THE ACTION OF CARBONIC OXIDE ON MAN.

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THE chief aim of the present investigation has been to determine experimentally the causes of the symptoms produced in man by carbonic oxide, and particularly the relation of the changes in the blood to the symptoms, to the percentage of carbonic oxide breathed, and to the period during which the inhalation is continued.

Method of estimating the saturation of blood with carbonic oxide.

In blood saturated, or partly saturated, with carbonic oxide, the presence of the carbonic oxide is usually ascertained by reducing the blood and then examining it with an ordinary spectroscope. There is however a more direct, and at the same time more delicate method of recognising the presence of carbonic oxide—namely by simple observation of the colour of the diluted blood. Undiluted blood when saturated with carbonic oxide and examined in bulk cannot be distinguished by its colour alone from blood saturated with air. After sufficient dilution, however, there is a striking difference. The normal blood gives a yellow, and the carbonic oxide blood a pink colour. Utilising this difference in tint I have determined the relative saturations of the hæmoglobin with carbonic oxide in different specimens of blood by determining the relative amounts of their differences in tint from the tint of normal blood.

By mixing dilute carmine solution with dilute oxyhæmoglobin solution it is possible to reproduce exactly the tint of dilute carboxyhæmoglobin. Hence carmine solution may be employed for estimating the percentage saturation of blood with carbonic oxide. If blood be diluted a hundred times, and a portion of the solution be saturated

with carbonic oxide, it requires somewhat more than an equal volume of carmine solution of about ·01 % strength to bring the unsaturated portion to the same tint and intensity of colour as the saturated portion. The exact relation of the carmine solution to the blood solution requires of course to be determined by trial, and if necessary adjusted.

In applying this method to human blood I employed narrow test-tubes, similar to those of Gowers' hæmoglobinometer, and each holding about 5 or 6 c.c. They were made from a piece of glass tubing of even bore, and of about $\frac{3}{16}$th inch internal diameter. 2·0 c.c. of water having been measured from a narrow burette into one of the tubes, ·02 c.c. of blood, obtained by pricking the finger, was measured off in the pipette of a Gowers' hæmoglobinometer, and mixed with the water in the tube. A similarly diluted solution of the blood was well shaken with carbonic oxide, or, more conveniently, with coal gas, and placed in another (shorter) tube, which was filled quite full and corked. This latter solution was prepared in a larger test-tube, or small bottle, which was filled with coal gas through a tube, and quickly closed with the thumb before the gas had time to escape.

Standard carmine was now (in the first four experiments) added from a narrow burette to the blood under examination, until the tint was the same as that of the saturated blood solution. When the tints became nearly equal the carmine was added in quantities of not more than ·2 c.c. at a time, and the points were noted at which there was just appreciably too little and just appreciably too much carmine, the mean between these points being taken as the correct result. The calculation of the percentage saturation is illustrated by the following example. 2·1 c.c. of carmine required to be added to every 2·0 c.c. of diluted normal blood to reproduce the saturation tint. With a specimen of partially saturated blood only 1·6 c.c. of carmine were required. In the latter specimen $\frac{2{\cdot}1 - 1{\cdot}6}{2{\cdot}1} = \frac{{\cdot}5}{2{\cdot}1} = 24\%$ of the hæmoglobin was combined with carbonic oxide.

To test the method defibrinated ox-blood was shaken up and divided into two portions. One of these was saturated with carbonic oxide by prolonged shaking in a large flask with coal gas several times renewed. Several definite mixtures were then made of the saturated with the unsaturated blood, and from these mixtures specimens were taken with the Gowers' pipette, and the percentage saturation estimated. The results were as follows:

TABLE I.

Actual percentage saturation	Saturation found		Percentage Error	
	Uncorrected	Corrected	Uncorrected	Corrected
50	52	55	+ 2	+ 5
	48	51	− 2	+ 1
100	89	101	− 11	+ 1
	90	102	− 10	+ 2
	90	102	− 10	+ 2
33	30	31·5	− 3	− 1·5
	33	34·5	± 0	+ 1·5
	27	28·5	− 6	− 4·5
67	67	72	± 0	+ 5
80	74	80	− 6	± 0
17	21	22	+ 4	+ 5
	15	16	− 2	− 1
8·5	10	10·5	+ 1·5	+ 2
20	17	18	− 3	− 2
	15	16	− 5	− 4
Average			− 3·4	+ 0·8

These results shew that the method is fairly accurate, and may be relied on to within about 5 %. Above about 70 %, however, the uncorrected results become distinctly too low, and are fully 10 % too low when the blood is completely saturated.

The reason for the low results is that when blood containing carbonic oxide is diluted with ordinary water a certain amount of dissociation of the carbonic oxide hæmoglobin must occur, due chiefly to the influence of the oxygen dissolved in the water. If a dilute blood solution be shaken with air containing carbonic oxide it will be found (see the dissociation curve, Fig. 3) that when the air contains about ·16 % of carbonic oxide the blood solution is half saturated. Since the coefficient of absorption of carbonic oxide in water is about ·024 at 15° such a blood solution will contain about $2{\cdot}4 \times {\cdot}0016 = {\cdot}004$ % of carbonic oxide in simple solution. Hence, if half saturated blood (containing about 10 % of its volume of carbonic oxide in the corpuscles) be diluted to $\frac{1}{100}$th, and half its volume of carmine solution be added, so that the resulting solution contains about ·066 % of its volume of carbonic oxide, about ·004 %, or 6 % of the total contained carbonic oxide, will be required to saturate the water sufficiently to prevent further dissociation of the carbonic oxide hæmoglobin. This will cause an error of 3 % in

the determination of the percentage saturation of the hæmoglobin. If, however, the hæmoglobin of the undiluted blood were fully saturated with carbonic oxide, a similar calculation will show that the error would amount to about 12 %. In the table the second column of results shows the percentages corrected for the error just referred to. It will be seen that when the correction is made the results are about as good for high as for low saturations. The correction is applied in the various determinations referred to in the paper.

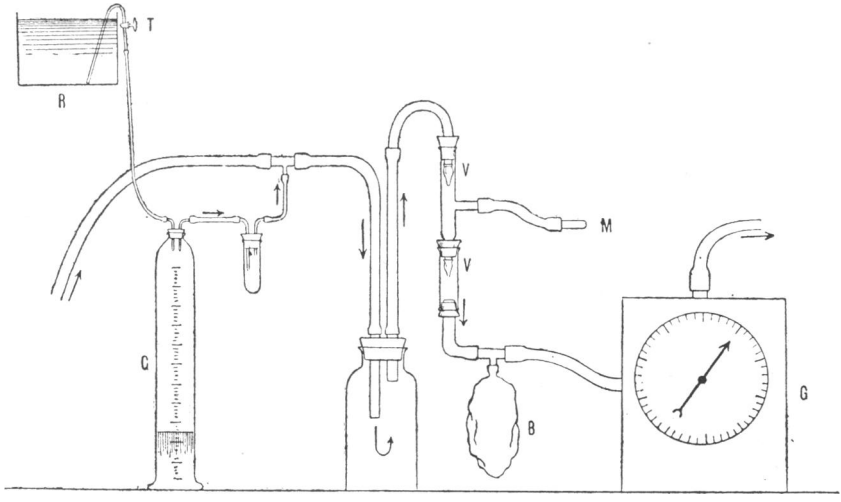
One disadvantage of the method as just described is that the value of the carmine solution alters appreciably with alterations in the tint of the daylight. It is thus not only necessary to restandardise the carmine solution frequently, but any percentage error caused by neglecting this precaution is as great with low as with high saturations of the blood. An error of 10 % in the value assumed for the carmine solution might thus cause a blood solution with a distinct pink tinge, and really containing hæmoglobin 10 % saturated, to be regarded as normal. For these reasons I have in each of the earlier experiments kept a tube of solution of normal blood for purposes of comparison, and for finally re-determining the value of the carmine. In the later and longer experiments I prepared beforehand several tubes of normal blood solution, and determined the saturation by adding the carmine not to the blood solution under examination, but to the normal blood. I then noted the quantities of carmine required to produce equality in tint (1) with the solution or solutions of blood under examination, and (2) with the saturated blood solution. This method is certainly preferable, and makes the results more accurate, but implies a modification in the mode of calculation, which will be evident from the following example. There required to be added to the normal blood solution ·5 c.c. of carmine solution to produce equality of tint with the blood solution under examination, and 2·2 c.c. to produce equality with the saturated blood solution. The percentage saturation of the solution under examination was therefore $\frac{\cdot 5}{2\cdot 5} \times \frac{4\cdot 2}{2\cdot 2} \times 100 = 38\,\%$. With this method not more than ·1 c.c. of carmine must be added at a time.

Experiments on Man.

The accompanying diagram shows the arrangement employed for enabling the subject to breathe for any required time air containing a definite percentage of carbonic oxide. In all the experiments I was myself the subject.

G is a gas meter through which an air-current of constant amount is kept up by means of an aspirator of the type used in the respiration apparatus which I have formerly described. The current employed varied from 8 to 15 litres per minute according to circumstances. The air-current follows the direction shown by the arrows. M is a mouth-

FIG. 1.



piece through which the subject breathes from the air-current, and VV are pieces of intestine soaked in glycerine and arranged in the ordinary way to act as valves, and prevent any passage backwards of air during either inspiration or expiration. B is a bladder so arranged as to take up the extra air driven forwards during expiration, and so prevent any resistance being felt, or any irregularity in the working of the meter. C is a tall measuring cylinder which is filled before the experiment with pure carbonic oxide. By allowing water to drip at a constant rate (regulated by the tap T) from the reservoir R, a constant slow current of carbonic oxide is driven into the main air-current in the direction shown by the arrows. The carbonic oxide bubbles through a test-tube containing water. This test-tube acts as a valve, and makes it possible also to count the number of bubbles which pass in a given time, and so make sure that the apparatus is working rightly. The bottle placed in the main air-current is for the insertion of a mouse when required for purposes of comparison, and serves also to insure thorough mixture of the carbonic oxide with the air.

The following are the notes of the more important experiments.

Several experiments of a preliminary character are omitted, and the notes of others are curtailed as much as possible.

EXPERIMENT I.

Percentage of CO = ·50. Duration 11½ mins.

A specimen of blood taken after ten minutes had a marked pink tinge on dilution, and gave a faint double band of CO hæmoglobin on reduction. There were no symptoms except unusual hyperpnœa after running upstairs.

EXPERIMENT II.

Percentage of CO = 0·39.

After 1½ min.	Mouse panting.
„ 3 „	Mouse very helpless. Sprawling on belly.
„ 7 „	Mouse same, has not moved since last observation.
„ 13 „	Mouse remains on its side when put there.
„ 15 „	Specimen of own blood taken. *Saturation* 23 %. Distinctly pink as compared with similar diluted specimen taken before the experiment. No symptoms yet.
„ 22 „	Slight feeling of palpitation. Pulse 102.
„ 26 „	Mouse remains on its back when put there. Have slight hyperpnœa, respiration being a little deeper than usual. Feel somewhat "abnormal."
„ 29 „	Respirations 18. Palpitation. Pulse 120. Feel distinctly "abnormal."
„ 30½ „	Blood taken again. Strong pink colour. *Saturation* 39 %. Still gives a double absorption band after warming with $(NH_4)_2S$.
	Stopped the experiment. Ran upstairs (24 steps) once. A little later became giddy, much out of breath, had palpitations and could not see so well as usual. On standing for two or three minutes felt all right again. Vision cleared, and hyperpnœa disappeared. Afterwards singing in ears.
After 4 min. from time of stopping.	Ran upstairs again. After about a minute had same symptoms as before, which again disappeared after a minute or two.
After 8 min. do.	Ran upstairs again with similar result, but symptoms not quite so marked as the first time.
„ 15 „ „	Blood taken again. *Saturation* 28 %.

After 45 min. from time of stopping. Blood taken again. *Saturation* 23 %. After warming with $(NH_4)_2S$ there was only a faint and doubtful indication of the double bands on examination with a small direct vision spectroscope. With the naked eye the pink colour of the diluted blood very distinct both before and after reduction with ammonium sulphide. Running upstairs twice still caused slight giddiness and dimness of vision, and more than the usual shortness of breath. As these symptoms passed off there was singing in the ears.

After 105 min. do. Blood taken again. Still distinctly pink on dilution. *Saturation* 18 %. In walking home a few minutes after this observation I became out of breath, with a very slight tendency to dimness of vision and palpitations, followed by slight singing in the ears.

„ 186 „ „ Blood taken again. Could not be sure of any pink colour. *Saturation* 5 %. On running up and downstairs a little later I could not detect any unusual symptoms.

Experiment III.

Percentage of CO = ·40. Duration 24 minutes.

At the end of the experiment the blood was taken. *Saturation* 27 %. No symptoms except unusual hyperpnœa, and slight giddiness after running once upstairs. Half an hour afterwards the blood *saturation was* 16 %, and there still seemed to be a little unusual hyperpnœa on exertion. After another hour the *saturation was* 10 %, and all symptoms had disappeared.

Experiment IV.

Percentage of CO = ·36. Duration 29 minutes.

After 18 minutes the blood *saturation was* 26 %. After 29 minutes *saturation was* 37 %. On walking up and down the room at end of experiment felt throbbing in the head and palpitations. On running upstairs twice became giddy, short of breath, etc. 15 minutes later the blood *saturation was* 32 %.

Experiment V.

Percentage of CO = ·41. Duration 29 minutes.

After 1½ min. Mouse showed some loss of power.
„ 3 „ Mouse remained on its side when put there.
„ 15 „ Own blood taken. *Saturation* 13 %.
„ 28 „ Very slight hyperpnœa and palpitations.

After 29 min. Blood taken again. *Saturation* 35 %. Experiment stopped. On running upstairs marked giddiness and impairment of both vision and hearing, which disappeared again after a minute or two.

After 15 min. from time of stopping. Blood taken again. *Saturation* 28 %. Still slight giddiness and marked hyperpnœa after running upstairs.

„ 45 „ „ Blood taken again. *Saturation* 19 %.

„ 80 „ „ Blood taken again. *Saturation* 10 %.

No headache or other abnormal symptoms followed the experiment.

Experiment VI.

Percentage of CO = 0·12. Duration 120 minutes.

After 5½ min. Mouse panting, and resting on its belly.

„ 11 „ Mouse still resting on its belly; when roused to any effort its legs sprawl.

„ 15 „ Own blood taken. Pink tinge just distinctly visible, but very slight. *Saturation* 8 %.

„ 33 „ Feel slight tendency to palpitations. Pulse 96. Mouse is much the same.

„ 46 „ Blood taken again. Pink tinge now very distinct. *Saturation* 18 %. On ceasing for a minute or two to breathe through the tube I could detect no abnormal symptoms.

„ 67 „ Pulse 84. Slight palpitations. Feel rather sleepy.

„ 90 „ Pulse 86. Blood taken. Somewhat deeper pink tinge than last specimen. *Saturation* 27 %. Immediately after the blood was taken I ran twice up and downstairs. This caused for a minute or two distinct dimness of vision and hearing, and a slight tendency to stagger, besides abnormal hyperpnœa. Resumed breathing after an interval of 8 minutes (which is allowed for in the succeeding time record). Mouse much the same, or if anything, more torpid.

„ 104 „ Beginning to experience slight hyperpnœa while sitting breathing the CO. Rate of respirations 12.

„ 120 „ Pulse 96. Hyperpnœa still quite distinct, and general feeling of uneasiness. Blood taken. Pinker than last specimen. *Saturation* 37 %. Stopped the experiment. On sitting quietly on a chair could still feel that the respirations were deeper than usual. I also felt dull and "abnormal."

	On running once upstairs I became very distinctly weak in the legs, and had to lean against a table. At the same time vision and hearing became markedly impaired, and there seemed to be some confusion of mind. The sound of the running water of the aspirator seemed to be far away, and to come much nearer after I had rested for a minute or two, vision clearing up correspondingly at the same time. While vision was impaired I found it difficult to distinguish the tints of the different specimens of blood.
	Two or three minutes later I ran upstairs again with the same results. The symptoms came on about half a minute after I reached the top of the stair. On testing with a watch hearing appeared distinctly impaired.
	On its removal the mouse could not move about, and was very torpid and cold, but it recovered without warming when replaced in its cage.
After 18 min. from time of stopping.	Distinct throbbing headache (which, however, did not last long) like that which follows the breathing of air containing much carbonic acid. Short of breath even on going very quietly upstairs.
„ 30 „ „	Blood taken again. Less pink than last specimen. *Saturation* 27 %. While resting have no difficulty in judging of the tints of the specimens.
„ 90 „ „	Blood taken again. Distinctly a little pink still. *Saturation* 20 %.
„ 105 „ „	Ran twice up and downstairs. More out of breath than usual afterwards, and slight tendency to dimness of vision for about half a minute.
„ 195 „ „	Blood taken again. Is just perceptibly pinker than usual. *Saturation* 11 %. No headache since last observation.

Experiment VII.

Percentage of CO = 0·21. Duration 71½ minutes.

After 16 min.	Pulse 91. No symptoms.
„ 20 „	Blood taken. Distinctly a little pink. *Saturation* 17 %.
„ 34 „	Very slight feeling of fulness and throbbing in head.
„ 37 „	Fulness and throbbing more distinct.
„ 40 „	Blood distinctly pinker than last specimen. *Saturation* 39 %.

After 43 min.	Feeling decidedly "abnormal." Slight hyperpnœa and marked throbbing.
„ 45 „	Pulse 104. Breathing distinctly deeper.
„ 54 „	Feel very decidedly abnormal. Vision seems not so good. Slight feeling of giddiness.
„ 59 „	Hyperpnœa more distinct. Beginning to look pale and yellowish, and "as if ill."
„ 61 „	Blood taken again. Pinker than last specimen. *Saturation* 44·5 %.
„ 63 „	Feel worse shortly after making any movement in my chair.
„ 65 „	Hyperpnœa marked, and slight confusion of mind.
„ 71 „	Blood taken. Very pink tint, slightly more so than last specimen. *Saturation* 49 %. Stopped experiment. Vision dim. Limbs weak. Had some difficulty in getting up or walking without assistance, movements being very uncertain.
After 2 min. from time of stopping.	Could walk fairly straight across the room. Could write on black board, but letters not formed as usual, and some mistakes in spelling, etc. Felt confused.
„ 5 „ „	Felt a little better.
„ 6 „ „	After walking four times up and down the room I staggered and nearly fell. On going on I was very unsteady, often nearly falling, and grasping uncertainly at various objects for support. Vision also very indistinct. I seemed to see things, and yet not recognize their details. I could not read until after a rest. The exertion caused considerable hyperpnœa, but this was not much noticed, as the other symptoms were so much more prominent.
„ 12 „ „	Said over the German numerals correctly up to 25. Still rather unsteady, and nearly fell when turned round.
„ 13 „ „	Attempted to walk along the line of one of the boards of the floor. Did so with much difficulty and great staggering and waving of arms.
„ 15 „ „	Immediately after the last exertion, and while still very confused, I was given oxygen to breathe out of a bag. The effect seemed to be distinct. After three or four seconds everything seemed to clear up suddenly, and I was able to walk steadily up and down the room carrying the bag. Face also was

said to improve in appearance, and no longer to look so "sickly." I breathed the oxygen for two minutes, and on ceasing continued to walk, and soon again became unsteady and confused.

After 22 min. from time of stopping. On walking quickly up and down the room I got very unsteady, and could not see distinctly, or hear the noise of a tap except faintly. At this point I again began to breathe from the oxygen bag, and the effect seemed distinct. After three or four seconds the confusion of mind and of perception disappeared completely, and I was able to run up and down the room with the bag, without any return of the confusion of mind. On stopping the oxygen I again began to feel confused after about a minute of walking. On trying to run vision rapidly became dim, and movements uncertain. Breathing the oxygen seemed once more to produce the same good effect, and it was also noticed that my voice seemed to become more natural.

„ 35 „ „ The symptoms now became much less marked.

During the whole of the evening after this experiment I suffered from headache, but had no nausea or marked loss of appetite. Within two hours of the experiment I ate dinner as usual. During the succeeding day I had slight headache.

As this experiment was pushed considerably beyond the point at which hyperpnœa began, wider tubing and a more free ventilation were employed than in previous experiments, and I believe that my respirations were deeper throughout the experiment. For this reason probably the absorption of carbonic oxide was somewhat more rapid than might have been expected from the results of some of the other experiments.

In this and the succeeding experiments the determinations were made by adding the carmine to normal blood solution, instead of to the tube under examination.

Experiment VIII.

Percentage breathed irregular on account of tubing becoming disconnected during the experiment. For the last 10 minutes ·43 %. Duration of experiment about 35 minutes.

At the end of the experiment the blood was taken. *Saturation* 56 %. For some time before the end of the experiment there were palpitations, giddiness, dulness of the senses, and distinct hyperpnœa. Shortly before the end of the experiment a specimen of blood gave *saturation* 48 %. At the

end of the experiment I could hardly stand, and could not walk alone without falling down. Neither breathing oxygen for a minute, nor lying down with legs and pelvis raised (which in a former experiment had seemed to cause improvement) had any immediate good effect, beyond what could fairly be attributed to rest alone. The symptoms and gradual improvement were as in former experiments.

Blood was again taken 50 minutes after the end of the experiment. *Saturation* 38 %. Marked giddiness still followed any considerable exertion, such as walking up and down the room.

Two hours after the end of the experiment the blood *saturation was* 32 %. There was still some giddiness etc. following exertion.

I had some headache until the next morning, when the blood was again examined, and found to give exactly the same result as before the experiment.

EXPERIMENT IX.

Percentage of CO = ·027. Duration 3½ hours.

After 1 hour. Blood just distinctly pinker than normal. *Saturation* 7 %.
After 2 hours. Blood looked about same as last. *Saturation* 11 %.
„ 2½ „ „ „ „ „ *Saturation* 15 %.
„ 3 „ „ „ „ „ *Saturation* 15 %.
„ 3½ „ „ „ „ „ *Saturation* 14 %.

No symptoms during the experiment. Perhaps very slight unusual shortness of breath and palpitations on running upstairs.

EXPERIMENT X.

Percentage of CO = ·021. Duration 4 hours.

After 1 hour. Blood looked hardly pinker than normal blood. *Saturation* 8 %.
„ 2 hours. Blood just pinker than normal. *Saturation* 13 %.
„ 3 „ „ „ „ „ *Saturation* 13 %.
„ 4 „ „ „ „ „ *Saturation* 13 %.

No symptoms during or after the experiment.

EXPERIMENT XI.

Percentage of CO = ·046 to ·044. Duration 4 hours.

After 1 hour. Blood had distinct pink tinge. *Saturation* 17 %.
„ 2 hours. Pink tinge very distinct. *Saturation* 28 %.
„ 3 „ Blood looked much same as last time. *Saturation* 28 %.
„ 4 „ „ „ „ „ „ *Saturation* 23 %.

There were no symptoms during the experiment, but on running upstairs

afterwards there was unusual hyperpnœa, with slight palpitations, etc. Another experiment of 4½ hours' duration, with a similar percentage (·048), gave a similar result, and the symptoms brought on by exertion did not increase after the first two hours. A mouse was not distinctly affected.

In another experiment with ·035 % I could not be sure at the end of two hours that any unusual symptoms were brought on by exertion. The blood had a faint pink tinge, and the saturation was estimated at 14 % in two determinations, made after one and two hours.

Several points come out clearly in these experiments, and may be discussed one by one.

Causes of the Symptoms produced by Carbonic Oxide.

The symptoms produced by carbonic oxide in a healthy and normal individual resemble very closely those produced by atmospheres in which the oxygen tension is considerably diminished, either by reduction of atmospheric pressure, or by reduction of the oxygen percentage. Relatively slight hyperpnœa, palpitations, and feeling of fulness in the head, together with a tendency to impairment of the senses and loss of power over the limbs, are the characteristic symptoms produced both by carbonic oxide and by a diminished supply of oxygen in the air breathed. The fact noted above that in the earlier stages of carbonic oxide poisoning these symptoms only occur after exertion is also characteristic of a moderately diminished oxygen supply, as shown by the records of mountain travellers.

The experiments further show that none of these symptoms occur until the blood is saturated to a considerable extent with carbonic oxide, and that both the increase and diminution of the symptoms during and after inhalation of moderate quantities of the gas run parallel with the changes in the saturation of the blood. In proportion as the saturation increases the symptoms increase: in proportion as the saturation diminishes the symptoms diminish.

As shown in repeated experiments the symptoms do not become appreciable during rest until the blood is about a third saturated, so that the oxygen carried by the blood is diminished by about a third. Now this is just about what might be expected on the hypothesis that these symptoms are due to want of oxygen. A glance at the causes given by Paul Bert at page 691 of *La Pression Barométrique* will show that the oxygen carried by the blood in a living animal was diminished by about a third when the oxygen tension of the atmosphere

breathed was diminished by about a half. The symptoms produced by a third saturation of the corpuscles with carbonic oxide should therefore correspond to those experienced by mountaineers at a height of about 18000 feet, or by persons breathing air in which the oxygen percentage is reduced to about 10·5. As a matter of fact there seems to be a pretty close correspondence Thus when the oxygen percentage in air is reduced to about 10 or 11 %, the breathing becomes just noticeably deeper, as shown by the tracings published by Lorrain Smith and myself[1].

In Experiments VII. and VIII. the blood was about half saturated with carbonic oxide, so that the oxygen must have been diminished to about half the normal, *i.e.* to less than the proportion in average venous blood. According to Bert's curves this amount of oxygen would correspond to an atmosphere in which the oxygen tension was diminished by two-thirds (a height of about 28000 feet, or air at ordinary pressure, and containing only 7 % of oxygen). The symptoms produced by the carbonic oxide were in this case hardly so urgent as those which are experienced in atmospheres with the oxygen tension diminished by two-thirds; this is probably due to the fact that the tension of the oxygen in the blood is higher in the case of carbonic oxide poisoning, and that for this reason what oxygen there is in the blood is more readily made available. The tension of the oxygen in the blood, and not merely its amount, is certainly of great importance, since blood which is half saturated with oxygen still contains more than sufficient oxygen, as regards quantity, to supply all the needs of the tissues; and yet with this half-saturated blood very urgent symptoms are produced.

On the whole there is thus every reason to attribute the symptoms produced by the carbonic oxide solely to diminution in the oxygen-carrying power of the blood.

There remains a further question as to how exactly want of oxygen produces these symptoms. At first sight it might seem tolerably certain that the direct cause of most of the symptoms must be diminution in the percentage of oxygen contained in the arterial blood supplying the central nervous system. There is, however, the following difficulty in accepting this explanation as by itself sufficient. The symptoms are brought on, or much aggravated, by any exertion. Now, were the affected parts of the central nervous system, and these parts only, concerned in the exertion, this fact would be quite intelligible

[1] *Journal of Pathology*, I. 180. 1893.

since it would be reasonable to assume that there would be an increased demand for oxygen in these parts, and consequently an increased deficit in the supply. But even moderate exertion causes such symptoms as loss or impairment of the senses, while there is no reason to suppose that the exertion specially affects one of the parts of the body concerned in sensation or perception. It does not seem likely that the blood passing through the lungs during the exertion takes up less oxygen than during rest. The available evidence goes towards showing that the blood is as fully saturated with oxygen during exertion as during rest[1]. The presence of the carbonic oxide would, moreover, tend to facilitate rather than retard the complete saturation of that part of the hæmoglobin not saturated with carbonic oxide. Possibly the key to the difficulty lies in changes in the blood supply to the brain caused by the exertion.

According to Roy and Sherrington[2] exertion normally causes an increased supply of blood to the brain. With a constant diminished supply of oxygen in the blood the circumstances are probably different, and in particular the heart may not be able to respond sufficiently to compensate for the fall of blood pressure produced by the increased flow of blood through the muscles. If this explanation be correct it seems possible that the cerebral symptoms produced by carbonic oxide or want of oxygen may even during rest be in part due to circulatory changes, and not merely to direct action of the abnormal blood on the nervous centres.

The Time-relations of Carbonic Oxide poisoning.

The experiments show clearly that the time required for an atmosphere containing carbonic oxide to produce symptoms of poisoning depends simply on the time required for the production of a certain degree of saturation of the blood. With a low percentage, as in Experiment VI., a much longer time is required than with a higher percentage, as in Experiment I.; but in either case the symptoms became distinctly appreciable during rest as soon as, and not before, the blood had had time to become saturated to about a third.

As a considerable interval elapses before the blood has been sufficiently saturated to produce symptoms, and as this interval is not due to a slow rate of absorption of the poison into the body, carbonic oxide presents a typical example of a cumulative poison.

[1] Geppert and Zuntz, *Pflüger's Archiv*, XLII. 189. 1888.

[2] This *Journal*, XI. 93. 1890.

The actual time required to produce the symptoms of poisoning must depend in the first place on the amount of air breathed in a given time as compared with the mass of the blood. A man has about 5 litres of blood, and the red corpuscles of this blood are capable of taking up about 1 litre of oxygen or carbonic oxide. To produce distinctly appreciable symptoms of poisoning it will thus be necessary that about 330 c.c. of carbonic oxide should be absorbed. Now a man at rest breathes about 7 litres of air per minute, and in the experiments this was about the quantity actually breathed through the apparatus. Thus, supposing that the air contained 1 % of carbonic oxide, 70 c.c. of carbonic oxide would be breathed per minute. Hence, if the whole of this were absorbed it would still take 5 minutes to produce definite symptoms. With ·5 % at least 10 minutes would be required, and with ·1 % at least 50 minutes. In Experiment I. (·39 % of CO) it required about 25 minutes to saturate the blood to a third. The minimum possible time, according to the above calculation, would have been about 12 or 13 minutes. Apparently, therefore, only about half of the carbonic oxide breathed was actually absorbed. If similar calculations be made for the other experiments it will be seen that, so long as the absorption was proceeding rapidly, they follow, roughly speaking, much the same rule. Whether the percentage of carbonic oxide was relatively large or small, about half of the carbonic oxide actually breathed was absorbed.

In the following table the times, calculated from the blood determinations as actually required to produce certain degrees of saturation, are given along with the times which would on the above assumption have been required, if the whole of the carbonic oxide had been absorbed.

TABLE II.

No. of Exp.	Percentage of CO in air breathed	To produce 50% saturation		To produce 33% saturation		To produce 15% saturation	
		Minutes actually required	Required if all the CO breathed had been absorbed	Minutes actually required	Required if all the CO breathed had been absorbed	Minutes actually required	Required if all the CO breathed had been absorbed
2	·39	—	—	24	12	10	5·5
3	·40	—	—	30	12	—	—
4	·36	—	—	26	13	11	6
5	·41	—	—	27	12	18	5
6	·12	—	—	107	40	38	18
7	·21	72	34	34	23	18	10
Average	·31	72	34	41	19	19	9

From this table it will be seen that the times actually required correspond roughly to the assumption that about half of the carbonic oxide breathed is absorbed.

Of the carbonic oxide inhaled at each breath in these experiments a certain proportion would not be absorbed because it never reached the alveoli, and, being a very insoluble gas, would not, as some other gases are, be taken up by the mucous membranes. As about 500 c.c. of air were inspired at each breath this proportion would amount to about a third if we assume, after Loewy[1], that the dead space due to the respiratory passages amounts to about 140 c.c., and add 30 c.c. for the tubing of the mouth-piece of the apparatus. Of the gas which did reach the alveoli a further proportion (about a third) was apparently also not absorbed, chiefly (as shown below) because the air did not remain long enough in the alveoli, but partly also because the average tension of the carbonic oxide in the blood passing through the lung was increasing appreciably. With very small percentages of carbonic oxide the absorption after a time ceases (Experiments IX. X. XI.). This cessation of absorption doubtless depends on the fact that the tension of the carbonic oxide in the blood of the lungs becomes equal to that of the air breathed.

In order to obtain still more direct evidence as to the proportion of carbonic oxide which escapes absorption with percentages well above those at which absorption might be considerably diminished by the cause just mentioned, I made a direct determination of the carbonic oxide in the inspired and expired air. The air was inspired from a bag, and the expired air collected in another bag. The bags were furnished with short pieces of rubber tubing, connected together by a T tube, through one limb of which I breathed. To avoid all extra "dead space" valves were dispensed with, and taps, opened and closed at each respiration, were employed for giving the air the required direction. The breathing was continued for 3 minutes, and the first four breaths were rejected, so as to wash out the lungs before the expired air was collected. The analyses were made by explosion of a sample of the air (freed from carbonic acid) with about 15 % of hydrogen, and subsequent determination of the carbonic acid formed.

The results were as follows:

	CO_2 %	CO %
Inspired air	·03	1·31
Expired air	4·29	0·57.

[1] *Pflüger's Archiv*, LVIII. 416. 1894.

It thus appears that 56 % of the carbonic oxide was absorbed. In this experiment the respirations were less frequent (8½ per minute) and deeper than in the other experiments, which probably accounts in part for the slightly higher percentage absorbed, since with deep inspiration the influence of the dead space in the air passages is less. Evidently the dead space cannot alone account for the incomplete absorption of the carbonic oxide.

From this and the previous experiments it follows that the time required to produce distinct symptoms of poisoning with carbonic oxide will be about double the time required to breathe 330 c.c. of it.

This conclusion obviously does not apply in the case of very high percentages, with which, as Heger has shown, death may occur before the whole of the blood has had time to pass through the lungs.

Just as the rapidity with which symptoms are produced by carbonic oxide depends on the rate at which the blood is saturated, so does the rapidity of recovery (with the moderate doses used in the above experiments) depend on the rate at which the carbonic oxide is got rid of. The data obtained in Experiments II. III. VI. and VIII. show that disappearance of the symptoms runs parallel with disappearance of the carbonic oxide from the blood. In man, as might be expected, this is a slow process. However quickly the carbonic oxide may have been absorbed it will disappear slowly. Even when the blood had been only a little more than a third saturated, as in Experiment VI., it was still about 10 % saturated after three hours; when it had been 56 % saturated, as in Experiment VIII., it was still about 30 % saturated after two hours. We may thus infer that in cases of severe poisoning by carbonic oxide, with the blood about 70 % saturated, it would take about 6 or 7 hours for the blood to return to a practically normal condition.

Time-relations of Carbonic Oxide Poisoning in different Warm-blooded Animals.

It is evident from the records of some of the above experiments that, with the same percentage of carbonic oxide, symptoms of poisoning occur far more rapidly in mice than in man. The reason for this is undoubtedly the following.

The amount of carbonic acid produced, and of oxygen absorbed, by different warm-blooded animals varies, as Rubner has shown, not according to the relative masses of the animals, but, roughly speaking,

according to the relative extents of their external surfaces. The mass of a man is about 3000 times the mass of a mouse, but the external surface of the man is probably only about 150 times that of the mouse. A mouse weighing about 25 grammes produces in one hour at ordinary temperatures about ·25 grammes of carbonic acid. A man weighing 70 kilos produces in the same time about 40 grammes. The mouse thus produces in an hour about 10 grammes per kilo body weight, while the man produces only about half a gramme. The exchange between air and blood in the lungs is thus about 20 times as rapid in a mouse as in a man. Consequently one would expect that a mouse would absorb a proportional amount of carbonic oxide about 20 times as rapidly as a man. The experiments bear out this explanation. Thus in Experiment I. (·39 % of carbonic oxide) the mouse was distinctly affected in 1½ minutes, whereas it took half-an-hour, or 20 times as long, to affect a man. In Experiment II. it took 5½ minutes to affect the mouse, and about 2 hours, or 20 times as long, to affect a man. As a general rule warm-blooded animals will be poisoned by given proportions of carbonic oxide (and probably also by other poisons) with rapidities varying as the extents of their surfaces in relation to their masses. Recovery from the carbonic oxide will, as a rule, follow a similar law. Thus a mouse recovers in a very short time as compared with a man.

An Indicator of Carbonic Oxide in Coal-mines, etc.

In introducing mice into some of the above experiments I had partly a directly practical object in view. The presence of carbonic oxide in the air is in certain cases a source of great danger in coal-mines and other places. Carbonic oxide is one of the gases formed by the explosion of an excess of fire-damp, or coal-dust in presence of air. It is thus a constituent of after-damp. It is still more frequently met with in connection with the spontaneous heating, or actual ignition, of coal, which is so common in certain colliery districts. It is also present in large quantities in the smoke of blasting powder, and of some other explosives. A miner usually trusts to his lamp to give him indications of the presence of dangerous gases in a mine. A lamp is, however, of no service in detecting small quantities of carbonic oxide in air. It is this fact which makes after-damp, smoke, etc. so dangerous to men who attempt to penetrate them while trusting to a lamp to give warning of any danger. There is no known chemical test for carbonic oxide which could under the circumstances be applied by unskilled persons and

which would give a sufficiently rapid indication of the presence of danger from carbonic oxide. The fact, however, that the respiratory exchange of a smaller warm-blooded animal is so very rapid as compared with that of a man, rendered it probable that such small animals as mice might safely be employed as indicators of the presence of carbonic oxide. While recently collecting samples of the gases from heated coal in Staffordshire collieries I have used mice with this end in view, and found that their symptoms gave timely warning of the presence of carbonic oxide in cases where it was present in poisonous proportions. The above experiments give more definite data as to the interval available for a man after a mouse has been rendered helpless by carbonic oxide. It will be seen that this interval is very considerable. The mouse is affected within a few minutes if it is affected at all, while a man will have an interval of 20 times as long. Even with 5 % of carbonic oxide the interval will be about 20 minutes.

As shown in a previous paper the poisonous action of carbonic oxide rapidly increases when the oxygen percentage (or tension) in the air breathed is abnormally diminished. Now, in the air of a coal-mine, where carbonic oxide is present there will always be more or less reduction in the oxygen percentage. This reduction is due partly to the presence of fire-damp, but chiefly to that of black-damp, which, as recently shown[1], is not pure carbonic acid, but a mixture consisting of about 85 to 90 % of nitrogen and 15 to 10 % of carbonic acid, and is formed in enormous quantities all over a mine, whether fire-damp be present or not. The reason why carbonic oxide becomes so much more dangerous in air partly deprived of oxygen is of a twofold nature. In the first place the oxygen tension in the alveoli is greatly diminished (proportionally much more than the oxygen tension in the outside air). With a given percentage of carbonic oxide the mass influence of the latter will therefore tell more on the hæmoglobin, and the blood will thus become saturated to a greater extent with carbonic oxide. In the second place, however, a given saturation of the blood with carbonic oxide will tell far more seriously when, as happens with an atmosphere very deficient in oxygen, the hæmoglobin is already only partially saturated with oxygen. A man can easily live in an atmosphere containing only 10 % of oxygen, although his hæmoglobin is probably only about $\frac{2}{3}$rds saturated with it; but if at the same time his available hæmoglobin is diminished by even as little as a third by carbonic oxide

[1] Haldane. *Proc. Roy. Soc.* LVII. 249. 1895. Haldane and Atkinson. *Trans. Fed. Inst. of Mining Engineers*, 1895, p. 549.

poisoning, he will certainly be rendered more or less helpless. Judging therefore from the effect produced on man by ·05 % of carbonic oxide in ordinary air (Experiment XI.) the same percentage would in time produce a fatal effect if present along with about 50 % of black-damp or fire-damp.

A further cause which may probably often hasten the action of carbonic oxide in coal-mines is hyperpnœa due to the presence of more than 3 % of carbonic acid (or 25 % of black-damp) in the air, or to muscular exercise. This hyperpnœa will bring more carbonic oxide into the lungs in a given time, and thus hasten its absorption.

Now all these causes except the last (muscular exertion) will equally affect the mouse. The latter thus has the advantage of indicating, not simply a certain given minimum percentage of carbonic oxide, but the minimum percentage which is actually dangerous in the atmosphere present.

Causes of the Absorption of Carbonic Oxide by the Blood.

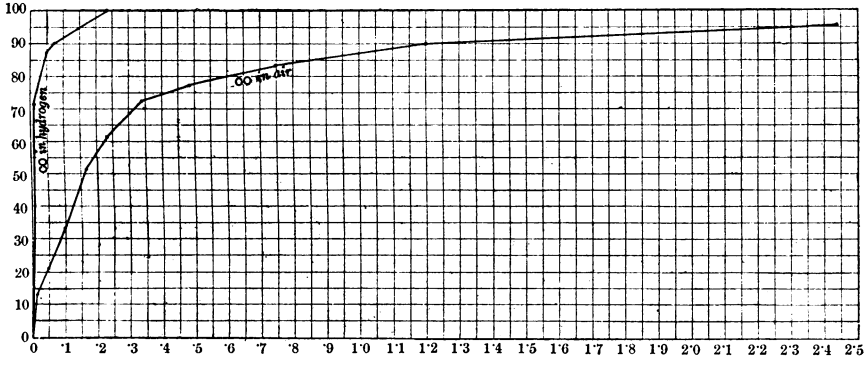
There are no reasons for believing that any other cause exists for the passage of carbonic oxide through the pulmonary epithelium than the difference of tension between the carbonic oxide in the alveoli and in the blood passing through the lungs. As I showed in a previous paper carbonic oxide is, apart from its action on the hæmoglobin, a physiologically indifferent gas, like hydrogen or nitrogen; and this being so it will simply diffuse through the living tissues, without entering into any sort of combination with them. The absorption of carbonic oxide by the blood corpuscles during life is, however, a less simple matter, and presents several points of great interest.

When a man or animal breathes air containing a very small percentage of carbonic oxide the gas continues to be absorbed by the blood for a certain time; but sooner or later a point is reached at which the absorption ceases. Thus in Experiment XI., with ·045 % of carbonic oxide in the air breathed, further absorption ceased when the hæmoglobin was about 25 % saturated. Two causes suggest themselves for this cessation of absorption. The first is that with very low carbonic oxide tension the compound of carbonic oxide and hæmoglobin is unstable, especially at the body temperature, so that only a portion of the hæmoglobin can remain in combination with carbonic oxide. The second possible cause is that the affinity of the oxygen of the blood for the hæmoglobin counteracts the affinity of the carbonic oxide, and so

prevents the formation of more than a certain proportion of carboxy-hæmoglobin. To decide as to the relative influences of these two causes I have made a number of experiments with blood solutions outside the body.

In the first series 1 % solutions of ox-blood were well shaken at a temperature of 17° to 18°, with air containing various percentages of carbonic oxide, and the percentage saturation of the hæmoglobin with carbonic oxide determined colorimetrically. The details of the method employed, and the individual results will be found in the succeeding paper. The average results are represented graphically in Fig. 2. On examining the curve it will be seen that with about ·16 % of carbonic oxide in the air the hæmoglobin is equally shared between the carbonic oxide and the oxygen. With double this percentage of carbonic oxide there are about two parts of carboxyhæmoglobin to one of oxyhæmoglobin, and in general the number of parts of carboxyhæmoglobin to

FIG. 2.



Dissociation curves of carboxyhæmoglobin in hydrogen and in air.
The ordinates represent percentage saturation of the hæmoglobin with carbonic oxide: the abscissæ represent percentage of carbonic oxide in the hydrogen or air.

one of oxyhæmoglobin is approximately equal to the percentage of carbonic oxide in the air divided by ·16. This result indicates that the sharing of the hæmoglobin between the carbonic oxide and the oxygen depends approximately not on the absolute amount of the carbonic oxide in the air, but on the proportion of carbonic oxide (divided by a constant) to the oxygen of the air, which may be taken as remaining constant, since the proportions of carbonic oxide added to the air do not appreciably reduce its oxygen percentage.

Assuming this to be strictly true, then if s represent the percentage

saturation of the hæmoglobin with carbonic oxide, and s' its percentage saturation with oxygen (at the oxygen tension of atmospheric air) and p the percentage of carbonic oxide present in the air, then it is clear that $\frac{s}{s'} = \frac{p}{\cdot 16}$. But $s' = 100 - s$, therefore $s = \frac{100\,p}{\cdot 16 + p}$. Employing this formula a curve may be constructed which will be nearly identical with that represented in Fig. 2.

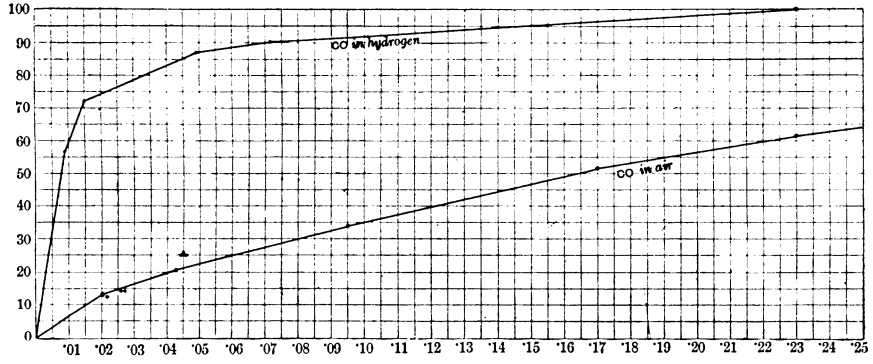
From the formula it is evident that the value of s can never exceed 100, however much the value of p may be increased. Hence one asymptote of the curve is the line indicating 100 % saturation. On the other hand the negative value of p can never exceed $-\cdot 16$, however much the value of s be increased in a negative direction. Hence the other asymptote to the curve is a line which would indicate $-\cdot 16$ % of carbonic oxide. The curve is thus a rectangular hyperbola with the asymptotes just specified, and passing through the point corresponding to 0 % saturation and 0 % of carbonic oxide in the air.

In order to obtain more direct evidence as to the dissociation of carboxyhæmoglobin by mere reduction of the carbonic oxide tension, apart from the influence of oxygen, I made a few experiments with mixtures of carbonic oxide and hydrogen (which was free from oxygen or traces of carbonic oxide). The method used was the same, but in order to facilitate the measurements the carbonic oxide employed for making the mixtures was first diluted to a tenth with hydrogen. The bottle in which the blood solution was shaken with the mixture was thrice as large, and allowance was made for the reduction produced in the carbonic oxide percentage of the mixture by the absorption of carbonic oxide by the blood solution. This allowance, and the greater size of the bottle, were necessitated by the fact that the amount of carbonic oxide absorbed by the blood was a considerable fraction of the whole carbonic oxide contained in the bottle. The shaking was also continued for a longer time, as the rate of absorption of the carbonic oxide must have been much slower. As, moreover, the hæmoglobin not combined with the carbonic oxide was reduced, and therefore altered in colour, the solution was gently agitated with air after removal from the bottle. By this means the uncombined hæmoglobin was reconverted to oxyhæmoglobin without any appreciable dissociation of the carboxyhæmoglobin.

The results of five experiments made in this way are shown in the curves in Figs. 2 and 3. These results are not numerous enough to show the exact form of the dissociation curve of carboxyhæmoglobin (in the concentration employed) but nevertheless correspond very closely

with the hypothesis that this curve is also a rectangular hyperbola, one asymptote being the horizontal line indicating 100 % saturation, and

FIG. 3.



Dissociation curves of carboxyhæmoglobin in hydrogen and in air.
The ordinates represent percentage saturation of the hæmoglobin with carbonic oxide: the abscissæ represent percentage of carbonic oxide in the hydrogen or air. The asterisks denote the percentage saturation of the blood and the percentage of carbonic oxide breathed in experiments IX. X. and XI.

the other a vertical line, which would indicate about −·0065 % of carbonic oxide. The experimentally determined curve appears to join the horizontal asymptote at ·23 % of carbonic oxide, but this only signifies that with ·23 % the percentage saturation was so high as to be incapable of distinction by the colorimetric method from complete saturation. It will be seen that even with ·05 % of carbonic oxide in the hydrogen the hæmoglobin was nearly 90 % saturated. Hence it is quite intelligible that with percentages higher than this in air the relative saturation of hæmoglobin with carbonic oxide and oxygen should practically speaking be a function simply of the relative proportions of oxygen and carbonic oxide.

The dissociation curve of carboxyhæmoglobin in much more concentrated solution has recently been investigated by another method by Bock[1], who also, in some of his experiments, employed ox-blood hæmoglobin, at nearly the same temperature. My results confirm his general conclusion that the dissociation curve rises very sharply up to a tension of about ·5 mm. (corresponding to about ·07 % of carbonic oxide in hydrogen at ordinary pressures) and afterwards very slowly. Still more recently Hüfner[2] has published the results of several experiments on

[1] *Physiologisches Centralblatt*, Sept. 1894, p. 385.
[2] *Archiv für (Anat. und) Physiol.* p. 213. 1895.

the same subject. He finds that with a tension of ·5 mm. of carbonic oxide a hæmoglobin solution at 31° C. is 87 % saturated.

With ·16 % of carbonic oxide in hydrogen, hæmoglobin solution is very nearly saturated with carbonic oxide, whereas with the same percentage of carbonic oxide in air the same solution is only half saturated. The difference between half saturation and complete saturation is evidently due almost entirely to the presence or absence of the atmospheric oxygen. It thus appears that at a tension of about ·16 % of an atmosphere the influence of carbonic oxide in forming carboxyhæmoglobin is about equal to the influence of the atmospheric oxygen (at a tension of 21 % of an atmosphere) in forming oxyhæmoglobin. The affinity of carbonic oxide for hæmoglobin would thus seem to be about $\frac{21}{\cdot 16} = 131$ times the affinity of oxygen for hæmoglobin. If allowance be made for the fact that ·16 % of carbonic oxide only produces 95 % saturation in the absence of oxygen, the relative affinities will be as 21 to ·15, or as 1 to 140.

Before applying the results just described to the interpretation of the causes of absorption of carbonic oxide by the blood, it is necessary to consider the possible influence of the higher temperature and greater concentration of the hæmoglobin in the living body. It does not seem *a priori* probable that either of these conditions can alter to any considerable extent the *relative* saturating powers of carbonic oxide and oxygen. Nevertheless I made several experiments in order to roughly test the question. When the bottle containing carbonic oxide in air was kept in a bath at 38° during the saturation, I found that with ·175 % of carbonic oxide the hæmoglobin was 52·4 % saturated, and with ·14 % of carbonic oxide 42·25 % saturated. These results are both practically identical with the results at lower temperatures. In a further experiment I placed ·75 c.c. of undiluted ox-blood in a dry flask of 1·5 litres capacity, which was then filled with air containing ·16 % of carbonic oxide. The blood was then spread about on the bottom of the flask in a thin layer, and left for about an hour and a half. The saturation with carbonic oxide was then determined by the method described at the beginning of the paper, and found to be 54 %. This result is, within the limits of experimental error, about the same as that obtained with the diluted blood. It thus appears that neither the increased temperature nor the increased concentration has any marked influence on the relative saturating powers of oxygen and carbonic oxide.

As the result of an experiment with carbonic oxide in hydrogen at a

temperature of 38°, I found that with ·0087 % of carbonic oxide the hæmoglobin of a 1 % blood solution was 48 % saturated after half-an-hour's shaking. As the bottle was closed airtight before being placed in the water-bath the actual tension of the carbonic oxide would be about ·0093 % of an atmosphere. This result, as compared with those at 18°, shows that, as might be expected, the rise of temperature diminishes considerably the saturating power of carbonic oxide, just as it does that of oxygen.

In Experiment XI. it was found that when ·045 % of carbonic oxide in air was breathed the last two specimens of blood were 28 % and 23 % (average 25·5 %) saturated. A glance at the curves on Fig. 3 will show that this saturation is about 4 % greater than would have been obtained by shaking blood with pure air containing the same percentage of carbonic oxide, but only about a third of what would have been obtained in the absence of oxygen. It is thus evident that, but for the influence of the oxygen tension of the blood passing through the lungs, thrice as much carbonic oxide would have been absorbed. It was thus, practically speaking, the oxygen tension of the blood, and not the mere lowness of the carbonic oxide tension, which prevented the further absorption of carbonic oxide by the blood.

The experiment is, further, of great interest, as it enables us to assign an approximate value to the oxygen tension of human arterial blood. The curve shows that had the oxygen tension been that of air (*i.e.* 21 % of an atmosphere) the blood would have been about 21·5 % saturated. Now in this case the relative saturating powers of the two gases would have been as ·045 × 130 = 5·85 to 21. But as the blood was actually 25·5 % saturated the relative saturating of the oxygen must have been reduced to about 17,—or 16 if allowance be made for the dilution of the carbonic oxide in the alveoli by aqueous vapour;—*i.e.* the oxygen tension in the arterial blood leaving the lungs must have amounted to about 16 % of an atmosphere. Now from the composition of the expired air, and the amount of the "dead space" of the air-passages, it may be inferred that the normal alveolar oxygen tension is about 14 % of an atmosphere. This is a somewhat lower oxygen tension than that of the arterial blood as deduced from the result of the experiment, but, considering the limits of error in the various determinations, it would be unsafe to conclude that during this experiment the oxygen tension in the arterial blood was really higher than that in the alveoli. It is nevertheless remarkable that Experiments IX. and X. also seem to indicate slightly higher oxygen tension in the arterial blood

than in the alveoli. Further experiments must decide whether the condition of the blood in carbonic oxide poisoning really furnishes any reliable additional evidence in support of Bohr's conclusion that the arterial may exceed the alveolar oxygen tension. It must, however, be borne in mind that the values obtained through such experiments are in reality minimum values. During the first part of the passage of the blood through the alveolar capillaries the oxygen tension in the blood must be very low, so that carbonic oxide will be very readily absorbed. After an atmosphere containing carbonic oxide has been breathed for an hour or two a time will come when the extra carbonic oxide absorbed in the first part of the alveolar capillaries will be driven off again by the increased oxygen tension in the second part; and unless there is sufficient time for the completion of the latter process the percentage saturation of the blood with carbonic oxide will indicate too low an oxygen tension for arterial blood.

A consideration of the conditions just referred to as existing in the alveolar capillaries would seem to afford the key to some facts as regards the absorption of carbonic oxide which at first somewhat puzzled me. A reference to the protocols of Experiments IX. X. and XI. will show that the point at which further absorption ceased was reached somewhat suddenly, and not, as might have been expected, gradually approached as a curve approaches its asymptote. This was probably due to the fact that in the first part of the alveolar capillaries absorption goes on nearly equally fast all through an experiment, so that the point is reached suddenly at which the excess of carbonic oxide taken up in the first part of the capillaries begins to be driven off again in the second part. The second part of the alveolar capillaries would thus seem to check the absorption of carbonic oxide much in the same way as that in which an overflow weir suddenly checks the rise of the water in a river when the water level has reached a certain point.

There can be little doubt that the disappearance of carbonic oxide from the blood when pure air is again breathed depends on dissociation of carboxyhæmoglobin in the blood of the lungs, and consequent diffusion outwards of carbonic oxide. Evidence already exists that if any carbonic oxide is oxidised in the body the quantity is at least very small[1], but the data obtained in Experiments II. and XI. render it possible roughly to test the hypothesis that diffusion outwards is the essential cause of the disappearance of the carbonic oxide. In Experi-

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

ment XI. it was found that with ·045 % of carbonic oxide in the air the blood became at the end of two hours about 25% saturated, and that this saturation did not increase further. Hence it may be provisionally assumed that a saturation of 25% corresponds to an average tension of about ·045% of an atmosphere of carbonic oxide in the arterial blood. Now in Experiment II. the blood was about 25% saturated half-an-hour after the end of the experiment, and it took at least two and a half to three hours more to reduce the saturation to a point beyond which carbonic oxide could no longer be detected with certainty in the blood. In the first case there was an initial driving force inwards of ·044% of an atmosphere of carbonic oxide, and in the second case an initial driving force of the same amount outwards. The passage outwards of the whole of the carbonic oxide required more than three hours, while the passage inwards of the corresponding amount required about two hours. Were it the case that oxidation of carbonic oxide within the body, or any other cause except diffusion outwards through the pulmonary epithelium, played an important part in causing the disappearance of carbonic oxide, one would have expected to find that under conditions such as those in the two experiments referred to the disappearance of the carbonic oxide would be more rapid than its absorption into the blood. The greater actual rapidity of the absorption would seem to be due to the following causes. Absorption must be hastened by the influence of the first part of the alveolar capillaries, in which, as already shewn, the oxygen tension, and therefore also the carbonic oxide tension, remains always much lower than in the alveolar air. On the other hand the disappearance of carbonic oxide from the blood must be correspondingly retarded by the same part of the alveolar capillaries, which will not merely give off no carbonic oxide to the alveolar air, but will reabsorb some of what has been already given off by the part in which the oxygen tension is high.

The Action of Oxygen in Carbonic Oxide Poisoning.

In the course of the experiments described above I endeavoured to ascertain whether the inhalation of oxygen causes a rapid partial relief in the symptoms of carbonic oxide poisoning. The reason for expecting such relief is that, as shewn in the previous paper[1], breathing pure oxygen causes the blood to take up in simple solution a quantity of oxygen sufficient to go a long way towards supporting life. In cases of

[1] This *Journal*, XVIII. 201. 1895.

carbonic oxide poisoning, unless death has occurred, the blood corpuscles will still always be capable of carrying to the tissues a considerable quantity of oxygen in combination with the hæmoglobin. When this quantity of combined oxygen is reinforced by the oxygen which goes into simple solution in the blood in presence of an atmosphere of pure oxygen, it might be expected that the total quantity in the blood would suffice to support life. Similarly one would expect that with the blood 50% saturated with carbonic oxide the symptoms would at once be relieved by breathing oxygen.

The experiments which I made on this subject were not conclusive. In No. VII. there was a marked amelioration in the symptoms, apparently due to the oxygen. In No. VIII., however, there was no distinct amelioration; and one or two further control experiments (not recorded) showed how difficult it was to obtain convincing evidence without pushing the experiments to a dangerous point. The evidence brought forward in the previous paper leaves no doubt, however, that the breathing of oxygen must not only hasten the elimination of carbonic oxide, but also provide to the tissues an important supply of dissolved oxygen.

Remarks on the Treatment of Carbonic Oxide Poisoning.

It is evident that in the treatment of cases of carbonic oxide poisoning the first point to attend to is the prompt restoration if necessary of a sufficient supply of oxygen to the tissues, and particularly to those of the central nervous system. The examination of a drop of highly diluted blood will at once give information as to whether, when the patient is seen, there is still any dangerous amount of interference with the oxygen carrying power of the blood. If it is not distinctly pinker than normal blood diluted in a similar manner it may be inferred that the patient is now suffering, not from present want of oxygen, but from the effects of previous want of it. If the diluted blood is markedly pink good effects may be hoped for from the administration of oxygen if it is at hand. Apart from the administration of oxygen vigorous artificial respiration should if possible be continued until the pink colour of the blood becomes indistinct. It will probably also be wise to keep the head low and the limbs raised, so as to increase if possible the blood supply to the central nervous system, which seems to be the part of the body most sensitive to want of oxygen. Another point which may probably be of importance is to

prevent fall of temperature due to diminished heat production. Such fall of temperature is an exceedingly probable secondary result of carbonic oxide poisoning. It is known to be one of the dangers of climbing at high altitudes, where the conditions as regards oxygen supply are similar to those in slight cases of carbonic oxide poisoning. My attention was first directed to this point by observations on mice, and subsequently by a fact communicated to me by one of the rescue party after the terrible colliery explosion in South Wales in 1894. It was noticed that some of the men found still alive, but suffering from the effect of after-damp, got worse and gradually sank when brought to the fresh air at the bottom of the downcast pit. At this point the air would be cooler and dryer than in the workings, besides which the air-current would be very rapid. As the men in the pit were clothed very lightly their removal to the fresh air might easily accelerate a fall in body temperature, with all its well-known consequences. Dr Stevenson has further informed me that in a case of slow poisoning with carbonic oxide examined by him and treated at Guy's Hospital some years ago it was noted that the extremities &c. were exceedingly cold. In this case inhalation of oxygen after the patient was brought in was not found of service. Whether or not fall of temperature plays a part in carbonic oxide poisoning in large animals such as man, it certainly does so in the case of mice. The fall is apparently accelerated by dilation of the blood-vessels of the skin. Warming the animal restores it; and possibly a similar restorative effect might be produced in man by warm baths, or some measure of the same kind, in cases where the body temperature has fallen. Such a degree of deprivation of oxygen as occurs in severe cases of carbonic oxide poisoning must certainly cause serious damage of a more or less lasting character to the tissues, and particularly, as shewn by the experiments of Böhm[1], to the central nervous system. On either the nature of this damage, or on means of treatment for it, such experiments as I have as yet made throw no further light. It is perhaps usually the damage to the central nervous system which causes death—in some cases long after the patient has been restored to pure air.

The Minimum Harmful or Poisonous Percentage of Carbonic Oxide.

It is of practical importance to obtain some idea as to the minimum harmful or poisonous percentage of carbonic oxide for man. The above

[1] *Archiv für exper. Path. u. Pharm.* VIII. 68. 1878.

experiments prove that this percentage is very nearly the same for man as for mice and other warm-blooded animals. Experiment XI. shows that ·05% in pure air is just sufficient to produce in time very slight symptoms in man. About the same percentage produces slight symptoms in mice, as shewn in the previous paper. The action on small animals such as mice depends, however, to some extent on temperature. With a low external temperature the metabolism of a mouse is much increased; consequently the demand for oxygen increases, and a given saturation of the blood tells more evidently, just as in the case of a man exerting himself moderately. If sufficient oxygen to meet the increased metabolism in the mouse is not provided the body temperature must fall. In man there is no marked increase of metabolism with a diminished external temperature, hence the poisonous percentage of carbonic oxide cannot vary from the same cause except in so far as external cold may cause a more rapid fall of body temperature in consequence of the poisoning.

In Experiment VII. it appeared that ·2% is a very dangerous percentage to a man. In this experiment the saturation of the blood was still increasing, although urgent symptoms had already shown themselves, and the percentage of oxygen in the blood had fallen to what would have been a dangerous extent had the same diminution been produced by breathing air in which the oxygen tension was diminished. That the symptoms were not of a still more urgent character was probably due to the fact that the tension of the oxygen still present in the arterial blood was normal and not reduced. For this reason a given diminution in the oxygen percentage of the blood is probably not so dangerous when produced by carbonic oxide poisoning, or loss of red corpuscles, as when produced by diminution in the oxygen tension of the air breathed. In the previous paper it was shown that at ordinary temperatures a little over ·2% may be fatal to a mouse, and there can be little doubt that ·3% would produce death sooner or later in man, though much larger percentages may be breathed for a short time with impunity. Thus, in the experiment described on p. 446, I breathed 1·3% for several minutes, and, knowing the cumulative action of the gas, and having calculated the interval of safety, I had no hesitation in doing so. Its cumulative action is nevertheless one of the causes which make carbonic oxide specially dangerous under certain circumstances, for, as shown in Experiment VII., a man may be half-an-hour in air containing a poisonous proportion of carbonic oxide and yet feel nothing, so that when the dangerous symptoms

supervene there may be nothing to direct suspicion towards the air, or, as often happens in coal-mines, it may be too late to escape.

Closely connected with the question just discussed is a further one as to the limit of time within which the percentage saturation of the blood (and consequently the severity of the symptoms) may increase when a given percentage of carbonic oxide is breathed. Experiments IX. X. and XI. show that with less than ·05% of carbonic oxide in the air breathed the maximum quantity had been absorbed within two and a half hours. With higher percentages of carbonic oxide in the air this time limit will certainly not be exceeded, since, as shown by the curve, the amount of carbonic oxide absorbed by the blood does not increase proportionally to increases in the percentage of the gas in the air. Hence about two and a half hours may be set down as the limit of time within which absorption continues.

Summary of Chief Conclusions.

1. The percentage saturation of the hæmoglobin of the red corpuscles with carbonic oxide may be estimated during life by a simple colorimetric method.

2. The symptoms caused by carbonic oxide depend on the extent to which the hæmoglobin has been saturated.

3. Carbonic oxide is a "cumulative" poison. The symptoms produced by it do not become sensible (during rest) until sufficient has been absorbed for the corpuscles to become about a third saturated. With half saturation of the corpuscles the symptoms become urgent. The symptoms are due solely to deficiency in the oxygen percentage of the blood, and are similar to those experienced by mountaineers and balloonists at high altitudes.

4. When air containing carbonic oxide is breathed, about half of the carbonic oxide actually inhaled is absorbed (except when absorption is coming to a standstill). The time required for the production of sensible symptoms in an adult man depends on the time required for the inhalation of about 660 c.c., or the absorption of about 330 c.c. of the pure gas.

5. The time required for the symptoms to appear (or disappear) in different animals is proportional to the respiratory exchange per unit of body weight, and is about 20 times as long in a man as in a mouse. Hence it is possible with safety to use a mouse as an indicator of the presence of poisonous proportions of carbonic oxide in an atmosphere

(in a coal-mine for instance) into which it may be necessary for men to penetrate.

6. The maximum amount of carbonic oxide capable of being absorbed by the blood from air containing a given small percentage depends almost entirely upon the relative affinities of oxygen and carbonic oxide for hæmoglobin, and the relative tension of the two gases in the arterial blood.

7. The affinity of carbonic oxide for hæmoglobin is about 140 times that of oxygen.

8. The oxygen tension of human arterial blood is approximately 16% of an atmosphere.

9. Distinct symptoms, appreciable during rest, are not produced by carbonic oxide in otherwise normal air until about ·05% of the gas is present. With about ·2% urgent symptoms are produced.

10. With a given percentage of carbonic oxide in the air breathed a certain percentage saturation of the blood with carbonic oxide is reached within about two and a half hours, and not afterwards exceeded however long the breathing of the vitiated air may be continued.

11. The disappearance of carbonic oxide from the blood when fresh air is again breathed is always much slower than the absorption of the gas, and is chiefly due to dissociation of carboxyhæmoglobin by the mass influences of the oxygen in the pulmonary capillaries, and consequent diffusion of the gas outwards through the alveolar epithelium.