The influence of pathological conditions on active absorption of oxygen by the lungs / by J. Lorrain Smith.

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THE INFLUENCE OF PATHOLOGICAL CONDITIONS ON ACTIVE ABSORPTION OF OXYGEN BY THE LUNGS.

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It is a matter of common clinical experience that the most varied types of disease involve some damage to the lungs in the form of congestion, œdema or inflammation, and that the danger to life is much increased in any case when such complications supervene.

The basis of this relationship is a subject the investigation of which would throw much light on the nature of respiratory disease. Apart from these abnormal conditions of the lungs, the study of which is of interest to general pathology, we have also to consider a large group of diseases in which the morbid process originates in a lesion affecting the lungs themselves.

The investigation of the function of the lungs which has been carried out by Dr Haldane and myself[1], has shown that the process of oxygen absorption is subject to variations of a purely functional kind. Some of the conditions under which these variations occur we investigated, but we confined our attention to those of a physiological nature. If we consider the relation of this activity to respiratory disease we are confronted with a large variety of conditions which cause more or less serious damage to the lung tissue, and which therefore have in all probability a most important effect on the vital function of oxygen absorption.

To simplify the investigation of this problem we may conveniently consider these conditions as forming two groups.

1. Conditions affecting the organism as a whole, as the state of fever and the infective process which fever usually accompanies.

2. Conditions in which the important element is some gross change in the lung tissue itself, such as congestion of the blood-vessels and exudation into the alveoli.

[1] This *Journal*, xx. and xxii.

It is not here maintained that these two phases of the problem are to be separated by any hard and fast distinctions. The purpose of the present investigation is to show how the activity of the lung is modified in conditions in which either the general or the local pathological change is the most prominent factor.

The method which has been applied in this research is identical with that employed in the study of oxygen absorption already referred to. The tension of oxygen in the blood circulating in the lung capillaries in the affected animal is measured by estimating the saturation of the hæmoglobin by carbonic oxide, the exact proportion of this gas present in the atmosphere breathed being known.

The only other method which has been applied to a study of the blood gases in similar conditions is that of estimating the amount of oxygen and carbonic acid which can be obtained from the blood by the vacuum pump in the febrile condition as compared with the normal. Geppert[1] has shown that, in the arterial blood of dogs suffering from the fever produced by injection of pus or other pyretic substances, there is no diminution in the amount of oxygen in the arterial blood; but on the other hand there is diminution of carbonic acid, and this is in direct proportion to the rise of temperature. We are without sufficient data in regard to the nature and conditions of the metabolism which occurs in the blood while in the lungs or in the arteries to enable us to interpret this result of Geppert's. Nor can we accept the observations on the amount of oxygen present in febrile blood as proving that the tension of oxygen is not diminished seriously as a result of fever.

Still less could we expect to obtain reliable data in regard to the activity of oxygen absorption by the lungs by estimating the amount of gas exchange in any given conditions. It is hardly necessary therefore to point out that the results which are now brought forward cannot be compared with any that have been hitherto otherwise obtained.

The great majority of the following experiments were carried out on mice. Mice are readily sensible to changes in the temperature of their surroundings, and a state of artificial rise of body temperature can be induced with the greatest ease. They are also probably the most susceptible amongst animals to infection with bacteria. Finally, it is easy by a method to be explained later, to induce in the parenchyma of the lung a condition of inflammatory irritation resulting in congestion and exudation to such an extent as to be fatal.

In the first series of experiments the effect of simply raising the

[1] Geppert. *Zeitschrift für Klin. Medicin*, 1881.

body temperature has been observed, and for this the classical method of the warm bath was used.

The animal while it breathed the atmosphere containing carbonic oxide had its temperature raised by means of a bath of warm water surrounding the bottle in which it was placed. This method, though not very precise, was sufficient for the purpose in view, as the aim of the experiment was to induce a condition in which the animal was manifestly beginning to suffer from high temperature. In this condition the animal's skin became congested and it lay extended so as to expose a heat losing surface as large as possible. It also became very feeble in its movements and dyspnœic. At the conclusion of a period sufficient for the saturation of the blood with carbonic oxide according to the tension in the atmosphere breathed the mouse was drowned and the colour ot the hæmoglobin estimated with carmine. A rough idea of the effect of the bath on the body temperature may be gained from three observations which were taken on normal mice in a current of air after they had been exposed to corresponding temperatures for a period similar to that used in the experiments. It was impossible to ascertain in each case the temperature of the mouse during or at the end of each experiment.

Observations on effect of bath on mouse temperature.

Temp. of Mouse	Time (before experiment)	Temp. of bath	Rate of meter. Litres per minute	
37·8° C.	6·50	40° C.	·526	
	6·55	41		congestion of skin
	7·3	41		
	7·6	40		
	7·15	41		
	7·15	40		
	7·18	42		
39·5° C.	7·20			
35·3° C.	11·2	42° C.	·566	
	11·7	45		
	11·13	41		congestion of skin
	11·15	45		
	11·30	42		
39° C.	11·32			
38·5° C.	3·55	43·5° C.	·526	
	3·58	45		
	4·7	46		congestion of skin
	4·10	44		
	4·12	47		
43° C.	4·18	44		

TABLE No. I. Experiments on the effect of raising the body temperature by the warm bath.

Animal	% of CO	Rate of ventilation in litres per minute	Duration of experiment in minutes	Temp. of bath	Saturation of hæmoglobin with CO	Oxygen tension of arterial blood	
Mouse	·088	·517	37′	36° C.	49·4	25·4	No congestion of skin
,,	·115	·441	41′	30	59·7	22·1	,, ,,
,,	·100	·424	45′	35	53·5	25·1	,, ,,
					Average	24·2	
,,	·094	·476	46′	35° C.	72·6	10·1?	
,,	·080	·434	30′	40	55·9	18·0	Skin congested &c.
,,	·064	·573	40′	40	49·5	18·3	,, ,,
,,	·073	·566	30′	42	49·5	21·1	,, ,,
,,	·070	·600	60′	41	50·3	19·4	,, ,,
			Average of last four experiments			19·2	
,,	·102	·526	29′	45° C.	66·8	14·4	Mouse collapsed
,,	·230	·354	25′	43	77·9	18·0	,, ,,
					Average	16·2	

The observations in Table No. 1 may be considered in three groups. In the first place, we have three observations showing that a bath at a temperature of not more than 35° C. will not in this (30′—45′) period cause signs of distress from heat nor any distinct change in the oxygen tension. A perfectly normal mouse may have a temperature of 39° C. and doubtless this fact accounts for the lack of effect from baths with a temperature of 35°. The tension here observed gives an average of 24·2. This though slightly higher than the normal already published (22·6 % and 23·8 %) is practically the same. It was pointed out in the paper referred to that there was some reason to believe that the precautions used to prevent the fall in body temperature, and consequent fall in arterial oxygen tensions, during an experiment, were not always successful in their purpose.

The next group consists of five experiments in which there were signs of distress from heat and congestion of the skin, and with this there is a distinct fall in the oxygen tension in spite of the hyperpnœa which would in itself tend to raise the oxygen tension. In regard to the first experiment where the temperature of the bath is low in comparison with the others, it is almost certain that some factor in addition to the heat was at work reducing the oxygen tension. It is introduced here however because no such explanation could be demonstrated. Leaving it aside the average tension is 19·2 %, a value distinctly

below that of the first group and also below the average of the normal results formerly published. Apart from the first observation in the group the results are fairly consistent with each other. In the third group are two experiments in which the temperature of the bath was raised distinctly over 40° C. This causes great collapse and in a short time the mouse dies from hyperpyrexia. The two observations gave an average of 16·2 %. A mouse can however live with a tension much lower than this, as may be seen in cases where observations with rarefied atmospheres have been made. On the other hand it is interesting to find that the value obtained in conditions where the body temperature has been reduced to a fatal point and where it has been raised to a fatal point are identical[1]. It suggests that with uninjured lungs this is the lowest point which can be reached in the presence of atmospheric air. The heat and cold both inhibit or paralyse the active process of absorption, and the value here obtained might be due to mere diffusion of oxygen from the alveoli. If this were the explanation however it is not easy to see how lower values in oxygen tension could ever be reached in the presence of atmospheric air. That such values are reached is clear from the case of tension at 10·6 % in the present table, and also from cases in a later table, No. V., where there has been damage to the lung tissue. The discussion of this point will be resumed when we have the other experiments before us. It is sufficient in the meantime to remark that this striking effect in the oxygen tension indicates a very serious interference with the activity of the lungs in the process of fever. Whatever may be the interpretation of the ascertained fact that it is of vital importance to an animal to preserve its oxygen tension at a level beyond what is required to saturate the hæmoglobin with oxygen, it is highly probable that in the condition of fever a high oxygen tension would be only the more necessary.

It should be pointed out here that the results detailed in the above table are in no wise inconsistent with those of Geppert in which he found the amount of oxygen contained in arterial blood undiminished by the onset of fever. According to the curve constructed from Hüfner's data on the dissociation of oxyhæmoglobin a tension of 14 % would leave the hæmoglobin nearly 98 % saturated.

The next series of experiments deals with the question of the effect on the oxygen tension of the toxic agents arising in the organism during a fatal microbic invasion. This series may be regarded as supplementary

[1] This *Journal*, XXII. p. 238.

to those just discussed and as contributing to the solution of the same problem. Mice were again used, and one reason in particular had weight in leading to the selection of them for this purpose.

TABLE No. II. Experiments on the oxygen tension of arterial blood after infection with bacillus pyocyaneus.

Animal	% of CO	Rate of ventilation. Litres per minute	Duration of experiment	Temp. of bath	Saturation of hæmoglobin with CO	Oxygen tension of arterial blood	Temp. of mouse
Mouse	·083	·588	30′	30° C.	55·3	18·5	37·5° C.
,,	·085	·588	36′	29	63·8	13·5	36·5
,,	·088	·588	37′	32	62·7	14·7	36·3
,,	·108	·468	30′	30	68·4	14·1	37
,,	·100	·535	33′	30	69·5	12·6	36·9
,,	·076	·639	30′	30	60·7	13·9	36·0
,,	·078	·674	20′	30	53·2	19·6	34·9
					Average	15·2	
					Average oxygen tension in normal mice	23 %	

In a paper which[1] Prof. Wesbrook and I published on the Occurrence of Fever in mice, we pointed out the fact that the only change in body temperature which we had been able to observe after infection with various microbes was a fall preceding death. We were unable to obtain any indisputable evidence that the rise which not infrequently occurs in rabbits, guinea-pigs and which is the rule in man, ever takes place in mice. It was therefore possible to observe the effect of a rapidly fatal infection on the activity of the lungs without the complication introduced by the existence of high temperature. The only precaution which was necessary in the case was to ascertain that the terminal fall in temperature had not yet commenced.

The observations on oxygen tension were taken 3—5 hours after the inoculation. The microbe used was an active growth of Bacillus Pyocyaneus which was fatal in 12 hours in doses of ·25 c.c. of a broth cultivation at least 24 hours old. Occasionally older cultivations were used but these were only more toxic. The manner in which this bacillus preserves its toxicity for mice makes it an extremely convenient one for a series of experiments such as those of the present research. That it has no special local effect on the lungs was another reason for using it on this occasion. The period which was allowed to elapse between the inoculation and the experiment in this case was very similar to that adopted by Geppert in his blood gas analyses after

[1] *Brit. Assoc. Reports* 1876. p. 974.

injection of pus into dogs, and which he found sufficient for establishing a marked departure from the normal in regard to the amount of carbonic acid in the arterial blood. The mice at the time of observation had become sluggish and unwilling to run about but otherwise they did not show any abnormality. If the observations were delayed till the infective process had become more developed, the experiment was too severe and the mouse died before sufficient time had elapsed for the hæmoglobin to become saturated up to the value for the tension of CO in the atmosphere breathed. This is seen in one experiment, the last one, which has been added to the table for the purpose of showing this point. The mouse died in 20 minutes. For the latter part of this period also its respirations were so feeble that the period should be reckoned still shorter.

In the remaining six experiments in the table it will be seen that the average tension is very much below the normal. In one only, the first, is there a value which might be regarded as approximating to the normal. It will further be noticed that the temperature of the mouse was in no case below the normal. In the last experiment, which failed because the mouse was too far gone, the temperature was below 35° C. but in others it was 36° C. or above it.

TABLE No. III. Experiments on the oxygen tension of arterial blood after infection with bacillus pyocyaneus, the air supply containing an excess of oxygen.

Animal	% of CO	Rate of ventilation. Litres per minute	Duration of experiment	Temp. of bath	Saturation of hæmoglobin with CO	Oxygen tension of arterial blood	Oxygen percentage of atmosphere breathed	Temp. of mouse
Mouse	·303	·526	31′	32° C.	54·1	73·1	76·6	38·2
,,	·306	·500	31′	31	57·1	65·5	87·9	36·5
,,	·207	·504	35′	32	52·0	53·5	79·6	37·5
,,	·165	·652	31′	30	41·0	67·5	86·3	33·5
				Average of infected mice		64·9	82·6	
				Average of normal mice in similar atmosphere		115·2	86·9	

The values for the oxygen tension here are further subject to the remark that had the mice been normal the saturation of the hæmoglobin to over 60 % would have given not the normal tension, but the increased tension which is established when the blood is saturated to this extent. The average here is scarcely more than 50 % of what it would have been had the mice retained the normal respiratory power.

The conclusion from this series is that one of the toxic effects of a

fatal infection is a distinct lowering of the oxygen tension. It occurs before the fall in temperature and is generally speaking independent of the temperature change. It should probably be regarded therefore as one of the essential effects of the intoxication, or in other words an effect which depends directly on the toxic agency itself, and therefore as an integral part of the process of infection.

A further series (see Table III.) of experiments was carried out with a view to showing with greater clearness if possible the extent of the paralysis. In the investigation of absorption of oxygen in the normal lung above referred to it was shown that an animal in atmospheres which contain oxygen at a higher tension than air still absorbs oxygen actively, and establishes in its blood a tension considerably higher than that of the atmospheres in question. If paralysis be present one would expect the animal to have lost the ability to establish this extremely high tension.

Table No. IV. Experiments on oxygen tension in arterial blood after infection with bacillus pyocyaneus, the animal being kept in air at a raised temperature.

Animal	% of CO	Rate of ventilation. Litres per minute	Duration of experiment	Temp. of bath	Saturation of hæmoglobin with CO	Oxygen tension of arterial blood	Temp. of mouse
Mouse	·070	·576	30′	40° C.	53·5	17·6	38·5° C.
,,	·067	·555	30′	38	46·7	21·5	39·0
,,	·060	·666	45′	40	52·3	15·6	38·0
,,	·060	·714	41′	40	53·5	15·1	38·0
				Average	17·4		

The mouse infected with pyocyaneus was supplied with a current of oxygen from a cylinder at the time it was breathing CO.

In table No. III. four experiments of this kind are recorded, and they show that to a greater or less extent the power of active absorption has been lost.

In regard to these it is interesting to compare the average with an average from normal mice in similar atmospheres quoted from the former paper. The fall is to a tension much below that of the atmosphere breathed—a point which roughly speaking corresponds to the value of 16 % in ordinary air.

This series therefore confirms the observations in ordinary air given in Table No. II.

Finally, in regard to this question, it seemed worth while to do one or two experiments (see Table No. IV.) on the combination of high temperature and infection, for this would form an approximation to the

effects of heat and toxic agents together, a condition which is the rule in man when he suffers from a microbic invasion.

Still more than in the former case has care to be taken to provide against the death of the animal before the requisite time for the experiment has been obtained.

Four experiments are given and the results differ in no way from those already recorded.

TABLE No. V. Experiments on the effect on the oxygen tension in the arterial blood of exposing animals to an atmosphere containing oxygen at a high tension.

Animal	% of CO	Rate of ventilation. Litres per minute	Duration of experiment	Temp. of bath	Saturation of hæmoglobin with CO	Oxygen tension of arterial blood	Oxygen tension in the air marked in % of an atmosphere	Duration of exposure to oxygen at a high tension	Length of time between the exposure and the observations of the oxygen tension in the arterial blood
Mouse	·117	·750	31′	30° C.	67·8	15·8	187 %	3	at once
,,	·121	·750	30′	32	65·0	18·5	168	3+3	,,
,,	·124	·750	30′	32	69·8	14·9	183	5	,,
,,	·120	·759	31′	30	75·7	11·2	183	5	5
,,	·139	·731	46′	33	61·1	24·5	188	7	16
,,	·133	·800	30′	30	66·7	18·5	181	10·5	at once
,,	·102	·800	30′	32	66·8	14·1	181	10·5	4
,,	·087	·731	38′	33	71·5	9·9	175	19	1
,,	·057	·860	36′	33	55·3	11·8	174	19	4
,,	·120	·769	40′	30	71·0	13·8	174	17	3
Lark	·062	·750	36′	30	62·7	10·6	183	14	12
,,	·038	·789	55′	30	47·1	12·4	174	16	at once
,,	·044	·750	48′	32	43·9	16·0	301	2·5	,,
,,	·043	·681	44′	30	40·1	17·9	305	1·75	12

It now remains to consider the relation of local changes in the lungs to the activity of oxygen absorption.

The most interesting local change to investigate is that which involves an irritation of the epithelial tissue of the lung of the simplest possible type. I have found that such a condition of lung tissue can be obtained in the following manner. The animal is placed in an air-tight chamber and subjected to oxygen at moderately high pressure. In a short time the lungs become affected, and if the pressure be kept up for a sufficient period, the animal dies with consolidation of the lungs from congestion and exudation into the alveoli. The higher the pressure the shorter the time during which the lungs are able to withstand the effects of the oxygen. It is unnecessary here to enter into full details of the observations I have made on this question.

They will form the subject of a paper to be published shortly. The one result which is made use of here is that in oxygen at a positive pressure of 35 inches of mercury the only impurity being about 15 % nitrogen, *i.e.* in a tension of oxygen less than two atmospheres, and in the absence of any other gas affecting respiration, a mouse will die with the lungs in the condition described in less than 24 hours. The lungs when tested post mortem sink in water, and when examined with the microscope the alveoli are found to be almost completely filled with exudate and the blood-vessels are extremely congested.

The observations on oxygen tension in this condition are of great interest, not only because they show the effect of these pathological changes on the activity of the lung, but also because they show that this effect is manifested early in the process. Why oxygen at high pressure becomes an irritant is a question which must be dealt with later.

In the table of results (No. V.) it will be seen that the experiments arrange themselves for the most part in groups of two. In each experiment two mice were placed in the chamber together and the oxygen tension of each taken at the end of the period of exposure to high pressure. It is to be noted that sometimes there is considerable difference between the two animals in regard to the tension in their arterial blood. This was noticed to depend on the resistance of the mice to the effects of the oxygen. A full-grown mouse for example is later in yielding to the oxygen than a half-grown one. Other circumstances doubtless enter in also to modify the results.

In regard to the experiment placed 5th in the table it should be noted that 16 hours had elapsed before the oxygen tension was taken. A second mouse similarly exposed had died at the end of the 7 hours. The one examined might have nearly recovered by the time the oxygen tension was observed. It was noticed in a number of the experiments that though the breathing had become very greatly embarrassed from exposure to oxygen the animals very frequently recovered in the most remarkable manner when replaced in air.

Four experiments on birds are included. They were carried out for the purpose of ascertaining whether the same effects are to be found in birds as in mice after exposure to oxygen. At the end of the period of exposure the bird was in each case dyspnœic, the first one recorded being more affected than the others. The lungs showed congestion and partial consolidation when examined post mortem.

The normal oxygen tension of larks is between 35 and 40 % of an

atmosphere and we have in one of these experiments a fall of fully 70 % of the normal tension.

In regard to the last two experiments a detail should be added which could not be easily brought out in the table. Previously to their exposure to the tension of 301 % of an atmosphere of oxygen they had been exposed to a moderate tension of 100—120 % for a period of 12 hours. They were then exposed subsequently, after an interval of some hours, to the high tension of 300 % of an atmosphere for the period stated in the table.

In regard to the mice, while the results do not proceed exactly according to the period of exposure to the high oxygen tension, yet on the whole this is so, and if we compare say an exposure of 3 hours with one of 19 hours or even shorter periods we find that the oxygen tension is lower after the longer period.

In comparing the tensions which are obtained after damage to the tissue of the lungs with those which are obtained by exposure to high temperature, or by the action of toxic agents, one interesting fact comes out. The diminished tensions which may be obtained by this method of local disturbance to the lungs are distinctly lower than the lowest obtained by the other means used in the present research. By means of the increased temperature a tension as low as 14·5 % was reached, by injections of bacillus pyocyaneus a tension of 12·6 % was reached, whilst by the latter method the tension falls as low as 9·9 %.

The gradation which is observed in the 3 sets of experiments suggests that we may in the study of oxygen tension in various pathological conditions not only find the explanation of various phenomena of respiratory disease, but also obtain data for estimating the clinical significance of disturbance to the respiratory functions in these conditions. The tables of results seem to indicate that when a disturbance by the active absorption of oxygen is local in the sense of being due to changes localised in the lungs, it is less grave than a similar disturbance due say to a rise in body temperature. In other words, there seems in the former case to be a wider limit within which the animal is able to survive. To interpret this fully however we would require to understand the reason why the organism normally maintains a high oxygen tension in its arterial blood.

Summary of Conclusions.

1. The oxygen tension of the arterial blood leaving the lungs is lowered to about that of the alveolar air by the general pathological processes which ordinarily occur in fever and in particular by rise of body temperature and by toxic agents of bacterial origin.

2. The oxygen tension is also lowered by pathological changes occurring in the lungs locally as a result of irritation by high pressure oxygen.

3. Among the experiments here recorded the lowest tensions observed in the cases where the animal suffers from some general condition are on the whole higher than the lowest tensions observed when the local changes in the lungs have been brought about.

4. The observations of oxygen tension show that interference with active absorption through the lung epithelium forms an integral part of many conditions of disease directly or indirectly associated with the lungs.

5. The fact, that the pathological conditions just referred to tend to reduce the oxygen tension of the arterial blood to about that of the alveolar air, affords striking confirmation of the conclusion that the absorption of oxygen by the lungs is an active physiological process and cannot be explained as due simply to diffusion.