THE PATHOLOGICAL EFFECTS DUE TO INCREASE OF OXYGEN TENSION IN THE AIR BREATHED.

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THE investigation which forms the subject of the present paper arose out of a series of experiments on the attenuation of microbes by oxygen at high pressure. Part of this series was carried out with the view of ascertaining the effect of the oxygen on animals which had been infected. It soon became apparent, however, that the oxygen at a tension of over 100% of an atmosphere produced pneumonia in the normal animal. It was therefore necessary to carry out a preliminary research in regard to this.

The literature of respiration records in connection with this question a considerable number of investigations, the most important of which were carried out by Lavoisier and others immediately after the promulgation of the combustion theory of respiration. According to various authors, definite effects were obtained by breathing pure oxygen. The respiratory exchange was increased, the circulation quickened, congestion of the lungs, or even inflammation and death, occurred. The theory was that addition of oxygen increased the pulmonary combustion, and thereby produced these pathological changes. This result was controverted by Regnault and Reiset in their classical investigation[1]. They showed that no increase in oxidation occurred and no pathological changes ensued on the exposure of animals to atmospheres rich in oxygen.

The question of the effect of oxygen took a new form in Paul Bert's research on the effects on animals of variations of barometric pressure. He discovered the fundamental law that the effects on all living organisms arising from variations in barometric pressure are entirely the result of the tensions at which the oxygen is maintained in the

[1] *Annales de Chimie*, p. 496. 1849.

various atmospheres. By exposing an animal to four atmospheres of oxygen, the same effect is brought about as that caused by increasing the barometric pressure of the air 20 times. In relation to the present investigation, the chief fact brought out is that oxygen at a tension varying from three to five atmospheres becomes toxic, and causes death in a definite form. The series of changes in the animal exposed to the oxygen, which Bert described, did not lead him to support the old combustion theory of respiration. He compares the symptoms with those of tetanus, or strychnine poisoning. The changes began with convulsions, and unless the tension were lowered in time, death of the animal ensued. In the experiments with small birds, he found that oxygen at a tension of $3\frac{1}{2}$ atmospheres caused the onset of the convulsions after about 5 minutes' exposure. If the tension of oxygen were kept at this level, the convulsions continued to occur with decreasing severity, and at longer and longer intervals, till the animal died. If, however, the tension of oxygen were raised at the beginning distinctly beyond this, death ensued in the first attack. Another feature of this condition, of great pathological interest, was that the animal exposed to oxygen seemed to be thrown into a status epilepticus, and even if the high tension were replaced by that of ordinary air, the convulsions which had begun in toxic atmosphere, continued till death followed. The longest duration of this condition which Bert records, was in the case of a dog where the effect lasted for 24 hours after the dog had been removed from the high oxygen tension.

Bert directs attention to a farther point in regard to the fatal effect of oxygen on different classes of animals. While a tension of oxygen equal to 300 % of an atmosphere produces convulsions in birds, a similar effect is not obtained in dogs till the tension rises to 380 %[1]. He states, however, that he does not consider his experiments as sufficiently precise in regard to this aspect of the subject.

Bert regarded the effects as those of an agent toxic to the nervous system. The oxygen must cause these effects either by direct action, being carried in the blood to the nerve tissue, or by some indirect means, as, for example, by an effect on the blood itself. He carried out a number of transfusion experiments, in which he drew blood from an animal suffering from the toxic effects, and injected it into a normal animal. His negative results led him to conclude that the convulsions were due to the direct action of the oxygen on the nervous system.

[1] *La Pression Barométrique*, 794.

He then endeavoured, by means of blood-gas analyses, to discover the quantity of oxygen which must be present in the blood before the toxic effect arises. While he states that his analyses do not permit of a conclusion as to any constant value[1], the average obtained in the case of the dog was about 30 vol. per cent. Bert's conclusion accordingly was that oxygen at a certain tension (which can be most correctly stated as a tension of the gas in the air breathed) becomes a direct nerve poison, and that it is in this way that excess of oxygen kills an animal.

It would, however, seem *a priori* improbable that an excess of oxygen, which is harmful to the nerve elements, should be without effect on the other tissues of the body. Indeed Bert's observations on the diminution of respiratory oxidation when the tension of oxygen in the air breathed has risen beyond 100 % of an atmosphere, and the occurrence finally of complete arrest, clearly suggest that the lungs are affected by the oxygen. Further, since the question involves essentially a study of the action of oxygen on the tissues, it is clear that the lung is the most favourable organ for this purpose. In fact, we might say that Bert's investigation breaks down in this respect because he has to deal with the relation of oxygen to the nerve elements, and yet has no means of accurately determining the tension of the gas in this tissue. In the case of all tissues other than the lungs, we find in the circulating blood, which intervenes to carry the gas to them from the lungs, a factor whose effect on the tension of the gas we have no means of estimating.

The animals used in the present research were chiefly mice and small birds, although a few observations were made on rats, guinea-pigs, and pigeons. The advantage of using the smallest animals for these experiments is that the total amount of oxygen consumed is small, and therefore several hours must elapse before there is any appreciable fall in the oxygen tension of the atmosphere in a chamber even so small as the one now described. To obtain the effects due to moderately high oxygen tensions, each experiment had to be carried on for several days, and in such cases the smallest animals require the least attention.

The apparatus consisted of a pressure chamber to which was attached a mercury manometer 10 feet in height. The chamber was constructed out of strong brass tubing of 6 in. diameter, and 15 in. in length. The capacity was almost exactly 6 litres. To permit observa-

[1] *La Pression Barométrique*, 794.

tion of the animal during the experiment one end of the chamber was made of thick glass. This was fitted very carefully, and the fittings were covered with a layer of modeller's wax. The opposite end of the chamber could be detached, and was formed out of a disc of gun-metal $\frac{3}{8}$ inch in thickness. This disc rested on a strong collar, and between it and the collar was placed an india-rubber washer. To close it down tightly, a number of bolts were used, arranged round the circumference on a plan similar to that adopted in constructing the lid of an autoclave. The inner surface of the chamber was painted white. Two pieces of brass tubing were soldered into openings in the metallic disc, and by means of them a current of air or oxygen could be passed through the chamber after it was closed. The oxygen was obtained from cylinders supplied by the Scotch and Irish Oxygen Company. The gas was manufactured by the peroxide of barium method, and contained no impurity except nitrogen. The india-rubber tubing was that used for the manufacture of bicycle pumps. In the middle of the india-rubber, in this form of tubing, there is a strong layer of linen. This was found sufficient for the highest pressures. Tubing composed of ordinary india-rubber is very apt to give way at about 3 atmospheres' pressure.

An experiment was carried out in the following manner. There was placed in the chamber along with the animal a supply of food sufficient for two or three days, and enough sawdust and cotton-wool to keep the animal dry and warm. In the chamber there was also a gauze basket containing finely granular potash lime, to absorb the carbonic acid as it was excreted. After the chamber was closed, a current of oxygen was set going, and allowed to pass through the chamber until the air had been entirely replaced. About 18 litres were usually passed through in this way, the amount being measured by a meter. The outlet tube was then clamped, and the oxygen allowed to pass in till the pressure rose to the level determined on. As the oxygen became absorbed, the pressure was occasionally raised, and in the long experiments samples were taken at intervals for analysis. In those experiments where the oxygen was fatal, a post mortem examination of the animal was made, and the tissues examined microscopically.

The lowest tension of oxygen which has been studied is 40 % of an atmosphere. Above this, at intervals, experiments have been carried out till a tension of 450 % of an atmosphere was reached. The aim in this series was to find the effects which arise with tensions approaching by degrees that required to produce the toxic effect described by Bert.

Exp. I. Two mice were placed in the pressure chamber, and, without washing out the air, oxygen was passed in till the mercury showed a few inches positive pressure. Analyses of the gas in the chamber were made daily, and these gave an average tension of 41·6 % of an atmosphere. The mice were carefully observed; but as they showed no abnormal symptoms, at the end of 8 days the experiment was concluded. The temperature of the chamber was on an average 19° C., but varied from 17° C. to 22° C.

This should be regarded as a control experiment. It tested the method in several respects, but chiefly as to whether mice resembled man in their resistance to the effects of a very moderate oxygen tension. There is a large amount of experience on record in which men in caissons have carried on severe mechanical labour in this tension without any harmful result. Indeed, it is held by some engineers that so much oxygen increases the working power. This experience, however, does not exactly correspond to the experiments just recorded, since the exposure to oxygen in the caissons is intermittent, while in the experiment it is continuous, and if there were any effect, even of a minor description, the fact that it was continuous would relatively increase its severity. It was found, as will be pointed out later, that mice have a remarkable power of recovering from the effects of high tension oxygen. The same is probably true of man, so that in the alternation between the ordinary atmosphere and the atmospheres where oxygen is at an increased tension, there would be much less danger than in an exposure which is continuous. The absence of effect, however, shows that mice are, roughly speaking, not less resistant than man to oxygen.

In the next experiments, the tension of oxygen was raised to 70—80 % of an atmosphere.

Exp. II. Two mice were placed in the chamber, and the oxygen tension raised. The average of the daily analyses gave a tension of 73·6 % of an atmosphere. On the 4th day of the experiment, one mouse was found dead, and when examined showed congestion and consolidation of the lungs. The other mouse survived exposure for 8 days, and continued to live for 9 days subsequently in ordinary air, when it died from some accidental cause.

Exp. III. The experiment was repeated with the slightly higher oxygen tension of 79·9 % of an atmosphere. It gave the same result. One mouse died on the 4th day. In this case the congestion of the lungs was not so well marked as in the former case. The other mouse survived a week, when the experiment was concluded.

As experiments on the effect of oxygen these observations are not decisive, as the tension is not yet sufficiently high; but, in the light of the further results to be recorded, they may be regarded as indicating that at this tension a point has probably been reached where the oxygen has an effect on the lungs, which varies according to the resistance of the individual animal. The result is very similar to the observations in caissons, where it is found that one worker suffers while others endure the exposure without showing any effects.

It is convenient at this point to allude to some precautions which were found necessary in conducting the experiments. Special care was taken to avoid any fallacy from a fall in the body temperature of the mice. Most of the experiments were carried out in a small room which was maintained for the purpose at a temperature of from 17°—20° C., and in some the pressure chamber was kept warm by a gas flame. Another precaution taken was to provide for the absorption of the carbonic acid. The gauze basket with granular moist potash lime was found most effective. The amount usually present was ·05 %—·1 %, and was never higher than ·5%. The purity of the oxygen was also tested. Examination was made especially for the presence of ozone, or any other gas which might act as an irritant to the lungs. No impurity except nitrogen, however, could be detected.

It will also be noticed that in most of the experiments two animals were used. The purpose of this was to have a check on accidental circumstances in each experiment. It was found that the mice differed considerably in their power of resistance to the action of oxygen. A young mouse for example gives way more quickly than one that is fully grown.

In the experiments which follow next in the series, the tension of oxygen was about 130 % of an atmosphere. The effect on the mice was uniformly fatal, and the immediate cause of death was inflammation of the lungs. Embarrassment of respiration set in some time before death, and the lungs were found post mortem to be extremely congested, with more or less complete consolidation. Other changes were observed; for example, congestion of other viscera (liver, spleen, kidneys); but these were not of constant occurrence, nor were they so pronounced as the changes in the lungs.

Exp. IV. Two mice were placed in the chamber, and the pressure was raised to give a tension of oxygen of 128·6 % of an atmosphere. The mice were at first very active, and ran about the chamber in a very lively manner, as if stimulated by the oxygen. After 48 hours, they became sluggish, and

after 90 hours, they were found dead. The pressure was raised at frequent intervals to give an average oxygen tension of about 130 % of an atmosphere.

Post mortem examination: A. The lungs were deeply congested, and sank in the fixing fluid (saturated solution of corrosive sublimate). Spleen slightly enlarged. Other organs normal. On microscopic examination, the tissue of the lungs showed intense congestion in the large and small blood vessels. The alveoli were to a great extent filled with an exudate, which was granular and fibrillated in appearance, but did not give the fibrin stain by Weigert's method, nor with eosin. The Weigert's stain showed one or two streptococci. These, however, were exceedingly few in number, and as the mice died overnight in a somewhat warm atmosphere, their presence was probably accidental. There were no leucocytes in the exudate. The pneumonic condition was universal, and could therefore be compared only with the earliest stages of croupous pneumonia. The exudate itself was probably the cause of the embarrassed respiration and the animal's death. It is inconceivable that with inflammation so extensive, the animal could have survived until the process had developed farther. B. The lungs of the second mouse showed similar changes. There were no micro-organisms to be found in the sections. The liver and kidney showed congestion in this case.

In the post mortem records of cases in which death ensued from the effects of caisson disease, the occasional congestion of the viscera, including the lungs, liver, and spleen, has been noted. This is a suggestive detail in the observations, since it tends to show that the effects of high oxygen tension are not limited to the nervous system (Bert), nor to the lungs, but may affect other tissues as well. Pavy's experiments on glycosuria arising from passing oxygenated blood through the liver add confirmation to this hypothesis[1].

Exp. V. Two mice were placed in the chamber, and the oxygen tension raised to 128·9 % of an atmosphere. Mice became sluggish after 48 hours. Both died in about 69 hours. Post mortem examination showed the lungs congested and consolidated: other organs normal in both animals.

Exp. VI. Two mice were placed in the chamber, and the oxygen tension raised to 129·7 %. Both mice were found dead in 40 hours, and the post mortem appearances were similar to the previous experiments.

Exp. VII. Two mice were placed in the chamber, and the oxygen tension raised to 114 %. The mice died with consolidation of lungs after 60 hours' exposure.

[1] *Proceedings of the Royal Society*, 1875 and 1876.

The result is perfectly uniform. The oxygen causes a general pneumonia, which slowly developes to the stage at which the lungs are filled with a fluid exudation. Owing to this condition the animal dies. The average oxygen tension is 125·3 %, and the average time of survival is 64 hours. The regularity of the occurrence of pneumonia from oxygen at this tension lends further probability to the theory that workers in caissons at 4·25 % atmospheres air pressure, or a tension of 88 % of oxygen, are exposed to dangers from the effect of the oxygen on the lungs. It is further evident that the tension which, without exception, produces fatal results in mice is very slightly beyond this.

The next question to decide was whether raising the tension of oxygen distinctly above this point would give the same results at a markedly shorter period. Accordingly the pressure was raised so as to give an oxygen tension of 180 % of an atmosphere.

Exp. VIII. Two mice were placed in the chamber, and the oxygen tension raised to 182·9 % of an atmosphere. The mice were very lively at first, and ate their food greedily. In 23 hours one mouse was dead. The other died in 27½ hours. Post mortem examination: lungs deeply congested and consolidated. Spleen slightly enlarged in one of the mice. The other organs were normal.

Exp. IX. A small mouse, half-grown, and a full-grown mouse were placed in oxygen at a tension of 176·7 % of an atmosphere. In 10½ hours, the small mouse had embarrassed respiration, and was dead in 21 hours. The other mouse was at this time taken from the chamber, but died 3½ hours later. On post mortem examination, the changes in the lungs were found to be the same in character as before, but hardly so marked.

Exp. X. Two mice were placed in the chamber, and the oxygen raised to a tension of 188·5 % of an atmosphere. One of them died in 7 hours. The other was removed from the chamber and recovered.

Exp. XI. A guinea-pig was subjected to an oxygen tension of 166·5 % of an atmosphere. After 12½ hours, its breathing was very laboured, and it was drowned. The lungs showed marked congestion and œdema. This experiment was performed as a control on the foregoing experiments. The chamber was, however, inconveniently small for a guinea-pig. The oxygen absorption was so great that there was a rapid fall in pressure.

Exp. XII. A lark was placed in oxygen at a tension of 175·8 % of an atmosphere. After 11 hours the breathing had become exceedingly embarrassed, and the bird was taken out. It survived till next morning, but continued dyspnœic. Its arterial oxygen tension was observed by the carbonic oxide method, and was 10·7 % of an atmosphere. The arterial

oxygen tension of a normal bird is 35—40 % of an atmosphere. The lungs were markedly congested.

Exp. XIII. Two larks were placed in oxygen at a tension of 173·3 % of an atmosphere. One bird died after 16 hours, with congestion and consolidation of the lungs. The arterial oxygen tension of the surviving bird was 12·4 % of an atmosphere.

Exp. XIV. Two mice were placed in oxygen at a tension of 189 % of an atmosphere. Both mice died after 27 hours' exposure. The lungs showed the same lesions as in the other experiments.

In comparing these experiments with those in which the oxygen tension was 130 % of an atmosphere, the chief point of difference to be noted is that the time of exposure which mice and small birds can endure is not more than about 24 hours. The lesions produced by the oxygen are the same as those seen in the former series of experiments.

This lesion was also studied in regard to the modifications of function which it induces in the lungs. In a paper which I published in this *Journal* (Vol. XXII.) on the arterial oxygen tension in various pathological conditions, I recorded a series of experiments to show that exposure of animals to oxygen at a tension of 170—180 % of an atmosphere caused in a short time a diminution in the power of the lungs to actively absorb oxygen, and that with a continuance of this exposure the arterial oxygen tension fell till it reached the level for which mere diffusion of oxygen from the alveolar air might account. The inflammation now described is a further stage of the same process.

In concluding this set of experiments it seemed desirable to make an observation on the effect on mice of air pressure similar to the oxygen pressure. Two mice were exposed to air at the pressure of two atmospheres, for 48 hours, but showed no symptoms. The reason for making this observation is that Bert did not include observations on mice in his experiments on the comparison of the effects of air and oxygen pressure.

The experiments which have so far been recorded show that at a very moderate tension of oxygen the lungs become inflamed, and that the time of onset of the inflammation is earlier the higher the tension. Further, there is apparently no marked difference between mammals and birds in this respect. The inflammation developes slowly, taking about 24 hours when the tension is 180 % of an atmosphere, to reach a fatal stage. The pneumonia is therefore a much more slowly developing effect than the nervous symptoms described by Bert, and in regard to it there is not the same differentiation of the different

classes of animals. It should be noted, however, that, in contrasting the effect on the lungs with that on the nervous system, we have to bear in mind the fact that in mice and birds the alveolar oxygen tension is probably about the same, and therefore the lung cells in mouse and bird are exposed to the same tension of oxygen in any given atmosphere. Since, however, the absorbing power of the lungs differs in mice and birds, there is no reason to suppose that in a given atmosphere the nerve tissue of the two animals is exposed to the same oxygen tension. In fact, experiments are given later which indicate that these tensions normally differ very considerably. To further clear up this question a series of experiments were carried out to investigate the relation of the pneumonic to the nervous effect, and with this purpose higher oxygen tensions were now employed.

Exp. XV. Two mice were placed in the chamber, and the oxygen tension raised half an atmosphere beyond that of the former experiments, viz. to 230 %. In 9¾ hours both mice suffered from very marked dyspnœa, when the experiment was concluded. The mice recovered. This experiment illustrated the striking fact, observed throughout, of the remarkable power of recovery from this condition.

Exp. XVI. Two mice were subjected to oxygen at a tension of 285 % of an atmosphere. They were at first very lively. In 3¾ hours both were dyspnœic. After 8¾ hours, one died with congested lungs. The other recovered.

Exp. XVII. A rat was subjected to oxygen at a tension of 268 % of an atmosphere. The large absorption of oxygen by the rat introduced a certain amount of fallacy into this experiment. In 5 hours the respiration was very much embarrassed, and the animal died overnight.

Exp. XVIII. Two mice were subjected to oxygen at a tension of 300 % of an atmosphere for 1 hour 8 minutes. They showed during this time nothing abnormal. The tension was then raised to 354·9 %. After breathing this atmosphere for 1¼ hours, they showed dyspnœa: *i.e.* 2 hours 35 minutes after the experiment began. After 10¼ hours, they were taken out of the chamber, and they both died immediately thereafter. The lungs of both showed the characteristic pneumonia.

Exp. XIX. Two mice were exposed to oxygen at a tension of 357 % of an atmosphere. They were both dead after 5 hours, with the characteristic consolidation and congestion of the lungs.

There was no evidence of convulsive effects although the tensions were now as high as some of those used by Bert; but as I have already pointed out, it was with birds that the "toxic effect" was obtained at this tension.

Bert's experiment was therefore repeated in the following manner:

Exp. XX. Two larks were placed in the chamber, and the oxygen raised to a tension of 301·4 % of an atmosphere. They at once became excited, and moved rapidly about the chamber. After 13 minutes' exposure to this tension, they were simultaneously thrown into violent convulsions. These recurred at short intervals. They began to subside in about an hour. After 2 hours 7 minutes, the chamber was opened. One of the birds remained in an unconscious condition, with occasional epileptiform convulsions, for about 1 hour after, when it died. The other survived, and was very active and restless for a while, but became later very sluggish. When it was fed by the hand, however, it shook off its drowsiness for a short time, and again assumed its normal activity. It survived in this condition for several days. There was a remarkably small amount of dyspnœa. The oxygen seemed to abolish the fatigue which would arise after a similar effect in a normal bird. There was scarcely any hyperpnœa even. There was nothing noteworthy in the post mortem appearances.

This experiment fully confirms Bert's observations. The symptoms of toxic action were of the nature of strychnine effects. The effects, further, persisted in one of the birds after it had been restored to ordinary air. It occurred to me that the difference between mice and birds, which had hereby been clearly established, might be due to a difference in their respiratory function, rather than to a difference in the reaction of their nervous system. Before the oxygen can reach the nervous tissue, it must pass through the lung cells and the blood, and both these elements may have an effect in modifying the tension, which differs in the two cases[1].

A certain amount of evidence is already in our possession in regard to the differences in arterial oxygen tension which are due to the lung cells. In the paper just referred to, by Dr Haldane and myself, we have brought forward experiments on the oxygen tension of the blood as it leaves the lungs, which prove that the active power of absorbing oxygen possessed by the lungs of small birds is much greater than that of mice. In ordinary air small birds have an arterial oxygen tension of about 35—40 % of an atmosphere, while mice have an oxygen tension of 20—25 %. We farther showed that when the oxygen tension of the air breathed was increased to 80 % of an atmosphere, the same difference in absorptive power was still observed.

If then the onset of convulsive effects be in any way dependent

[1] This *Journal*, xxii. p. 231.

on the power of actively absorbing oxygen at a given tension, say 300 % of an atmosphere, it should be possible to abolish the effect by paralysing the functional activity. I have already referred to the experiments which have been published showing the manner in which this paralysis can be effected by exposing the bird to a moderately high tension for some hours[1]. This experiment was accordingly carried out as a preliminary to observing the effect of an oxygen tension of 300 % of an atmosphere.

Exp. XXI. Two birds were exposed to a tension of 140 % of an atmosphere. The tension, further, fell very considerably during the night. After 12 hours, the birds were taken from the chamber. They were quieter than normal, but showed no signs of difficulty in breathing. One of the birds was taken 2½ hours later, and was placed in oxygen at a tension of 300 % of an atmosphere. It remained in this atmosphere for 2 hours 38 minutes without showing the faintest tendency to convulsions. It showed dyspnœa after an exposure to the high tension of about 45 minutes. The experiment was concluded, and the bird was taken out. Its arterial oxygen tension in ordinary air was then observed, and found to be 16 % of an atmosphere, or less than 50 % of the normal. The lungs were markedly congested. The remaining bird was similarly examined 10 hours after it had been exposed to the oxygen at the moderate tension. It remained in oxygen at a tension of 300 % for 1 hour 15 minutes, and showed only dyspnœa. The arterial oxygen tension, observed next day, was 19 % of an atmosphere.

Exp. XXII. A control experiment was carried out at this stage, which consisted in exposing to oxygen at a tension of 300 % a normal bird and a bird whose lungs had been damaged previously by a moderate tension of oxygen. After 12 minutes the normal bird had convulsions while the other bird hopped about unconcernedly.

There are accordingly two phases of the oxygen effect. The one consisting in the slowly developing inflammatory effect seen most prominently in the lung tissue. The other a rapidly developing effect on the nervous tissue, which we may in the meantime describe as functional. In these experiments, we have seen oxygen at a tension of 300 % of an atmosphere giving rise to the inflammatory effect in mice in 5 hours. The same tension gave rise to the tetanic effect on the nervous system, in birds, in about 12 minutes. In what sense the two phases of oxygen effect resemble each other is obscure. Both effects persist after the animals have been restored to ordinary air, and this, since it is frequently inconsistent with recovery, we may regard as

[1] This *Journal*, xxii.

indicating a profound change in the tissue cells. It is also clear that the onset of the effect on the lungs acts as a protection from the nervous effects. It is probably in this way that the explanation may be arrived at of the subsidence of the nervous effect after some time.

A further experiment was made to ascertain if a tension of oxygen distinctly lower than 300 % could bring about convulsive effects.

Exp. XXIII. A bird was placed in the chamber and the pressure raised to 255 % of oxygen, at 11.23 a.m.

11.44 Suspicion of convulsions.
12.27 Restlessness, but no convulsions.
12.30 Pressure raised to 287 %—dyspnœa.
12.33½ Convulsions.
12.37 Experiment stopped.

From this experiment it is clear that below a tension of about 270 % of an atmosphere oxygen does not cause convulsive effects on birds.

It still remained to ascertain at what tension the nervous effects could be obtained in mice. Curiously enough, Bert, though he complains of the difficulty he experienced in obtaining oxygen in sufficient quantity for his experiments, did not make observations on mice. Hence there are on this point no data.

Exp. XXIV. A mouse was exposed to oxygen at a tension of 414 % of an atmosphere at 11.5 a.m.

11.20 No convulsions. Pressure raised to 450 %.
11.37 Mouse showed mild convulsions.
11.43 Convulsions more distinct.
11.55 Mouse removed from chamber. It was now sluggish in its movements.

Exp. XXV. The preceding experiment was repeated with two mice. They were exposed to a tension of 450 % of an atmosphere from the beginning of the experiment. One mouse died from the oxygen early in the exposure. The other showed convulsions after an exposure of 20 minutes.

The convulsions in neither of these experiments were so severe as those which were seen in the case of the birds.

These experiments again clearly exhibit the difference between mice and birds in respect of the nervous symptoms of oxygen poisoning, and we have seen that this difference can be to a certain extent abolished by damaging the lungs of the birds. The question which now presents itself is whether or not the bird with its arterial oxygen tension lowered

by damage to the lungs, would show the convulsive effects at the very high tension of 4·5 atmospheres of oxygen, at which they occur in mice.

Exp. XXVI. Two birds were exposed to oxygen at a tension of 166 % of an atmosphere for 10½ hours. They were then exposed to a tension of 308 % at 12.17 p.m.

12.47 Birds showed no sign of convulsions. Tension raised to 373 % of an atmosphere.

1.10 Birds still showed no signs of convulsions. Pressure raised to 450 % of an atmosphere. Convulsions set in at once.

1.30 Chamber opened. One bird was dead. The other was dyspnœic, and remained so for some hours afterwards.

The nervous effect therefore was only retarded by the paralysis of active absorption. The exact point at which the nervous effect returned would doubtless vary with the condition of the lungs. The following two experiments prove the same conclusion, though in a slightly different manner. If it be true that the onset of the lung effect is protective from the nervous effect, we should, in place of a preliminary exposure to a low tension, be able to raise the tension very gradually, by successive stages, until we reach the tension of 4·5 atmospheres before causing the convulsive effect. The experiments now recorded give the times of exposure at different stages, in order that this might be accomplished.

Exp. XXVII. A bird was exposed to oxygen at a tension of 239 % of an atmosphere at 1.45 p.m.

3.15 Tension raised to 252·9 %.

3.35 Bird became restless.

3.47 Tension raised to 271 %.

3.52 No convulsions.

4.15 Tension raised to 300 %.

4.38 Bird quiet. Dyspnœic. Tension raised to 324 %.

4.49 A few small spasms, but no convulsions.

5.3 Tension raised to 342 %.

5·7 Convulsions.

5.19 Experiment stopped.

Exp. XXVIII. A bird was placed in oxygen at a tension of 269·7 % of an atmosphere, at 12.40 p.m.

12.50 Restlessness. No convulsions.

1.10 Still restless, but no convulsions. Tension raised to 287 %.

1.12 Bird quieter. Slightly dyspnœic.

1.30 No convulsions. Tension raised to 303·4 %.
1.43 Convulsions, which subsided.
1.50 No trace of convulsions. Tension raised to 309·7 %. Small clonic spasms at once, which subsided.
2.5 No further development. Tension raised to 342 %. Bird now quiet. Dyspnœic.
2.10 Dyspnœa.
2.19 Dyspnœa increasing. Tension raised to 342 %.
2.25 Tension raised to 365 %. Bird quiet. Co-ordination difficult.
2.35 Tension raised to 408·9 %. Dyspnœa.
2.40 Convulsions. Apparatus burst.

In both these experiments the tension was carried distinctly beyond that which usually causes convulsions, and probably had the stages been taken more slowly it might have reached a still higher point.

Bert attempted, by means of direct observations on the quantity of oxygen which could be obtained from the blood of animals exposed to the high tension, to determine the conditions under which the tissues of the nervous system became poisoned. His hypothesis was that the saturation of the hæmoglobin of the blood was not complete till a very high tension had been reached, and that the tension which gave rise to convulsions corresponded with that at which not only was the hæmoglobin saturated, but the gas was beginning to pass into solution in the liquid part of the blood. The tissues, further, are supposed to be anaërobic, and the fatal effect was the result of the oxygen directly acting on the anaërobic elements[1].

Whilst this explanation of the dissociation of oxyhæmoglobin is incorrect, and the theory of the tissues also unsupported, it is important to remember that the "toxic" effect is due to tension, and not to quantity, of oxygen in the blood. It is possible to diminish the quantity of oxygen in the blood, and yet to bring about the convulsions at the oxygen tension of 300 % of an atmosphere, and the following experiment was carried out with this object.

Exp. XXIX. A bird was placed in the chamber, and beside it a bottle with a wide mouth inverted in a capsule containing water. In the bottle was a volume of carbonic oxide sufficient to give about ·4 % tension at a pressure of three atmospheres. When the oxygen tension had been sufficiently raised to make it safe to do so, the bottle was overturned, and the carbonic oxide gas allowed to escape into the chamber. When the oxygen

[1] *La Pression Barométrique*, p. 1154.

tension reached 300 % of an atmosphere, the convulsions set in as usual. At the end of this experiment, the blood of the bird was examined and the hæmoglobin was found to be 38 % saturated.

General Résumé.

It remains in conclusion to draw attention to the physiological and pathological investigations with which the one just recorded is in immediate connection.

It may be regarded in the first place as supplementary to the investigation on the normal process of respiration of oxygen, which has been carried out by Dr Haldane and myself. In that investigation we showed that the absorption of oxygen by the lungs is an active physiological process. The experiments just described show that at a tension a good deal higher than that of ordinary air, oxygen has the effect on the lungs of an irritant, and produces inflammation.

In the second place the experiments show that the toxic effects described by Bert occur at a tension which is much higher than that required to produce the inflammatory effect on the lungs. Further, it is shown that when the lungs are damaged the tension required for the production of this toxic effect is markedly higher than that required when the lungs are normal.

A subject on which these experiments have a direct bearing is the pathology of caisson disease. Since this subject requires separate investigation, I do not propose to discuss it fully at present. It is clear, however, that Bert in his experiments in regard to it, directed his attention chiefly to the effects of rapid decompression, to which he is inclined to ascribe the disease. Since workers in caissons are occasionally in 4·25 atmospheres of air pressure, they are undoubtedly within, at most, a very short distance of an atmosphere dangerous from the oxygen alone. Bert's investigations do not take into account the possible oxygen effects, and if we read the records of post mortem examinations of cases dying from caisson disease, not only is there a large amount of evidence regarding the congestion of the lungs and other viscera, similar to that produced in the mice in these experiments, but there is a scarcity of fatal accidents when caissons burst and decompression is instantaneous. Further, Bert admits that the only point on which all observers agree is that the risk of accidents to the workers is proportional to the time of exposure to the high pressure[1].

[1] *La Pression Barométrique*, p. 512.

It is unnecessary at present to adduce further evidence to show that the oxygen tension of the high pressure atmosphere is probably to be regarded as taking a part along with rapid decompression in the production of caisson disease. For investigation of this subject experiments must be conducted on lines differing from those now described.

Apart from the special interest of caisson disease, the experiments have a bearing on the general pathology of inflammation. The fact to which I would especially draw attention is that the inflammatory condition of the lungs is in a sense directly continuous with the normal process of respiration. The transition from the physiological to the pathological stage is imperceptible. Oxygen which at the tension of the atmosphere stimulates the lung cells to active absorption, at a higher tension acts as an irritant, or pathological stimulant, and produces inflammation.