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He was sent to bed and the following morning was cystoscoped. This examination revealed a villous growth of the bladder lying to one side of the left ureter. Both ureters were secreting normally. He had no further bleeding whilst in hospital. Three days later, he was operated on. After anaesthesia with ether, the bladder was washed out and distended with boric lotion. A supra-pubic cystotomy was next performed and the bladder slung up with two stout silk sutures. With the aid of retractors the tumour could be seen lying in the position shown by the cystoscope. An assistant next put a finger in the rectum and pushed the bladder forward. This however did not assist in making the tumour more get-at-able and was given up. An electric head lamp was used to give a good illumination. With some difficulty a purse-string suture was placed round the base of the growth, and this was then cut away. The base was next cauterized freely, and the suture tightened. Very little bleeding took place. The bladder seemed perfectly healthy and it was decided to close it completely. This was done in the usual manner by Lembert sutures.

The after history was uneventful. The bladder and skin wound healed by first intention. The patient was only catheterized twice and no catheter was tied in. A few blood clots were passed at first but the urine was clear on the second day. It was fortunate that the growth did not invade the ureteral orifice, as this would have necessitated transplantation of the ureter, and very considerably added to the difficulties of the operation.

I have to thank Lieutenant-Colonel R. Tilbury Brown, C.M.G., D.S.O., R.A.M.C., for his permission to publish this case.

Lecture.

ANOXÆMIA AND ITS EFFECTS AS SEEN IN GAS POISONING.

By C. G. DOUGLAS, C.M.G., M.C., D.M.

By the term "anoxæmia" is implied a condition in which the rate of supply of oxygen by the arterial blood is insufficient for the requirements of the tissues of the body. Such an insufficiency may arise from a variety of causes: deficiency of oxygen in the atmosphere, interference with the free gaseous interchange between the blood and the air in the lungs, a diminution in the capacity of the blood to transport oxygen in the normal quantity (no matter whether that alteration is due to circulatory failure, to excessive haemorrhage, to abnormal destruction of red blood corpuscles within the body or to anaemia of some other origin, or to some factor which so alters the haemoglobin in the blood that it is no longer capable of combining with the normal proportion of oxygen even when there is no impediment to the entrance of oxygen from the air in the lungs into the blood), or lastly any cause that may hinder the free liberation of oxygen from the oxyhemoglobin in the red corpuscles as the blood traverses the capillaries in the tissues.

1 A lecture delivered at the Royal Army Medical College, February 9, 1921.
The almost instantaneous loss of consciousness that occurs when we breathe an atmosphere devoid of oxygen—the mental failure, loss of muscular power and co-ordination, and the weakening of the heart's action which ensue in even normal people when subjected experimentally to atmospheres in which the oxygen concentration is seriously lowered—the headache, nausea, weakness and misery which result from more prolonged exposure to atmospheres moderately impoverished of oxygen, a train of symptoms which we meet with in mountain sickness—all these phenomena must bring home to us the paramount influence on the cells of the body of a proper supply of oxygen. We can understand, too, that anoxæmia, if it should develop at a time when the body is already affected by some gross pathological change, may well constitute a factor of overwhelming importance.

In this lecture I am going to confine myself to the question of the extent to which anoxæmia may be a direct or contributory cause of serious symptoms, if not of death, in cases of gas poisoning which may occur during military operations, and I am naturally led to speak first of all about the effects produced by those poisonous gases which were deliberately used for offensive purposes and figured so largely during the recent war.

As you are aware a great number of different toxic gases were used both by the Germans and by the Allies, but we can fortunately dismiss some of these at once, since, whatever their military value as harassing or neutralizing agents, they did not in practice produce a type of effect that would cause deficiency of oxygen to manifest itself in the body. This statement holds good for the pure lachrymator substances such as xylyl bromide used by the Germans in their earlier type of gas shell, or ethyl iodochloroacetate which was used by the British, or the chlorarsine compounds contained in the German Blue Cross shell. It is true that these substances are capable of causing pulmonary lesions of the most serious type, provided that they occur in relatively high concentration in the atmosphere breathed, a fact which has been proved experimentally on animals, but their boiling point is so high that the requisite concentration to produce this effect was never actually attained in the field, and their action was therefore limited to profound sensory irritation of the eyes, upper respiratory passages, etc., an effect which was quite sufficient to disable the opposing troops temporarily. Hydrocyanic acid, which was extensively used by the French and ourselves in gas shell, need not detain us, for this gas does not lead to anoxæmia in the strict sense. It is a true tissue poison, and the vital activity of the cells and organs of the body may be abolished even though the oxygen carrying power of the blood is unimpaired: the tissue cells simply cease to make use of the oxygen that is carried by the blood, the immediate cause of death being failure of the respiration and of the heart.

We are left, therefore, with the so-called acute lung irritant gases, of which the best known are chlorine, phosgene, trichlormethyl-chloroformate, chloropirin and nitrous fumes,¹ and the remarkable vesicating agent mustard gas or

¹ Though nitrous fumes were not responsible for any serious casualties during the warfare on land, they offered a problem of considerable importance during naval warfare owing to the liability of the propellant charges of guns to get set on fire during action. See in this connexion Surgeon-Lieutenant Fairlie: "Poisoning by Nitrous Fumes," Naval Medical History of the War, Journal of the Royal Naval Medical Service, vol. vi, p. 66, 1920.
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218 dichlorethyl-sulphide. I propose to deal first of all with the acute lung-irritant gases.

The most dangerous symptoms which arise in poisoning by the acute lung irritants are due to the onset of acute pulmonary œdema, for the exudation into the alveoli, if considerable in quantity, is capable of causing death by asphyxiation just as certainly as does drowning. The concentration in the atmosphere breathed which is necessary to cause a serious degree of pulmonary œdema differs with the different gases of the group, phosgene, trichloromethyl-chloroformate and chloropirin exhibiting a greater toxicity in this respect than chlorine or nitrous fumes. In addition, however, to the effects that these gases produce in the alveoli of the lungs they are liable to exert a marked irritant action on the mucous membrane of the trachea and bronchial tubes, which may be rendered evident by congestion, necrosis of the epithelium and formation of inflammatory exudate. This inflammatory action on the mucous membrane of the air tubes varies in prominence according to the particular gas to which the person has been subjected. Thus phosgene may induce a sufficient degree of pulmonary œdema to cause death without any very definite changes being produced in the mucous membrane of the air tubes, save perhaps in the smallest bronchiolo. On the other hand the pulmonary œdema resulting from exposure to chlorine or chloropirin is always accompanied by very definite inflammatory changes in this situation. This distinction appears to correspond roughly with the differences of sensory irritant power of the different gases, that is with their power to cause pain, lacrimation, and violent coughing.

A great deal of information is now available regarding the actual pathological changes which result in the lungs from the action of the acute lung-irritant gases. The main changes can of course be determined by an examination of the organs at autopsies on fatal cases of poisoning in the case of man, and the full sequence of events has been exhaustively studied in experiments on animals. For the full details of these experimental results, I will refer you more particularly to the accounts published by Edkins and Tweedy 1 and by Dunn 2 in England, and to a recent description of the investigations made in the United States which has been edited by Winternitz 3. You are doubtless conversant with these pathological changes, and I need not here do more than summarize the main features briefly.

A period of delay intervenes before any definite alteration makes its appearance in the lungs. The first sign of pulmonary œdema that can be recognized is an accumulation of fluid in the interstitial tissue of the lungs accompanied by a marked distension of the lymphatics, and this is quickly followed by the appearance of œdema fluid in the alveoli, which can at this stage be recognized practically universally throughout the lungs. In the course of the next few hours the alveolar œdema extends and becomes more intense. As time goes on the dis-

1 Edkins and Tweedy: Report No. 2 of the Chemical Warfare Medical Committee published by the Medical Research Council, April, 1918.
2 Dunn: Report No. 9 of ditto, published September, 1918; Report No. 20 of ditto, published March; 1920.
of the alveoli. Some parts of the lung, mainly those from which drainage by the lymphatics would appear to be difficult, exhibit a solid alveolar edema, the alveoli being filled with fluid to the complete exclusion of air, whilst the edema in other areas may be comparatively slight. Yet even in the latter case there is a great tendency for the fluid to lie against the alveolar walls hindering access of air to them. The degree of change which may occur in the mucous membrane of the bronchial tubes is very variable. Sometimes, as may be the case in phosgene poisoning, the damage is comparatively trivial and confined to the terminal bronchioles, though even in these cases the bronchioles leading to the lobules of the lung where the edema is solid may become blocked with exudation and epithelial débris. Such damage is far more striking after poisoning with chloropicrin or chlorine, and affects in the main the mucous membrane of the small and medium air tubes, though even the larger air tubes and trachea may be seriously affected. In these cases the desquamated epithelial cells and coagulated exudate may form casts which seriously obstruct the entrance of air into the alveoli beyond, the obstruction being further accentuated by the engorged and edematous condition of the submucosa. The capillary network between the alveoli may also be damaged by the gas, evidence of this damage being afforded by thrombosis in the alveolar capillaries in the neighbourhood of the entrance of a bronchiole into a lobule of the lung, though the capillaries in the more peripheral part of the lobule may appear intact. The more severe the dose of gas the more extensive is the capillary thrombosis. The American observers have drawn attention to the possible obstruction of capillaries from compression by strands of fibrin deposited in or upon the alveolar walls. As the inflammatory changes develop in the lungs the even expansion of the lungs by the respiratory movements must be greatly interfered with. Complete or partial obstruction of the bronchial tubes by debris and exudate, and the flooding of alveoli with edema fluid will greatly impede the entrance of air into some parts of the lung, while the remaining parts of the lung into which air can penetrate will become overdistended, and the weakened alveolar walls may be actually torn by the increased breathing movements or bouts of coughing. Acute or disruptive emphysema will result from this, and as one might expect this condition is most pronounced in those cases which exhibit the greatest degree of obstruction in the bronchial tubes. In the case of pure phosgene poisoning acute emphysematous changes in the lung may play but a small part, though such changes are always prominent when severe poisoning is produced by either chloropicrin or chlorine. During the war different lung-irritant gases were often used simultaneously by the Germans, particularly in gas shell, and the liability of the casualties to show emphysematous changes varied considerably. Pathological changes in other parts of the body than the respiratory apparatus are of an indefinite character after exposure to the lung-irritant gases, and appear to be secondary to the asphyxial condition which ensues from the pulmonary lesions.

You will see that the essential lesions are the gross exudation of fluid into the alveoli of the lungs, inflammatory and necrotic changes in the mucous membrane of the bronchial tubes, acute emphysema, and capillary thrombosis or obstruction. What we have evidently to consider are the precise effects that will be produced by these various changes, for that knowledge is essential if we are to adopt the right lines of treatment.
It is of course apparent that changes in the lungs of the type I have indicated must seriously interfere with the respiratory exchange between the blood and the air, but we must consider in greater detail how far we are to attribute the symptoms to hindrance of oxygen absorption and how far to hindrance of excretion of carbon dioxide. This aspect of the question has been studied extensively by Haldane, and he has dealt with it in a lecture given before this College in October, 1919. I need not therefore do more than recapitulate the main points in his argument.

The interposition of a layer of oedema fluid between the alveolar epithelium and the air in the lungs must of necessity offer a hindrance to the entrance of oxygen into the blood and the escape of carbon dioxide from the blood. Carbon dioxide is, however, far more soluble in water than is oxygen, and it will therefore pass far more easily through the alveolar epithelium and the overlying oedema liquid than will oxygen for any given difference of the partial pressures of the gas in the blood and in the alveolar air. Any increase in the breathing will cause a material lowering of the partial pressure of carbon dioxide in the alveolar air and so facilitate the escape of this gas from the blood, but the small proportional increase in the partial pressure of oxygen in the alveolar air will have little effect in promoting the entrance of oxygen into the blood. Provided therefore that the accumulation of oedema fluid in the alveoli is the only factor that we have to reckon with we can see that it might be possible for the patient to exhibit symptoms of profound deficiency of oxygen without affording any evidence of material retention of carbon dioxide.

If, however, in addition to the development of oedema the structure of the lung becomes disorganized by the development of areas of acute emphysema and of partial collapse, the proper distribution of air through the lung at each breath will be upset. The areas of partial collapse will be ill-ventilated, and though the emphysematous areas may be over-ventilated, this over-ventilation may be unable to compensate for the deficiency of ventilation in the collapsed areas owing to the relatively small proportion of alveolar wall and capillaries to the air contained in the emphysematous spaces. The net result will be that the carbon dioxide concentration in the alveolar air, and therefore in the arterial blood, will become higher than normal; we shall, in fact, have a condition in which severe deficiency of oxygen is accompanied by some degree of carbon dioxide retention.

In both these cases, however, it is the hindrance to the oxygen intake that is responsible for the really serious effects on the body. Accumulation of a certain excess of carbon dioxide does not cause nearly so widespread or disastrous results as profound shortage of oxygen. Moreover, the great sensitiveness of the respiratory centre to any rise of carbon-dioxide pressure in the blood implies that accumulation of carbon dioxide will be accompanied by great hyperpnoea, which will lead to a corresponding increase in the rate of elimination of carbon dioxide. Deficiency of oxygen, if accompanied by increase of carbon-dioxide concentration, can, it is true, stimulate the respiratory centre; but such an effect is but slight when compared with the action of carbon dioxide.

The question now arises as to the effect that will be produced by capillary
thrombosis or vascular obstruction in the lungs. If these effects are very extensive and severe, as might well be the case in the most severe type of gas casualty who succumbs very quickly after exposure, we can see that they might become a very important accessory factor in causing death, but Dunn's observations on animals have shown clearly that death may ensue when the thrombosis is limited to but certain parts of the lobules, and the fact that the cyanosis in the majority of even serious gas casualties can be relieved by the administration of oxygen points to the fact that in such cases the shortage of oxygen arises from the hindrance to the entrance of this gas into the blood owing to the presence of the fluid in the alveoli, rather than to capillary obstruction, and at the same time suggests that there can be no material passage of venous blood through the non-aerated portions of the lung where the alveoli are completely filled with oedema fluid. The nature and significance of the vascular changes that can be observed in the lungs of animals after exposure to lung-irritant gases have been critically discussed by Barcroft in a lecture given at this College in October, 1919, and he makes it clear that the circulation through the non-aerated parts of the lungs is shut down—at least while the animal is resting.

In this connexion I would call your attention to what one sees in cases of ordinary lobar pneumonia. As you know, a patient may have a considerable part of his lungs consolidated, and yet exhibit little or no cyanosis. Were the circulation still continuing freely through the hepatized parts, where the alveoli are so blocked with exudate that no air can enter them, we should expect the blood leaving the lungs to have a much lower oxygen saturation than normal, seeing that part of it would have passed through aerated parts of the lungs, and part would have had no opportunity of gaining oxygen, and we should therefore expect cyanosis to be pronounced. Actually it would appear that in such a case there is an almost complete cessation of the circulation through the consolidated areas, and that the aerated portion of the lungs is practically sufficient to provide for the patient's oxygen requirements during rest (it must be remembered that the normal lungs are capable of meeting the demands of the body even though the rate of oxygen consumption rises to ten times the resting figure, a value which can easily be reached in severe muscular work).

By the kindness of Professor Meakins, of Edinburgh, I am able to show you X-ray photographs of the lungs from a case of lobar pneumonia, in which the blood vessels have been injected with an opaque preparation; and you will see that though the circulation through the lobe which is in the stage of red hepatization appears to be only moderately diminished, there is a general lack of the injection in the blood-vessels in the lobe in the stage of grey hepatization, only a few of the larger vessels being apparent in this region.\(^1\)

Haldane\(^2\) has pointed out that when severe deficiency of oxygen is accompanied by an increase in the concentration of carbon dioxide in the blood, there is reason to believe that the capillaries in the tissues will be dilated and the flow of blood to the veins increased. The heart will therefore be called upon to pass

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on blood to the arteries at a faster rate, but in the absence of a proper supply of oxygen it may fail to meet the strain, and dilatation of the right side of the heart and venous engorgement will give evidence of this. Owing to the dilatation of the capillaries, the lips and face will exhibit a full blue or plum-coloured cyanosis. When, however, the shortage of oxygen is unaccompanied by retention of carbon dioxide, there will be no capillary or venous engorgement, but the grey ashen colour of the patient's face and the obvious indications of circulatory failure will bear witness to the severity of the anoxæmia.

What we have to face therefore in the hours which follow exposure to the acute lung-irritant gases is the risk of death from sheer deprivation of oxygen. Any retention of carbon dioxide which we are likely to encounter in these cases need not cause us misgiving: in fact it is an actual advantage if the deficiency of oxygen is accompanied by some degree of carbon dioxide retention, for this will have a beneficial effect on both respiration and circulation, and will in addition ensure that there is no diminution in the ease of liberation of oxygen from the haemoglobin as the blood passes through the tissues, since an increase in the pressure of carbon dioxide in the blood (or more strictly: the increase in the hydrogen ion concentration to which this gives rise) causes oxygen to dissociate from oxyhaemoglobin at higher partial pressures. One may note in this connexion that the cases showing congested cyanosis, i.e., those cases in which the deficiency of oxygen was probably associated with retention of carbon dioxide, were not in practice so grave as those which were distinguished by ashen pallor.

This acute stage when death from asphyxia is imminent is practically limited to forty-eight hours or so; in fact some eighty per cent of the deaths from acute lung-irritant gases occurred in France in the first twenty-four hours. When once the critical period is safely passed the chances of ultimate recovery are good. Experience both with men and animals shows that reabsorption of the fluid from the lungs is rapid, and that the structural damage of the tissues of the lungs and of the capillary vessels may be healed to a surprising extent. Though emphysema may remain in some cases it is remarkable how complete recovery may be in the majority. Numerous instances are on record in which men who were on the border line of death in the acute stage returned to combatant service in one or other of the various theatres of the war after the lapse of some months. In our experience during the war bronchopneumonia was an uncommon complication amongst those who survived. Convalescence was sometimes delayed by a train of symptoms in which neurasthenia and a mild degree of anoxæmia dependent on an unnaturally rapid and shallow type of breathing played a part, but I do not intend to enter into this aspect of the question as it has been dealt with by Haldane in the lecture to which I have alluded.

The immediate aim of treatment of these cases will be obvious. What we have to do is to try to tide the patient over the acute period in order to give time for the natural recuperative processes to come into play. We cannot of course rectify the damage that has been done in the lungs, nor can we bring about the immediate reabsorption of the oedema fluid, but we can take steps to combat the anoxæmia. Clearly we must prevent the patient from undertaking any muscular exertion, for if the portion of the oedematous lung which is still functioning is inadequate to transmit oxygen to the blood at a fast enough rate when the patient is at rest and his oxygen requirements minimal, any wilful increase in the oxygen
consumption of the tissues can only spell disaster. Let me remind you that if one stands up one's oxygen consumption is considerably above the figure obtained when one is lying down, whilst walking at only two miles per hour will raise the oxygen consumption to between twice and thrice the lying value. We ought too to keep the patient warm not only to combat shock but to prevent any shivering or undue increase of muscular tone which might occur if the body temperature tended to fall and would entail an increase in the oxygen consumption in the muscles concerned.

The next thing we can do is to try to increase the rate of transmission of oxygen through the œdema fluid and the pulmonary epithelium into the blood. The rate of diffusion of a given gas through a layer of liquid is determined by the solubility of the gas in the liquid and by the difference in the partial pressure of this gas on the two sides of the liquid, and we can easily raise the partial pressure of oxygen in the alveolar air by giving the patient oxygen to breathe. The only difficulty arises in the selection of the best method of administration of oxygen. Some methods are hopelessly inadequate, others entail the use of so much oxygen that it may prove impossible to keep up the supply of the gas. What we have to aim at is to raise the concentration of oxygen in the air in the lungs to such a point that the gas will traverse the œdema liquid and the pulmonary epithelium at a rate sufficient to saturate the haemoglobin to the normal extent as the blood passes through the pulmonary capillaries: the relief of the cyanosis will indicate when we have attained this concentration. There is no need to raise the concentration of oxygen in the air in the lungs above the value which is found just sufficient to relieve the cyanosis, for the haemoglobin is now as saturated with oxygen as it is during normal life, and any further increase in the partial pressure of oxygen only implies a very trifling gain in the amount of oxygen held in simple solution in the blood. As a rule a quite moderate addition of oxygen to the air breathed by the patient will suffice.

In the earlier days in France, the nitrous oxide anaesthesia apparatus was employed for oxygen administration. This was certainly effective, but the fact that pure oxygen was used demanded a supply of the gas that could hardly be kept up, and a further disadvantage lay in the fact that pure oxygen if administered continuously for any length of time was known to have an irritant effect on normal lungs. A great improvement was introduced by Stokes in August, 1916, when he adopted the simple method of allowing a small stream of oxygen to pass through a soft rubber catheter which was introduced through the nose of the patient so that the open extremity lay in the nasopharynx. It was easy by this means to treat a number of cases simultaneously. About the same time Haldane introduced his apparatus for the administration of oxygen, and later on this was supplied in considerable numbers to the medical units in France. The advantage of the Haldane apparatus is that oxygen only passes to the patient during inspiration and none of the gas is wasted during the patient's expiration, while the delivery of oxygen can easily be adjusted so that it is kept continuously at the rate necessary just to relieve the cyanosis. If I am sitting still under normal conditions

2 Report No. 10 of Chemical Welfare Medical Committee, published by the Medical Research Council, October, 1918.
circumstances my alveolar air contains about fourteen per cent of oxygen when I am breathing ordinary air, and if under the same circumstances I administer oxygen to myself by the Haldane apparatus at a rate of two litres per minute the percentage of oxygen in my alveolar air rises to about thirty-four per cent; that small addition of oxygen to the inspired air has in fact sufficed more than to double the concentration of oxygen in my alveolar air. Under these circumstances I should only be breathing about eight litres of air per minute. A gassed case would of course be breathing a good deal more owing to his hyperpnea, and a greater rate of oxygen flow would be necessary to attain the same concentration of oxygen in his alveolar air. Very often, however, the cyanosis of such cases can be relieved by the administration of oxygen by the Haldane apparatus at the rate of three litres per minute, and it is not often that one has to exceed a rate of oxygen flow of five litres per minute.

The relief of the cyanosis is in itself a clear indication that the haemoglobin of the blood is being properly oxygenated, but Meakins has recently determined by accurate analysis the effects of oxygen administration in various patients suffering from pulmonary complaints who exhibited signs of anoxemia accompanied by cyanosis. Both Stadie and Meakins have found that the haemoglobin of the arterial blood of normal persons obtained by direct puncture of the radial artery is about ninety-five per cent saturated with oxygen, and that in pneumonia accompanied by cyanosis there is a definite reduction of the oxygen saturation of the haemoglobin in the arterial blood. In a case of lobar pneumonia accompanied by a moderate degree of cyanosis Meakins found that the arterial blood was from eighty-two to eighty-five per cent saturated with oxygen; administration of oxygen by the Haldane apparatus at the rate of two litres per minute raised the saturation of the haemoglobin to ninety-one per cent, and at the rate of three litres per minute to ninety-seven per cent, a value actually in excess of the normal.

A case of acute pulmonary oedema from gas poisoning will exhibit cyanosis for several days. The cyanosis is of course most marked during the first forty-eight hours and then lessens progressively as the oedema fluid is absorbed and the functional capacity of the lungs regained. The cyanosis is an indication of shortage of oxygen, and long continued shortage of oxygen acts prejudicially on the body. Obviously then our aim should be to keep the cyanosis relieved, and this implies continuous oxygen administration over several days. It is therefore desirable that we should use some method of administration which allows the oxygen to be used with the greatest economy. In practice one can however safely intermit the oxygen supply for short periods; this will often prove a relief to the patient, and will admit of giving him nourishment and of attending to him.

To show how one may proceed in these cases I may quote to you two cases that I treated just after the first Haldane apparatus had been sent to France for trial. The first patient had been gassed twenty-nine hours previously during a gas trench mortar bombardment, and when I first saw him he was semi-

comatose, with face pale and leaden coloured, and speech incoherent. His pulse was 130-140 in rate, and very weak and irregular, and his respirations over fifty per minute and fairly deep. Administration of four litres of oxygen per minute by the Haldane apparatus improved his colour greatly, and with five litres per minute the colour of his lips and face became almost normal: we therefore kept up the oxygen administration at the latter rate with intermissions of ten minutes every half hour. Beside the change in colour there was a remarkable improvement in the pulse. Within a minute or two of starting the oxygen the pulse rate fell to 120 and became regular and of much better tension, but whenever we left off the oxygen administration both colour and pulse quickly deteriorated. After three hours' treatment with oxygen the respirations had fallen to forty-four and seemed less deep, and the patient was becoming more sensible. We continued the oxygen administration, and after a further twenty-four hours the patient's general condition showed distinct improvement, and he was far more conscious. Respirations were still forty-four but the hyperpnoea was distinctly less; the pulse was 120 in rate and regular and strong. Cyanosis returned on stopping the oxygen but it was not as deep as on the previous day, and we were able to cut down the oxygen supply to four litres per minute without causing the cyanosis to return. Administration was kept up continuously with intermissions of ten minutes every half an hour. The following day the oxygen could be safely cut down to three litres per minute, and it was given for half an hour at a time with intermissions of half an hour. The pulse was now 100 per minute in rate and of good quality; the respiration rate was forty, and the hyperpnoea much diminished. Later in the day it was possible to cut the oxygen down to two litres per minute. The following morning the oxygen was reduced to one litre per minute, and in the evening the administration was stopped altogether as the cyanosis did not return.

The second case had been gassed ten hours before I saw him by the gas shell which penetrated his billet. In the interval he had been treated intermittently with pure oxygen by means of a nitrous oxide inhaler. When I first saw him his condition was very grave and he appeared to be moribund. His pulse was hardly palpable and it was impossible to count the rate, and he exhibited a livid cyanosis. Five litres of oxygen per minute given by the Haldane apparatus caused a considerable improvement in colour, but even with ten litres per minute the colour did not seem to me to become quite normal. Continuous administration of oxygen was started with the rate of oxygen delivery of six litres per minute. The pulse became palpable in a few minutes, though it was of somewhat fluctuating quality; its rate was now 120 per minute. Half an hour after starting the oxygen the respiration rate was fifty-two and the breaths were not deep. Three hours later the pulse was 112 per minute, and though weak it was quite regular; the respiration rate was fifty-eight. The patient objected to having the mask removed, and when it was taken off he soon made feeble efforts to regain it: I may add that during the period I am describing the mask of the apparatus was never removed for more than a minute or two at a time. Two hours later the pulse was 108 in rate and slightly stronger, the respiration rate being still fifty-eight. The patient still continued to resist the removal of the mask, and appeared to be able to sleep as long as he was having oxygen. At the end of another two hours the pulse and respiration rates were unchanged, but the
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colour of the face whilst the oxygen was being administered was now very
definitely better than it was during the first hour of oxygen administration.
After a further two hours and a half the pulse rate had fallen to 100, the respira-
tion rate being fifty-four. Five litres of oxygen per minute now caused a marked
improvement in colour, and the administration was therefore continued with this
rate of delivery. If the rate of oxygen supply was reduced to three litres per
minute there was far less relief of the cyanosis. At the end of another hour and a
half, i.e., about twelve hours from the commencement of the continuous oxygen
administration, the pulse, though weak, was very definitely stronger than at the
start, its rate being 102, the respiration rate had dropped to forty-eight per minute.
The patient was more conscious and did not look so moribund while the oxygen
was being given, but when the oxygen was stopped his condition deteriorated
rapidly and cyanosis became extremely marked. The oxygen treatment was
continued subsequently and the patient eventually made a good recovery. It was
possible to transfer him to England on the tenth day and he rejoined his
regiment in France within a year.

I have quoted these cases in detail because I think that they will bring home
to you the reality of the dangerous effects of deficiency of oxygen on the central
nervous system and on the heart. You will notice how quickly the relief of the
cyanosis is followed by a great improvement in the quality of the pulse and by a
reduction in the rate of the heart beat and the disappearance of irregularity in its
action, how coma may give place to consciousness, and how the patient's
unwillingness to be deprived of the oxygen may indicate the relief of the dis-
comfort which he is experiencing. Stop the oxygen and the condition of the
patient rapidly deteriorates. The improvement, striking as it is within a brief
time of commencing the oxygen administration, becomes progressively greater as
the administration is persisted with.

These instances will serve, too, to emphasize a point which I have already
alluded to, namely, the necessity of administering the oxygen continuously in cases
of this type where one is endeavouring to tide over an acute but transitory condi-
tion of asphyxia. I feel that, in the past at all events, medical men have not
infrequently failed to recognize in their true light the serious effects that accompany
any grave and continued shortage in the oxygen supply to the tissues of the body,
effects that cannot be remedied by infrequent administrations of oxygen for but a
few minutes at a time. I recall in this connexion that I have seen in France a
patient suffering from acute pulmonary oedema, and deeply cyanosed, to whom
oxygen was being administered for but five minutes every hour: yet the oxygen
apparatus was standing by the bedside all the time in perfect working order, the
cyanosis could be relieved immediately, and no great supply of oxygen was required
to accomplish this, and the patient offered no resistance to the application of the
mask since he found relief during the oxygen administration.

You will notice that in speaking of treatment with oxygen I have confined
myself to the use of portable apparatus for its administration. Another method
that may be employed is to place the patient in a closed chamber in which the air
has been artificially enriched with oxygen. Such a method has obvious advan-
tages. The patient is unhampered by any apparatus and the work of those
attending him is facilitated. Against the advantages must, however, be set certain
disadvantages. Such a chamber is costly to build and requires attention in the
running, while some system for preventing carbon dioxide from accumulating in the air must be adopted, and the risk of fire must be carefully guarded against. Evidently it would be difficult to establish an oxygen chamber anywhere but in a permanent hospital, and the number of cases that could be treated simultaneously would be limited. Chambers of this type were built in England during the war and used with excellent results, and there is little doubt that the method will be developed further in the future for clinical use. A portable apparatus is, however, clearly essential in the field and can hardly be supplanted in ordinary medical practice owing to the limitations of the chamber method.

I have already drawn your attention to the venous engorgement and signs of right-sided dilatation of the heart which may be distinguished in the full blue cases of cyanosis, and the evidence of cardiac failure in the grey ashen cases will be clear from the descriptions I have given. Any failure of the circulation can but accentuate the anoxæmia determined by the pulmonary lesions and help to establish a vicious circle. There is yet another factor to take into account which I have not so far mentioned and that is a concentration of the blood with a rise in the hæmoglobin and red corpuscle content which occurs in all gas casualties suffering from severe pulmonary oedema, a concentration dependent, no doubt, on the abstraction from the body of the fluid exuded into the lungs, on the general condition of shock, and probably in some degree on the anoxæmia. An alteration of this character in the blood implies an increase in viscosity, and though such an increase may be tolerated with impunity in normal persons under certain circumstances, e.g., at high altitudes, where an increase in the number of red cells and in the hæmoglobin is one of the adaptive changes shown by the body to compensate for the reduced oxygen pressure in the atmosphere, it may well prove a serious factor in cases of gas poisoning in which the pulmonary capillaries have been damaged and very likely offer an increased resistance to the flow of blood. Should this effect develop you can well understand how the strain may prove too much for a heart already profoundly affected by the deficiency of oxygen.

In considering the effects of anoxæmia in these cases we must not, therefore, confine our attention solely to the primary cause of the shortage of oxygen which is to be found in the hindrance imposed on the passage of oxygen from the alveolar air into the blood; we must take into account the secondary cause dependent on circulatory failure in one or another form, and be prepared to adopt suitable treatment to counteract its effects. The importance of venesection was emphasized by Macaulay and by Irvine in cases of acute pulmonary oedema arising from accidental poisoning with nitrous fumes on the Rand, and it was on the basis of this experience that venesection was first seriously practised in France when dealing with gas casualties resulting from cloud gas attacks. Of the value of venesection in the cases showing venous engorgement and full blue cyanosis there can be no doubt, and the rapidity with which the abstraction of blood is followed by an amelioration of the patient's condition such as diminution of the cyanosis, and distinct reduction of the dyspnæa, headache and general discomfort, suggests that

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in the main the treatment owes its effect in these cases to an immediate relief of an embarrassed circulation at a critical period when the heart is beginning to fail and its right side to dilate under the strain. Numerous experiments, particularly by the American observers, have established the beneficial effects of venesection on animals poisoned by the acute lung-irritant gases, but the point remains in doubt whether the abstraction of blood will hinder the exudation of fluid into the lungs or promote its re-absorption when once œdema has been established, and experiments made on animals by English observers have given but inconclusive results in this respect. Venesection of the grey, ashen cases that showed no venous engorgement was found to be of no benefit, and in fact sometimes appeared to do harm, and in this class of case the question of the possible benefit of infusion of saline must be considered. In the earlier days in France this treatment was not adopted, for the reason, I think, that fear was felt that the procedure might lead to a serious accentuation of the pulmonary œdema, though I believe that one or two grey cases were infused at a later period with apparently some benefit. The German official medical pamphlet issued during the war mentions that infusion had been tried in a few cases with beneficial results, but the treatment was not recommended enthusiastically. Towards the close of the war Colonel Underhill\(^2\) and other American investigators brought forward a number of valuable results (loc. cit.) which they had obtained in a long series of experiments on animals which enabled them to make a strong case for treatment by infusion. They were of opinion that the concentration of the blood and the consequent alteration of viscosity was a real factor which contributed to a fatal issue, and that infusion would help to check the increase in viscosity. It would appear, therefore, that we overestimated the risk of infusion in these cases, and we might have been well advised to make a careful trial of the method in the grey cases, being guided by Underhill's suggestion that an index of the desirability of infusion could be obtained by following the haemoglobin concentration of the blood. Apparently when once pulmonary œdema has been well established infusion of saline can be practised without accentuating the exudation. Venesection in itself will very likely lead to dilution of the blood owing to the tendency for liquid to be drawn in from the tissues to replace the volume of blood abstracted from the circulation. It should not be forgotten that though venesection may at first appear undesirable in any particular case, the improvement resulting from oxygen administration or perhaps from infusion of saline may so alter the picture as to suggest that venesection may prove of benefit at a somewhat later stage.

I have now taken up a great deal of time with a discussion of anoxæmia, as it may occur after poisoning by the acute lung-irritant gases, and I have done so because I feel that we have here a particularly important type of case. We are faced by an acute shortage of oxygen which is determined primarily by the conditions in the lungs, and is secondarily accentuated by changes in the circulation which are largely at all events dependent on the primary anoxæmia. Immediate asphyxia is the real threat to life, and in comparison with this the part played

\(^1\) Report No. 13 of Chemical Warfare Medical Committee, published by the Medical Research Council, November, 1918.

by secondary bacterial infection of the damaged tissues is as a rule of minor importance. It is true that secondary infection with consequent bronchopneumonia was of frequent occurrence in the experiments on dogs made by the American investigators, and they laid much stress on these sequelae. In Dunn's experiments on goats, on the other hand, recovery almost invariably occurred without septic complication, which suggests that they more nearly represent the conditions which prevailed in man, for I have told you that in France our experience was that bronchopneumonia was an uncommon sequela.

The case is quite different when we turn to the effects produced by mustard gas (dichlorethyl-sulphide). This substance has a delayed but intense inflammatory action on the skin, the conjunctivae and the mucous membrane of the respiratory passages. It may be discounted as a direct cause of acute pulmonary oedema, save perhaps in exceptionally severe cases, and it is only very rarely that the intensity of the primary inflammatory reaction may lead to so much blockage of the bronchial tubes by false membrane and exudation as to threaten death from asphyxia. A fatal result practically invariably depends on the secondary bacterial infection of the damaged and necrotic mucous membrane of the bronchial tubes and the development of severe bronchopneumonia with some degree of associated pulmonary oedema. As this condition becomes established cyanosis, which was absent in the earlier stages, may begin to make its appearance. In such a case there is, however, a further danger than simple anoxæmia, for the body has to contend with the bacterial intoxication. We may give oxygen to such a case and find it followed by relief of the cyanosis and by an improvement in the heart's action, and yet we may be unable to stave off a fatal issue. It is clearly right in such cases to persist with oxygen treatment, for if we can get such obvious signs of the relief of anoxæmia, we can be certain that we are putting the body in a better condition for fighting the infection, though in the end the infection may get the upper hand. We may prolong life and give the patient a chance of pulling through in virtue of his own recuperative powers. If we can prevent the shortage of oxygen from developing it may just make the difference between life and death, though oxygen will not cure the pulmonary lesions, nor is it likely to influence the bacterial infection directly. When you recollect how severely the tissues of the body feel any shortage of oxygen you will see the wisdom of administering oxygen whenever you have reason to believe that cyanosis is dependent on the failure of the blood to get properly oxygenated in the lungs.

I do not, however, want to leave you under the impression that anoxæmia only arises from changes in the lungs which prohibit the free entry of oxygen into the blood. Leaving the question of the poisonous gases used for offensive purposes, let us for a moment turn our attention to the effects produced by two other poisonous gases; the occurrence of which may be regarded as due to accidental causes rather than to the deliberate action of man. The first of these is carbon monoxide. This gas is evolved in large quantities, as you are aware, on the explosion or detonation of explosives. It was met with, therefore, during mining operations owing to the explosion of hostile mines or camouflets, and was responsible for a considerable number of casualties. It penetrated into deep dug-outs when a high explosive shell, with a delay action fuse, burst in the vicinity, and rendered the blow back from guns and machine-guns a source of danger.
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Casualties were sometimes caused by this gas owing to its occurrence in the fumes arising from coke braziers or in the exhaust gases of motor vehicles. Carbon monoxide has in itself no action on the lungs; its poisonous action depends solely on the fact that it can combine with haemoglobin and thus hinder the red corpuscles from fulfilling their proper function as transporters of oxygen, and were it not for this property it would be a purely inert gas so far as the body is concerned.

Carbon monoxide combines with haemoglobin to form a dissociable compound just as does oxygen, but the affinity of carbon monoxide for haemoglobin is roughly 240 times that of oxygen. When blood is exposed to an atmosphere containing both carbon monoxide and oxygen the proportions of carbon monoxide haemoglobin and oxyhaemoglobin which are formed are determined by the laws of mass action, the haemoglobin dividing itself between the two gases according to their relative partial pressures. Thus if blood is saturated outside the body with normal air (20·9 per cent of oxygen), containing 0·085 per cent of carbon monoxide, the haemoglobin will finally become equally divided between the two gases, or fifty per cent saturated with carbon monoxide. If the concentration of carbon monoxide in this air is raised to 0·255 per cent, equilibrium will be reached when the haemoglobin is seventy-five per cent saturated with carbon monoxide; if it is reduced to 0·028 per cent, equilibrium will occur with the haemoglobin twenty-five per cent saturated with carbon monoxide. A similar partition of the haemoglobin in the blood between carbon monoxide and oxygen occurs when a man breathes air containing a small proportion of carbon monoxide, and as the oxygen carrying power of the blood is progressively diminished symptoms of anoxæmia begin to show themselves. Yet reduction of the oxygen carrying power of the blood by saturation of a certain proportion of the haemoglobin with carbon monoxide has a far more severe effect than reduction of the haemoglobin to a similar degree by some form of anæmia, for with partial saturation of the haemoglobin with carbon monoxide the dissociation of any oxygen carried by the haemoglobin is rendered more difficult, the oxygen being in fact liberated in the tissues at far lower partial pressures than would otherwise be the case.

With massive doses loss of consciousness may be rapid, and death may be preceded by convulsions. With more moderate doses the symptoms develop gradually since the gas is only absorbed slowly, and present a typical picture of the effects of progressive and uncomplicated anoxæmia. Loss in power of the limbs, giddiness, confusion of mind, and breathlessness and palpitation on the least exertion are succeeded by apathy and complete helplessness, the failure in the intellectual powers gradually passing into complete unconsciousness which may finally terminate in a painless death. The extent to which the symptoms develop is dependent on the degree of saturation of the haemoglobin with carbon monoxide, which is eventually reached under the mass influence of the carbon monoxide and the oxygen in the air breathed, and on the length of exposure when once equilibrium is attained.

Here again a recognition of the way in which carbon monoxide exerts its effects on the body suggests the proper lines of treatment. As carbon monoxide is a

dissociable compound, the unfettered mass influence of the oxygen in the air begins to expel the gas from its combination with haemoglobin as soon as an atmosphere free from carbon monoxide is reached. This process is slow owing to the high affinity of carbon monoxide for haemoglobin, but in an hour or two the blood will be entirely freed from the gas. The normal alveolar air in the lungs only contains about fourteen per cent of oxygen when ordinary air is breathed, so that the administration of pure oxygen will render the expulsion of carbon monoxide six times as fast. The right procedure is therefore to administer pure oxygen continuously to the patient (taking precautions that the expired air is not rebreathed), when we may expect the whole of the carbon monoxide to be expelled from the haemoglobin, and the normal oxygen carrying power of the blood to be restored after half an hour to an hour. Artificial respiration may sometimes be necessary at first if the breathing threatens to fail, and in any case it is obvious that rest is essential. You should note that in this case we use pure oxygen for a short time with the deliberate object of hastening the expulsion of carbon monoxide from the blood, and that when once the oxygen carrying power of the blood has been rendered normal there is no value in continuing the oxygen administration. The purpose for which the oxygen administration is required is quite different from that which we discussed when dealing with acute pulmonary oedema. In spite of the fact that all the carbon monoxide has been got rid of from the blood the patient may not recover consciousness for a number of hours, and he may even die without regaining consciousness. This gives you some idea of the profound damage which may have resulted in the body during the period of severe anoxæmia, and evidence of a less degree of damage is not infrequently seen in cases that recover in the shape of partial paralysis, mental disturbance or cardiac dilatation.

I want to contrast the grave symptoms of anoxæmia that are seen in carbon monoxide poisoning with the effects produced by another poisonous gas which causes a diminution in the oxygen carrying power of the blood. I refer to the action of arseniuretted hydrogen. This gas is apparently strictly cumulative in its action, the effects produced being practically proportional to the product of the concentration of the gas and the duration of exposure. Thus exposure of animals for about six minutes to one part of arseniuretted hydrogen in 1,000 of air causes death to occur about twenty-four hours later, and the same result ensues after an exposure for twelve hours to a concentration of one part of the gas in 100,000 of air. The gas acts upon the red corpuscles of the blood causing intense haemolysis, and this effect seems to be at the bottom of the symptoms. In slight cases there is only jaundice and anaemia, associated with a feeling of malaise, nausea and pains about the body. In more severe cases there is haemoglobinuria as well as jaundice, and bad secondary anaemia. In bad cases vomiting sets in in an hour or two with intense pain in the back, weakness, fainting and collapse, haemoglobinuria is intense and acute nephritis occurs with casts in the urine. Death seems to be due either to the nephritis, or to the want of oxygen caused by the destruction of the red corpuscles and loss of haemoglobin. The nephritis appears to be largely dependent on the accumulation of haemoglobin or its derivatives in the kidney. Peripheral neuritis is a not uncommon symptom in the later stages of non-fatal cases.

We never encountered this gas during the warfare on land, but a certain
number of cases occurred amongst the crews of submarines, since in certain instances small amounts of arseniuretted hydrogen were formed during the charging of the accumulators, the lead plates of which at times contained traces of arsenic. A good description of these cases has been recently given by Surgeon Lieutenant-Commander Dudley, R.N. The symptoms were moderately severe in some of the cases, but fortunately no fatality occurred. Some of the cases admitted to hospital showed only two million red corpuscles per cubic millimetre with a haemoglobin percentage reduced to half the normal amount. Yet in spite of this symptoms of actual shortage of oxygen were extremely slight. Unusual breathlessness on exertion was probably to be attributed to this cause, and perhaps the headache which was a constant and troublesome feature should also be ascribed to some shortage of oxygen.

A man whose haemoglobin is fifty per cent saturated with carbon monoxide is in a helpless condition—his mental power is profoundly affected; he staggers like a drunken man if he attempts to walk and probably collapses with any exertion—yet a reduction of the haemoglobin by fifty per cent in a case of arseniuretted hydrogen poisoning gives no such evidence of grave deficiency of oxygen. I have already given you a clue to the explanation of these differences. The presence of carbon monoxide profoundly modifies the dissociation of oxygen from the haemoglobin, oxygen being yielded up by the haemoglobin with far greater difficulty than usual as the blood passes through the tissues. There is, however, no such influence when the haemoglobin has been merely reduced in amount in the blood in consequence of the haemolysis caused by the arseniuretted hydrogen. The haemoglobin that is left will pick up oxygen in the lungs and yield it up in the tissues just as it does under normal conditions, and the reduction in the total oxygen carrying power of the blood can be counteracted by an increase in the circulation rate. If, however, the oxygen requirements of the tissues when the body is at rest demand that the blood shall be circulated at a rate considerably above the normal, it is clear that the power to meet any increase in the oxygen requirements must be greatly limited. Hence one finds that muscular exertion demands more of the circulation than it can accomplish, and the failure of compensation is shown by the unusual degree of breathlessness which hinders the subject from doing more than a very moderate degree of muscular work. We should find an analogous state of affairs in any other condition of severe anaemia.

Finally let me quote an instance of anoxæmia which occurred during the war under circumstances quite different from any that I have hitherto mentioned. A grain ship which had been sunk at sea was eventually salvaged and towed into harbour. Some time later a party of men was set to work to clear the hold. At first all went well, though on one or two occasions the men noticed a curious dizziness and weakness of the limbs which passed off quickly if they stopped work for a few moments. One day, however, the working party immediately after descending into the hold was overcome without previous warning by dizziness, loss of power of the arms and legs, and loss of consciousness. It was possible to drag some of the men rapidly from the hold when they quickly recovered, and no symptoms developed later on, though some had headache for a

time, but three men died before they could be rescued. It was possible to exclude carbon monoxide definitely on this occasion, nor was there anything pointing to the fact that the men had been overcome by such a gas as sulphuretted hydrogen which might have been generated in the decomposing cargo. There is little doubt that what really happened was that the men entered unknowingly an atmosphere grossly deficient in oxygen owing to the absorption of oxygen from the air in the hold by the sodden grain. The fact that none of them had noticed any marked breathlessness on entering the hold on the previous days suggests that the reduction of oxygen in the atmosphere was not accompanied on this occasion by any material accumulation of carbon dioxide, though the slight symptoms that they did experience pointed to something being wrong with the air.

I have tried to-day to give you some idea of the different conditions under which we had to face symptoms due to anoxæmia during the war as a result of gas poisoning, and to show you that we have got to reckon with different causes for this anoxæmia. I have dealt with the treatment of these cases only in so far as it is founded on a knowledge of the factors at work and itself helps to explain and emphasize these factors: I had no intention of entering fully into the question of treatment. I want you to appreciate the relative importance of anoxæmia in the different types of casualties, and to see that though under some circumstances acute anoxæmia may constitute the gravest danger that threatens the patient, at other times it forms but a contributory factor in the course of an illness in which perhaps the danger arising from secondary infection or more directly from some further toxic property of the gas occupies the most prominent position. Yet I hope you will agree with me that even in the latter case the alleviation of the prejudicial effects of deficiency of oxygen on the cells of the body may just turn the balance and make the difference between life and death.

Current Literature.

Pneumonia.—Review from Medical Science Abstracts and Reviews, September, 1920, of the Medical Research Council. Zander describes an extensive outbreak of severe pneumonia due to Friedländer's bacillus which occurred in a prison camp between December, 1916 and April, 1917. There were 411 cases with 144 deaths, a mortality of 36 per cent.

Bacteriology. — Spooner has collected the results of the bacteriological examination in 2,950 cases of lobar pneumonia, 1,103 being under his own observation at a U.S.A. base hospital. Twenty-nine per cent were caused by type 1 pneumococcus, 21 per cent by type 2, 11 per cent by type 3, 39 per cent by type 4.

A new method of typing pneumococcus is described by Hirshfeld, Loewe, and Wallach, based on the observations of Rosenow and also of Longcope, that a coagulum is formed if pneumococci are grown in the blood of a pneumonia patient (J. Am. M., Aug., 1919, 73, 170-1). This clotting is thought to be due to the production of acids probably from the glycoproteins of the blood serum. This

1 Frederick (Journal of Hygiene, vol. xix, p. 205, 1920), gives data which shows how rapidly the oxygen may be used up when vegetable matter is stored in ill-ventilated spaces.