THE ABSORPTION AND ELIMINATION OF VOLATILE SUBSTANCES THROUGH THE LUNGS:

ANAESTHESIA, POISONING BY GASES AND VAPOURS
IN INDUSTRY, TREATMENT OF ASPHYXIA.*

BY

YANDELL HENDERSON, PH.D.,
PROFESSOR OF APPLIED PHYSIOLOGY, YALE UNIVERSITY.

THE art of anaesthesia is usually treated as if its scientific basis were distinct and peculiar. In fact, however, the inhalation of volatile substances, gases or vapours with strong pharmacological actions, is not confined to anaesthesia. We have used illuminating gas in our houses, and have inhaled at least its combustion products for two generations past; and now the motor car adds its exhaust gas to the air we inhale in the streets. Petrol is an anaesthetic, although a poor one.¹ The use of gases in war; the increasing pollution of the atmosphere with the gases and vapours of industry; the use of oxygen in the treatment of pneumonia—all of these are subjects which have points in common with inhalational anaesthesia. I propose in this lecture to refer to such collateral subjects, for the sake of the information and experience that can be extracted from them, throwing light on the art of administering a volatile anaesthetic.

The Importance of Volatility.

It is no mere accident that the substances which we use as anaesthetics for surgical purposes are volatile. There are, indeed, non-volatile anaesthetics, solids and liquids. They find use in experimental work on animals when the subject is not to be kept alive. But with the exception of morphine, which is scarcely an anaesthetic, they are not used to any extent upon patients. Why is it that in general the volatile anaesthetics are preferred to those which are non-volatile? The answer is, I think, that for surgical anaesthesia the patient must be very profoundly drugged—more profoundly than in any other condition for which drugs are used; so profoundly, in fact, that death would almost inevitably follow if the condition were continued for many hours. The fact that the substances used as anaesthetics are volatile enables them to be absorbed extremely rapidly up to the high concentration in the blood necessary for an anaesthetic action upon the nervous system. Their volatility also allows a more rapid elimination than is possible for any non-volatile substance.

Volatility, the property of forming a gas or vapour, is a quality of the utmost importance in determining the physiological effects of substances that may gain entrance to the body, or to which the body may be exposed. Volatility renders a substance capable of entering and leaving the body through the lungs. The differences between absorption and elimination through the lungs, on the one hand, and, on the other hand, absorption from the alimentary canal and elimination through the kidneys, are of far-reaching but not generally appreciated significance. There are in chemistry and physics certain much used principles called the gas laws: the laws of Boyle, of Henry, and of Charles. These laws have no direct bearing upon absorption from the stomach or excretion through the kidneys, and little application therefore to solids and liquids. We do not yet know with any degree of precision the laws controlling absorption from the stomach and intestines and excretion through the kidneys. But the gas laws dominate absolutely, in respect to the absorption and elimination of volatile substances through the lungs, and afford the foundation for the toxicology, the pharmacology, and the therapeutics of gases and vapours.

A substance taken in through the lungs may act so much more rapidly and intensely than when taken in through the stomach that it is hard to believe that the cause in the two cases is the same substance. As an illustration let us take lead. Ordinarily, lead poisoning, as seen in painters,

type-setters, and other trades, is a slowly progressing chronic condition affecting the teeth, the alimentary canal, and some voluntary muscles. Recently it was discovered that a compound of lead with some organic groups, in particular tetra-ethyl lead, which is a volatile liquid, has the property of greatly increasing the efficiency of motor-car engines. The addition of only 0.1 per cent. of this substance to gasoline or petrol is sufficient to alter the character of the explosion in the cylinders of the engine, so as to afford a much smoother working and a possibility of greater efficiency. Following up this discovery a combination of the largest industrial concerns in America undertook to manufacture and sell this material. We sanitarians, who are more interested in the welfare of the human machine than in greater efficiency in motor-car engines, protested that an immense industrial and public health hazard would be involved in such a use of lead; and we have succeeded in having the whole matter referred to a commission for study. But the point that I wish to call to your attention is that at nearly every stage of the development, manufacture, and distribution of this substance there were outbreaks of poisoning. The symptoms of poisoning by this volatile lead compound were, however, quite unlike ordinary lead poisoning. Even physicians with the widest experience in industrial diseases were at first inclined to deny that the fatalities were essentially due to lead. The sequence of symptoms was usually insomnia, visual delusions, and violent mania, soon leading to death. Encephalitis and mania are, indeed, described in the literature, but are seldom seen, as the result of the swallowing of lead. The inhalation of lead dust usually induces the slow form of poisoning. But when lead in a truly volatile form is inhaled the effect is acute, and is primarily upon the brain.²

These facts illustrate the difference between the effects of the absorption of lead or any other substance from the alimentary canal, and absorption from the lungs. It is scarcely possible, or at least exceedingly rare, for absorption from the stomach to be so rapid as to produce simultaneously the same concentration or pressure of a soluble substance in the stomach, in the arterial blood, and in the brain. But we have learned that with a large number of volatile substances the natural and usual relation is that the pressure and concentration of the substance in the lungs instantly produce the same pressure and a corresponding concentration of the substance in the arterial blood, and almost immediately the same pressure and concentration of the substance in the brain. Absorption from the lungs is not only more rapid than from the stomach, but more rapid than from subcutaneous injection, and practically more rapid even than from intravenous infusion.

As regards the elimination of any substance, the lungs are incomparably the most rapid channel. A substance which, even with the aid of diuresis, will be excreted through the kidneys only in the course of days, may be excreted through the lungs within a few hours. The lungs should, therefore, be used for the therapeutic elimination of all harmful substances that are volatile. The method of increasing the volume of breathing so as to obtain a maximal pulmonary ventilation for such therapeutic purposes was described in my previous lecture.

If a further illustration is needed, it is afforded by a comparison of ethyl ether with ethyl alcohol, the latter in the form of Scotch whisky. The pharmacological actions of ethyl alcohol and ethyl ether upon nerve tissue are fundamentally almost the same. But how different are the common uses of the two liquids! How different are the commonly observed effects upon the users induced by the two substances! Alcohol is indeed capable of being burned to some extent in the body; ether is not. But fundamentally it is not this property that produces the differences between the symptoms, the intensity, and the duration of alcoholic drunkenness and ether anaesthesia. Essentially the differences in the two conditions are due to the facts (1) that ether is far more volatile than alcohol, (2) that alcohol is far more soluble in blood than ether, and is therefore less rapidly ventilated out of the blood in the lungs, and (3) that it is customary to take alcohol in liquid form into the stomach, while ether is taken in vapour through the lungs

* The second of two lectures under the auspices of the Dental Board of the United Kingdom, delivered at the Royal Society of Medicine, London, October 23rd, 1925. The first lecture was published in the JOURNAL for December 19th, 1925 (p. 1170).

Applications of the Gas Laws.

Recently Haggard and I³ have formulated the applications of the gas laws in this field. We have confirmed and amplified the conclusion reached by Cushny.¹⁴ Without attempting to go too much into detail I may here give you a summary of the principles at which we have arrived and which control the absorption, distribution, and elimination of what we may call non-reacting gases. By a non-reacting gas we mean one which is taken up, held, and given off again by the blood and tissue fluids of the body in simple solution, which undergoes no alteration in the body, but is both absorbed and eliminated simply by diffusion from and into the air of the lungs and into the urine. It may or may not have pharmacological action. Examples of such gases are nitrogen, methane, and ethyl ether. The first has been studied by Haldane, Boycott, and Damant,⁴ in relation to caisson disease, the compressed-air illness of deep-sea divers. Ether has recently been investigated from this standpoint by Haggard. The absorption and elimination of such gases depend upon four main factors.

1. The rate at which a gas is absorbed into the body and the amount the body can hold vary greatly according as the gas is more or less soluble. In general, the solubility of a gas in blood is only slightly less than its solubility in water. Its solubility at the temperature of the air in the lungs determines its behaviour. The capacity of the various tissues to dissolve gases varies widely; it is low in bone and often very high in fat; but with most gases the average for the body as a whole is probably nearly the same as the solubility in blood. This, at least, is true of ether, as Haggard has found. The total amount of any gas that the body will take up is dependent both upon its solubility and upon the concentration in the air breathed.

2. The rate of absorption is directly proportional to the concentration of the gas or vapour in the air breathed. The concentration in the air is generally best expressed in milligrams of the substance per litre of air. The concentration that is effective is, however, not exactly the concentration in the air of the room; it is the concentration when the air is warmed to body temperature and saturated with moisture. It is the somewhat reduced concentration under these conditions, as they obtain in the lungs, which induces diffusion into the blood passing through the lungs. At the saturation point the total amount of the gas in the body is directly proportional to the concentration in the atmosphere, with which the blood and body as a whole have come into equilibrium. From twice as high a concentration the body will absorb twice as much of the gas.

3. The third factor determining the rate of absorption is the pulmonary ventilation. It depends upon the volume of air breathed, and the amount of the gas thus brought into contact with the blood in the lungs, but not that which merely enters the dead space. As we shall see, respiration is particularly important in respect both to absorption and elimination in the case of quite soluble gases and vapours, such as ethyl ether; but it is comparatively unimportant in respect to relatively insoluble gases, such as nitrogen.

4. The circulation is the fourth factor, and is largely determinative of the rate of absorption and elimination of gases of relatively low solubility, while for such gases respiration plays a comparatively small part. Thus a condition which would double the volume of air breathed per minute would only slightly affect the entrance or exit of such a gas, so long as the circulation remains constant. But if the circulation were doubled, so that twice as much blood would flow through the lungs each minute, even with respiration unchanged, the rate of absorption and elimination of such a gas would be nearly doubled.

For the various factors concerned in these processes and conditions we use the following symbols:

L = Effective pulmonary ventilation in litres per minute—that is, respiration *minus* the volume of air which merely enters the dead space.

C = Concentration of the gas in milligrams per litre of inspired air, when warmed to body temperature and saturated with moisture as it is in the lungs.

K = Coefficient of distribution of the gas between equal volumes of lung air and pulmonary blood. For ordinary conditions complete and instantaneous equilibrium between arterial blood and lung air may be safely assumed. Thus, if for a certain gas such as the

vapour of ethyl ether K is 15, this figure means that there is always in the blood leaving the lungs, and in the arterial blood, 15 times as much of that gas in one litre of blood as in one litre of alveolar air; and that this holds true alike during absorption, equilibrium, and elimination of the gas.

G = The volume of blood, expressed in litres or kilos, in active circulation in the body—in other words, the effective blood volume at the time.

B = Circulation, defined as the number of litres or kilos of blood flowing through the lungs in one minute.

A_c = Concentration of the gas in the arterial blood in milligrams per litre.

V_c = Concentration of the gas in the mixed venous blood in the right heart in milligrams per litre.

W = Body weight in kilos.

Using these symbols we derive the following expressions:

(1) LC = the amount of the gas inhaled into the lungs per minute.

(2) $LC \times \frac{L}{BK + L}$ = amount of the gas again exhaled from the lungs per minute.

(3) $LC \times \frac{BK}{BK + L}$ = amount of the gas absorbed per minute into the blood, before any of the blood completes the round of the circulation, and returns to the lungs from the venous side—that is, the initial rate of absorption.

(4) $\frac{LCK}{BK + L}$ = amount of gas in milligrams absorbed per litre of blood flowing through the lungs.

(5) $\frac{LCKG}{BK + L}$ = amount of gas absorbed during the first complete circulation of the blood, which is accomplished in the time $\frac{G}{B}$, a period less than one minute even during bodily rest.

(6) $\frac{LCKG}{BK + L} \times \frac{G}{W}$ = amount of the gas brought back to the lungs by the venous blood during the second round of the circulation.

The amount of the gas which the blood brings back to the lungs from the venous side is added to that which the breathing takes into the lungs, and the sum of the two quantities is distributed between the arterial blood and the expired air in accord with their relative volumes and with the coefficient of solubility. The distribution is always in the ratio $BK : L$.

These expressions signify that during absorption the arterial blood contains at first far more of the gas or vapour than the venous blood. But as the inhalation of a constant concentration of a gas in the air continues, the concentrations in the arterial and venous blood gradually approach the same value—namely, that of saturation for the concentration of the gas in the air. At all times the mixed venous blood flowing back from the body contains an amount of the gas per litre which is the same as the average concentration in the body as a whole at the moment (in milligrams of the gas per kilo of body weight). During absorption, therefore, especially in the earlier stages, the concentration in the venous blood is far below that in the arterial blood. During elimination, on the contrary, the venous blood has a concentration which is the average of the concentration in the body as a whole, while that of the arterial blood is lower than the venous by the fraction thrown off in the breath. Thus

(7) $V_c \left(1 - \frac{L}{BK + L}\right) = A_c$, the arterial concentration during elimination.

The amount of any gas that the body will hold is defined by the expression:

(8) CKW = amount of gas in the body at equilibrium with C in the air.

Evidently the maximum amount of a gas that can be absorbed is not a fixed absolute quantity, but is proportional to the concentration of that particular gas in the air. When respiration and circulation remain uniform and normal, the rate of absorption is such that, if a certain percentage of saturation is taken up in one minute, the same percentage of the remaining unsaturation will be absorbed in the second minute, and so on thereafter. Thus if saturation be taken as 100 and if 1 per cent. of this amount is absorbed in one minute, 1 per cent. of 99 will be absorbed in the second minute; and 1 per cent. of 98.01 in the third minute, and so on. The absorption is thus comparatively rapid at

first, then slower, and finally infinitely slow. It is not practical, therefore, to determine the time when equilibrium of intake and elimination will be reached, but it is often convenient for purposes of calculation to use the time required to reach 50 per cent. saturation, $\frac{CKW}{2}$, or some other percentage of saturation.

If we let t_x represent the time required to reach the percentage of saturation x , we may calculate this time in minutes by means of the expression

$$(9) \quad t_x = \frac{2.3 \times W(BK + L)}{LB} \log \frac{1}{1-x}.$$

The use of the half-saturation time, or the time of any definite percentage of saturation, is particularly convenient because it is the same for all concentrations of any one gas, so long as respiration and circulation are uniform. But the greater the solubility of a gas, the longer is the time required to reach half-saturation, and the greater the absolute amount constituting half-saturation.

For an average human adult at rest with normal volume of respiration and circulation, the time of half-saturation for a gas or vapour of $K=15$, such as ethyl ether, is about two and a half hours, while for one of $K=0.014$, nitrogen, it is about seven minutes, and for 90 per cent. of saturation about twenty-two minutes. For a child, owing to the more active metabolism and greater relative volume of breathing and circulation in relation to body weight, the time required to reach half-saturation, or any other definite percentage, is correspondingly less. The same relation holds true in an adult when respiration and circulation are increased by exercise, or by the pharmacological action of the gas itself, or in any other way.

The absorption of any absolute amount of gas—for example, the anaesthetic amount of ether—is effected very slowly when a low concentration of the gas is inhaled, but with a far more than proportional rapidity when the concentration in the air is high. The rates of absorption are not expressed by straight lines, but by exponential curves, which rise rapidly at first and then more and more slowly. In the absorption curves of all concentrations of a given gas points having equal abscissae have ordinates which are proportional to the concentrations. An absolute amount in millilitres may therefore be only a relatively low percentage of the saturation limit (CKW) of a high concentration, but a high percentage of the limit, or even exceed the limit, for a low concentration.

The influence of respiration, circulation, and the solubility of the gas upon the time required to reach 50, or any other, per cent. of saturation is expressed by the formula:

$$(10) \quad \frac{t_x}{t'_x} = \frac{\frac{BK + L}{LB}}{\frac{B'K' + L'}{L'B'}}.$$

Using this formula and substituting various values of K , so as to see the effect that solubility has, not only on the rate of absorption but also on the parts played by respiration and the circulation in effecting absorption, we reach results of great utility. Thus with a gas of a solubility as low as 0.01, even a doubling of the respiration scarcely affects the rate of absorption or of elimination, while a doubling of the circulation of the blood induces a nearly proportional increase of the rate of absorption and elimination. On the other hand, with a gas of solubility 10, alterations of the circulation of the blood have an entirely negligible effect, while the rates of absorption and elimination rise and fall almost in proportion to the volume of respiration. This is shown in the following table.

	B=B'=1.		L=L'=1.	
	L=1.	L'=2.	B=1.	B'=2.
$K=0.01$	$\frac{1.01}{1}$	$\frac{2.01}{2}$	$\frac{1.01}{1}$	$\frac{1.02}{2}$
$K'=10.0$	$\frac{11}{1}$	$\frac{6}{1}$	$\frac{11}{1}$	$\frac{21}{2}$

Irritant Gases.

From the standpoint of a physician interested in industrial diseases, and from the standpoint of the use of gases in war, the irritant gases have a peculiar importance. For us, in connexion with the topic of this lecture, irritation of the lungs is chiefly of interest because it occasionally follows ether anaesthesia. Ether vapour in high concentration is well known to be an irritant. If, then, sufficiently large amounts of ether are to be introduced into the lungs without resorting to very high concentrations in the inhaled air, there is obviously only one way to effect the purpose. This is by increasing the volume of air breathed by means of an inhalation of carbon dioxide as a preliminary to the initiation of anaesthesia.

The laws of absorption which we have just now considered teach us that if the ventilation of the lungs is increased to twice its ordinary amount, and the concentration of the inspired ether vapour is reduced to one-half, we may induce the absorption of the same amount of ether as is effected by a small volume of breathing and a high concentration of the vapour in the inspired air. The first combination avoids the irritant action of ether on the lungs, the second subjects the patient to it.

In general the effects of the irritant vapours follow a law worked out in my laboratory by Haggard.⁵ This law is that the more soluble the gas the more it attacks the upper respiratory tract; the less soluble it is the more liable it is to act chiefly upon the deeper parts—the bronchi and the lungs. The more soluble substances, such as ammonia, are largely absorbed on the damp walls of the nares, pharynx, larynx, and trachea. They also excite the respiratory reflexes of coughing and closure of the glottis; and the lungs are thus protected. With substances such as phosgene and the higher oxides of nitrogen the comparatively slight solubility and relatively slight immediate irritation allow the chief action to be effected in the lungs themselves. So the patient may feel quite well for some hours afterward, and then develop an acute pulmonary oedema and die on the slightest exertion.

The nature of pulmonary congestion and oedema is still obscure, and the causal connexion of anaesthesia and post-operative pneumonia is not wholly clear. I suspect that if the lungs of patients were regularly examined every few hours for a day or two after anaesthesia, râles and other indications of irritation would be found in a considerable proportion of cases, even among those who fortunately recover without developing pneumonia. It is well recognized, as the result of observations on gassed soldiers during the war, that asphyxia is a consequence of the congestion and oedema of the lungs induced by irritant gases. It is not generally realized that the opposite relation is also possible, and that asphyxia, even partial asphyxia, may induce severe pulmonary effects, even when the gas causing the asphyxia has in itself no direct irritant action whatever. Thus it was found by David⁶ that mere oxygen deprivation by excess of nitrogen may induce pulmonary congestion in animals. We have found that in dogs slowly asphyxiated with carbon monoxide the congestion of the lungs may be so acute that a lobe of lung is scarcely distinguishable at first glance in its density and colour from a lobe of the liver, so intense is the congestion. Yet it is absolutely certain that carbon monoxide is entirely devoid of direct irritant action.

Of course, pneumonia following anaesthesia is a bacterial infection; but without a predisposing disturbance of physiological conditions the lungs would resist the invasion and infection. We cannot assign with certainty the relative importance of such factors as the chill induced by ether, when volatilized on an open mask, the irritation induced by highly concentrated ether vapour in the lungs, the anoxaemia and acapnia, and the slow emergence from coma, all characteristic of a vast number of anaesthetics. But this aspect of the matter I would emphasize: that all of these hazards may be eliminated together by the procedures described in my previous lecture.

Carbon Monoxide Asphyxia.

I cannot urge too strongly that the study of anaesthesia, at least with volatile anaesthetics, is merely a branch of

a larger subject—that of gases and vapours in their physiology, toxicology, therapeutics, and industrial and sanitary aspects. Sanitary science has a vast fund of knowledge regarding foods, water supplies, and corresponding subjects; and this knowledge is now extensively applied. But it is only recently that pollution of the air that we breathe has begun to receive adequate consideration. My reason for directing attention to this matter now is that all phases of the physiology of gases are mutually contributory. Anyone interested in the volatile anaesthetics will profit by including some acquaintance with the industrial gases. So I propose to devote the remainder of this lecture to certain aspects of carbon monoxide as it now affects the lives of all civilized men.

It is well established that the number of deaths each year in any city due to its illuminating gas rises in direct proportion, or even in more than direct proportion, to the amount of carbon monoxide in the gas. In those cities where coal gas of low carbon monoxide content is supplied asphyxiations are few. In New York City at the other end of the scale, where the gas contains nearly 30 per cent. of carbon monoxide, the number of deaths from carbon monoxide asphyxiation runs up toward 500 a year. A part, but only a part, of this mortality is suicide; the despondent New Yorker turns on the gas, just as a despondent Londoner jumps into the Thames.

In recent years the automobile has enormously increased our exposure to carbon monoxide. But knowledge has been accumulated now which we may at least hope will provide the basis for much needed reform. In America tunnels are being introduced, particularly in New York, where the Hudson River is nearly three-quarters of a mile wide; too wide for bridges and inconvenient for ferries. The ventilation of such a tube, with a double line of vehicles moving through it, raised special problems. The chemical aspects of these problems were referred to Mr. A. C. Fieldner⁷ of the United States Bureau of Mines, while the physiological aspects were referred to me for investigation. Mr. Fieldner and I, and our co-workers, developed a standard for tunnel ventilation, which has been adopted, not only in America but also in England, on the advice of Dr. J. S. Haldane, for the tunnel to be constructed under the Mersey River at Liverpool. Experience in a similar tunnel at Pittsburgh, Pa., has now demonstrated the safety of this standard, and the danger (before ventilation was installed) in failing to maintain it.

FIG. 1.—Showing the relation of carburettor adjustment in the ratio of air to gasoline (petrol) to efficiency, power, combustion of fuel, and amounts of carbon dioxide and carbon monoxide produced in an automobile engine.

The sum and substance of Fieldner's very extensive tests on a large number of passenger cars and trucks are summarized in Fig. 1. It shows at a glance the general behaviour of the motors now used in automobiles and the extent to which the fuel is consumed. Roughly, in any one car, the distance travelled, the number of strokes of the engine, and the amount of air drawn into and discharged from the cylinders are proportional quantities. So

the greater the amount of fuel in proportion to air—that is, the richer the mixture to which the carburettor is set—the greater the fuel consumption per mile and the less the efficiency. Unfortunately the richer mixtures afford greater power, especially for starting and hill climbing; and carburettors are usually set to deliver a pound of fuel for each 12 lb. of air. If the manufacturers and the owners of motor cars were truly interested in saving fuel the engines could be adjusted to an efficiency requiring only 1 lb. of fuel to each 15 lb. of air. The saving of fuel would amount to 20 or even 30 per cent.

FIG. 2.—Showing the carbon monoxide dissociation curve of blood (solid line) and the percentage saturation after one hour in various concentrations of the gas (broken line).

We might leave this whole matter to engineers for solution, except for the fact that it also involves a health hazard which is reaching serious proportions. With a full supply of air the combustion in an explosion engine may be nearly complete; its products in that case are carbon dioxide and water vapour. With the excessively rich mixtures habitually employed the combustion is, on the contrary, extremely incomplete; one-third of the fuel value is unconsumed. Thus, as shown by the straight lines which cross in the figure, the proportion of carbon dioxide decreases rapidly and that of carbon monoxide increases rapidly with the richness of the mixture. As we see in the figure, exhaust gas usually contains about 6 per cent. of carbon monoxide, an amount which, if discharged in any quantity into a confined space, is intensely poisonous. It is not merely this concentration, but rather the absolute amount of carbon monoxide that is important. The amount is approximately 1 cubic foot per minute for each 20 horse-power. This means that from even the smallest car commonly used in America there is enough carbon monoxide to render the atmosphere of a small closed garage of 10 by 10 by 20 feet deadly in less than ten minutes. As is well known, the victims of carbon monoxide poisoning often lose the power to stand or walk before any other symptom warns them of their danger. Neglect to open the garage doors before starting a car is thus an increasingly common cause of death in spite of extensive public warnings.

In the physiological part of the investigations we first studied in detail the fundamental matter of the combination which carbon monoxide makes with the haemoglobin of the blood and the general nature of carbon monoxide asphyxia. Our observations verified in every detail the fundamental work of Haldane. We then proceeded to determine the rate at which men and women exposed to atmospheres contaminated with exhaust gas will absorb carbon monoxide, and the physiological effects of various amounts for periods of one hour.⁸

The results of these investigations are expressed graphically in Fig. 2. Here the upper curve is the well known theoretical dissociation curve of carbon monoxide and haemoglobin in the presence of air; the lower curve expresses very practical information as to the approximate percentage of saturation that a man will develop in one hour, if he is sitting still in an atmosphere containing the amount of carbon monoxide shown in the scale below the abscissa. This curve and the scale are drawn for a normal volume of breathing. If respiration were doubled these percentages of saturation would be attained in half an hour,

and the curve would therefore represent the percentages of saturation attained in this time by a man breathing air containing the amounts of carbon monoxide indicated.

On this basis I recommended 0.04 per cent., or 4 parts of carbon monoxide in 10,000 of air, as the maximum concentration allowable in air to be breathed for such a period as that required to pass through the Hudson River tunnel, a period probably of a quarter to half an hour. As this standard has been very widely adopted, it is important that I should emphasize the fact that it applies only to quite short periods of time. Any standard for the contamination of air with carbon monoxide must specify, not only the amount of carbon monoxide, but also the time of exposure. Thus the full sanitary rule which we developed is as follows: When the time of exposure is measured in hours and the concentration is measured in parts of carbon monoxide per 10,000 of air, then if the product of the time multiplied by the concentration equals 3, no perceptible physiological effect results. If the product equals 6, there is a just perceptible effect, perhaps a slight headache and lassitude; if it equals 9, severe headache and nausea result; if it equals 15 the condition is dangerous; if it rises above 15, the conditions are such as will be quickly fatal. If the subject is making any muscular exertion and his breathing is increased, the figures for the products of time and concentration that are comfortable and safe are reduced from 3 to 2, or 1, or even less; for the rate of absorption varies directly with the volume of the breathing.

Conditions in Streets and Garages.

With this rule in mind we proceeded to determine the extent of the contamination of the air in the streets of New York City, where traffic is congested.⁹ The general results of our investigations show that concentrations of 1 part of carbon monoxide in 10,000 of air are rather common, and indicate that the conditions in crowded streets are on the verge of being definitely injurious for persons who are exposed in them for many hours. In garages the conditions are often far up in the scale of unhealthiness, and headaches are common.¹⁰ The conditions in assembling and repair shops are much worse; indeed, they are so bad that the mechanics have severe asphyxial headaches, often accompanied by nausea and extreme unreasonableness of temper, several times each week. Altogether the automobile trade in America is one of the most unhealthy in modern industry.

To a considerable extent these conditions are unnecessary. The carburettors and engines of cars could be adjusted so as to conserve fuel and decrease the amount of carbon monoxide produced. While Governments are gravely considering the world's dwindling supply of petroleum, the manufacturers of cars have as yet done little to help in overcoming the serious health hazard involved in the wasteful consumption and incomplete combustion of petroleum products. It is, indeed, surprising that when all automotive engineers know that a slight change and a negligible increase of cost would effect such great improvements, conditions are allowed to continue as wasteful and as unhealthy as they are in America now. Owing to the general use of less highly powered cars here in Great Britain conditions seem to be distinctly better. In my opinion, the high tax here of £1 per year per rated horsepower is a measure of distinct sanitary advantage.

Pending more fundamental improvements, there is a device by which the air in streets, and especially the conditions in garages and repair shops, could be greatly improved. This device is the so-called vertical exhaust. It involves merely a continuation of the exhaust pipe vertically upward at the back of the car so as to discharge the exhaust gases upward out of the level at which we inhale air through our noses and mouths. A vertical exhaust pipe is in effect merely a chimney. To discharge exhaust gas below a car in the manner now customary has the same disadvantage that would be produced if all stoves and furnaces were vented through basement windows. It is just as important to employ the ancient device of the chimney upon motor cars as it is upon locomotives and other engines. Although exhaust gas is a relatively colourless form of smoke, its constituents are actually more toxic

than are those of most of the smoke produced from the burning of coal. I believe that, with the increasing use of cars, vertical exhaust will ultimately be required, at least on all city taxicabs and omnibuses.

The Elimination of Carbon Monoxide from the Blood.

Finally, I wish to return for a few minutes to a topic to which I referred also in my previous lecture: the treatment of acute carbon monoxide poisoning. Within a few hours after profound but not fatal poisoning with carbon monoxide no trace of the gas is found in the blood. It has been eliminated through a reversal of the process through which it was absorbed. And yet for days, months, and even for life, structural degenerations and functional derangements, usually either nervous or cardiac, may continue. They are the sequelae of the injury wrought by oxygen deficiency and its concomitants, while the gas was still in the victim's blood.

The investigations to which I have already referred drew our attention to the question of the rate at which the gas is eliminated. Haggard and I¹¹ thus came upon a point which had previously been overlooked and which suggested the therapy—perhaps it should rather be called a prophylaxis—which has come into extensive use. We had previously determined the rate of elimination of carbon monoxide in men who had reached saturations of 20 or 30 per cent. Haldane has recorded the rate of elimination after saturations of 40 or even 50 per cent. His data and ours both indicate an elimination during the first hour of about one-half the amount of carbon monoxide previously absorbed. No one, however, had studied the rate at which carbon monoxide is eliminated during the first hour or two after a gassing which has produced a saturation of the blood of considerably more than 50 per cent. with coma and its accompaniments. There is a fundamental difference between the behaviour of subjects gassed to the point of coma and that of those in whom the saturation does not exceed 50 per cent., and the duration of exposure is not prolonged. Under the latter conditions the subjects breathe practically normal volumes of air, and their metabolism at most is only slightly perverted.

Our observations on subjects more profoundly poisoned soon showed that when the degree of saturation of the blood rises to figures above 50 per cent. and definite asphyxia is threatened, there is excessive breathing which markedly reduces the body's store of carbon dioxide. We found that when the victim is afterwards removed from the poisonous atmosphere the breathing, lacking its normal stimulus, remains at a very low level for an hour or more. The body lacks the carbon dioxide needed to maintain an efficient ventilation of the lungs. The elimination of carbon monoxide during this time is therefore very slight. Although the body is surrounded by fresh air the asphyxiation continues within the tissues. Even the administration of oxygen has no great effect, for it is not adequately inhaled. Until a sufficient amount of carbon dioxide is reaccumulated in the blood and tissues efficient breathing does not return, and the injurious conditions within the living cells of the nervous system and heart are thus continued long after the body is surrounded by pure air. When, as in our experiments, the period of gassing is brief but acute, most of the asphyxia, during which the harm is wrought, probably occurs after the subject is removed from the poisonous atmosphere. It is largely during this time that the autolytic and necrotic processes are so intensified as to be thereafter irreversible. Evidently the abbreviation of the post-gassing period of depressed breathing and its continued asphyxia are of critical importance in preventing permanent damage.

Dogs were used in our experiments. They were placed in a glass-walled gassing chamber through which was passed a current of air and enough city illuminating gas to produce a concentration of 0.3 to 0.4 per cent. of carbon monoxide. Up to the point of unconsciousness the picture presented by the subjects resembled closely that of slow anaesthesia with ether. At first the animals were restless, then a stage of excitement set in, followed by muscular weakness. Respiration became more and more vigorous, culminating as coma developed in violent and prolonged hyperpnoea.

After five or ten minutes of unconsciousness the animals were removed from the gassing chamber, and at frequent intervals thereafter for a couple of hours small samples of blood were taken and analysed for carbon monoxide. The experiments fall into four groups: (1) those in which the subjects were allowed to recover spontaneously; (2) those in which they were made to inhale oxygen; (3) those in which they were made to inhale air to which 8 to 10 per cent. of carbon dioxide had been added; (4) those in which they were made to inhale oxygen containing 8 to 10 per cent. of carbon dioxide.

The results of these four groups of experiments are shown by the curves in Fig. 3. It is here seen that animals left

FIG. 3.—Showing the rate of elimination of carbon monoxide from the blood in dogs, (a) untreated, (b) under inhalation of oxygen, (c) air and CO₂, (d) oxygen and CO₂.

to recover spontaneously have a very slow rate of elimination during the first half or three-quarters of an hour. In those treated with oxygen the elimination is at first scarcely more rapid, for the animals do not breathe any better; indeed, in some cases they breathe even less when oxygen is administered than when they are left to recover spontaneously. Such slight benefit as pure oxygen affords is seen in the greater rapidity of elimination in the latter part of the first hour, or the first part of the second hour. With inhalation of air and carbon dioxide, as in the third group of experiments, the curve starts downward immediately and falls in a practically straight line. This is due to the increased respiration, which provides sufficient fresh air to start the elimination of carbon monoxide immediately. Finally, the fourth curve shows that under inhalation of oxygen containing carbon dioxide the blood of the subjects was practically freed from carbon monoxide within twenty minutes. The augmented breathing and high concentration of oxygen together rapidly displace carbon monoxide from the blood.

Later we were able to follow essentially the same sequence of events in the human victims of gas poisoning.¹² Both the hyperpnoea during gassing and the depression of respiration after removal from the poisonous atmosphere were verified. The slow elimination during the first hour or two has been verified in patients who received no inhalation, while, on the contrary, rapid elimination was found in all cases where a mixture of oxygen and carbon dioxide was administered. The mixture generally employed is 5 per cent. carbon dioxide and 95 per cent. oxygen. This treatment has now saved a large number of lives, and has come into very general use in America. In two respects its benefits have exceeded even our hopes. It seems to prevent the subsequent development of pneumonia, a fact which is probably due to the overcoming of the initial pulmonary congestion. The treatment has also proved capable of effecting complete restoration without subsequent nervous sequelae even in patients gassed for considerable periods. Its most brilliant successes, however, have followed applications to men who have been gassed acutely but for short periods of time, as in the case of workmen exposed to the

fumes from blast furnaces, or those overcome by illuminating gas while working in a sewer or a trench in the streets, or men in the city fire brigade, who, as they say, have been "eating smoke" while fighting a fire. In such cases the subject may have been not only unconscious, but so nearly dead that artificial respiration was necessary at the beginning of the inhalation, and yet after fifteen or twenty minutes' inhalation he is in many cases not only conscious and breathing naturally, but able to get on his feet and go back to work.

In preparing for the treatment of poisoning by the various gases and vapours of modern industry the question sometimes arises whether to provide cylinders containing the mixture of oxygen and carbon dioxide, or merely carbon dioxide to be mixed with air as it is wanted. For all those volatile poisons which cause the blood to be deficient in oxygen, inhalation of oxygen and carbon dioxide is superior to air and carbon dioxide. But the intoxications which cause no oxygen deficiency can be treated with air and carbon dioxide quite as effectively as with oxygen alone, as in the past. Even for treating asphyxial cases in some industries here in Great Britain, air and carbon dioxide probably offer some important practical advantages over oxygen and carbon dioxide.¹⁵ Carbon dioxide is relatively cheap, and the supply of one cylinder lasts much longer than a cylinder of oxygen and carbon dioxide. For the many non-asphyxiant volatile toxic substances to which modern man exposes himself (for example, various alcohols, petroleum products, benzole, etc.) air and carbon dioxide are the logical and effective antidote. The aim is to stimulate the breathing of the patient, and to maintain it for an hour or more at such a large volume as will ventilate the poison out of the blood by way of the lungs, and thus clear the body and especially the brain. Oxygen does not stimulate respiration; carbon dioxide does.

REFERENCES.

- ¹ Haggard, H. W.: *Journ. Pharm. and Exper. Therap.*, 1920, xvi, p. 401.
- ² Hamilton, Reznikoff, and Burnham: *Journ. Amer. Med. Assoc.*, May, 1925, p. 1481.
- ³ Henderson and Haggard: *Amer. Journ. Physiol.*, June, 1925, p. 194.
- ⁴ Haldane, Boycott, and Damant: *Journ. Hygiene*, 1908, vol. viii, p. 342.
- ⁵ Haggard: *Journ. Indust. Hygiene*, 1924, vol. v, p. 390.
- ⁶ David, O.: *Zeit. f. klin. Med.*, 1912, vol. 74, p. 404.
- ⁷ Fieldner, Straub, and Jones: *Journ. Indust. and Engin. Chem.*, 1921, vol. 13, p. 55.
- ⁸ Henderson, Haggard, Teague, Prince, and Wunderlich: *Journ. Indust. Hygiene*, 1921, vol. iii, pp. 79-92 and 137-146; also *Journ. Indust. and Engin. Chem.*, 1922, vol. 16, p. 229.
- ⁹ Henderson and Haggard: *Journ. Amer. Med. Assoc.*, 1923, vol. 81, p. 385.
- ¹⁰ Ciampolini: New York State Department of Labor Bulletin, 1924.
- ¹¹ Henderson and Haggard: *Journ. Pharm. and Exper. Therap.*, 1920, vol. xvi, p. 11.
- ¹² *Ibid.*: *Journ. Amer. Med. Assoc.*, 1922, vol. 79, p. 1137.
- ¹³ Henderson, Y.: *Ibid.*, September, 1924, p. 758; also Drinker, C. K.: *Journ. Indust. Hygiene*, 1925.
- ¹⁴ Cushman, A. R.: *Journ. Physiol.*, 1910, vol. xl, p. 17.
- ¹⁵ Haldane, J. S.: *Trans. Inst. Mining Engin.*, 1925, lxxviii, p. 271.

CHANGE OF TENSION ON THE LENS CAPSULES DURING ACCOMMODATION AND UNDER THE INFLUENCE OF VARIOUS DRUGS.*

BY

BASIL GRAVES,

SURGEON, ST. PAUL'S EYE HOSPITAL, LIVERPOOL; TEMPORARILY, POST-GRADUATE CLINICAL LECTURER, DEPARTMENT OF OPHTHALMOLOGY, BELLEVUE HOSPITAL, NEW YORK UNIVERSITY, ETC.

A PATIENT came in 1924 wearing glasses for his one sound eye. I questioned him about the other eye which does not, unaided, possess useful sight; no evidence of the presence of a lens can, by ordinary methods of examination, be seen in this eye which has absolutely clear media and normal (6/5) vision with a *plus* 14 lens. The slit-lamp reveals the following features: A tiny scar-track (C, Fig. 1) through the cornea; at the bottom of the anterior chamber a tiny brown spherical object (X) which is doubtless an encapsulated or partially disintegrated minute foreign body; a minute prick (K) in the pigment-layer of the iris at the pupil-margin opposite the corneal scar; and finally, opposite this, a small rather oval hole (a) in an absolutely clear and otherwise intact anterior lens-capsule (A). The posterior lens-capsule (P) is equally clear and wholly intact. No vestige of lens-matter remains between these two clear and thin capsules: it has all dissolved out with a completeness

* Read by invitation on May 5th, 1925, before the sixty-first annual meeting of the American Ophthalmological Society, Washington, D.C.