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REFLEXOGENIC AND CENTRAL STRUCTURES IN OXYGEN POISONING[1]

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SINCE the work of Bert [1878] it has been recognized that oxygen at high barometric pressure exerts acute deleterious effects on animal organisms. The entire story as to just how this oxygen poisoning is brought about is not yet known. There can be little doubt, however, that one of the most important factors is the upset in the carriage of carbon dioxide, which results from the failure in the reduction of oxyhaemoglobin at the tissues when an animal breathes pure oxygen at pressures greater than 3 atm. This explanation was first suggested some years ago by Gesell [1923], who had observed that the susceptibility of rats to high oxygen was increased when a small amount of carbon dioxide was added to the respired oxygen. A more direct attack of this problem was made later [Bean, 1929] in experiments in which dogs were exposed to pure oxygen at pressures of from 3 to 5 atm. Oxygen pressures above 3 atm. (the point at which there would theoretically be a failure of the normal reduction of haemoglobin) caused an increased blood acidity, a decreased heart rate and a lowered oxygen consumption, all of which support the contention of haemoglobin involvement. Moreover, shortly thereafter Campbell [1929] found an increased carbon dioxide pressure, high enough to be toxic, in the tissues of rabbits breathing pure oxygen at 3½ atm. That there is a failure of normal reduction of haemoglobin under high oxygen was demonstrated in experiments in which blood colour changes were followed continuously in dogs [Bean, 1931]. Experiments of Hill [1933] have indicated the importance of carbon dioxide in oxygen poisoning. Another group of investigators who had concluded [Behnke, Shaw, Shilling, Thomson & Messer, 1934] that carbon dioxide played no significant role in oxygen poisoning later reversed their opinion and state: "Carbon dioxide tensions which are wholly innocuous when associated

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with oxygen pressures of less than 1 atm., prove highly toxic when associated with oxygen at 4 atm. of pressure" [Shaw, Behnke & Messer, 1934]. It is quite possible there are other contributing factors to the production of oxygen poisoning. Recent experiments of Campbell [1937] indicate that the thyroid gland and external temperature play important roles, and apparently high oxygen also has some direct toxic influence on isolated frog muscle [Bean & Bohr, 1938].

The site of action of the accumulated carbon dioxide, increased acidity and perhaps additional factors in the production of the convulsive seizures of oxygen poisoning has been little more than a subject for speculation. Conceivably several structures might be either contributory to, or perhaps entirely responsible for, such seizures in animals exposed to oxygen at high barometric pressures. In the present study we have attempted to determine the importance of some of these structures which might be peculiarly involved in the induction of these convulsive attacks.

Apparatus and methods

The chamber in which the experimental animals were exposed to high pressure was essentially that, with few modifications, which has been described earlier [Bean, 1931; Bean & Haldi, 1932]. This chamber permits the continuous recording of respiration, blood pressure and heart rate, changes of blood *p*H and volume flow on smoked paper of a long-roll kymograph. A glass window provides for direct continuous observation of the animal which is at all times completely under the control of the operator—as much as though the operator were himself present in the chamber. The temperature may be regulated at will. Intravenous injection may be controlled simply by the manipulation of two stopcocks. Continuous observation of colour changes in the circulating blood and the sampling of circulating arterial or venous blood are easily accomplished. Uni- or bilateral blockage of the vagus nerves is attained by circulating cooled solution from the outside through tubular hooks in which the nerves have been previously slung. These hooks are insulated from the surrounding tissue in which they are buried. Removal of the cold blocks—referred to below as deblocking—is attained simply by stopping the circulation of the cooled fluid.

Given such regulating devices as our apparatus affords, we cannot subscribe to the views of some investigators [Behnke *et al.* 1934] concerning experiments in which the pressure chambers have been of such size as to prohibit the entrance of the operator. Not only have we found the chamber employed in our present and earlier investigations admirably

suited to the various problems undertaken, but we also recognize obvious advantages, such as greater ease of compression, temperature regulation and the economy accruing from the use of such a chamber for animal experiments. More important, however, is the equally obvious fact that such apparatus eliminates the quite unnecessary risk to the operator of the long recognized deleterious effects of high oxygen pressure. In many experiments on high oxygen pressure, data may lose their objectivity or are distorted by the subjective effects of the high oxygen pressure where the operators are themselves exposed along with the experimental animal. That high oxygen pressure and even high air pressure make the exposed operator incapable of properly recording or observing objectively is clearly brought out by these same advocates of large chambers: Under 10 atm. of air..."A simple task, the palpation of the pulse of another worker was accomplished only with extreme difficulty" [Behnke, Thomson & Motley, 1935]; and from an earlier report, a human subject under 4 atm., "after breathing oxygen for 43 min....suddenly experienced a transient syncope associated with a blanching of the face, sweating of the hands and absence of the radial pulse" [Behnke, Johnson, Poppen & Motley, 1934*a*]. Damant [1930], and Hill & Phillips [1932] report subjective effects and altered cerebration as a result of exposure to increased pressure. It is apparent then that wherever the investigations on high oxygen pressure permit, the regulation of the experiment and the observations should be made by an operator from without the compression chamber, regardless of its size.

The experimental animals used in our present study were dogs, partially or totally decerebrated. Such preparation served a twofold purpose, viz. (1) helping to determine whether convulsive seizures induced by high oxygen pressure can occur in the absence of the cerebral cortex and lower nuclei of the cerebrum, (2) eliminating the use of any prolonged chemical anaesthesia and thereby also the possibility that any reaction which might occur during or subsequent to exposure to high oxygen pressure could be due to pain attendant upon a lowered chemical anaesthesia. This last-mentioned point is of considerable significance, since it has been found that high oxygen pressure rapidly lowers chemically induced anaesthesia [Bean, 1931] to such degree that the movement and reaction of the animal can very easily be misinterpreted as oxygen poisoning.

The decortication and decerebration were carried out under a number of different transient anaesthetics, morphine urethane, Evipal or ether. Except for those few experiments in which the thalamus was left intact the cerebrum was removed down to the level of the superior colliculi.

After sufficient time (usually 1–1½ hr.) had elapsed for the transient anaesthesia to wear off, the animal was exposed in the chamber to oxygen at from 3 to 5 atm. pressure. Blood pressure, heart rate, and respiration were recorded and the animal's behaviour closely observed.

Results and discussion

The onset of oxygen poisoning was, with very few exceptions, first manifest by an alteration in breathing and frequently by twitching of some facial or neck muscle. There was usually an early hyperpnoea, jerky and irregular respiratory movements which later changed to a slowed deepened dyspnoeic breathing. The expiratory effort became progressively more pronounced and prolonged. Not infrequently apnoeic periods appeared in the expiratory phase, some as long as 25 min. have been recorded and observed; pronounced periodic breathing was not an uncommon reaction [Bean, 1932]. Tonic convulsive expiratory movements involving the greater part of the body musculature occurred. The convulsive seizures frequently spread also into the inspiratory phase. In addition to these manifestations of oxygen poisoning, tonic and clonic movements of the limbs unrelated to the respiratory cycle, dilatation of the pupil, emesis, excessive salivation, relaxation of the sphincters with resulting defaecation and urination, have been commonly observed.

While severe convulsive attacks may appear suddenly, the oxygen poisoning is a gradual process beginning with the failure in the reduction of oxyhaemoglobin. That there is wide individual variation in the susceptibility to high oxygen pressure is explained in part at least by a correspondingly wide individual variation in the response to carbon dioxide. For these reasons it would appear dangerous to set any time limit of exposure for which an animal can be assured of safety from oxygen poisoning.

The cerebrum and oxygen poisoning. Three experiments were performed on animals, from each of which the cerebrum had been removed down to the thalamus. Exposure of these animals to 5 atm. of oxygen resulted in convulsive seizures typical of those described as oxygen convulsions. Twelve other animals, in which decerebration had been carried to the level of the superior colliculi, reacted to high oxygen pressure in an essentially similar manner.

Reflexogenic zones and oxygen poisoning. Since the onset of oxygen convulsions is first manifest by an upset of breathing, and since also the seizures in the more advanced stages are so intimately associated with respiratory movements, a consideration of causative or contributory

mechanisms must include those reflexogenic zones which play important roles in the control of breathing, viz. the carotid sinuses and bodies, the aortic and pulmonary sensory areas served by the vagi.

Bilateral denervation of the carotid sinuses and bodies was performed on ten decerebrate dogs. This procedure, like decerebration alone, did not prevent the occurrence of either the disturbances in breathing which precede the actual convulsive seizures or the convulsive seizures themselves. Considering the individual variations in the reactions of animals to high oxygen pressure these sinus denervation experiments clearly indicate that the functioning of the carotid sinus or carotid body receptors is not essential to the occurrence of either the early respiratory disturbances or the convulsions. It is recognized nevertheless that these structures with innervation intact cannot be dismissed as being unaffected by high oxygen pressure. Indeed, one might well expect that in exposure to high oxygen pressure the resulting accumulation of carbon dioxide, increased acidity and lowered oxidation would bring about some stimulation of the chemoreceptors of the carotid bodies with consequential changes in cardiac, respiratory and vasomotor activity.

In non-decerebrate animals with intact sinuses and anaesthetized with morphine urethane, exposure to high oxygen pressure causes a slowing of the heart [Bean, 1931]. In our present experiments this bradycardia was found to be much less pronounced in decerebrate sinus denervated animals. Apparently, therefore, the intact sinus mechanism does contribute to the production of this slowing. However, the fact that a high oxygen bradycardia occurs in the denervated sinus preparations indicates involvement of additional cardiac control mechanisms.

The onset of severe oxygen convulsive seizures was attended by a sharply increased heart rate superimposed upon the bradycardia just mentioned. This tachycardia has been recorded from animals not only with intact, but also with denervated sinuses. It cannot be attributed, therefore, to increased carotid sinus or carotid body activity. The more probable explanation is either a gross inadequacy of the sinuses and bodies to meet, even at their highest state of efficiency, overwhelming demands, or an actual decrease or complete paralysis of function of the sinus and carotid body receptors or their central connexions by accumulated carbon dioxide and acidity.

Vagi and oxygen poisoning. The vagal trunks mediate afferent impulses from aortic and pulmonary endings which play important roles in reflex regulation of breathing and circulation. Does high oxygen pressure induce the respiratory convulsions of oxygen poisoning by action on

these endings? Investigation of the possible role of the vagi in oxygen poisoning was begun with preliminary experiments on non-decerebrate rats anaesthetized with morphine and urethane. In each of such experiments two litter mates were used; in one of these the vagi were sectioned; the other animal was used as control. Although the early experiments presented no conclusive results, due in part to the depth of anaesthesia required, they did suggest that the intact vagi may function in a protective manner to delay the onset of oxygen convulsions. In our later experiments on dogs no attempts were made to isolate either the aortic or the pulmonary branches of the vagi, so the corresponding reflexogenic zones were considered together although they may act quite independently. In several experiments decerebrate dogs were vagotomized by complete transection of both vagi, but in most of the experiments on the vagi cold block (2–5° C.) was employed.

Cold blockage of the vagus nerves of decerebrate dogs, applied before the onset of the symptoms of oxygen poisoning failed to prevent, and cold blocking or sectioning these nerves after the onset of poisoning failed to relieve, the poisoning reactions already manifest. In fact, such vagal treatment usually hastened the onset and exalted the poisoning reactions. Vagal cold block applied before raising the oxygen pressure or in the early part of the period of exposure to the increased pressure established a slowed deepened dyspnoeic breathing with convulsive expiratory movements similar to and in many instances identical with that mentioned above which occur in the more advanced stages of oxygen poisoning. This effect of vagal cold blockage at atmospheric pressure is illustrated in Fig. 1, part 1. The animal in this experiment had been decerebrated under transient ether anaesthesia, and, as was typical of such, was more responsive to experimental procedures than were those decerebrated under transient Evipal anaesthesia.

Vagal cold block applied after some time of exposure to high oxygen pressure, but before the onset of the convulsive seizures, induced the convulsive respiration which frequently continued after deblocking, apparently maintained by the oxygen effect itself. Such vagal block effect of high oxygen pressure was relieved by decompression to atmospheric pressure or by substituting air at an equally high pressure, for the oxygen. Such results are illustrated in Fig. 1 A, B, C, D, the records of which were obtained from an experiment in which Evipal had been used during the decerebration. Part A shows the effect of cold blocking and deblocking the vagi while the animal breathed oxygen at atmospheric pressure. In contrast to the blockage response in animals decerebrated

under ether there was no dyspnoeic prolonged expiratory phase and no convulsive movements. Vagal cold block applied to this animal after it had breathed oxygen at 60 lb. gauge pressure for 25 min. gave rise to the record shown in part B. This response more nearly approximated that observed in the animals decerebrated under ether (Fig. 1, part 1), in that the prolonged dyspnoeic expiratory phase with convulsive muscular movements was present. The vagal blockage effect persisted for some time after deblocking and there followed an apnoeic period of 12 min. (not shown in the figure) before the return to the preblock type of breath-

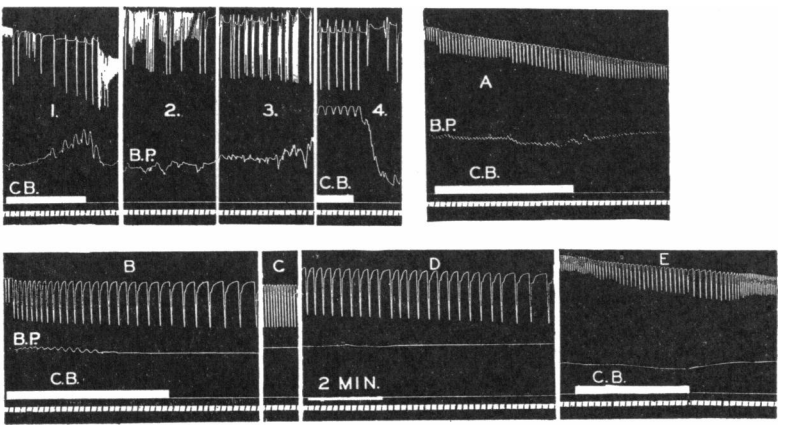

Fig. 1. High oxygen effects and vagal cold blockage: 1, 2, 3, 4, dog decerebrated under *transient* ether anaesthesia; A, B, C, D, decerebration under transient Evipal anaesthesia. In each, from above downward, respiration (upstroke = Expiration) blood pressure (*B.P.*), Signal (*C.B.* = cold block applied to vagi), time (2 min. = 2 minutes). For more complete explanation see text.

ing as seen in part C. High oxygen pressure had evidently increased the response to vagal cold blockage. After the exposure to high oxygen pressure had been continued for 32 min. more (87 in all), the breathing, as shown in part D, had become practically identical with that of part B. Not only are the records B and D identical, but also the accompanying convulsive muscular movements were essentially similar. High oxygen pressure acting alone in this instance (part D) had induced reactions indistinguishable from those previously induced by cold blocking the vagi after a short exposure to high oxygen pressure (part B). It is noteworthy also that this reaction (Fig. 1, part D) was very similar to that produced by vagal cold block alone, applied at atmospheric pressure in dogs decerebrated under ether. After the return of the animal to

atmospheric pressure (Fig. 1, part E) the response to vagal cold blockage approximated that which occurred before compression. The results of this experiment indicate that high oxygen pressure enhances the effects of vagal cold blocking; and that high oxygen pressure acting alone may eventually induce vagal blockage effects, in all probability by blocking out vagal influences on central mechanisms.

Vagal cold blockage and high oxygen pressure act in a similar manner on animals prepared under ether anaesthesia. Illustrative of this are the records shown in Fig. 2: A, the effect of vagal cold blockage while breathing oxygen at atmospheric pressure before compression; B, the response to vagal cold blocking and deblocking after breathing oxygen at 60 lb. pressure for 70 min.; C, the respiratory record after 20 min.

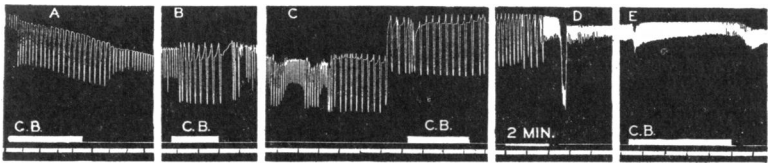

Fig. 2. Increasing reaction to vagal cold blockage as high oxygen exposure is prolonged; onset of convulsive type of breathing and vagal blockage effect of high oxygen; reversal of effects by substituting room air at high pressure for the high oxygen. From above downward, respiration (upstroke = Expiration), Signal (*C.B.* = cold block applied to vagi), time (2 min. = 2 minutes duration). The long displacement of the respiratory record in D is an artefact due to an additional rinsing of the spirometer with room air at high pressure. See text.

more exposure to oxygen at 60 lb. when the high oxygen pressure of itself had induced a response essentially similar to that induced earlier by the vagal cold block. Application of the cold block at this stage (C) was without any further significant effect, the oxygen having already given rise to a maximum blocking action and the attendant convulsive expiratory movements. Rapid relief from this convulsive breathing and the accompanying tonic and clonic body movements was attained by replacing the spirometer oxygen with room air at the existing chamber pressure (60 lb.). This is shown in Fig. 2, part D. Vagal cold block applied during the breathing of air at 60 lb. pressure was, in contrast to that during high oxygen pressure or before compression, remarkably ineffective (Fig. 2, part E). The subsequent shift of the animal back to breathing high oxygen pressure (not shown in figure) was attended by a return of the effectiveness of vagal cold blocking and also the return of the vagal block effect of the high oxygen pressure itself, similar to that

shown in parts B and C. Decompression to oxygen at atmospheric pressure resulted in the disappearance of the signs of oxygen poisoning, but the sensitivity of the vagi to blocking fell to a much lower level than that prevailing previous to exposure to the high oxygen exposure (part A).

The rapidity of recovery from the vagal block effects and convulsive manifestations of high oxygen poisoning, when the oxygen was replaced by room air at an equivalent pressure, was not dependent upon the integrity of the carotid sinuses or bodies. Evidence for this is shown in Fig. 3, which was recorded from a decerebrate denervated sinus animal. Here convulsive movements and the vagal block effect of high oxygen pressure (part D) were relieved by a shift to room air, and this, even before the change to air which occupied a period of less than 3 min., was completed. Apparently the causative agent in oxygen poisoning was effective on central structures aside from any influence it may have had on reflexogenic zones.

The vagi and bradycardia of oxygen poisoning. With the purpose of investigating the relationship of the vagi to the bradycardia of oxygen poisoning which occurs in decerebrate animals with intact or denervated sinuses and in non-decerebrate anaesthetized animals as mentioned above, several experiments were carried out in which the vagi were sectioned previous to exposure to the high oxygen pressure. It was found that the tachycardia resulting from such vagal sectioning was not significantly altered by the subsequent exposure to high oxygen pressure. Evidently the high oxygen bradycardia is mediated by the vagi, and any slowing influence which may be exerted by the oxygen directly on the heart or through the sympathetic innervation may be completely masked by the tachycardia of vagal sectioning.

The tachycardia which occurred so frequently with the onset of severe convulsive seizures and which was superimposed upon a heart previously slowed by high oxygen, might possibly be explained as due to a secondary blocking of efferent vagal fibres. In this connexion it is noteworthy that Hill & Macleod [1903] observed in the frog's heart that the vagus nerve endings "appear to be paralysed by exposure to high oxygen". It seems likely, therefore, that high oxygen pressure can produce a central vagal block and thus alter breathing; that it can initially slow the heart by efferent vagal impulses and secondarily increase heart rate by blocking the inhibitory action of the vagi.

In these and earlier experiments [Bean, 1931] on high oxygen pressure, it was found that unless there occurred muscular spasm and convulsive seizures, the changes in blood pressure were not at all pro-

nounced. The more usual change when such did appear was a slight gradual rise. The records in Fig. 1 show the blood-pressure changes in an experiment performed on a decerebrate dog with carotid sinus innervation and vagi intact. Here, after breathing oxygen at 60 lb. pressure for 45 min. (part 2), the blood pressure had altered only slightly. Five minutes later, however, with the onset of severe convulsive seizures and tachycardia the blood pressure increased sharply (part 3). If a vagal block action of high oxygen was in any way responsible for this change, such blocking action had not reached a maximum since application of the cold blocks to the vagi resulted in a still further increase in blood pressure and respiratory convulsive movements (part 4).

A similar blood-pressure response to high oxygen pressure occurs in decerebrate animals after denervation of the carotid sinuses and bodies.

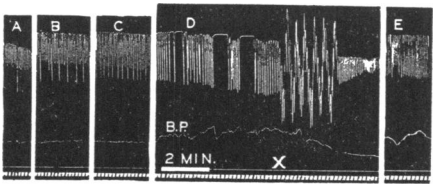

Fig. 3. Denervated sinus, decerebrate dog; A, breathing oxygen at atmospheric pressure; B, 5 min. after compression to 5 atm. of oxygen; C, 30 min. after compression; D, 58 min. after compression when convulsions had begun. At *X* the oxygen was replaced by room air at 5 atm. (the very wide swings of the respiration record are due to spirometer rinsing). Part E was recorded after having returned from breathing air at 5 atm. to oxygen at the same pressure.

This is illustrated in Fig. 3. The blood pressure, after the animal had been breathing oxygen at 60 lb. pressure for 50 min., increased by only 3 mm. Hg (part C). With the onset of convulsive seizures, the blood pressure rose appreciably (part D). Replacement of the oxygen by room air at 60 lb. pressure dispelled the convulsive movements and turned the rising blood pressure downward.

If high oxygen pressure causes any generalized peripheral vasoconstriction, as is thought by some to be the case [Behnke, Forbes & Motley, 1935*a*], experimental evidence [Behnke *et al.* 1935*a*; Bean, 1931] indicates the brain is exempt from vasoconstriction. The experiments of Hill [1908] on the bat's wing and the frog's foot showed that at air pressures as high as 70 atm. (equivalent to 14 atm. of oxygen) there was no observable change in the peripheral blood vessels. Aside from the question of vasocontriction, however, there can be little doubt but

that the muscle spasm and tachycardia are contributing factors in the sharp rise in blood pressure which takes place during convulsive attacks of oxygen poisoning.

It has been stated [Shaw *et al.* 1934] that oxygen poisoning in the anaesthetized dog first manifests itself by a drop in blood pressure and that this drop constitutes the criterion of oxygen poisoning. In later work on man it was found that there occurred no change in blood pressure as a result of exposure to high oxygen pressure [Behnke *et al.* 1934*a*]. A subsequent report [Behnke *et al.* 1935*a*] concludes that a rise in blood pressure is an early manifestation of oxygen poisoning. Although our earlier and present data indicate in general a rise in blood pressure under high oxygen pressure, they indicate definitely that blood pressure change is not a good criterion of oxygen poisoning. Our experimental results as shown in Fig. 1 are at variance with the results of experiments on dogs anaesthetized with sodium barbital in which a fall in blood pressure "is the constant and early sign of oxygen toxicity and always precedes the convulsive seizure" [Behnke *et al.* 1935*a*]. If one is looking for an early sign of oxygen toxicity, the respiratory record offers a more reliable indicator. Individual variation in susceptibility to oxygen poisoning is considerable, but rare indeed have been the exceptions which fail to show an early alteration in breathing, such as an hyperpnoea or dyspnoea, as a result of exposure to high oxygen pressure. The prompt increase in respiratory minute volume when our animals, either with intact or denervated sinuses or intact or sectioned vagi, were exposed to increased oxygen pressure bears this out.

The respiratory minute volume (expressed in c.c. per kg. body weight) of seventeen decerebrate dogs was measured in as many experiments. Fifteen of these showed a pronounced increase in respiratory minute volume within 5 min. or less after the oxygen pressure had been raised to 60 lb. One of the remaining two showed a delayed increase after an initial decrease which lasted 18 min. The other in which there was a decreasing minute volume preceding compression failed to show any increase in minute volume after compression, and died after 60 min. of exposure. Of these seventeen experiments, one group of six was carried out on dogs in which both the vagi and sinuses were left intact; a second group of six was carried out on dogs in which the carotid sinuses were denervated, but the vagi left intact; the third group of five experiments was performed on dogs with sinuses left intact, but the vagi either sectioned or cold blocked. The first group, i.e. those animals with both vagi and sinuses intact, showed the most marked increase in respiratory

minute volume as a result of exposure to high oxygen pressure. The second group, those animals with intact vagi and denervated sinuses, showed much less increase in respiratory minute volume on compression than the first group, but somewhat more than the third group in which the vagi had been sectioned and the sinuses left intact. The two animals which failed to show an immediate minute volume increase on compression belonged to this last group. These results indicate that the receptors of the aortic bodies and the carotid sinuses and bodies, contribute to the early increase in respiratory minute volume of oxygen poisioning.

Oxygen poisoning is in large measure a reversible effect. It should be emphasized, however, that decompression to atmospheric pressure after prolonged exposure to high oxygen pressure may be attended with considerable difficulty even when sufficient time is allowed to prevent bubble formation. Decompression to atmospheric pressure on several occasions resulted in a failure of respiration which could be relieved by partial recompression. It is possible that this respiratory failure may have been due to an alteration in membranes and their permeability to oxygen at the lung. It may also have been due to some irreversible alteration in the cells of the regulatory mechanism, as a result of prolonged high concentration of carbon dioxide, increased acidity or perhaps some deleterious effect of oxygen itself.

Summary

1. Decorticate and decerebrate dogs were exposed to oxygen at from 5 to 6 atm. pressure in a chamber equipped so that observations and experimental procedures could be carried out with the animal continuously and completely under the control of the operator from without.

2. Neither the cortex nor basal ganglia are essential to the induction of oxygen poisoning reactions which must arise from sites below the superior colliculi.

3. While the carotid sinuses and bodies, the aortic and the pulmonary vagal sensory endings contribute to oxygen poisoning by increasing the respiratory minute volume, they are not essential to the occurrence of oxygen convulsions.

4. The results suggest that high oxygen pressure enhanced the effectiveness of vagal cold block and acts to paralyse the normal vagal influence on the controlling mechanism of respiration.

5. The bradycardia of oxygen poisoning is largely dependent upon the integrity of vagal-cardiac fibres. The tachycardia which frequently

accompanies the convulsions is due in part to a depressing or paralysing action of accumulated carbon dioxide, acidity or direct toxicity of oxygen on nerve connexions of the sinus region.

6. Although there usually is a gradual rise in blood pressure, with a sharp increase during convulsive seizure, blood-pressure change is not a good criterion of the onset of oxygen poisoning. The earliest indication of poisoning effects is usually an alteration in breathing.

7. Since there is a wide individual variation in susceptibility to oxygen poisoning it appears unwise to set any specific time limit for safety from oxygen poisoning.

8. The results of these experiments are entirely compatible with the view that the accumulation of carbon dioxide and increasing acidity of the tissues consequent upon a failure in reduction of haemoglobin and a resulting upset in the carriage of carbon dioxide by the blood is one of its most important causative factors in oxygen poisoning. It is recognized, however, that there may be other and more direct toxic effects of high oxygen pressure on the tissues.

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