THE EFFECT OF EXCESS OF CARBON DIOXIDE AND OF WANT OF OXYGEN UPON THE RESPIRATION AND THE CIRCULATION. By LEONARD HILL and MARTIN FLACK.

(From the Physiological Laboratory of the London Hospital Medical College.)

Historical Introduction.

Paul Bert in his classical researches published in *La Pression Barométrique*[1] found that death occurred in a closed space, the oxygen supply being ample, when the partial pressure of CO_2 rose to 30 % in the case of mammals, to 24—28 % in the case of birds, to 13½—17 % in that of reptiles. Bert also determined that the percentage volume of CO_2, during the respiration of air containing 30—40 %, might rise to 120 in venous blood, to 116 in arterial, and to 40 in the tissue fluids; 10—15 being the normal amount in the last (dog). When the arterial blood contained as much as 80—90 % the animal was completely anæsthetic, the blood-pressure high, the heart beat frequent, but life was not endangered. The animal quickly recovered on breathing air, consciousness being speedily regained.

This anæsthetic effect of carbon dioxide has been confirmed by several workers, and its employment in combination with oxygen as a useful anæsthetic has been advocated (Gréhant, Benedicenti, etc.).

As is well known pure CO_2 is an irrespirable gas, and like other irrespirable gases, such as the halogens and their H compounds, and ammonia, etc., it produces spasm of the glottis.

The spasm is a reflex effect (the Holmgren-Kratschmer reflex) depending upon the excitation of the nasal mucous membrane and upon the integrity of the fifth nerve. Kratschmer showed that, after section of both fifth nerves, the closure of the glottis no longer occurred when these gases were inhaled or blown into the nose.

Zagari[2] has made observations upon the effect of the inhalation of CO_2 through a tracheal cannula, and concluded that the central effect produced by such an inhalation is preceded by a reflex one, resulting in inspiratory spasm of the diaphragm. The trigeminal excitation he says produces an expiratory reflex. Zagari found that the reflex was from the main bronchi rather than from the bronchioles. The bronchial muscles can be excited to contract by small doses of CO_2 (4 %). This contraction disappears upon section of the vagi; Einthoven, however, attributes it to a central effect.

Trying for us the effect of inhalation of a high percentage of CO_2 M. Greenwood found that he was unable to breathe the following: pure CO_2; 64·61 CO_2, 8·65 O_2; 38·24 CO_2, 9·11 O_2; but that he was able to breathe without spasm of the glottis a mixture of 15·3 CO_2, 14·47 O_2, although marked evidence of dyspnœa attended the effort. We have noticed also that mixtures containing about 20 % CO_2 bring about partial closure of the glottis so that a peculiar whooping sound is produced with each attempt at inspiration.

Haldane and Lorrain Smith[3] found on breathing air containing 18·6 % CO_2 that in one to two minutes there resulted profound dyspnœa attended by great discomfort, throbbing in the head, mental dullness and cyanosis. Speck[4] says that the first breath of 11·5 % CO_2 was unpleasant and that disagreeable sensations with dimness of vision quickly resulted. Speck says also that increasing the percentage of CO_2 in the inbreathed air from ·95 to 11·51 produced a nearly five-fold ventilation of the lungs (from 7·0 litres to 32·5 litres per minute); at the same time the number of respirations was trebled and the depth of breathing doubled. At 7 % there was as much CO_2 in the inhaled as in the exhaled air, and at 11 % there was more CO_2 in the inhaled than in the exhaled, thereby showing that not only no CO_2 was being given out but some of the inspired CO_2 was being retained in the body. Loewy and Zuntz[5] observing the ventilation to be 6·46 litres per minute when pure air was breathed found that, on adding CO_2 to the inspired air until the expired contained 5·28 %, the ventilation rose to 13·44 litres per minute and to 19·45 litres when the CO_2 in the expired air reached 6·66 %. These authors also obtained similar results from rabbits showing the effect of CO_2 upon the ventilation of the lungs.

The greatest effect in increasing the volume occurred with 15 % CO_2, the higher percentages diminishing the same by producing narcosis.

Loewy[6] suggests that the inhalation of a known percentage of CO_2 might be used as a method for testing the condition of the respiratory

centre when under the influence of drugs or in pathological states, and in fact has used this method for that purpose. He finds that the centre (tested by this method) is not affected during sleep or by chloral, but is depressed by morphia. Filehne[7] also says it is easy to produce apnœa by blowing in air, even on vagotomised rabbits when under morphia;

CO_2 content of inspired air	Breathing volume
0	838 c.c.
3·9	1269
4·7	1524
4·9	1783
11·5	2281
51·2	1406
8·0	1635
0	680

and that this is only done with the greatest difficulty when the centre is normal. Loewy points out that CO_2 in low percentages has no paralytic effect upon the centre. This is shown by the fact that the breathing volume increases and diminishes in a definite proportion as the partial pressure of CO_2 is raised or lowered. Loewy also directs attention to the fact that subjective feelings accompanying altered breathing only occur with comparatively high pressures of CO_2, becoming evident when the expired air contains 6 % and reaching a higher point when the expired air contains 8 %. One of the most interesting communications of recent date upon this subject is that of Haldane and Priestley[8] in which they demonstrated the exquisitely sensitive control which is exerted by the partial pressure of CO_2 in the alveolar air upon the respiratory centre. With 1·74 % CO_2 in the inspired air the lung ventilation was increased 43 %, and so perfect was the adjustment that the increase in percentage in the alveolar air was within the limits of experimental error. On breathing 4 % the alveolar tension rose 0·3 % and ventilation was increased 177 %; on breathing 5·28 % the alveolar tension became 0·85 higher than usual and ventilation 4·74 times as great. They conclude that an increase of ·2 % in the alveolar tension of CO_2 doubles the normal breathing volume and that it is produced when the CO_2 in the inspired air contains about 3 %, only then too do we become conscious of increased respiration. During work however 2 % becomes very noticeable because the effect is multiplied by the increased production of CO_2 in the body.

As to the influence of an excess of CO_2 in the air breathed upon the working capacity of a man, we can quote results which have been

obtained with the different forms of breathing apparatus for use in mines. In the case of a man working with the "Shamrock" type of dress[1] Dr P. Wetzke[9] found that 23,500 kgmm. of work were the most that could be done by a man in 120 minutes, the CO_2 rising to 2·5 % in 60 minutes and to 4·8 % at the end of the period. With the "Dräger" dress 37,500 kgmm. were accomplished in 125 minutes; the CO_2 reached ·5 % in 85 minutes, and 1·85 % at the end of the time. With the "Fleuss-Siebe-Gorman" dress, one of us (L. H.) found a powerful man able to do 46,950 kgmm. of work in 120 minutes, the CO_2 remained below ·5 % for 110 minutes and rose at the end to 1·2 %. The analyses of the contents of the breathing bag were made immediately after each working period. The work consisted of lifting a weight of 60 lbs. either by hand or by means of a foot pedal. When the CO_2 was allowed purposely to rise to 2 % or more, the power to do work was greatly decreased, as in the case of the "Shamrock" dress.

This diminution may be due to three causes (1) the increased work done by the respiratory muscles, (2) the depressing effect of CO_2 upon the heart, (3) the depressing effect of CO_2 upon muscle.

In considering these three causes there is ample proof that the first occurs, and we have little doubt that the dyspnœa is the main cause of the lessened working power. The respiratory mechanism prevents any large increase in CO_2 tension (Haldane and Priestley), and we have no evidence that a small increase in CO_2 tension affects muscle, nerve or heart.

As to the influence of larger amounts of CO_2 on these structures we can quote the experiments of Waller and of v. Lhota. Waller[10] states that "on isolated nerve the effect of little CO_2 is an augmented reaction, of much CO_2 a diminution or abolition followed by augmentation, upon isolated muscle the regular effect is augmentation, and upon isolated heart the regular effect is diminution." His "little" and "much" signify short or long exposure to the same partial pressure, *e.g.* that in expired air. Friedländer and Herter[11] found that after CO_2 poisoning the motor nerves were just as excitable as before (at the same position of the coil). Stimulation of the central end of the sciatic nerve gave no effect in deep CO_2 narcosis, showing that the centre was paralysed. In an atmosphere of pure CO_2 v. Lhota[12] found that the contraction of frog's muscles rapidly took on the characteristics of fatigue, that such muscles were preserved from exhaustion and when

[1] The dress has been improved since these results were obtained.

returned to pure air had a greater working capacity than control muscles which had been excited in air. In this connection Winterstein[13] finds that strychnine convulsions are prevented in a frog by putting it into 80 % CO_2 and concludes that CO_2 has a paralysing effect upon the processes of dissimilation. In one experiment after the injection of strychnine on placing the frog in pure CO_2 the animal became paralysed in 5 minutes; and when returned to the air became excitable again in 8 minutes. In 80 % CO_2 and 20 % O_2, the paralysis was not quite complete even after an hour. These results agree with those of Verworn[14], who shows that the excitability of the cord under the influence of strychnine depends partly upon the removal of waste products and partly upon want of oxygen. Perfusion of the cord with O free saline produces a return of excitability but perfusion with oxygenated saline causes far more. In connection with these experiments we may recall some observations made by one of us (L. H.) as long ago as 1893, which led to the conclusion that excised frog's muscles when tetanised *in vacuo* give off hardly any more CO_2 than when left at rest.

Fletcher[15] has noted similarly that five gastrocnemii in a current of N gave out ·05 c.c. of CO_2 per half hour during rest and ·07 c.c. during tetanisation; while five other gastrocnemii taken from the opposite limbs of the same five frogs and placed in O_2 had an output which reached ·095 c.c. during rest, and ·233 c.c. during activity. It was also noticed by Fletcher that fatigue came on much more rapidly in those in the nitrogen, than in those kept in oxygen, and that fatigued muscles if allowed to rest in oxygen recovered much more rapidly and perfectly than if allowed to remain in nitrogen. He noticed moreover that frog's muscles kept in oxygen never passed into *rigor mortis*. In the case of mammalian muscle Winterstein (*Pflüger's Archiv*, CXX. p. 225. 1907) finds that excitability is preserved for 27 hours in 2—4 atmospheres of O_2 at 37° C., and for 5 hours in 1 atmosphere. Hopkins and Fletcher[16] have shown that lactic acid is produced in a resting excised muscle kept under anærobic conditions, but not if kept in oxygen; also that from muscles, in which considerable lactic acid formation has been induced by tetanisation, a good deal of the lactic acid disappears when placed in oxygen.

In regard to the effect of small doses of CO_2 upon metabolism, Gréhant has brought evidence to show that it is lowered, but the evidence is far from conclusive.

Conflicting views have been held as to the relative importance of

oxygen-want and excess of carbon dioxide in the production of dyspnœa and asphyxia. In the case of fish and arthropods it is stated that dyspnœa results only from oxygen-want and not from CO_2 excess and that apnœa can be produced by filling the intestine with O_2 (Babák and Dédek, *Pflüger's Archiv*, CXIX. p. 483. 1907). Lombroso (*Pflüger's Archiv*, CXIX. p. 1. 1907) finds that mechanical obstruction of the movements of the mouth or gill-plate affects the breathing rhythm just as much in a fish out of water as in water, so that oxygen-want is not the factor in this case. In the case of mammals Rosenthal insisted on the importance of oxygen-want while Traube laid stress on CO_2 excess. Pflüger [17] carried out experiments to clear up the conflicting results and showed that severe symptoms of dyspnœa occurred when the CO_2 % in the blood actually was lessened so that in this case oxygen-want was the chief factor. Excess of CO_2 in blood he said could likewise produce dyspnœa but this is endured for a much longer time than that of oxygen-want. Friedländer and Herter [11] found that 20 % CO_2 could be breathed by rabbits for as long as an hour without any peculiar phenomena of poisoning, excepting increased cardiac and respiratory activity. Depression only resulted from a day-long exposure to such an atmosphere. When 30 % of CO_2 was administered the phenomena of depression quickly ensued, breathing soon ceased, the animal dropped to the ground, and temperature gradually diminished until death occurred. With 70 % the phenomena were limited to a few minutes. Benedicenti [18], working under Rosenthal, used percentages of CO_2 of 10, 12, 15 and more. He found that the CO_2 exerted a purely narcotic effect and did not excite the respiration, or at any rate only for a short time! With 30—35 % CO_2 there was no dyspnœa, but narcosis occurred in 30—45 minutes, the pupils widened and corneal reflex was almost abolished. This reflex did not vanish until CO_2 was 40—50 % and in such doses animals lived $1\frac{1}{2}$ hours—a result contrary to that of Paul Bert. Benedicenti's results were contradicted by those of Zuntz and Loewy [5], of Kropeit [19] and of Plavec [20]. Plavec found with increase in CO_2 up to 30 % an increasing greatness in the breathing volume, it then began to diminish with the onset of narcosis. With 5 % CO_2 the dyspnœa was very significant and with 10 % a marked rise of blood-pressure and slowing of the pulse became evident. The maximal CO_2 dyspnœa was 2—3 times as great as that produced by oxygen-want, *e.g.*

Atmosphere breathed	Breathing depth 1·4	Normal 1
Hydrogen	,, frequency 1·3	,,
	,, volume 1·8	,,
10 % CO_2	Breathing depth 2·4	,,
10 % O_2	,, frequency 1·5	,,
80 % air	,, volume 3·6	,,
30 % CO_2	Breathing depth 2·7	,,
20 % O_2	,, frequency 1·6	,,
50 % air	,, volume 4·3	,,

According to Winterstein[13] all the excitatory phenomena produced by CO_2 are of reflex origin. He has published blood-pressure curves purporting to show that the same results are obtained by blowing CO_2 into the nose and exciting the fifth nerve, as on inhalation through a tracheal cannula.

Mares[21] has carried out the most recent and complete investigation on this subject. He shows that rabbits have a far greater resistance to CO_2 than have dogs—a fact which may explain the divergent results of earlier workers. Rabbits can breathe for a relatively long time a mixture of 80 % CO_2 and 20 % oxygen, and quickly recover from the results of breathing the same when supplied with pure air. Mares states that respiration in the case of CO_2 excess becomes in the course of the first minute very greatly deepened, with the expiratory pauses longer, so that the number of respirations may be reduced to half in the first five minutes. In a later stage there occur breathing pauses extending to 1 minute. Friedländer and Herter[11] give a graphic account of the effect of breathing excess of CO_2 on an unanæsthetised animal:—"Upon allowing a rabbit to breathe 60—80 % CO_2 with 20 % O_2 most powerful respiratory effects immediately occur, combined with general extensor spasms of the greatest intensity. The pulse slows from 280 to 116 per minute with the first breath. This excitatory stage lasts but a short time, in 30—40 seconds, the animal falls to the ground completely narcotised and irresponsive to all forms of excitation. The respiration though still visible ever becomes slower and weaker, and finally very seldom and of minimal volume. The body temperature falls rapidly. Nevertheless the animal lives for more than a quarter of an hour, in fact until respiration finally ceases and the blood-pressure sinks to zero." "On allowing the animal to breathe air again, recovery takes place very rapidly. After 30—90 seconds very rapid and powerful respirations occur, at the same time reflex movements return and the animal makes spontaneous movements, at first often of a very powerful and cramp-like nature. These pass away and the animal is again in its

normal state." In these animals ecchymoses and œdema of the lung were caused by the violence of the convulsions. In cases of death the heart frequently still gives weak rhythmic movements in the auricle and both auricle and ventricle will react to mechanical and electrical stimulation.

Kropeit[19] says that the symptoms on breathing CO_2 with sufficient O_2 are exactly the same as those on breathing H_2 (O_2-want). Mares[21] draws a distinction between the effects and describes the results of O-want upon the respiration. He allowed the animals to breathe freely from a supply of N_2, so that the mechanical effects which result from closure of the trachea were prevented. In the first stage the respirations became notably deepened and somewhat more frequent; the dyspnœa is often ushered in by a very deep breath. It is accompanied by symptoms of anxiety and excitement and is of short duration, the breathing soon becoming very shallow and finally ceasing—"the præterminal pause." The excitatory stage is closed by powerful clonic-tonic spasms. The præterminal pause has been ascribed by Landergren (cf. Mares[21]) to the excitation of the vagus centre and consequent inhibition, by others to the exhaustion of the respiratory centre from O-want, and by Högyes[22] to the exhaustion of the respiratory muscles by the fits. The last explanation is certainly wrong. The pause is followed by terminal breaths, single or in groups, or by very deep cramp-like inspirations accompanied by snapping movements of the mouth, working of the alae nasi and movements of the whole head. These respirations are due to the incoordinate action of the dying respiratory centre (Richet, Mares), while according to Landergren[21] they result from the interference of exciting and inhibitory influences on the respiratory centre.

With CO_2 excess the blood-pressure shows a preliminary rise and then sinks to near the abscissa. No marked slowing of the heart is observed but the systoles become less and less powerful until at last they may finally cease. In these respects the effect upon the heart is entirely different from that of O-want. After the CO_2 excess is removed the systoles gradually recover in force again and the blood pressure steadily returns to its original height.

On the other hand in O-want the blood-pressure usually rises with the onset of dyspnœa. The heart then becomes infrequent, beating irregularly with powerful systoles. At the end of the stage of spasms, the heart may be almost entirely inhibited, not beating more than once a minute, the blood-pressure falling almost to zero between such beats. The blood collects in the dilated cavities as the pressure sinks—the heart

becomes weaker and weaker and death results from its failure. Upon the admission of air, the heart escapes from vagus inhibition, and beating with great force quickly drives the blood-pressure to a height.

The effect of CO_2 is a direct one upon the heart muscle and can be set aside by the removal of the CO_2 and massage of the heart.

Heart muscle is apparently resistant to O-want. Strecker[23] found that the excised mammalian heart could beat for a comparatively long time with a poor oxygen supply. Magnus[24] found that the mammalian heart could preserve its contraction for some time when hydrogen was sent through the coronary circulation. The heart of a curarised mammal may go on beating for half an hour after discontinuing artificial respiration. The hearts of mammals can be recovered after hours and even days—even after freezing (Hering). Bernstein and Fr. Müller[25] found in animals poisoned with chlorate of magnesium, until 70 % of the hæmoglobin was turned into methæmoglobin and only 3—4 % O_2 was left in the blood, that the animals could go on living for an hour or more. E. G. Martin (*Amer. Journ. Physiol.* xv. 1905) observed that strips of the turtle's heart stop in oxygen-free saline but were "characterised by the ease with which oxygenation produces recovery." It is clear from all these observations that the heart beat is only arrested by complete want of oxygen, and then is only arrested and not killed by such complete want, at any rate not for a long period of time.

As to the effect of oxygen-want upon the respiration, according to Speck[4] symptoms begin to appear when the partial pressure of oxygen falls below 10·5 % of an atmosphere. Friedländer and Herter[26] say that dyspnœa is scarcely noticeable in rabbits at 12·7 % but becomes very marked at 7 %. v. Terray[27] states that it is not noticeable in dogs and rabbits until below 10·5 %. In men Loewy finds that the breathing volume begins to increase when the O_2 falls to 15 %. Haldane says that hyperpnœa from want of O_2 occurs when the O pressure in the air breathed reaches 13 % or when the alveolar O pressure is 8 % of an atmosphere. The hyperpnœa is accompanied by a tendency to dizziness and by a loss of muscular power, disturbances of sensation, nausea, headache and marked psychical disturbances, similar in some respects to those of alcoholic poisoning.

The altitude at which men are affected on mountains depends on their power to keep up the oxygen tension in the blood, and this depends on the vigour of their circulation and on whether they are shallow or deep breathers, that is to say, on the relative proportion of the volume

of the dead space to the tidal air. In the case of Zuntz[28] at Berlin and on the top of Monte Rosa, the following table shows the relation between the actual and the reduced breathing volume.

	Barometric pressure	Breathing volume	Reduced breathing volume (at 0 and 760)	Alveolar O tension
Berlin	758	4·75	4·27	103·7
Monte Rosa	425	7·6	4·2	57·0

The reduced breathing volume of Zuntz and his co-workers was lessened on the top of Monte Rosa although the actual breathing volume was largely increased in all cases but one. The frequency of respiration was not affected in any uniform way. Jaquet and Stähelin[29] also found the reduced breathing volume of resting men in high altitudes less than it is in the plains. Mosso[30] found on Monte Rosa that the power to hold the breath voluntarily for a period was one-third of that in Turin. In sealed chambers Bert[1] found that death occurs when the oxygen partial pressure sinks to for cats 4·4, for sparrows 3·6, for guinea-pigs 2·5, for kittens 2·2. Tadpoles, according to Amerling (*Pflüger's Archiv*, CXXI. p. 363. 1908), are paralysed by O-want much sooner when old than when young. Tadpoles of 5 mm. length ceased to move when deprived of oxygen in 7 h. 30 min., when 15 mm. long in 1 h. 15 min.

The symptoms of mountain sickness occur at much lower altitudes in the case of mountaineers than in the case of men exposed to a low pressure in a pneumatic chamber or in a balloon ascent. The cause of the sickness is in all cases want of oxygen, and the difference seems to be due to the excessive, and in many cases unaccustomed, work on the heart in the case of the former. The dyspnœa from want of oxygen, just as that in cases of failing circulation, washes out the CO_2 from the blood and "the increased ventilation," as Haldane and Priestley[8] point out, "cannot materially increase the supply of oxygen, but can very materially decrease the CO_2 pressure." "Cyanosis, accompanied by all the effects of want of oxygen but unaccompanied by marked effect of CO_2 upon the respiratory centre, is thus produced; hence while cyanosis produced by hindrances to respiration or to respiratory exchange in the lungs would be accompanied by intense hyperpnœa due mainly to CO_2, circulatory cyanosis may be accompanied by only slight hyperpnœa." Mosso[30] noted the tendency to group breathing or Cheyne-Stokes respiration on the top of Monte Rosa, and attributed the symptoms of mountain sickness to the diminished partial pressure of CO_2 in the alveolar air. Zandell Henderson (*Amer. Journ. Physiol.* XXI. p. 126.

1908) maintains that the fall of blood-pressure, which occurs on excessive ventilation of the lungs by a bellows, is due to the washing out of CO_2 from the blood, and that shock generally is due to acapnia. His paper affords as far as we can find no evidence which prevents our attributing his results to the mechanical obstacle to the pulmonary circulation given by rapid and powerful positive ventilation. In pathological cases of Cheyne-Stokes respiration, where the centre is in an abnormal state of nutrition, Pembrey[31] showed that either administration of excess of O_2, or a low partial pressure of O_2 or a partial pressure of 2 % CO_2 in the inspired air, made respiration regular. The excess of O_2 acts by preventing O-want hyperpnœa which lowers the CO_2 tension of the blood and thus sends the respiratory centre into apnœa. The lessened partial pressure of O acts by keeping the centre constantly excited, and the added CO_2 also keeps the centre in a state of continuous excitement. Pembrey finds that these patients are far less susceptible to CO_2 than the normal individual, and even by a tension of 11 % CO_2 are only made to breathe regularly with no signs of dyspnœa.

The effect of oxygen-want upon the working power of the body has been tested by U. Mosso[30] with the ergograph. His records show that at Turin 3·48 kgm. metres of work could be performed before fatigue set in, whereas at the top of Monte Rosa it occurred when 2·828 kgm. metres had been accomplished.

Whymper found that it took 11·4 mins. to walk a mile in London and 11·58 in Quito. Trained Alpinists however, like the guides and mountain soldiers, are able to perform extraordinary severe physical tasks at high altitudes.

With regard to the effect of O-want upon metabolism, the Zuntz school have thoroughly established the fact that high altitudes increase it to a notable degree. Such an increase has not yet been observed in pneumatic chambers owing probably to the short duration of the exposures.

Part I. Observations on Animals.

Our experimental observations have been made upon cats and dogs and also upon man. We propose to consider first those made upon animals. The animals were anæsthetised with chloroform or ether during the operative procedures, while the observations were made during light anæsthesia, or with the animals under the influence of morphia. The blood-pressure was recorded by a mercury manometer connected

with the carotid artery, and the respiration by means of a bellows or tambour recorder connected either with a side tube of the tracheal cannula, or with the armlet of a sphygmometer surrounding the body of the animal. The respiratory tracings thus indicate the change in sign, but not the actual change in volume. The animals were made to breathe from an indiarubber bag containing in the one case varying concentrations of CO_2 combined with an ample supply of O_2, and in the other case nitrogen. In this second case a solution of sodium pyrogallate was placed in the bag which was well shaken, so that the O_2 and CO_2 exhaled by the animal were rapidly absorbed.

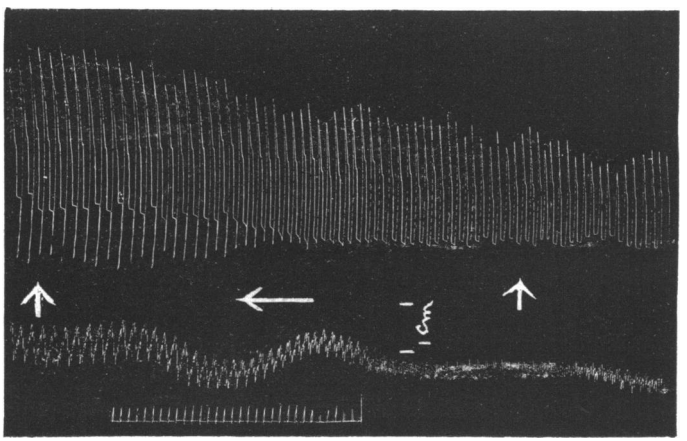

Fig. 1. $\times\frac{1}{3}$. Cat. Expired air breathed between the arrows. Time in seconds.

The influence of excess of CO_2.

Fig. 1 shows the effect of breathing 6·56 % CO_2, 14·5 % O_2, the vagi being cut. An increasing hyperpnœa is accompanied by a slight rise of blood-pressure, which however is interrupted at one stage. Fig. 2 represents a case in which the CO_2 is 6·4, O_2 9·65. The effect upon both respiration and circulation is more immediate and more marked, showing that the effect of O-want is here adding itself to that of CO_2 excess.

The third tracing (Fig. 3) shows the result of breathing 15·38 CO_2, 7·83 O_2 the sample being taken at the end of the experiment. The respiration becomes very dyspnœic and actually convulsive in type. The blood-pressure rises considerably, the heart beating powerfully during the period of administration. The respiration and circulation

do not become normal again until a period of two minutes has elapsed after the removal of the bag.

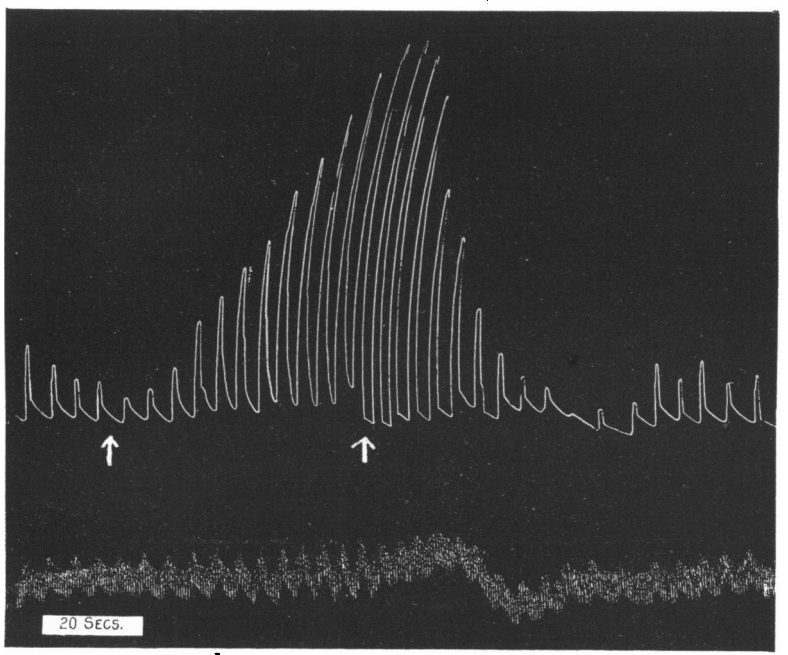

Fig. 2. $\times \frac{2}{5}$. Dog. Between the arrows $\begin{matrix} 6{\cdot}4\ CO_2 \\ 9{\cdot}65\ O_2 \end{matrix}$ breathed.

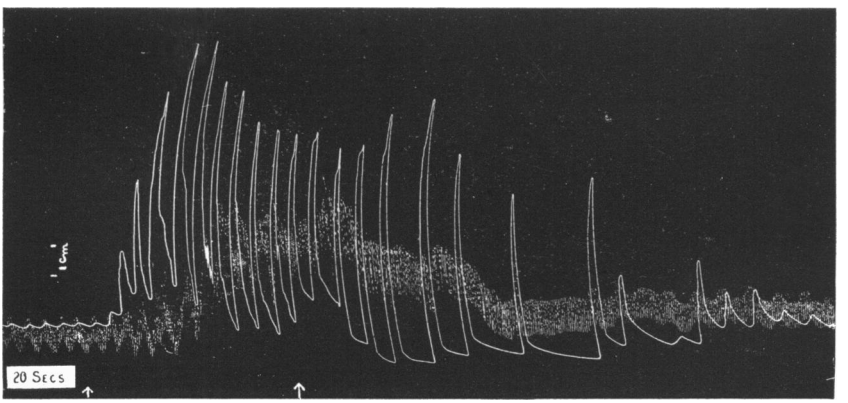

Fig. 3. $\times \frac{1}{2}$. Dog. Breathing of $\begin{matrix} 15{\cdot}38\ \% \ CO_2 \\ 7{\cdot}83\ \% \ O_2 \end{matrix}$ between arrows. Respirations convulsive.

In Fig. 4 is shown the effect of breathing 21·7 % CO_2 with excess of O_2. In Fig. 5 the percentage of CO_2 is 34·6 % and O_2 in excess.

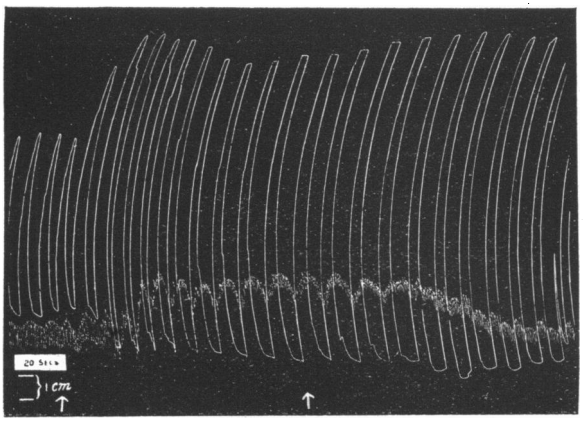

Fig. 4. $\times \frac{2}{3}$. Dog. 21·7 % CO_2 breathed between the arrows.

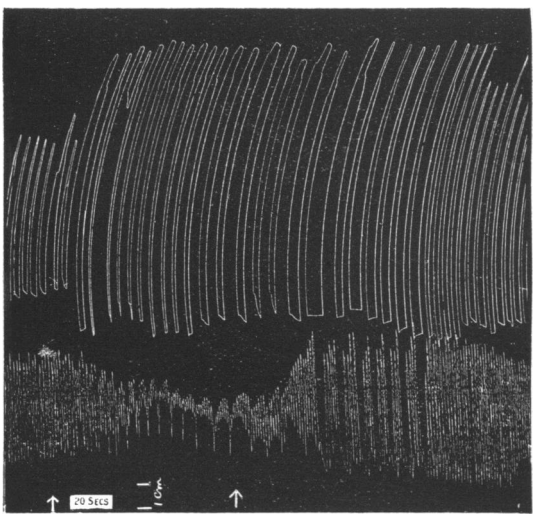

Fig. 5. $\times \frac{2}{3}$. Dog. $\begin{matrix}34{\cdot}6\ CO_2 \\ 11{\cdot}6\ O_2\end{matrix}$ breathed between the arrows.

In Fig. 6 there is 65·28 CO_2 with excess of O_2 while in Fig. 7 the CO_2 is pure.

The tracings show well the effect of CO_2 excess upon the respiration

and upon the circulation. It will be seen that there is an increasing excitatory effect upon the respiration from 6 % to 35 % where it reaches a maximum, although the effect of any percentage between 15 and 35 % is almost immediate. Above 35 % the respiration is evidently depressed, so that with 60 % the respiratory movements are far less marked, and with 80 % cessation of respiration occurs after a few small inspirations. Therefore up to 35 % CO_2 has an excitant effect upon the respiration, but beyond this limit the effect is distinctly depressant.

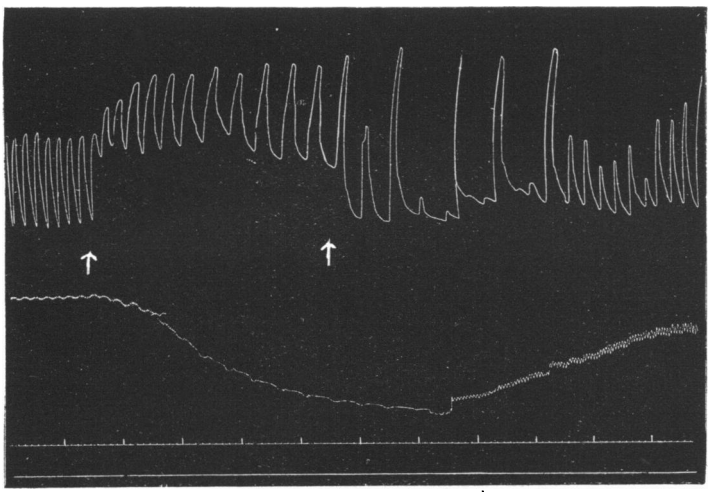

Fig. 6. $\times \frac{2}{3}$. Dog. Breathing of $\frac{65{\cdot}28\ CO_2}{16{\cdot}98\ O_2}$ between the arrows. Time in seconds.

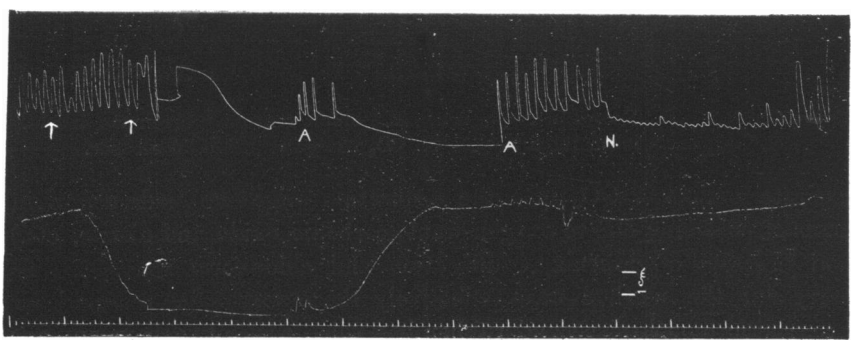

Fig. 7. $\times \frac{2}{3}$. Dog. Breathing of pure CO_2 between arrows. Artificial respiration at A. Natural breathing at N. Time in seconds.

The effect upon the blood-pressure is also well seen in the tracings, the results expressed in the following table well amplify them.

It will be seen that the most marked effect upon the blood-pressure is from 15—22 % (Fig. 3), at 34 % (Fig. 5) it is just beginning to fall, and with very high percentages it falls precipitously to the base line (Figs. 6 and 7).

Table showing the effect of different percentages of CO_2 upon the blood-pressure.

Per cent. CO_2	Effect on blood-pressure		Per cent. CO_2	Effect on blood-pressure	
6·56	10 mm.	Rise	34·6	10 mm.	Fall
6·4 (9·65 O_2)	12	Rise	43·9	60	Fall
7·1	no effect		44·18	80	Fall
15·38	76 mm.	Rise	65·26	114	Fall
21·7	38	Rise	80·66	120	Fall to base line
22·6	86	Rise	82·66	150	Fall to base line
26·28	8	Rise	Pure?	120	Fall to base line

The effect of CO_2 upon the respiration during very deep chloroform narcosis was also investigated. When breathing had become exceedingly shallow the inhalation of expired air at once remarkably increased the ventilation of the lungs, the effect passing away as the expired air was withdrawn (Fig. 8). We would suggest that the

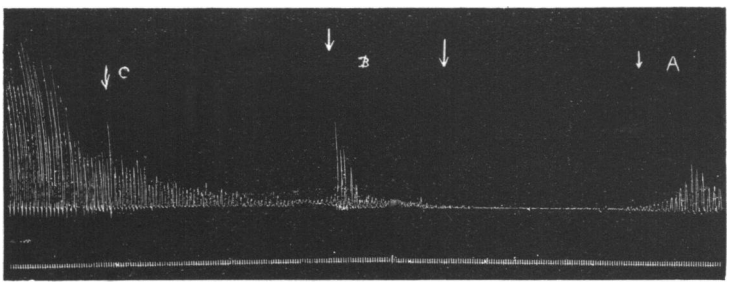

Fig. 8. $\times \frac{2}{3}$. Cat. Record of respiration. A. Chloroform on between the arrows. B. CO_2 on between the arrows. C. CO_2 on again. Time in seconds.

excitatory effect of CO_2 upon the respiration might be made use of in cases of poisoning due to oxygen-want (carbonic oxide and nitrite, etc.) and in cases of drowning, suffocation and chloroform syncope. To carry out the method most effectively there would be required an anæsthetic mouth-piece and rubber bag filled with oxygen in and out of which the operator has respired several times. This is then given the patient to breathe while artificial respiration is done. If oxygen is

not handy expired air itself serves as a suitable mixture. We may here recall the old method of resuscitation by blowing into the patient's mouth, which has undeservedly fallen into disrepute. The blowing and the artificial respiration should be used together. Champneys (*Artificial Respiration*, p. 145. 1887) urges the value of this method in reviving new-born children. The mouth of the child is covered with a towel and direct mouth to mouth inflation employed. The nose of the child must be left open as a safety valve and care must be taken not to rupture the lung by blowing too hard. Entrance of air into the stomach he says is of no account. In the case of a tubercular midwife this method led to the infection of twelve children.

The mode of action of excess of CO_2.

In order to settle the mode of action of excess of CO_2, as to how far it was central, reflex or in the case of the heart direct, we have not only made experiments before and after division of the vagi, that is to say after section of the afferent nerves from the air tubes and lung, but we have also carried out a series of injection experiments. In these we have injected the animal's own defibrinated blood which has been thoroughly shaken up with high percentages of CO_2 and O_2. The injections were made either into the jugular vein or into the peripheral end of the carotid artery.

Fig. 9 shows the effect of an injection of 30 c.c. of such blood into the jugular vein. The blood-pressure falls owing to the direct action of the gas on the heart, while the respiration is only affected at a later stage when the gas reaches the respiratory centre. We find that it takes from 12—14 seconds to affect the heart, which agrees well with Stewart's pulmonary circulation time for dogs of moderate size, namely 9—10½ seconds. The respiratory effect occurs in about double the time. On injecting such blood very slowly into the jugular vein of a cat, the cardiac and respiratory effects came on together (Fig. 10). The

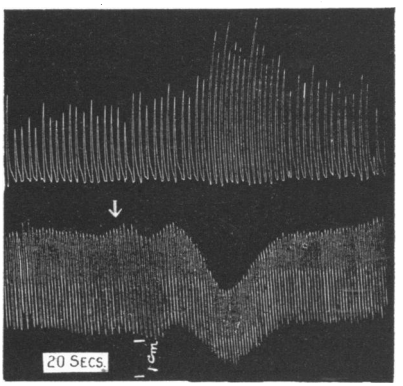

Fig. 9. ×½. Dog. The arrow marks the injection of 30 c.c. of CO_2 and O_2 sat. blood into the jugular vein.

respiration becomes slightly increased and the blood-pressure slowly falls during the first stage, while in the second stage respiration is altogether inhibited and the blood-pressure falls markedly (86 mm.) accompanied by vagus inhibition.

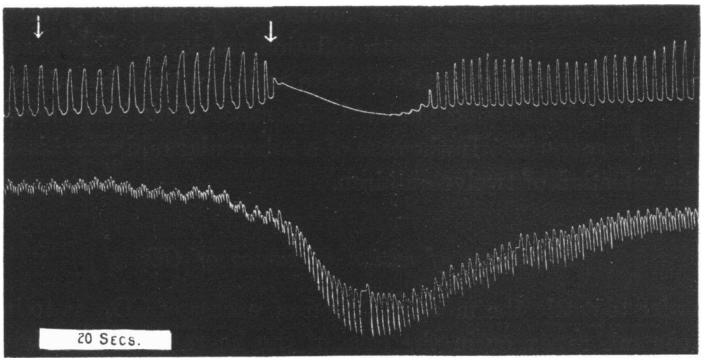

Fig. 10. $\times \frac{3}{5}$. Cat. Injection between arrows of 16 c.c. of CO_2 and O_2 sat. blood.

In the next tracing (Fig. 11) is shown the effect of the injection of such blood into the peripheral carotid artery of the same animal as in Fig. 9. The respiration and blood-pressure are affected simultaneously within a second or two of the injection. The blood-pressure is lowered not because of the direct action upon the heart, but on account of the excitation of the vagus centre, which occurs at the same time as the effect on the respiratory centre. In another experiment injection into the peripheral carotid of CO_2 blood produced spasm, then cessation of respiration, the heart showing signs of inhibition during the spasm, and the blood-pressure rising considerably during the period of cessation of the respiration. The effects of the carotid injection are so immediate and striking, and occur with such small quantities of blood,

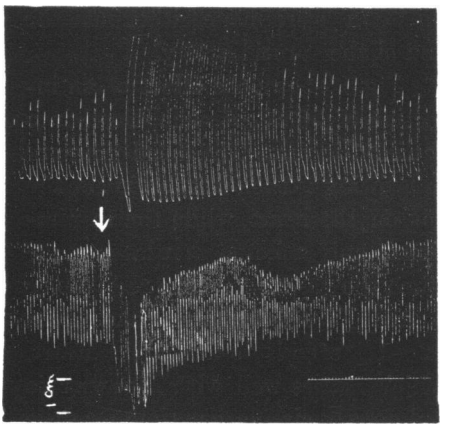

Fig. 11. $\times \frac{1}{2}$. Dog. The arrow marks the injection of 20 c.c. CO_2 and O_2 sat. blood into peripheral carotid. Time in seconds.

even with 5 c.c., that it is impossible for us to consider that these effects are produced reflexly by stimulation of afferent nerves such as the trigemini, but that they are due to direct stimulation of the respiratory centre in the medula.

Winterstein's assertion that CO_2 acts reflexly through the trigemini cannot be upheld in the face of the effects of minute changes of alveolar pressure of CO_2 obtained by Haldane and Priestley.

It is interesting to note that the injections into the jugular show that a small dose of blood saturated with CO_2 passes through the lungs without the excess being altogether got rid of.

There is evidence (cf. Heinz, *Hdb. d. Path. u. Pharm.* Bd. II. pp. 590, 598, 610) that reflex excitation of the breathing centre may be brought about by intravenous injection of such drugs as veratrine, nicotine, atropine; these act upon the terminations of the vagus in the lung. These reflexes are easily suppressed by narcosis and are abolished by division of the vagi. We have no evidence in our injection experiments that CO_2 produces a similar reflex effect. As we have said the results occur at such an interval of time after the injection as to make us believe that they are central in origin. Division of the vagi moreover has no effect.

The effects of CO_2 on the heart can always be quickly recovered from, even if the blood-pressure has sunk to zero. A small intake of air by normal or artificial means suffices to send the blood-pressure quickly up again, and normal breathing rapidly follows. In cases where the blood-pressure sinks to zero heart massage is also required.

Excess of CO_2 in moderate doses up to 25 % produces as we have seen a rise in blood-pressure. There is no evidence of this rise being of reflex origin (from the trigemini or vagi), since it usually occurs later than the effect upon the respiratory centre and comes on whether the vagi be intact or not. There is no evidence to be found in our records that it is due to increased force of the heart beat; injection of small doses of CO_2 saturated blood produces a fall, and when CO_2 is breathed in slightly higher doses the blood-pressure falls, and the force of the heart beat is diminished owing to the direct depressant effect of CO_2 on the heart. The increased respiration cannot in any way cause this rise of blood-pressure, since the blood-pressure falls after removal of the bag containing CO_2 some time before the respiration returns to its normal state.

Bayliss found on perfusing the iliac arteries of a frog with Ringer's solution saturated with CO_2 that a marked increase in the rate of flow

took place; the same occurred with 1 in 10,000 lactic acid. On the other hand Bier (*Virchow's Archiv*, CXLVII. pp. 256, 444, CLIII. pp. 306, 454) says that after the artery to a limb has been compressed for 10 minutes, an active hyperæmia follows in that limb even when the vaso-motor centre is being excited by asphyxia. The hyperæmia is however quickly set aside by the entry of the asphyxial blood into the limb, to return again on allowing the animal to breathe. If we suppose the vessels of the limb dilate owing to the effect of the local drop in blood-pressure in spite of the increasing activity of the vaso-motor centre, we must grant that the constriction, which follows the entry of the asphyxial blood, is due to the local effect of CO_2.

We have no evidence to offer which excludes the peripheral effect. The respiratory and cardio-inhibitory centres are both excited and so probably the vaso-motor centre is likewise, but our injection experiments show only spasm of respiration and inhibition when the CO_2 blood is driven directly into the brain.

Upon removal of the CO_2 there follows no great and rapid rise of blood-pressure as occurs on recovery from O-want. In the latter state the vessels are still constricted when the heart with a fresh supply of oxygen beats powerfully, in contrast with its depressed action after CO_2. The school of v. Basch has shown that while the pressure in the left auricle is raised quickly by compression of the aorta, owing to failure of the left ventricle to empty, it is not at first raised by asphyxia but even lowered. This effect is ascribed to the asphyxial blood stimulating the centre of the augmentor nerves of the heart (Openchowski, *Pflüg. Arch.* XXVII. p. 233).

We made a few observations on the effect of injection of other acids such as acetic and butyric, in weak concentration (·2 %). These acids added to Ringer's solution and injected into the peripheral carotid produced an excitatory effect on the respiratory centre similar to that caused by CO_2. But such acids effect such complicated changes in the blood (hæmolysis, agglutination, precipitation of proteids and changes in chemical equilibrium) that it is impossible to conclude from such experiments that the CO_2 effect is due to its acidic properties.

The effect of oxygen-want.

In Fig. 12 the dog was allowed to breathe from a bag which contained 4·52 of oxygen and no CO_2 at the moment when the respiratory symptoms became most marked. The respirations gradually

increase in intensity and finally become arrested for a short time. There is but little effect on the blood-pressure. In Fig. 13 the bag contained 2·09 of O_2 and no CO_2. The animal in this case was a cat.

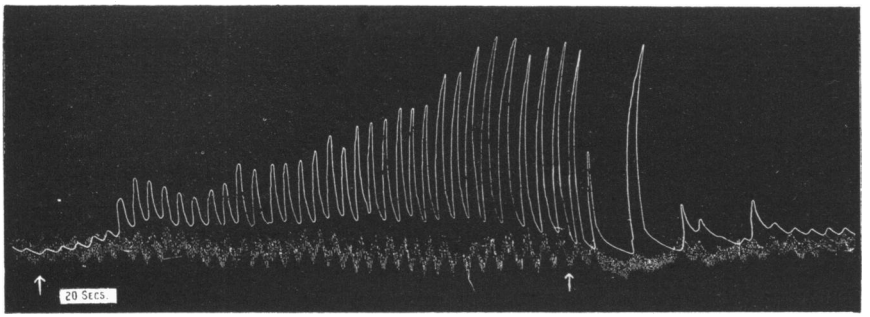

Fig. 12. $\times\frac{2}{3}$. Dog. Between the arrows $\frac{4\cdot52\ O_2}{0\ CO_2}$ was breathed.

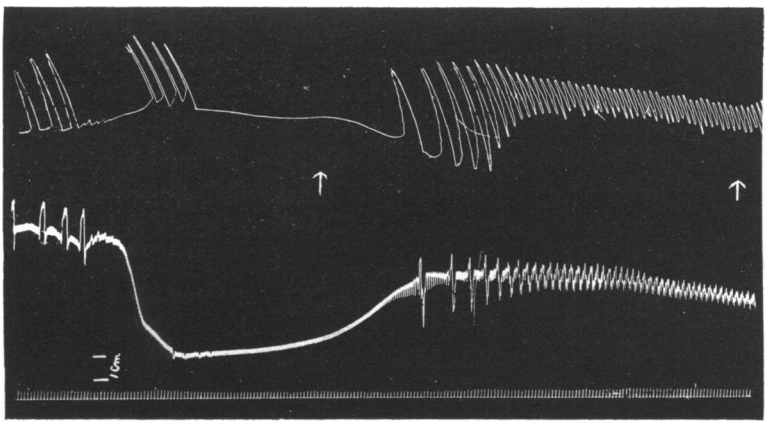

Fig. 13. $\times\frac{2}{3}$. Cat. Breathing between arrows $\frac{2\cdot09\ O_2}{0\cdot0\ CO_2}$. Time in seconds.

The respiration slowly increases in intensity and finally becomes arrested for a long period. The blood-pressure gradually rises, to fall again with the arrest of respiration. The heart beats become smaller and smaller but when the blood-pressure has become very low four convulsive gasps occur, and as the bag has been removed this brings about an immediate recovery of the blood-pressure and of the respiration. The blood-pressure rises considerably above its former level on recovery; as was generally the case in these observations. This rise points to the

state of vaso-constriction excited by oxygen-want, and as we have mentioned this subsequent rise above normal never occurs upon recovery from inhalation of excess of CO_2.

In the next tracing (Fig. 14) the bag contained ·24 % O_2 and no CO_2. The respirations gradually increase to a maximum and then a prolonged pause occurs, broken at intervals by spasmodic respirations. The blood-pressure rises during the first stage and then falls. The inhibitory effect exerted on the heart by the vagus centre is well marked.

Fig. 15 shows the effect of oxygen-want upon a cat. It is much the same as with the dog. There is the same increase in depth in the first stage, followed by convulsions, spasmodic breathing, cardiac inhibition and fall of blood-pressure. Convulsive respirations next occur at long intervals, and finally a very prolonged respiratory pause with marked fall of blood-pressure, which however rose when the respiratory pause was broken by a single deep convulsive breath of fresh air. Respiration recovered subsequent to a second convulsive breath which occurred after another long pause.

The rest of our experiments on oxygen-want we have summarised in the table next given. The same general features are seen in all—gradual onset of dyspnœa, inhibition of the heart when the vagi are intact, generally a rise of blood-pressure, convulsions and convulsive breathing, followed by long respiratory pauses and fall of blood-pressure. Recovery is rapid and marked by a rapid rise of blood-pressure to above original level.

To ascertain the mode of action of oxygen-want we have made a series of injections of blood saturated with carbonic oxide into the jugular vein and into the peripheral carotid. In the first case the symptoms have been slight, if any; the heart has a reserve supply of contractile material with oxygen in chemical combination and thus is not influenced by the temporary passage of a stream of deoxygenated blood through the coronaries. In the second case the medullary centres have shown signs of excitation, the nervous system, as is well known, being exceedingly susceptible to conditions of deficient oxygenation. The respiration becomes increased in depth as Fig. 16 shows, but not to the same extent as with CO_2 blood. We succeeded in one case in exciting the vagus centre and producing inhibition of the heart, but this is a later effect in asphyxia and is not easily produced by a temporary injection of deoxygenated blood. O-want brought about by ligation of all the cerebral arteries, is followed by excitation of all three centres, by spasm of respiration, cardiac inhibition

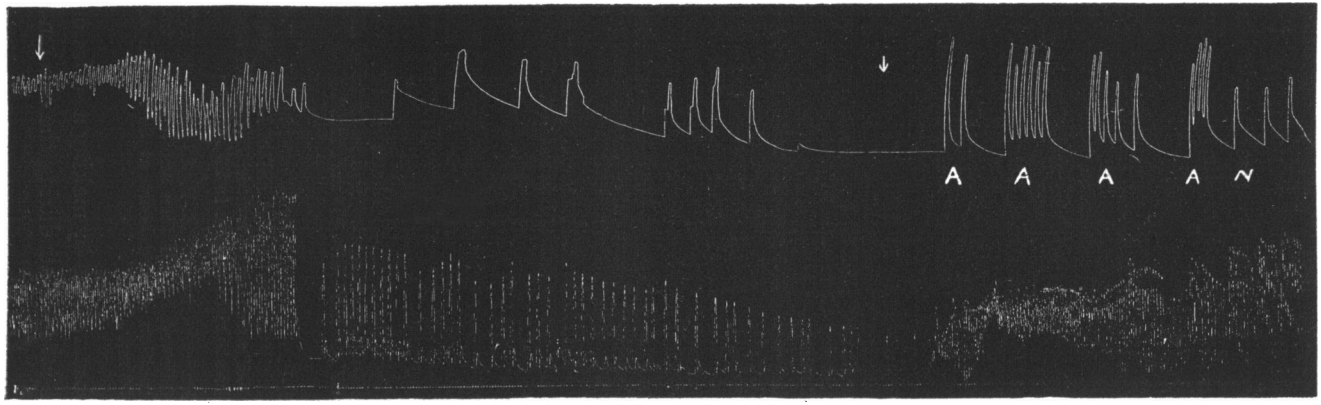

Fig. 14. $\times \frac{2}{3}$. Dog. Vagi intact. Breathing nitrogen between arrows. Sample at end $\begin{matrix}\cdot 0\ CO_2 \\ \cdot 24\ O_2\end{matrix}$. Artificial respiration at A. Natural breath at N.

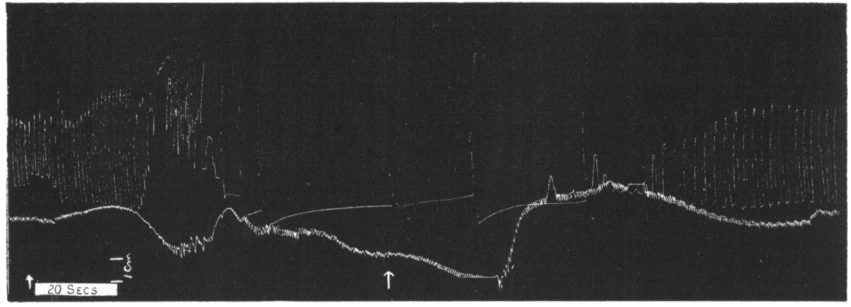

Fig. 15. $\times \frac{2}{3}$. Cat. Nitrogen breathed between the arrows.

and rise of blood-pressure (cf. Hill, *Phys. and Path. of Cerebral Circulation*, 1896). This vagus stimulation in O-want is protective in nature, since Barcroft and Dixon [32] have shown that vagus stimulation cuts the oxygen consumption down to $\frac{6}{10}$ in the case of the heart while the CO_2 output is even more considerably reduced.

Table showing effect of O-want upon the respiration and circulation.

	Respiration	Circulation
Cat Vagi intact	Gradual onset marked 32—77″, convulsions 86″, arrest at 105″	Rise hardly perceptible, marked inhibition of heart 56—86″. Fall B.-P. begins 51″, at 118″ fallen 80 mm. Recovered 114 mm. in 10″.
Dog Vagi cut	Marked effect 45—93″, from 106″ onwards two gasps in 57″	No rise B.-P. No inhibition of heart. Fall B.-P. begins 45″ and fell 92 mm. by 132″. Recovered 128 mm. in 42″.
Dog Vagi intact	Marked effect 55—101″, after this 4 breaths in 75″	Very slight rise B.-P. in 30″. Marked inhibition of heart 37—85″. Fall B.-P. begins 80″; fell 80 mm. by 182″: rose on recovery 52 mm. in 34″ and 100 mm. in 2 mins.
Dog Vagi intact	Marked dyspnœa 29—67″, convulsions and arrest did not set in	Marked rise B.-P. after slight fall had risen 50 mm. in 31″. Inhibition of heart not marked. No fall B.-P. during administration of gas. After removal of bag quickly fell to original level followed by subsequent rise of 30 mm.
Cat Vagi cut	Very gradual onset of dyspnœa marked at 54″, convulsion at 61″	No rise of B.-P. No inhibition of heart. Fall B.-P. begins 41″, fallen 46 mm. by 78″. Rose 104 mm. in 12″.
Dog Vagi intact	Marked dyspnœa 75—117″, after this 2 breaths in 20″. Convulsions just beginning when bag removed	Marked rise of B.-P. 52 mm. beginning at 88″. Inhibition of heart at 70″. No fall of B.-P.
Dog Vagi intact	Marked 37—130″ followed by convulsive type of breathing, 11 breaths in 135″	Very gradual rise of B.-P. 44 mm. in 100″. Marked inhibition of heart 24—37″, and from 64″ onwards, followed by gradual fall 70 mm. in 100″.
Dog Vagi cut	Gradual onset dyspnœa, marked 53″. Convulsions at 103″ followed by arrest, 1 breath in 30″	Slight rise of B.-P. 18 mm. in 44″. No inhibition of heart. Fall not marked till 98″, at 105″ falls 103 mm. in 9″.
Dog Vagi cut	Gradual onset dyspnœa—marked 60—101″ followed by arrest	B.-P. rises gradually 30 mm. in 54″. No inhibition of heart. Fall of B.-P. begins 101″ and falls 56 mm. in 75″. After first breath rises 94 mm. in 22″.
Cat Vagi intact	Very marked dyspnœa 20—26″, convulsions at 30″, arrest of respiration 65″	Gradual rise of B.-P. 18 mm. in 17″ followed by fall then another rise. Inhibition of the heart at 30″. Fall of 56 mm. in 53″.

We sought finally to complete our observations by making a series of investigations on the composition of the alveolar air during the different stages of asphyxia.

The trachea was closed by connecting a vacuum tube with the tracheal cannula for a certain period of time, varying in different observations from a few seconds to several minutes. The tap of the vacuum tube was turned and a sample of the contents of the lung obtained. The tables given below show what were the conditions of the respiration and of the circulation and the corresponding partial pressures of oxygen and CO_2. It will be seen that the oxygen in the alveolar air falls away more rapidly than the CO_2 increases.

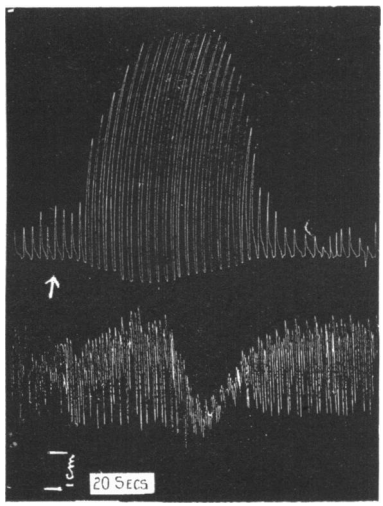

Fig. 16. $\times \frac{1}{2}$. Dog. Injection of 15 c.c. CO blood into peripheral carotid. Time in seconds.

The symptoms of asphyxia are due both to oxygen-want and to CO_2 excess. The first effect on the breathing occurred when the CO_2 was 6·46 and the oxygen 13·13; an evident influence both on blood-pressure and respiration occurred with the CO_2 at 6·6 and O_2 at 11·23. Cardiac inhibition was noted with CO_2 at 9·26 and O_2 at 8·31. The final symptoms of asphyxia are O-want effects. The highest figure reached by the CO_2 is 13·22 % at the end of 404 seconds, the oxygen in the same time having fallen almost to zero (·141 %).

Table showing the content of alveolar air in different stages of asphyxia.

	Duration of closure of trachea	Alveolar air content	Observations
April 30, 1907.	Cat: vagi intact.		
Tube I	42″	7·10 CO_2 5·16 O_2	Respiration much increased in intensity; B.-P. fallen 16 mm.; no previous rise; heart partially inhibited.
II	34″	7·60 CO_2 5·53 O_2	Convulsions. B.-P. fallen 16 mm.
May 15, 1907.	Dog: vagi intact.		
Tube I	106″	9·184 CO_2 6·72 O_2	Convulsions. B.-P. raised 12 mm.
II	?	10·41 CO_2 3·48 O_2	Convulsions and partial arrest of respiration. B.-P. raised 60 mm. Heart partially inhibited.
III	55″	9·62 CO_2 5·18 O_2	Very marked convulsions. B.-P. raised 24 mm., heart partially inhibited.
IV	16″	9·26 CO_2 8·31 O_2	Respiration convulsive. B.-P. raised 14; heart partially inhibited.
V	91″	10·63 CO_2 2·09 O_2	Convulsions and arrest of respiration. B.-P. beginning to fall after marked rise (34 mm.) Heart partially inhibited.
May 28, 1907.			
Tube I	16″	6·80 CO_2 8·80 O_2	Respirations convulsive. B.-P. raised 6 mm. No inhibition of heart.
II	27″	7·30 CO_2 7·60 O_2	Convulsive respiration. B.-P. raised 10 mm., partial heart inhibition.
III	47″	7·35 CO_2 5·84 O_2	Convulsions. B.-P. raised 20 mm., partial heart inhibition.
IV	89″	8·42 CO_2 3·06 O_2	Convulsions and partial arrest of respiration. B.-P. raised 28 mm., partial heart inhibition.
V	201″	9·47 CO_2 1·13 O_2	Respiration arrested, occasional gasp. Heart almost totally inhibited, occasional heart-beat coincident with gasp. B.-P. fallen 92 mm.
June 5.	Dog: vagi intact.		
Tube I	51″	7·79 CO_2 7·99 O_2	Respiration spasmodic. Some inhibition of heart. B.-P. raised 30 mm.
II	154″	8·85 CO_2 3·91 O_2	Respiration almost arrested; evacuation of fæces. Heart partially inhibited. B.-P. raised 70 mm.
III	9″	6·46 CO_2 13·13 O_2	Respiration very slightly increased. Heart and B.-P. not affected.
IV	35″	6·60 CO_2 11·23 O_2	Respirations becoming spasmodic. B.-P. raised 10 mm.
V	404″	13·22 CO_2 ·141 O_2	Respiration arrested. Heart very much diminished in frequency and force, after a period of inhibition. B.-P. fallen 100 mm.

Summary to Part I.

The effect of CO_2 excess:—

(1) At first hyperpnœa increased with rising partial pressure to convulsive breathing, especially marked in percentages from 15 to 30 %. Above 30—35 % the depressant and narcotic effect becomes more and more marked, so that with very high concentrations the excitatory effect is transitory and followed by respiratory arrest.

(2) With moderate doses the blood-pressure is raised and the vagus and vaso-motor centres excited; the most marked effect occurs with 10—25 %. Higher concentrations the blood-pressure falls owing to the depressant effect upon the heart muscle; from this effect the heart may be easily recovered by pure air and massage. The narcotic effect on unanæsthetised animals has been fully demonstrated by the authors we have cited above.

(3) The excitatory effect of small percentages of CO_2 on the respiratory centre leads us to urge that a mixture containing air or preferably oxygen and 5 % CO_2 should be employed in the resuscitation of cases of carbonic oxide and nitrite poisoning, of the apparently drowned, of suffocation and chloroform syncope. The simplest method of effecting this is to blow into the patient's mouth at the same time as artificial respiration is performed.

The effect of oxygen-want:—

(4) The dyspnœa is much more gradual in onset and terminates in a convulsive stage often of great intensity. This is followed by prolonged pauses broken at intervals by spasmodic respirations.

(5) The blood-pressure is usually raised but not always, the vagus centre is markedly excited, particularly during the convulsive stage of respiration. The blood-pressure rapidly falls subsequent to the convulsive stage, and upon recovery rises above the former level in a very short time. The heart is not so rapidly depressed by O-want as it is by CO_2 excess.

Part II. Observations on Man.

To carry our research to a further stage, we have made a series of observations upon ourselves and upon a number of medical students, with a view to investigating the composition of the alveolar air when the breath is held as long as possible. Shortly after making the preliminary experiments we ascertained from Dr Pembrey that he and

some of his pupils had already made some observations on similar lines. Dr Pembrey was kind enough to place such information as he had already obtained at our disposal. We have made these observations (1) under ordinary conditions, (2) after breathing oxygen, (3) after muscular exercise, and we have contrasted them with the results obtained by breathing in and out of an anæsthetist's indiarubber bag in the place of holding the breath. We made this contrast in order to see whether holding the breath had any mechanical effect upon the circulation, and whether our results were influenced by any such mechanical effect.

TABLE I.

Subject	Normal alveolar air CO_2	Normal alveolar air O_2	After holding the breath without oxygen CO_2	After holding the breath without oxygen O_2	Time held in secs.	Holding breath after three breaths of oxygen CO_2	Holding breath after three breaths of oxygen O_2	Time held in secs
L. H.	5·88	13·94	7·26	11·29	?	—	—	—
L. H.	6·2	13·0	8·32	10·20	32	—	—	—
L. H. (in a research 2 years ago L. H.'s CO_2 was 5·0)			5·89	8·54	23	—	—	—
L. H.	—	—	6·87	9·02	25	7·58	35·93	65
L. H.	—	—	—	—	—	7·86	excess	55
L. H.	—	—	—	—	—	8·87	excess	55
A. K.	—	—	6·90	10·39	45	—	—	—
M. G.	5·67	12·93	6·82	9·08	40	8·25	44·33	130
	—	—	6·85	9·02	40	—	—	—
	—	—	7·03	9·00	35	—	—	—
O. G.	—	—	6·95	9·96	30	—	—	—
M. F.	5·54	14·00	7·02	8·92	38	—	—	—
M. F.	5·54	14·00	7·31	9·23	35	8·01	31·60	55
M. F.	—	—	—	—	—	8·00	excess	89
S.	—	—	7·47	9·14	48	—	—	—
A. T. W.	—	—	6·76	11·90	135	—	—	—
L.	5·52	12·91	7·30	10·01	70	—	—	—
C. M. R.	6·35	13·06	6·96	10·52	35	—	—	—
G. E. V.	5·32	12·30	7·06	10·09	20	—	—	—
H. H. D.	5·40	12·36	6·80	11·31	35	—	—	—
H. N.	5·51	13·43	7·70	9·28	40	8·07	excess	90
E. H. R.	4·15	15·01	6·32	9·65	32	7·06	,,	72
W. R.	4·05 (two samples)	16·12	7·26	11·44	35	7·80	,,	40
Be	5·06	13·67	6·66	10·81	38	8·32	,,	58
H. B. W.	4·75	13·90	6·81	8·93	51	8·127	,,	105
F. S.	4·40	14·34	5·28	11·10	30	7·61	,,	62
I.	5·13	15·07	8·08	6·12	77	10·005	,,	160
Br.	5·06	15·20	6·625	11·21	42	7·80	,,	88
P.	6·02	15·52	6·30	11·32	53	7·92	,,	98
W.	5·53	14·61	6·21	10·32	38	7·86	,,	79

Table I shows in the first column the composition of the normal

alveolar air as obtained by the Haldane and Priestley method. Between the mouth-piece and the long tube from which the samples were taken we interposed a short piece of collapsible tubing. This we could clamp with a strong pair of rubber coated forceps immediately at the end of the expiratory effort, and thus relieve the subject from the necessity of closing the end of the tube with his tongue, an operation difficult to do after holding the breath to the breaking point.

Column II shows the composition of the alveolar air after the breath was held as long as possible after a normal quiet inspiration. The figures show that there are individual variations and also variations in the same individual under different conditions in daily life. One of the most important factors seems to be that of pluck or resolution to withstand discomfort, and this in the same individual varies according to the state of his nervous system, that is whether he be fresh or fatigued. This is well seen in the case of L. H.; in one instance he broke down with 7·26 CO_2, 11·29 O_2 in his alveolar air, in another when in a more vigorous condition at 8·32 CO_2, 10·20 O_2. The longest period of holding the breath that we have come across is one of 135 seconds, but in this case the student was so "done" that he could not expire sufficiently (300 c.c.) to obtain a sample which we considered satisfactory. This heroic effort was followed by a day's headache, and a refusal to repeat the performance.

In the case of I. who held his breath for 77 seconds the CO_2 rose to the high figure of 8·08 while the oxygen fell to the extraordinarily low one of 6·12 O_2. In most cases it will be seen that the breaking down point occurs when the oxgyen has fallen to 11—9 %. In the case of L. H. immediately after giving a lecture he broke down when the CO_2 had reached 5·89 %, a much lower figure than usual, but the oxygen was found to be but 8·54 %, a very marked drop. It will be seen also that in all cases the fall in the oxygen percentage is much greater than the rise in that of the CO_2; this led us to suspect that the breaking down point is fixed rather by the fall of oxygen than by the rise of the CO_2.

The third column of Table I shows the effect of taking three quiet breaths of oxygen before the holding of the breath. Oxygen want is thus altogether eliminated, and we see that in every case (for the samples were always taken following one another) the period over which the breath can be held is extended, in most cases greatly, and also that the partial pressure of the CO_2 is raised. Under these conditions the breaking point occurs approximately at 8 % CO_2. In the case of I. the

CO_2 went up to 10 % and the period for which he could hold the breath was more than doubled. In the case of M. G. the period was more than trebled. The symptoms which produce the breaking down are quite different in the two cases. In the one case (without oxygen) there is throbbing in the head, sometimes dizziness and a feeling of oppression in the chest, in fact some of those who held on longest described their feelings as those of "being about to die." One student fainted without any warning to the observer after having held his breath for about 15 seconds. He remembers observing the watch for that period and then both he and the watch fell to the ground.

In the second case (when oxygen is breathed before the experiment) the whole conditions are far more pleasant. There is a marked absence of anxiety, the second hand of the watch seems to slip round much more quickly, the breaking point is reached more suddenly; the urgent symptoms being: headache, breaking out into a profuse perspiration, an increasing and finally imperative desire to breathe.

In Table II column III are shown the results obtained on breathing in and out of a rubber bag in the place of holding the breath. In all cases but one (M. F.) the bag was filled with the air expired from the lung by a deep expiration, and this air was breathed in and out until the breaking point came when the contents of the bag were analysed. It will be seen (we have inserted column 1 from Table I for comparison) that this arrangement allows the CO_2 to go higher and the oxygen to go lower, very markedly so in the two cases who had the resolution to persist longest. In these cases the oxygen fell to the extremely low figures of 5·11 and 4·40 respectively; M. G. fainted for a moment or so, while E. H. R. became of such a marked blue-white colour that we made him desist from the experiment.

The results (columns I and III, Table II) therefore show clearly that holding the breath does produce some mechanical obstruction to the circulation by the cessation of the respiratory pump. In breathing in and out of a bag the blood containing oxygen in the outlying parts of the body can be brought into play and circulated freely to the coronary arteries and to the brain; at the same time the CO_2 can be removed from the tissues by the more efficient circulation and so its percentage in the alveolar air rises.

In column IV the same experiments were repeated but the bag was filled with oxygen in order to eliminate the influence of oxygen-want. Under these conditions we reached the extraordinary high figure of 10 and even 10·7 % CO_2 in the alveolar air; the time also is lengthened

from two to four or even five minutes. The symptoms become those well known to occur with a high partial pressure of CO_2. At first the inhalation is free and pleasant, then it deepens more and more and finally the hyperpnœa becomes so excessive that the whole effort of the man is given to gasping for breath. At this stage there is marked headache, the skin is flushed and the body bathed in perspiration. The shortness of Table II is accounted for by the exceedingly unpleasant character of the experiments.

TABLE II.

Subject	After holding breath CO_2	After holding breath O_2	Time held in secs.	After three breaths of oxygen CO_2	After three breaths of oxygen O_2	Time held in secs.	Breathing expired air from bag CO_2	Breathing expired air from bag O_2	Time in secs.	Breathing oxygen from bag CO_2	Breathing oxygen from bag O_2	Time in secs.
L. H.	6·87	9·02	25	7·58	35·93	65	7·80	8·39	80	8·77	43·86	165
M. G.	**6·82**	**9·08**	**40**	**8·25**	**44·33**	**130**	**7·96**	**5·11**	?	**10·70**	**41·82**	**330**
M. F.*	7·31	9·23	35	8·01	31·60	55	(9·76	12·30	215)*	10·16	excess	250
H. N.	7·70	9·28	40	8·07	excess	90	7·82	8·36	100	10·01	34·56	240
E. H. R.	**6·32**	**9·65**	**32**	**7·06**	**excess**	**72**	**8·22**	**4·40**	**125**	**10·29**	**32·89**	**255**

* Started with pure air, not expired, therefore no O-want effect.

The next series we give (Table III) shows the influence of severe muscular work on the power to hold the breath. We also give the results (1) of the normal alveolar air, (2) of holding the breath under normal conditions, (3) of holding the breath after three breaths of oxygen obtained on the same individuals at the same time of experiment.

TABLE III.

Subject	Normal alveolar air CO_2	Normal alveolar air O_2	After holding breath under normal conditions CO_2	After holding breath under normal conditions O_2	Time in secs.	Holding breath after three breaths of oxygen CO_2	Holding breath after three breaths of oxygen O_2	Time in secs.	Holding breath after muscular exercise CO_2	Holding breath after muscular exercise O_2	Time in secs.
W. R.	4·05	16·12	7·26	11·44	35	7·80	excess	40	8·87	11·70	12
Be	5·06	13·67	6·66	10·81	38	8·32	,,	58	7·93	13·82	9
H. B. W.	4·75	13·90	6·81	8·93	51	8·127	,,	105	7·12	11·46	10
F. S.	4·40	14·34	5·28	11·10	30	7·61	,,	62	7·77	10·23	10
I.	5·13	15·07	8·08	6·12	77	10·005	,,	160	9·95	8·901	14
Br.	5·06	15·20	6·625	11·21	42	7·80	,,	88	7·64	12·86	10
P.	6·02	15·52	6·30	11·32	53	7·92	,,	98	7·29	13·38	9

The duration through which the breath can be held is greatly shortened to 8—11 seconds, the CO_2 partial pressure rises far more quickly (approximately three times) and to a greater height, while the oxygen does not fall to the same extent as when the breath is held under normal quiet conditions. In the case of I. the individual peculiarities are shown to the same extent as before. In the former paper (Proceedings of this *Journal*, July 12, 1907) we gave a table

showing the alveolar tension and body temperatures of athletes immediately after several races.

The results there given show that the body temperature may under such conditions rise as high as 103°—105° F. The alveolar tensions we reprint as Table IV.

TABLE IV.

Subject	Race	Alveolar tensions CO_2	Alveolar tensions O_2	Observations when samples taken
W. V. F.	½ mile	4·62	17·43	Immediately after race.
R. M. L.	½ mile	6·0	16·40	,, ,, ,,
,,	1 mile	4·57	15·65	About 1 minute after race.
,,	1 mile	4·86	17·05	After running from course into dressing room.
J. F. P.	1 mile	4·40	16·54	Immediately after race.
		(5·16	14·62	before race).
,,	7 laps of 3 miles	4·22	15·32	Immediately after race.
H.	1 mile	5·12	16·0	About 1 minute after race.
,,	3 miles	4·53	14·94	2 mins. after race panting subsiding.
H. P.	1 mile	3·74	17·8	Immediately after race.
,,	3 miles	5·33	15·39	,, ,, ,,
,,	3 miles	4·44	16·30	,, ,, ,,
		(5·27	14·42	before race).

It will be seen that in all cases the partial pressure of CO_2 is low and that of oxygen high pointing to the conclusion at first sight that the ventilation was more than ample, and that the dyspnœa could not be ascribed to excess of CO_2 but rather to increased bodily temperature (Pembrey) and to the products of incomplete muscular metabolism such as lactic acid (Zuntz, Fletcher and Hopkins).

The new experiments however show that the CO_2 production is so active that the tension becomes almost doubled on holding the breath for some ten seconds, and the question arises whether the alveolar air is really in equilibrium with the blood. Our injection experiments in Part I of this paper show that even small doses of blood containing excess of CO_2 can pass through the lungs without being altogether freed of its excess, and it seems possible that during exercise there may be a higher tension of CO_2 in the blood than there is in the alveolar air. Moreover it will be seen from Table III that the CO_2 tension at the breaking down point after muscular exercise equals or approaches that when the breath is held after breathing oxygen. It therefore seems that the CO_2 tension of the blood may after all be a chief cause of the dyspnœa of muscular exercise.

In Table V we give results obtained after holding the breath a number of times in succession. In each case the breath was held after the subject thought that he had returned to a normal state of respiration subsequent to the previous holding of the breath.

TABLE V.

Subject	Alveolar air before exp. CO_2	Alveolar air before exp. O_2	Alveolar air after exp. CO_2	Alveolar air after exp. O_2	Times breath held in seconds
L. H.	6·20	13·00	6·50	12·46	35, 40, 35, 45, 45.
M. G.	5·56	13·85	6·37	13·57	35, 38, 33, 45, 50, 48, 50.
M. F.	5·40	14·21	6·09	14·20	30, 40, 38, 40, 30, 38, 37.
C. M. R.	6·35	13·06	6·75	13·24	33, 35, 49, 40.
G. E. V.	5·32	12·30	6·30	13·43	40, 50, 45, 50.
H. H. D.	5·40	12·36	6·09	13·55	35, 38, 43, 38, 42, 33, 40, 32, 32, 31, 34.
H. N.	5·51	13·43	6·51	14·31	40, 55, 57, 65, 70, 75.
E. H. R.	4·15	15·01	4·55	14·08	32, 43, 48, 44, 46, 56, 44, 47.
L.	5·52	12·91	6·16	12·32	70, 70, 100, 80.
F. S.	4·40	14·34	4·71	15·01	29, 43, 40, 45, 60, 45, 45, 45, 45, 43, 55, 60, 45, 60, 60, 55.
R.	4·05	16·12	4·80	14·81	30, 20, 18, 36, 42, 48, 45.
Be	5·06	13·67	4·53	15·79	25, 30, 36, 40, 35, 43, 51, 42.

It will be seen that on the whole the partial pressure of CO_2 tends to get higher, and the periods of holding the breath longer; the former is particularly marked. This is to be explained by the increased respiration which follows each period of holding the breath, whereby the blood is better oxygenated, and the results offer further proof that the power to hold the breath depends more upon the supply of oxygen than upon the amount of CO_2 present.

To contrast the results we obtained upon dogs during asphyxia with those on man we analysed samples of the alveolar air after holding the breath over gradually increasing intervals. Table VI shows the result.

TABLE VI.

Subject	Time in secs.	Alveolar air CO_2	Alveolar air O_2	Subject	Time in secs. start	Time in secs. finish	Alveolar air CO_2	Alveolar air O_2
L. H.	Normal	5·54	14·0	M. F.	0	10	5·54	14·0
,,	After 15	6·64	10·32	,,	5	15	5·72	13·7
,,	,, 25	7·23	8·68	,,	10	20	6·01	12·7
,,	,, 35	7·58	8·66	,,	15	26	6·17	10·16
M. G.	Normal	5·95	13·39	,,	25	33	6·56	9·23
,,	After 10	6·17	10·81	,,	30	38	7·31	8·94
,,	,, 20	6·21	10·01					
,,	,, 30	6·88	9·81					
,,	,, 40	6·60	9·56					

It will be seen that the oxygen goes down much more than the CO_2 rises and that the difference in the case of the oxygen is greater in the earlier stages than in the last, owing no doubt to the impediment to the circulation through the lungs produced by holding the breath, and partly perhaps to inhibited metabolism.

The last experiment of this series is one which confirms the results obtained by Speck and others (cited in the Introduction). Mixtures containing excess of oxygen and increasing percentages of CO_2 were breathed in succession from a bag. It was found that when the CO_2 was 4·78 % in the bag to begin with, the final amount reached 9·11 %; while when the mixture contained 13·32 % CO_2 at the beginning the final amount in the bag was 10·31 %, showing that in this case the body had got rid of no CO_2 but had actually absorbed 3 % of the CO_2 in the bag.

SUMMARY[1] TO PART II.

The conclusions to be drawn from these experiments are :—

(1) That the inability to hold the breath depends more upon oxygen-want than upon CO_2 excess.

(2) That the power to hold the breath is greatly extended by having an excess of oxygen in the lungs.

(3) Breathing freely in and out of a small closed space extends the power to withstand excess of CO_2 and want of oxygen, because the circulation is not mechanically impeded as it is when the breath is held.

(4) When excess of oxygen is breathed from a closed space the CO_2 tension rises to 10 % and over before the breaking point occurs. At this partial pressure CO_2 is rapidly accumulating in the body.

(5) In muscular exercise CO_2 excess rather than oxygen-want seems to be the excitant of the hyperpnœa.

(6) Finally our experiments show that while Haldane and Priestley are correct in saying that normally respiration is regulated by the tension of the CO_2 in the alveolar air, in cases of obstructed aëration of the blood, diminished oxygen tension is the more potent agent.

[1] A summary of Part I has been given on p. 103.

LIST OF REFERENCES.

(1) Paul Bert. La Pression Barométrique, p. 610. 1878.
(2) Zagari. Arch. f. Physiol. p. 37. 1891.
(3) Haldane and Lorrain Smith. Journ. Path. and Bacteriol. I. p. 168. 1892.
(4) Speck. Physiol. d. menschlichen Athmens. p. 131. 1892.
(5) Loewy und Zuntz. Arch. f. Phys. p. 397. 1897.
(6) Loewy, A. Pflüger's Arch. XLVII. p. 601. 1890.
(7) Filehne. Arch. f. exp. Path. u. Pharm. X. p. 442. 1879.
(8) Haldane and Priestley. This Journal, XXXII. p. 255. 1905.
(9) Wetzke. "Tests of Life-saving Apparatus." Reprint from "Kohler und Erz" Part I. 1907.
(10) Waller. Proceedings Physiol. Soc. p. XVI. 1896. This Journal, XX.
(11) Friedländer und Herter. Zeitschr. f. physiol. Chem. II. p. 99. 1878–9.
(12) v. Lhota. Arch. f. Phys. 1902. Suppl. p. 45.
(13) Winterstein. Arch. f. Phys. 1900. Suppl. p. 177.
(14) Verworn. Arch. f. Phys. 1900. Suppl. p. 152.
(15) Fletcher. This Journal, XXIII. p. 10. 1898; XXVIII. pp. 354, 474. 1902.
(16) Fletcher and Hopkins. This Journal, XXXV. p. 247. 1907.
(17) Pflüger. Pflüger's Arch. I. p. 61. 1868.
(18) Benedicenti. Arch. f. Phys. p. 408. 1896.
(19) Kropeit. Pflüger's Arch. LXXIII. p. 438. 1898.
(20) Plavec. Pflüger's Arch. LXXIX. p. 195. 1900.
(21) Mares. Pflüger's Arch. XCI. p. 529.
(22) Högyes. Arch. f. exp. Path. u. Pharm. V. p. 86. 1876.
(23) Strecker. Pflüger's Archiv. LXXX. p. 161. 1900.
(24) Magnus. Centralb. f. Phys. XXXVI. p. 133. 1902.
(25) Bernstein u. Fr. Müller. Arch. f. Phys. p. 498. 1907.
(26) Friedländer u. Herter. Zeitsch. f. physiol. Chem. III. p. 19. 1879.
(27) v. Terray. Pflüger's Archiv. LXV. p. 383. 1897.
(28) Zuntz, etc. Höhenklima u. Bergwanderungen, p. 228. 1906.
(29) Jaquet u. Stähelin. Arch. f. exp. Path. u. Pharmak. XLVI. p. 274. 1901.
(30) Mosso. "Life of Man in the High Alps," p. 3. 1898.
(31) Pembrey. Transactions Med. Chir. Soc. XC. pp. 49, 83. 1907.
(32) Barcroft and Dixon. This Journal, XXXV. p. 195. 1907.