directly by the aerotonometer, or indirectly by means of the blood-pump. In 1867 Pflüger published[1] a number of experiments in which he showed that arterial blood, especially if kept warm, immediately on leaving the body uses up part of its own oxygen. He observed that there is always a distinct darkening in the colour of arterial blood within a few seconds of its being shed. He also found that when blood was received straight from an artery into hot water in a very large vacuum (of 8 litres) instead of being pumped out in the ordinary way with a blood-pump possessing a 3 litre vacuum, the percentage by volume of oxygen obtained from the arterial blood was higher by from $0.2\,\%$ to $10\,\%$—on an average $1.98\,\%$. Hence on an average $9\,\%$ at least of the whole oxygen contained in arterial blood would seem to disappear very quickly after the blood leaves the body. This disappearance would account for a lowering in the oxygen tension of the shed blood from $21\,\%$ to about $3.5\,\%$ of an atmosphere, according to Hüfner's dissociation curve. Even if only $0.5\,\%$ by volume of oxygen (*i.e.* $2\,\%$ of the total quantity) had time to disappear before the blood passed through the aerotonometer, the oxygen tension would be lowered from $21\,\%$ to about $11\,\%$.

Some of Fredericq's later experiments[2] seem to afford strong confirmation to these suspicions. He found (experiment no. VII.) that when the animal was breathing a mixture containing $84.6\,\%$ of oxygen, the oxygen tension of the arterial blood, as determined by the aerotonometer, was nevertheless only $56.2\,\%$ of an atmosphere. This is just such a result as might be expected on the supposition that the oxygen tension falls considerably between the artery and the aerotonometer. On the diffusion theory supported by Fredericq, one would expect the oxygen tension of the aerotonometer, if the latter indicated correctly, to be about equal to the alveolar oxygen tension. With the high percentage of oxygen used by Fredericq oxygen would diffuse into the blood about 5 times as rapidly as usual, although the blood could only

[1] *Centralb. für die med. Wissensch.*, 1867, pp. 321, 722.
[2] *Centralb. für Physiologie*, 1894, p. 34.

take up a very little more of the gas. Hence, if the oxygen tension of the blood is only a little below that of the alveolar air under ordinary conditions, the difference ought to be still less, on the diffusion theory, when a mixture rich in oxygen is breathed. The difference actually found by Fredericq was, however, much greater.

These considerations tend to throw grave doubts on the results obtained by the aerotonometer; and, unless it can be shown that there is no loss of oxygen by the arterial blood in reaching or passing through the aerotonometer, it would seem that no stress can be laid on the low oxygen tensions inferred from blood-gas analyses, or from the experiments of Herter, Fredericq and others with the aerotonometer[1]. With Bohr's hæmataerometer, through which there is a very rapid flow of blood, the danger of a too low result would seem to be less.

Description of the New Method employed.

The method we have employed avoids the probable sources of fallacy of the aerotonometer, and at the same time presents the further advantage of being applicable under normal conditions to the animal or man experimented on. The experiments described in the present paper were all made on man.

The principle of the method has already been indicated in a recent paper by one of us[2], and is briefly as follows. The subject of the experiment continues to breathe air containing an exactly known very small percentage of carbonic oxide until a point is reached at which the percentage saturation of his hæmoglobin with carbonic oxide becomes constant. Now the final saturation with carbonic oxide of hæmoglobin solution brought into contact with gas containing carbonic oxide and oxygen depends on the relative tensions of the carbonic oxide and oxygen in the liquid, so that if the tension of carbonic oxide, and the final saturation of the hæmoglobin be known, the oxygen tension can be inferred[3]. Hence if in the living subject both the carbonic oxide tension in the blood leaving the lungs, and the final saturation of the hæmoglobin with carbonic oxide, are known, the oxygen tension of the blood leaving the lungs can be calculated. But the carbonic oxide tension of the blood

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[1] The carbonic acid tensions indicated by the aerotonometer may be considerably too high, since blood on being shed rapidly becomes less alkaline, so that its carbonic acid tension must rise.

[2] This *Journal*, xviii. p. 455. 1895.

[3] *Ibid.*, p. 450. See also the experiments given below.

leaving the lungs will (after absorption has ceased) be that of the inspired air, after allowance has been made for dilution of the latter by aqueous vapour. Therefore from a knowledge of the percentage of carbonic oxide breathed by the subject of the experiment, and of the final saturation of his blood with carbonic oxide, the oxygen tension of his arterial blood may be calculated.

The apparatus for continuously administering a given percentage of carbonic oxide to the subject of the experiment was exactly the same (including the mixing bottle and a spring clamp for the nose) as that described and figured in the previous paper. As regards regularity of working and complete comfort to the subject this apparatus left nothing to be desired. In the present experiments we took the additional precaution of analysing each time the gas left in the large measuring cylinder (C. Fig. 1, previous paper) at the end of an experiment, and allowing for the impurities found to be present. As these impurities could only consist of air or traces of carbonic acid we usually contented ourselves with determinations of the carbonic acid and oxygen or nitrogen. The latter gas was determined by absorbing the whole of the carbonic oxide and oxygen by means of ammoniacal cuprous chloride solution, and measuring the residue, which consisted of nitrogen. The amount of air could be calculated from the nitrogen or oxygen, as we found from several analyses in which the various gases were separately determined.

The method of determining the percentage saturation of the hæmo-globin with carbonic oxide was shortly described in the previous paper; but on account of the importance of these determinations a more full description seems desirable. A number of narrow test-tubes of exactly equal diameter (about $\frac{1}{4}$ inch) and each holding about 6 c.c. were taken, and 2·0 c.c. of water (saturated with air) were measured off from a narrow burette into each. At the beginning of an experiment 2 cubic millimetres of the blood of the subject were measured off in the ordinary way by means of a Gowers' hæmoglobinometer pipette into each of about six of the tubes, and the solutions well mixed. Each tube thus contained 2·0 c.c. of a 1°/₀ solution of the blood of the subject. 4 c.c. of the same solution were also thoroughly saturated with coal-gas and placed in another shorter tube (of the same diameter), which was filled full and corked up. In this tube the hæmoglobin was of course completely saturated with carbonic oxide. After the subject had breathed the carbonic oxide for a sufficient time 2 cubic millimetres of his blood were again measured off, and diluted with water in one of the tubes as before.

The solution in this tube was pinker than that in the tubes previously prepared. The relative degree of pinkness was determined as follows. A standard solution of carmine[1] was added from a narrow burette to one of the tubes of normal blood solution until its tint was the same as that of the blood under examination. Not more than ·05 to ·1 c.c. of carmine was added at a time, and the mean value was taken between what was just too little and just too much carmine. Addition of the carmine was then continued until the tint was equal to that of the blood solution saturated with carbonic oxide. Supposing that ·45 c.c. of carmine was required to produce equality of tint with that of the blood taken during the experiment, and 2·5 c.c. to produce equality of tint with that of the saturated blood, then, as 2·5 c.c. of carmine in 4·5 c.c. of liquid were required to produce saturation tint, and only ·45 c.c. of carmine in 2·45 c.c. of liquid to produce the tint of the blood under examination, the percentage saturation of the latter could be calculated by the following sum:

$$\frac{2 \cdot 5}{4 \cdot 5} : \frac{\cdot 45}{2 \cdot 45} :: 100 : x,$$

$$\therefore x = 33 \cdot 1.$$

A slight correction is required on account of the fact that carboxy-hæmoglobin is partly dissociated when diluted to a hundredth with water saturated with air. In a solution saturated with air and containing hæmoglobin 33°/₀ saturated with carbonic oxide the tension of the latter gas would, as shown below, amount to ·05°/₀ of an atmosphere. Accordingly, since the coefficient of absorption of carbonic oxide at 15° is ·025, water saturated with carbonic oxide at ·05°/₀ tension would contain in solution 2·5 × ·0005 = ·00125°/₀ by volume of carbonic oxide. But as blood saturated with carbonic oxide contains in combination about 20°/₀ by volume of the gas, the same blood diluted to a hundredth would contain ·2°/₀; and as ·00125 = ·6°/₀ of ·2 we must add ·6°/₀ to 33·1 in order to obtain the true result (33·7°/₀) in the above calculation. The similar allowances necessary with different saturations of the blood are as follows[2].

10°/₀	·2°/₀	40°/₀	·8°/₀	70°/₀	2·6°/₀
20	·3	50	1·1	80	4·4
30	·5	60	1·6	90	10·0

[1] For details as to the mode of preparation of this solution see this *Journal*, xviii. p. 465. 1895.

[2] This table of corrections is correct, as shown below, only when the titrations are made in winter daylight such as prevailed when our experiments were made. In the much

To determine the oxygen tension of the arterial blood of the subject from the percentage saturation of the hæmoglobin with carbonic oxide it is necessary to know accurately the percentage saturation of blood, or blood solution, which has been thoroughly shaken outside the body with air containing known percentages of carbonic oxide. A number of data on this point were given in the paper already referred to. As however great accuracy was now necessary, and the precaution had not been taken of analysing each time the residue of carbonic oxide contained in the burette used in making the mixtures[1], we began an entirely new set of determinations, in which the residue was always analysed, and the impurities (usually about 3 to 5 %) allowed for.

The result showed that the saturations previously obtained were markedly lower, so that we at first thought that the carbonic oxide formerly used had in spite of every care contained a considerable percentage of air. The new determinations were made about Christmas, whereas the old ones had been made in summer. On continuing the new series in April we were however much astonished to find that the results were mostly again about the same as the old ones, although there could now be no doubt as to the correctness of the percentages of carbonic oxide. After noticing that the high results were only obtained towards evening we at last found that bright daylight has a most marked action in diminishing the stability of carboxyhæmoglobin, and that the varying intensities of the light explained the irregularity of the results. When air containing even as much as ·1 % of carbonic oxide was shaken with blood solution in bright sunlight no pink colour at all could be observed in the solution; yet when the bottle was taken into the dark, or covered with a cloth, the ordinary-marked pink colour at once appeared on shaking. The experiment could be repeated again and again, the colour alternately appearing and disappearing, so that it was evident that the carbonic oxide was not oxidised or otherwise destroyed, but remained in the air of the bottle. Its affinity for the hæmoglobin must have been diminished by the sunlight to at least a

brighter daylight available in spring and summer the corrections would be larger unless special means were taken to partially darken the room. The following table gives the corrections necessary in a well-lighted room in summer. The data on which the table is based are given in a former paper (this *Journal*, XVIII. p. 451).

10 %	·2 %		40 %	1·5 %		70 %	4·0 %
20	·5		50	2·0		80	7·5
30	1·0		60	2·8		87·5	12·5

[1] See this *Journal*, XVIII. p. 463.

twentieth. On performing a corresponding experiment with hydrogen containing a trace of oxygen we could not observe any distinct action of the light on the stability of the oxyhæmoglobin, so that only the affinity of carbonic oxide, and not that of oxygen, would seem to be affected by the light. The Röntgen rays had no appreciable action on the stability of the carboxyhæmoglobin. The results given at p. 518 were obtained by shaking in bottles protected from the daylight by means of a cloth. The method employed was exactly the same in other respects as before, but with the greater precautions used, and the avoidance of light, the results were very concordant. A small correction was introduced for the very slight reduction in the percentage of carbonic oxide in the air of the saturating bottle produced by the absorption of carbonic oxide by the blood solution introduced. Experiments were made

(1) with 1 °/₀ solution of human blood at about 15° C.
(2) „ „ „ „ ox-blood and sheep's blood at about 15° C.
(3) „ „ „ „ human blood at 37° C.
(4) „ „ „ „ ox-blood at 37° C.

The results, as might be expected, were practically the same whether human blood, ox-blood, or sheep's blood was taken, and whether the determinations were at 15° or at 37° C. For this reason we have made one common curve from the whole of the data (Fig. 1). The individual results from which the curve is constructed are given at the end of the paper, together with an example of a single determination.

If the oxygen tension of arterial blood (the blood leaving the lungs) were the same as that of air we should expect that with a given percentage of carbonic oxide in the air breathed, the final saturation of the blood within the body would be the same as the saturation of blood when shaken outside the body with air containing the same percentage of carbonic oxide as in the air breathed. If the oxygen tension of arterial blood were lower or higher than that of air we should expect the final saturation within the body to be correspondingly higher or lower than in the blood outside the body. To calculate the exact arterial oxygen tension it is necessary to bear in mind that the percentage saturation of the blood depends practically on the relative tensions of the oxygen and carbonic oxide. The carbonic oxide tension, after absorption has ceased, will be that of the dry inspired air, after allowance has been made for the dilution of the latter with the aqueous vapour (about 6 °/₀) required to produce saturation at 37° C. The

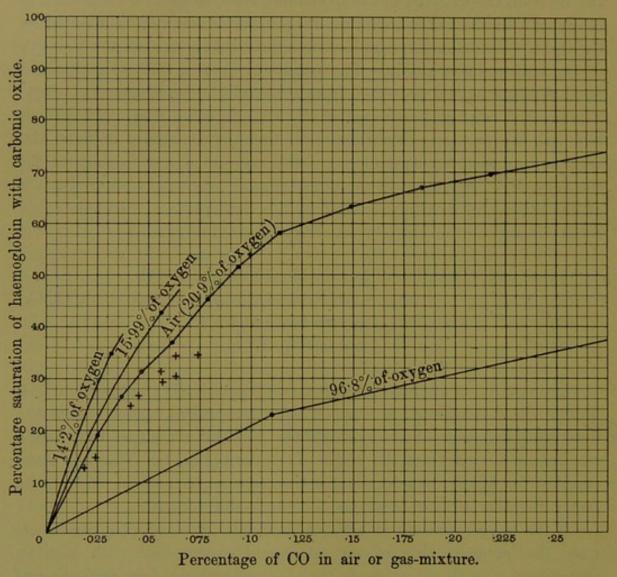method of making the calculation will be evident from the following
example.

FIG. 1.   The crosses indicate the results of the experiments on the oxygen tension of
the human arterial blood.

Let us suppose that the percentage of carbonic oxide breathed was
·060, so that after absorption had ceased the alveolar carbonic oxide
tension was ·0564 °/₀ of an atmosphere: also that the blood was found
to have become 47 °/₀ saturated when absorption had ceased.   With
·0564 °/₀ of carbonic oxide in presence of air (20·93 °/₀ of oxygen), the
blood outside the body would have become 35 °/₀ saturated, and the
relative mass influences on the hæmoglobin of the carbonic oxide and
oxygen would have been as 35 to 100 − 35, or as 35 to 65.   But the
saturation actually found in the blood of the body was 47 °/₀; hence the
relative mass influences of the two gases were as 47 to 100 − 47, or as

47 to 53, or as 35 to 39·5. Hence as the mass influence of the carbonic oxide was the same in both cases, the tension of the oxygen in the blood of the living body must have been reduced in the proportion of 65 : 39·5, or from 20·9 to 12·7.

To practically test this mode of calculation we made experiments in which blood solutions were shaken with gas-mixtures containing besides nitrogen various percentages of oxygen and carbonic oxide. The results were as follows:

		Percentage saturation of hæmoglobin with carbonic oxide	
		Calculated	Found
(1) 96·8°/₀ of oxygen and 3·2°/₀ of nitrogen	a. 0·376°/₀ of carbonic oxide	48	47·2
	b. 0·11°/₀ ditto	22·2	23
(2) 14·2°/₀ of oxygen and 85·8°/₀ of nitrogen	0·032 of carbonic oxide	32	35
(3) Expired air 15·99°/₀ of oxygen, and 4·06 of carbonic acid	a. ·046 ⎫ average ·056 b. ·063 ⎬ c. ·060 ⎭	37·0 ⎫ average 41 43·7 ⎬ 42·4 ⎭	40·8 ⎫ average 42·5 40·2 ⎬ 46·4 ⎭
(4) Pure hydrogen	0·036 carbonic oxide	100	97

These experiments show that the method of calculation employed is perfectly correct.

In making the experiment on man we found that the best percentages to employ were from about ·045 to ·06°/₀ of carbonic oxide. With lower percentages the change in tint of the blood was less marked, so that errors of titration told more seriously. With higher percentages, on the other hand, the condition of the subject evidently became abnormal, and the experiments, if of sufficiently long duration, were followed by severe headache and lassitude, lasting for many hours.

The following is a record of the results of the experiments.

Exp. 1. Subject A, 23/12/95. Corrected percentage of CO = ·049 for first 1½ hours: afterwards ·043.

After 1 hr. 22 mins. saturation of blood = 19·1 °/₀ ∴ oxygen tension = —
„ 2 hrs. 0 „   „   „   = 24·1 „   „   „   = 26·8 °/₀
„ 2 „ 33 „   „   „   = 24·8 „   „   „   = 25·8 „
„ 3 „ 25 „   „   „   = 25·3 „   „   „   = 24·7 „

Average 24·7 °/₀   25·8 °/₀

EXP. 2. Subject B, 25/12/95. Corrected percentage of CO for first 40 minutes = ·086, for next 45 minutes = ·073, for next 20 minutes = ·087, for next 85 minutes = ·078.

After 1 hr. 14 mins. saturation of blood = 33·1 % ∴ oxygen tension = —
,, 1 ,, 56 ,, ,, ,, = 36·6 ,, ,, ,, = 28·5 %
,, 2 hrs. 29 ,, ,, ,, = 42·2 ,, ,, ,, = 22·5 ,, *
,, 2 ,, 50 ,, ,, ,, = 42·0 ,, ,, ,, = 22·9 ,, *
,, 3 ,, 10 ,, ,, ,, = 47·1 ,, ,, ,, = 16·8 ,, *

* Minimum values only.

During this experiment the working of the apparatus was irregular, owing to temporary slowing two or three times of the ventilation current, particularly after the second determination. The subject felt abnormal, and was giddy on standing up at the end. The experiment was followed by severe headache, lasting for about 12 hours. For further remarks see below, page 512.

EXP. 3. Subject A, 26/12/95. Corrected percentage of CO = ·061 throughout.

After 1 hr. 20 mins. saturation of blood = 24·1 % ∴ oxygen tension = —
,, 1 ,, 50 ,, ,, ,, = 29·1 ,, ,, ,, = 27·5 %
,, 2 hrs. 12 ,, ,, ,, = 29·1 ,, ,, ,, = 27·5 ,,
,, 3 ,, 37 ,, ,, ,, = 29·1 ,, ,, ,, = 27·5 ,,
,, 3 ,, 3 ,, ,, ,, = 29·1 ,, ,, ,, = 27·5 ,,
Average 29·1 % 27·5 %

EXP. 4. Subject B. 27/12/95. Corrected percentage of CO for first 70 minutes = ·082, thereafter = ·067.

After 1 hr. 33 mins. saturation of blood = 32·4 % ∴ oxygen tension = 26·7 %
,, 2 hrs. 5 ,, ,, ,, = 33·1 ,, ,, ,, = 25·5 ,,
,, 2 ,, 34 ,, ,, ,, = 37·8 ,, ,, ,, = 21·0 ,,
,, 2 ,, 54 ,, ,, ,, = 33·1 ,, ,, ,, = 25·5 ,,
Average 34·1 % 24·7 %

EXP. 5. Subject A, 28/12/95. Percentage of CO = ·067 throughout.

After 1 hr. 15 mins. saturation of blood = 26·6 % ∴ oxygen tension = —
,, 1 ,, 45 ,, ,, ,, = 29·5 ,, ,, ,, = 30·6 %
,, 2 hrs. 11 ,, ,, ,, = 30·5 ,, ,, ,, = 29·2 ,,
,, 2 ,, 36 ,, ,, ,, = 30·5 ,, ,, ,, = 29·2 ,,
,, 3 ,, 10 ,, ,, ,, = 30·5 ,, ,, ,, = 29·2 ,,
Average 30·25 % 29·5 %

EXP. 6. Subject C, 31/12/95. For 40 minutes percentage of CO = ·068 %. Thereafter = ·059 %.

After 1 hr. 24 mins. saturation of blood = 27·9 % ∴ oxygen tension = —

,,	2 hrs. 0	,,	,,	,,	= 30·0 ,,	,,	,,	= 25·4 %
,,	2 ,, 24	,,	,,	,,	= 31·7 ,,	,,	,,	= 23·9 ,,
,,	2 ,, 38	,,	,,	,,	= 33·1 ,,	,,	,,	= 22·3 ,,

Average 31·1 %   23·9 %

EXP. 7. Subject A, 5/1/96. Percentage of CO = ·078 % for first 2¾ hours. Thereafter reduced to = ·055 %.

After

1 hr. 20 mins.	sat. of blood	= 23·4 % ∴	oxygen tension =		—		
1 ,, 40	,. ,,	,,	= 30·5 ,,		,,	,,	= —
2 hrs. 4	,, ,,	,,	= 34·9 ,,		,,	,,	= 30·6 %
2 ,, 23	,, ,,	,,	= 35·5 ,,		,,	,,	= 29·8 ,,
3 ,, 12	,, ,,	,,	= 35·5 ,,		,,	,,	= [19·2 to 29·8 %]
4 ,, 0	,, ,,	,,	= 35·5 ,,		,,	,,	= [19·2 to 29·8 ,,]

Average 35·2 %   30·2 %

In this experiment we intended to ascertain whether a reduction by ·023 % of the percentage of CO breathed would be followed by a corresponding reduction in the saturation of the blood. No appreciable reduction was, however, observed within 1¼ hours (see p. 514).

EXP. 8. Subject B, 6/1/96. Percentage of CO = ·0476 throughout.

After 1 hr. 37 mins. saturation of blood = 28·8 % ∴ oxygen tension = 23·8 %

,,	2 hrs. 8	,,	,,	,,	= 27·8 ,,	,,	,,	= 23·8 ,,
,,	2 ,, 38	,,	,,	,,	= 27·8 ,,	,,	,,	= 23·8 ,,
,,	3 ,, 8	,,	,,	,,	= 27·8 ,,	,,	,,	= 23·8 ,,
,,	3 ,, 38	,,	,,	,,	= 26·9 ,,	,,	,,	= 24·9 ,,
,,	3 ,, 58	,,	,,	,,	= 26·4 ,,	,,	,,	= 25·5 ,,

Average 27·4 %   24·3 %

To the above we add the results of two experiments (Nos. 9 and 10) given in the former paper[1]. The stock of gas used for filling the cylinder for these experiments was analysed and found to contain 93·3 % of carbonic oxide. The gas in the cylinder must therefore, judging from the other experiments, have contained about 10 % of air, and the percentage of carbonic oxide in the air breathed has been corrected on this basis. We have not added the results of experi-

[1] This *Journal*, XVIII. p. 44. 1895.

ment 11 of the former paper, as the gas used was not analysed. The results however agree closely with those of the experiments given in the present paper.

Exp. 9.　Subject B, 10/7/95.　Percentage of CO = ·025 %.

After 1 hr.	0 mins.	saturation of blood =	7 %	∴ oxygen tension =	—
„	2 hrs.	0 „	„	„	„	= 11 „	„	„	= —
„	2 „	30 „	„	„	„	= 15 „	„	„	= 26·9 %
„	3 „	0 „	„	„	„	= 15 „	„	„	= 26·9 „
„	3 „	30 „	„	„	„	= 14 „	„	„	= 29·1 „

Average　14·7 %　　　　　　　　　27·6 %

Exp. 10.　Subject B, 12/7/95.　Percentage of CO = ·019.

After 1 hr.	saturation of blood =	8 %	∴ oxygen tension =	—
„	2 hrs.	„	„	= 13 „	„	„	= 22·7 %
„	3 „	„	„	= 13 „	„	„	= 22·7 „
„	4 „	„	„	= 13 „	„	„	= 22·7 „

Average　13 %　　　　　　　　　22·7 %

The results of the experiments are shown graphically in Fig. 1. The crosses represent the average results of each experiment. In representing the percentages of carbonic oxide breathed allowance is made for dilution of the air with aqueous vapour within the lungs. The curves represent the results obtained outside the body with carbonic oxide and air, and other gas mixtures. The data from which the curve for air is constructed are given at page 518.

Taking all the determinations in which a steady result was obtained the average oxygen tensions found were as follows.

Experiment	1	25·8 % of an atmosphere.
„	3	27·5 „	„
„	4	24·7 „	„
„	5	29·5 „	„
„	6	23·9 „	„
„	7	30·2 „	„
„	8	24·3 „	„
„	9	27·6 „	„
„	10	22·7 „	„

Average　26·2 %

The alveolar oxygen tension for man has recently been carefully calculated by Loewy. He bases his calculations (1) on the composition

of expired air, (2) on the assumption, which can hardly be avoided, that the expired air is mixed with a quantity of air occupying the "dead space" between the opening of the nose or mouth and the alveoli, (3) on the fact that the air in the alveoli is saturated at 37° with moisture, and therefore diluted with about 6% of aqueous vapour. As the result of measurements of the volume occupied by plaster casts of the air-passages he estimates the dead space at about 140 c.c., and he confirms this estimate by the results of careful experiments which enabled him to assign maximum and minimum values to the extent of the dead space[1]. In this way he estimated the alveolar oxygen tension as about 12·6 to 13·5% of an atmosphere. The mean of four experiments during rest was 13·15%[2].

If we accept this value it follows from the results of our experiments that the oxygen tension of human arterial blood is normally about twice as high as that of the air in the pulmonary alveoli. This being so it follows that diffusion alone does not explain the absorption of oxygen through the lungs.

This conclusion is of such high importance that it is necessary to test it in every way possible.

Several possible sources of fallacy will at once suggest themselves.

1. *Sources of error in the titrations.*

To test the degree of accuracy of the blood titrations we made a number of known mixtures of defibrinated blood saturated with coal gas with the same blood shaken with air. In each case a drop of the known mixture was placed upon a finger, and 2 cm. of it measured off with the pipette, and the saturation with carbonic oxide estimated with carmine, just as in the determinations during an experiment on blood from a living subject. As the Belfast coal gas was found to contain on an average about 20% of carbonic oxide a slight correction was made for the carbonic oxide (about 0·5%) present in simple solution in the saturated blood. The results were as follows.

	Calculated		Found	Error
I	51·2%	*a.*	48·6%	− 2·6%
		b.	50·9	− 0·3
II	51·2	*a.*	50·2	− 1·0
		b.	51·7	+ 0·5

[1] *Pflüger's Archiv*, LVIII. p. 416. 1894.
[2] Loewy, *Untersuchungen über die Respiration und Circulation &c.*, 1895, p. 26.

	Calculated	Found		Error
III	51·2	*a.*	50·9	− 0·3
		b.	51·4	+ 1·2
IV	68·1	*a.*	69·0	+ 0·9
		b.	69·0	+ 0·9
V	68·1		68·8	+ 0·7
VI	51·2		54·0	+ 2·8
		Average error		+ 0·3

These results show that the limit of error in the estimations of the saturation of the blood with carbonic oxide is within 3 %, and that there is practically no tendency to a constant error in one direction or the other. Errors from mistakes in titration thus cannot appreciably affect the average results, and errors in the oxygen tensions obtained in individual experiments cannot well exceed about 3 % of an atmosphere.

2. *Effects of dilution of the hœmoglobin.*

The dissociation curve (Fig. 1) for hæmoglobin outside the body was obtained with dilute blood solutions, and it might seem possible, though not probable, that a different curve might be obtained with undiluted blood in which the red corpuscles were intact. We tested this possibility as follows. About ·3 c.c. of blood, taken quite fresh from one of ourselves, was defibrinated, and placed, by means of a pipette inserted air-tight through the cork, in a flask of about 600 c.c. capacity, which had been filled with the mixture of air and carbonic oxide. The blood was spread in a thin layer over the bottom of the flask, which was then completely immersed in a water-bath at 37° C., and kept in gentle motion for at least an hour, so as to insure saturation of the hæmoglobin to the maximum extent. We found half-an-hour insufficient, and if the blood was left standing quietly, even an hour did not produce more than half the final saturation.

The results were as follows:

% CO in air	% saturation of hæmoglobin
·057	35·4
·058	34·3
·038	31·9
Average ·051	33·9

The average result with dilute solutions of blood was 33·2, so that undiluted blood gives practically the same result as diluted blood.

3. *Effects of carbonic acid.*

It might be suspected that the presence of carbonic acid in the venous blood and pulmonary alveoli might in some way alter the relative affinities of carbonic oxide and oxygen for hæmoglobin. That this is not the case, however, is shown by the three experiments with expired air (containing $4·06°/_0$ of carbonic acid) quoted on page 507.

4. *Had absorption of carbonic oxide completely ceased when the determinations of oxygen tension were made?*

As regards the answer to this question we believe that the experiments leave no room for reasonable doubt. During the first $1\frac{1}{2}$ hours the saturation of the blood increased rapidly. The determinations show that at the end of about $1\frac{1}{2}$ hours this rapid absorption suddenly ceased. There might be a slight apparent increase or diminution afterwards, but except in experiment 2 we believe that these slight changes were only apparent. They are within the limits of error in titration, and reference to the notes shows the apparent difference to have been brought about by slight changes in the quantity of carmine necessary to reproduce the tint of complete saturation. In many cases the light was failing and at the same time changing in quality towards the end of the experiment, and when this was the case less carmine was needed to reproduce the saturation tint. Experiment VIII., which was the longest of the series, was purposely begun very early, so as to avoid the failing light, and in this case there was not the slightest apparent increase in the saturation during the 2 hours 21 minutes succeeding the first $1\frac{1}{2}$ hours. We were thus quite convinced that there was no fallacy due to incomplete cessation of absorption. In experiment II. there was an apparent increase, after the first two hours, of the saturation of the hæmoglobin; in this experiment, however, owing to irregularity in the water pressure employed for aspiration, the air current two or three times slowed down, particularly after the second determination, so that the percentage of carbonic oxide breathed became temporarily much higher than stated. During these periods the saturation of the blood must have rapidly increased[1]. To get rid of this increase several hours would probably have been required, since the conditions for the giving-off of carbonic oxide were enormously less

[1] See this *Journal*, xviii. p. 456. 1895.

favourable than the conditions for increased absorption during the periods when the percentage of carbonic oxide in the air was increased. The same considerations completely explain the fact that in experiment No. VIII., in which the percentage of carbonic oxide breathed was purposely reduced from ·078 to ·055 there was no appreciable diminution in the saturation of the blood after $1\frac{1}{4}$ hours. It was shown in a former paper that, even after breathing fresh air for three hours, about a third of the carbonic oxide which had been previously absorbed still remained in the blood [1].

5. *Is carbonic oxide oxidised within the body?*

It is an old opinion, due originally, we believe, to Bernard, that carbonic oxide is oxidised within the body, and thus got rid of. This theory seems to have been put forward to explain the disappearance of carbonic oxide from the blood consistently with the erroneous belief that carboxyhæmoglobin is not dissociated in presence of air.

Were it the case that carbonic oxide is oxidised to any appreciable extent within the living body the method we have employed would give erroneous results. It was thus necessary to examine this question with great care. Careful investigations as to whether carbonic oxide is oxidised in the living body were made by Gaglio [2].

He placed an animal with a known volume of carbonic oxide in a Regnault and Reiset's respiration apparatus for some hours, at the end of which time he carefully determined by combustion the residual carbonic oxide, air being led through the apparatus so as to wash out all the carbonic oxide, and enable the animal to get rid of all the carbonic oxide present in its blood. The percentage loss of carbonic oxide in the body of the animal and in the apparatus was as follows in these experiments:

	% of loss out of total CO used
No. 1	3·1
„ 2	2·2
„ 3	4·1
„ 4	2·2
„ 5	2·8
Average	2·9

[1] This *Journal*, xviii. p. 438.　　　[2] *Archiv für exper. Pathol.* xxii., p. 236. 1887.

In a control experiment, with no animal in the apparatus, the percentage loss was found to be exactly the same ($2\cdot8\,\%$) as the average loss when an animal was present. Hence no carbonic oxide was oxidised in the body of the animal.

The question has also been investigated by Martin[1], whose experiments do not seem, however, to have been carried out by such an accurate method. He found that (in two experiments) there was a loss of 11 and $7\cdot5\,\%$ of the carbonic oxide employed. This small loss may, however, have easily been due to an experimental error.

To obtain independent evidence we made the following experiment. Carbonic oxide was breathed until the blood was $33\,\%$ saturated. The subject was then made to breathe through a tin vessel containing potash lime into and out of a bladder, oxygen being at the same time supplied through a side tube in sufficient amount to prevent the bladder from collapsing. The saturation of the blood with carbonic oxide was now determined, and the determination repeated at intervals. As no appreciable quantity of carbonic oxide could escape through the lungs with this arrangement, any diminution in the saturation of the blood with carbonic oxide would indicate the occurrence of oxidation of carbonic oxide within the body. The results of the experiment were as follows:

3 minutes after beginning to breathe into bag. Saturation of blood $33\cdot3\,\%$
10   ,,   ,,   ,,   ,,   ,,   ,, $33\cdot3$,,
50   ,,   ,,   ,,   ,,   ,,   ,, $33\cdot3$,,
1 hour   ,,   ,,   ,,   ,,   ,, $33\cdot3$,,

A sample of blood taken 35 minutes after the experiment ceased was $25\,\%$ saturated.

This experiment shows that within an hour there was no appreciable disappearance of carbonic oxide from the body when escape through the lungs was prevented. Another similar experiment, in which, however, the blood was only $18\cdot5\,\%$ saturated, gave exactly the same result. Oxidation, or disappearance in any other way, of the carbonic oxide present in the body, cannot therefore affect the accuracy of our method of determining the oxygen tension.

[1] *Comptes Rendus*, cxv. 835. 1892.

6. *Does carbonic oxide pass freely through the pulmonary epithelium?*

It might be imagined that the pulmonary epithelium actively resists the passage inwards of carbonic oxide, and that for this reason the carbonic oxide tension in the blood can never become as high as in the alveoli. If it be once admitted that in the taking up or giving off of gases through the pulmonary epithelium the latter may play an active part, there seems no inherent improbability in the view that the epithelium may actively oppose the passage of carbonic oxide inwards by diffusion. There are, however, many facts which render this view exceedingly improbable. In the first place it is evident from our own experiments, and those in the previous paper[1] that when a given percentage of carbonic oxide is breathed the gas is absorbed with great ease and rapidity up to a certain point of saturation, at which absorption suddenly ceases (after about $1\frac{1}{2}$ hours in the experiments recorded above). This point varies with the percentage of gas breathed. The sudden cessation of the absorption can hardly be otherwise explained than on the assumption that a point is reached at which the carbonic oxide absorbed in the first part of the alveolar capillaries begins to be driven out again in the succeeding part, where the oxygen tension is high (see the previous paper, p. 456). Were the cessation of absorption due to active resistance on the part of the alveolar epithelium, one would not expect the absorption to be so very rapid and complete (allowance being made for the dead space), nor the cessation of absorption to occur so sharply, nor the point of cessation to vary so definitely with the percentage of carbonic oxide breathed.

Finally we must refer to the evidence presented in another previous paper by one of us[2], that carbonic oxide is in its action on living protoplasm simply an indifferent gas, like nitrogen or hydrogen, which appear to diffuse freely through all the tissues. It was shown in the paper referred to that a tension of a whole atmosphere of carbonic oxide is not poisonous to a mouse, provided that oxygen at two atmospheres' pressure is also present, so that a sufficient amount of oxygen in simple solution in the blood is supplied to the animal; also that cockroaches, which are exceedingly sensitive to the action of gases, will live quite

[1] This *Journal*, xviii. p. 430. In the previous paper it was estimated (p. 446) that usually about half the carbonic oxide inhaled is absorbed up to the point where absorption suddenly ceases. From the more accurate data obtained in the present paper it would seem, from a similar calculation, that in reality about 70 % is absorbed.

[2] This *Journal*, xviii. p. 201.

well for a fortnight in an atmosphere containing 80 % of carbonic oxide. The same animals are almost instantly rendered insensible by a corresponding percentage of carbonic acid.

Our investigations as to possible sources of fallacy in the method employed have thus led to purely negative results; and, as there appear to be sources of very serious error in the aerotonometer method of Pflüger we can at present see no reason to doubt the accuracy of the very high values which we have obtained for the oxygen tension of arterial blood. Our experiments thus strongly support the conclusion originally arrived at by Bohr, that diffusion alone does not explain the interchange of gases between the blood and the air of the pulmonary alveoli.

A considerable part of our work was carried out in the Chemical Laboratory of Queen's College, Belfast, and we beg to express to Professor Letts our thanks for his kindness in placing the resources of the laboratory at our disposal.

SUMMARY OF CHIEF CONCLUSIONS.

1. The oxygen tension of human arterial blood as it leaves the lungs is about 26·2 % of an atmosphere, or 200 millimetres of mercury.

2. Diffusion alone does not explain the passage of oxygen from the air of the pulmonary alveoli to the blood.

APPENDIX.

I. *Results of experiments in which $1\,°/_0$ blood solutions were shaken in the dark to saturation with mixtures of carbonic oxide and air.*

Percentage of CO in the air used		Percentage saturation of hæmoglobin with CO	Percentage of CO in the air used		Percentage saturation of hæmoglobin with CO
	·051	34·3	Ox blood	·025	19·0
	·0585	35·0	at about	·065	39·1
	·060	36·8	15° C.	·102	56·9
	·076	45·2		·140	60·4
	·078	46·5	Sheep's blood		
Human blood	·090	47·25	at about	·059	37·5
at about	·090	51·1	15° C.	·114	55·0
15° C.	·109	56·7		·035	25·9
	·115	59·1		·039	26·9
	·159	65·6	Human blood	·064	35·9
	·183	66·9	at 37° C.	·075	45·7
	·228	69·4		·117	58·6
	·430	85·0	Ox blood	·044	30·5
			at 37° C.	·045	28·2
				·206	69·0

Protocol of a single experiment.

Readings of burette delivering carbonic oxide		Readings of meter (correct) measuring air current in litres per minute
6·25 P.M.	14·0	0·47
6·26	12·8	0·47
6·27	11·6	0·47
6·28	10·45	
6·29	9·3	
6·30	8·1	

$$5\,)\,\overline{5\cdot9}$$

1·88 c.c. per minute, ∴ percentage of CO = ·251

Corrected for CO absorbed by hæmoglobin = ·244

Further corrected for impurity of CO   = ·228 $°/_0$

Titration with carmine up to tint of solution taken from saturating bottle

2·4 c.c.	not enough		3·4 c.c.	right
2·8 ,,	,,		3·6 ,,	right
3·0 ,,	not quite enough		3·8 ,,	slightly too much.
3·2 ,,	right			

Mean = 3·4.

Titration up to saturation tint

6·0 c.c.	not enough		7·2 c.c.	right
6·4 ,,	not quite enough		7·6 ,,	slightly too much
6·8 ,,	right			

Mean = 7·0.

∴ percentage saturation $= \dfrac{3\cdot4}{8\cdot4} \times \dfrac{12}{7} \times 100 = 69\cdot4\,°/_0$.

Analysis of residual gas from burette.

Nitrogen in gas burette	$= 5\cdot04$
+gas taken for analysis	$=15\cdot76$
$\therefore$ gas taken	$=10\cdot72$
After absorption of CO_2	$=15\cdot76$
$\therefore CO_2$	$= 0\cdot00$
After absorption of CO and O_2	$= 5\cdot59$
$\therefore N_2$ in gas taken	$= 0\cdot55 = \cdot696$ of air $= 6\cdot50\,^0/_0$
$\therefore$ CO in gas taken	$=10\cdot024 = 93\cdot50\,^0/_0.$

II. *Protocol of an experiment (No. 3) on the oxygen tension of arterial blood.*

Subject A. Breathing began at 11.13.

Readings of large meter (correct)		Readings of measuring cylinder.	
11.8 A.M.	659 litres	30 cc. (20 drops of water per 10 seconds)	
11.23	793	140 (21 ,, ,, ,,)	
11.43	971	255 (17 ,, ,, ,,) *	
11.58	1105	340 (17 ,, ,, ,,)	
12.13 P.M.	1240	425 (17 ,, ,, ,,)	
12.28	1371	510 (17 ,, ,, ,,)	
12.58	1636	680 (17 ,, ,, ,,)	
1.13	1768	770 (17 ,, ,, ,,)	
1.28	1901	855 (17 ,, ,, ,,)	
1.43	2033	940 (17 ,, ,, ,,)	
1.58	2166	1025 (17 ,, ,, ,,)	
2.13	2298	1110 (17 ,, ,, ,,)	

* At 11.31 the rate of delivery of water into the measuring cylinder was altered to 17 drops per 10 seconds.

The percentage (uncorrected) of CO breathed was thus perfectly constant throughout the experiment after 11.31, and $=\dfrac{1\cdot110-\cdot255}{2298-971}\times100=\cdot0644.$

Analysis of residual gas from cylinder.

Volume taken $=20\cdot165.$

After absorption of $CO_2=20\cdot155$

$\qquad\qquad \therefore\quad CO_2=\quad\cdot01\ =0\cdot05^0/_0.$

After absorption of $O_2=19\cdot955$

$\qquad\qquad \therefore\quad O_2=\quad\cdot20\ =0\cdot99^0/_0=4\cdot74^0/_0$ of air.

$\therefore$ the CO contained $4\cdot79^0/_0$ of impurity.

$\therefore$ the true percentage of CO breathed was $\cdot061.$

Determination of the saturation of the blood with CO.

1) at 12.33 P.M.

A. *For tint of sample.*

$\cdot2$ c.c. of carmine, not quite enough.

$\cdot3$,, ,, right.

$\cdot4$,, ,, slightly too much.

B. *For tint of full saturation.*

2·2 c.c. of carmine, not quite enough.
2·4　　,,　　　　,,　　　right.
2·6　　,,　　　　,,　　　right.
2·8　　,,　　　　,,　　　slightly too much.

$\therefore$ saturation of sample $=\dfrac{\cdot 3}{2\cdot 3}\times\dfrac{4\cdot 5}{2\cdot 5}\times 100=23\cdot 5 \%$.

Corrected for dissociation $=23\cdot 9\ \%$.

(2)　at 1.3 P.M.

A. *For tint of sample.*

·3 c.c. of carmine, not quite enough.
·4　　,,　　　　,,　　　right.
·5　　,,　　　　,,　　　slightly too much.

B. *For tint of full saturation.*

2·6 c.c. of carmine, not quite enough.
2·8　　,,　　　　,,　　　right.
3·0　　,,　　　　,,　　　slightly too much.

$\therefore$ saturation of sample $=\dfrac{\cdot 4}{2\cdot 4}\times\dfrac{4\cdot 8}{2\cdot 8}\times 100=28\cdot 6\ \%$.

Corrected for dissociation $=29\cdot 1\ \%$.

(3) at 1.25 P.M., (4) at 1.50 P.M., and (5) at 2.16 P.M., gave exactly the same results as (2).

Calculation of oxygen tension.

CO tension in the (dried) air breathed was ·061 % of an atmosphere.

$\therefore$ CO tension in the (moist) air of the pulmonary alveoli was ·057 % of an atmosphere. Now with the same CO tension in pure air outside the body hæmoglobin would become 35 % saturated, whereas the arterial blood only became 29·1 % saturated. Hence in the arterial blood the oxygen tension must have been increased above atmospheric oxygen tension (20·9 % of an atmosphere) in the proportion of

$$\frac{29\cdot 1}{100-29\cdot 1}\ \text{to}\ \frac{35}{100-35},\ \text{or from 20·9 to 27·5.}$$