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NOXIOUS GASES

and the

PRINCIPLES OF RESPIRATION
INFLUENCING THEIR ACTION

Second and Revised Edition

by

YANDELL HENDERSON

and

HOWARD W. HAGGARD

FROM THE LABORATORY OF APPLIED PHYSIOLOGY
YALE UNIVERSITY

American Chemical Society
Monograph Series

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GENERAL INTRODUCTION

American Chemical Society Series of Scientific and Technologic Monographs

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic monographs on chemical subjects. At the same time it was agreed that the National Research Council, in coöperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical development. The American Chemical Society named as Trustees, to make the necessary arrangements for the publication of the monographs, Charles L. Parsons, secretary of the society, Washington, D. C.; the late John E. Teeple, then treasurer of the society, New York; and Professor Gellert Alleman of Swarthmore College. The Trustees arranged for the publication of the A. C. S. series of (a) Scientific and (b) Technologic Monographs by the Chemical Catalog Company, Inc. (Reinhold Publishing Corporation, successors) of New York.

The Council, acting through the Committee on National Policy of the American Chemical Society, appointed editors (the present list of whom appears at the close of this introduction) to have charge of securing authors, and of considering critically the manuscripts submitted. The editors endeavor to select topics of current interest, and authors recognized as authorities in their respective fields.

The development of knowledge in all branches of science, especially in chemistry, has been so rapid during the last fifty years, and the fields covered by this development so varied that it is difficult for any individual to keep in touch with progress in branches of science outside his own specialty. In spite of the facilities for the examination of the literature given by Chemical Abstracts and by such compendia as Beilstein's Handbuch der Organischen Chemie, Richter's Lexikon, Ostwald's Lehrbuch der Allgemeinen Chemie, Abegg's and Gmelin-Kraut's Handbuch der Anorganischen Chemie, Moissan's Traité de Chimie Minérale

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Générale, Friend's and Mellor's Textbooks of Inorganic Chemistry and Heilbron's Dictionary of Organic Compounds, it often takes a great deal of time to coördinate the knowledge on a given topic. Consequently when men who have spent years in the study of important subjects are willing to coördinate their knowledge and present it in concise, readable form, they perform a service of the highest value. It was with a clear recognition of the usefulness of such work that the American Chemical Society undertook to sponsor the publication of the two series of monographs.

Two distinct purposes are served by these monographs: the first, whose fulfillment probably renders to chemists in general the most important service, is to present the knowledge available upon the chosen topic in a form intelligible to those whose activities may be along a wholly different line. Many chemists fail to realize how closely their investigations may be connected with other work which on the surface appears far afield from their own. These monographs enable such men to form closer contact with work in other lines of research. The second purpose is to promote research in the branch of science covered by the monograph, by furnishing a well-digested survey of the progress already made, and by pointing out directions in which investigation needs to be extended. To facilitate the attainment of this purpose, extended references to the literature enable anyone interested to follow up the subject in more detail. If the literature is so voluminous that a complete bibliography is impracticable, a critical selection is made of those papers which are most important.

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Foreword

Gases differ fundamentally from solids and liquids in their physical behavior: a substance in volatile form may exhibit properties, even in its chemical action, widely different from those of the same substance as a liquid or a solid. Accordingly, poisonous gases and vapors have characteristic effects upon men and animals exposed to them distinct from noxious substances in solid and liquid form. This book deals primarily with the special features of toxic action dependent upon volatility.

Respiration, the function of absorbing and eliminating volatile substances, differs no less fundamentally from the physiological processes by which solids and liquids are ingested and excreted. Consequently an understanding of the toxicology of noxious gases must be based on the special features of the physiology of respiration.

Owing to these considerations, the classification and description of volatile poisons are necessarily different in some respects from those usually employed in toxicology as well as from those which chemistry would suggest. Systematic description of their actions must be based in part upon their chemical character, in part upon their physical properties, such as volatility and solubility, in part upon their pharmacological and toxicological actions, and in part upon their special relations to respiration. The mode of classification adopted here is practical rather than strictly logical.

The literature primarily devoted to the particular topic of volatility as a factor in toxicology is small as yet, but is increasing rapidly. The first edition of this book was, in fact, the first modern monograph in its special field. Indeed, until the principles controlling respiration had been established, no systematic treatment of the absorption and elimination of gases was possible. On the other hand, the literature of industrial medicine and toxicology in general is enormous, and nearly all of it is involved as the background of noxious gases. To refer to the entire background would swell this book to many times its present size; it would also be superfluous, for the literature of

the general effects of poisons is fully summarized with references in text- and handbooks which are readily available. But these works deal chiefly with solid and liquid poisons and their entrance into the body through the alimentary canal. It is only with the special features due to volatility and entrance through the lungs that we are concerned. It has seemed best, therefore, to confine the references given here to two purposes: (1) particular points, usually on toxic concentrations, and (2) general references placed at the end of the chapters, through which the reader may find his way to works in which the original literature of industrial medicine and toxicology is reviewed and referenced. In particular, we recommend for this purpose the well-known work of Dr. Alice Hamilton on "Industrial Poisons in the United States" (New York, 1925), which presents an admirable account of this general field and references to its literature. The extensive German literature is reviewed by F. Flury and F. Zernik in "Schädliche Gase" (Berlin, 1931). The state of knowledge seventy-five years ago is shown in "Die Lehre von den Schädlichen und Giftigen Gasen" by H. Eulenberg (Braunschweig, 1865).

Only those gases which occur in industry are dealt with here; their use in war is not discussed. References to works dealing with chemical warfare are, however, given at the end of Chapter 8 on irritant gases. It should be added, by way of "giving the Devil his due," that immensely valuable measures of protection against industrial gases have resulted from the study of war gas defense.

As this book has been written for the practical use and information of chemists, engineers and others engaged in industry, a rather full description of the function of respiration has been included. It has not seemed necessary to give extensive references to the original articles on respiration in journals of physiology; but at the end of the chapters dealing with respiration a number of monographs and reviews have been cited from which the reader may obtain both an extensive survey and further references.

It is the function of the physician to recognize disease and to apply such treatment as may be known. Unfortunately, in respect to many of the industrial diseases, his best efforts can do little to repair damaged bodies. It is the function of the

lawyer, when the health or life of the industrial worker has been impaired or destroyed, to win for him or his family a money compensation. At best the functions of both the physician and the lawyer are exercised only after the harm has been done and the suffering inflicted. The aim of this book is not so much to contribute to treatment or to aid in the winning of compensation as to make available the knowledge, the principles and the techniques upon which measures of prevention and of safety in industry must be based.

Safety in the chemical industries requires, first, that no substance shall be used until its toxicological character has been thoroughly investigated and defined. Safety requires next that standards shall be established for the concentrations, never to be exceeded, of all such substances in the air of the rooms where men and women work. For many substances two or more standards are needed: one so low that no harm can result even when the period of exposure is the full working day every day in the year: the other, or others, higher but applying only to shorter periods of exposure. And after these standards have been determined, the third essential for safety is that such precautions shall be taken and such efficient ventilation shall be installed and maintained that the air in working places is never vitiated beyond these standards.

New Haven, Ct.
April, 1942

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HOWARD W. HAGGARD

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Chapter 1

General Survey of the Field

The use of gases and the defenses against them became a subject of immense importance during the World War of 1914-1918. Gas warfare was exceeded by no other feature of military affairs. No subject caused more anxiety to national leaders, or received a greater amount of thought and investigation by scientific experts, or took a stronger hold upon popular imagination. Although unused in the present war, at least up to this time (1942), attack by means of poisonous gases has been an ever-present threat to armies, navies and the civil populations of all nations: a threat that has required elaborate measures of defense.

Gas Hazards of Industry

The gas hazards of modern peaceful industry and the defenses against them are no less important. This is almost the only field in the whole range of modern sanitation in which the number of fatalities throughout the civilized world has increased year by year. This increase can and should be checked. Nevertheless, it is a safe prediction that long after the zymotic diseases have been controlled, or even in large part eliminated, deaths from gas asphyxiation will still occur.

The reactions between a living man and the atmosphere about him are so immediate, so continual and so much a matter of course, that the normal individual passes days, even years, without a thought of breathing. Several times each day he thinks of food and not infrequently of digestion. He is interested in the principles of alimentation; he gladly accepts scientific knowledge and takes elaborate precautions in food and drink. But of respiration and the gaseous substances which he takes into his body through his lungs he is generally oblivious. On such matters even educated and thoughtful people are now usually uninformed. And yet the way that most people die is by cessation of respiration.

In modern industry volatile substances are used in enormous quantities. They occur as raw materials, as products, and as agents of manufacture. Chemical processes play a continually increasing part in industry. Throughout the whole of modern society the products of petroleum, for instance, are articles of daily and hourly use. Substitutes and blends of other volatile substances are appearing on the market. The inhalation of gases and vapors foreign to pure air is thus almost universal. It is fortunate that not all volatile substances are extremely toxic, but comparatively few are entirely free from all effects.

Respiration as an Avenue of Absorption

It is essential that the gases which may affect human life should be treated apart from harmful solids and liquids and in relation to breathing. Between the gaseous state of matter on the one hand, and solids and liquids on the other, there is not only a fundamental difference from the physical and chemical standpoints, but an even more important distinction physiologically. Solids and liquids are usually swallowed and thus pass into the system by way of the digestive tract. Volatile substances, on the contrary, are inhaled. The toxicology of solids and liquids must be studied with the functions of the alimentary canal as a background. The action of gases upon the body can be treated effectively only with the fullest reference to the physiology of respiration.

Respiration is fortunately a function regarding which knowledge is more nearly, so to speak, on an engineering basis than any other process of the body. We are now able to control the volume of breathing of a patient so that the ventilation of his lungs is immediately increased 2 to 6 or more times the normal resting amount, and it may be so maintained for hours. The otherwise slow elimination of many volatile substances is thus greatly accelerated and the period of their stay in the body and their ill effects are correspondingly reduced.

General Classification of Gases

Viewed as problems of respiration it is possible, as we trust this book will demonstrate, to establish, in regard to the action of gases, a set of broad and very practical conceptions for application to hygiene and therapy. A classification of gases merely

from the chemical standpoint would not serve this purpose. Gases as distinct chemically as hydrogen and nitrogen are yet identical in their physiological action, whereas some of the gases which are classified together chemically are wholly unlike in the reaction which the body makes to them.

The classifications commonly used in pharmacology and toxicology are also an inadequate basis for dealing with volatile substances. Although the character of the drug action is of interest, knowledge of it helps but little in the directly practical problems of preventing absorption and hastening elimination: the essentials of prophylaxis and therapy. For these problems we need to consider such respiratory data as the figure which defines the solubility of the gas in the blood and determines its distribution between the air and the blood in the lungs. This is the fundamental factor in such diverse matters as the rate of initiation and termination of ether anesthesia and the development or prevention of caisson disease from work in compressed air.

From the standpoint of respiration, gases may be classified as follows:

(1) **Irritants.** Gases of this class injure the air passages or the lungs, or both, and induce inflammation of the surfaces of the respiratory tract.

(2) **Asphyxiants.** (a) Simple asphyxiants: physiologically inert gases like nitrogen and hydrogen which, when breathed in high concentrations, act mechanically by excluding oxygen. (b) Chemical asphyxiants: substances which, by combining with the hemoglobin of the blood or acting upon some constituent of the tissues, either prevent oxygen from reaching the tissues or prevent the tissues from using it.

(3) **Volatile Drugs and Drug-like Substances.** These gases exert little or no specific effect upon the lungs; they act after they have been absorbed into the blood and transported to the tissues of the body.

This group includes a large number of volatile hydrocarbons of wide industrial use. The acute effects are usually upon the nervous system to induce intoxication and anesthesia, which may terminate in respiratory failure. For some, the action is largely limited to these functional disturbances; others, however, may injure organs of the body; and some are capable, even in

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concentrations which do not produce anesthesia, of causing serious chronic poisoning if the exposure is prolonged.

(4) **Inorganic and Organometallic Substances.** This fourth group includes a large number of poisonous elements and compounds occurring in industry in volatile form and exerting a wide variety of toxic actions after their absorption into the body.

Treatment of Poisoning

As the effects of the four main classes of noxious gases are widely different, so also the treatments for poisoning by them differ greatly. In the treatment of some forms of poisoning the prime factor is the rapid elimination of the poison through the the same channel as that by which it entered: that is, through the lungs. For this purpose, augmented breathing is induced by inhalation of carbon dioxide diluted with oxygen. Quite different is the treatment of the inflammation and edema of the lungs induced by the irritant gases. In this condition complete bodily rest and inhalation of oxygen—without carbon dioxide—are the means of enabling the body to obtain and conserve oxygen and, if successful, to escape death by suffocation. Again different is the treatment of the poisoning induced by gases and fumes that exert little or no harmful action upon the lungs or blood, but act systemically. In such conditions treatment is essentially the same as that administered when the intoxicant has entered the body through channels other than the lungs.

Prevention of Poisoning

The prime means of prevention are such volumes of room ventilation and such exhaust drafts from places where noxious gases are liberated as will prevent the building up of toxic concentrations in the respired air. Such measures must be based on standards for degrees of atmospheric contamination that do not injure health. The standards differ according to whether the periods of exposure are as short as minutes or as long as months. When the conditions in an industry are such as to render these protective measures impracticable, such devices as gas masks, hose masks and self-contained oxygen-breathing apparatus must be employed.

Chapter 2

Elements of Respiration

The life of a man or animal consists, to a large extent, in the use by the body of chemical energy to do mechanical work and liberate heat. The processes involved are many and complex, but in their sum total they amount to an oxidation of carbonaceous substances—in effect, a low-temperature combustion. The foodstuffs, after absorption from the alimentary canal, are brought to the tissues by the blood and there stored or built up into the living cells ready for use when fuel is needed. Little or no combustion occurs in the blood or in the lungs; it takes place wholly in the living cells of the tissues. The oxygen required for the combustion is absorbed from the air in the lungs into the blood and is transported by the blood to the tissues. Similarly the carbon dioxide produced by the combustion is transported by the blood from the tissues to the lungs. In order to maintain these exchanges between the lungs and the tissues the blood is kept in continual rapid flow in a circuit from the lungs to the tissues through the arteries and from the tissues to the lungs through the veins. The lungs are ventilated by the movements of breathing. The blood is circulated by the pumping action of the heart. The oxidation of organic substances in the tissues is controlled by the nervous system to maintain the tone of the muscles and to liberate the energy with which they work. Together these three processes constitute that major function of life which, in the broadest sense, is termed respiration.

The Vital Combustion

The amounts of oxygen required to burn each of the organic foodstuffs in the body and the amounts of energy liberated by these combustions have been accurately determined. Consequently it is a simple matter to estimate the energy expenditure of the body at any time by merely determining the amount of oxygen consumed and calculating from it the corresponding amount of heat of combustion. On the basis of these determina-

tions we know that a liter of oxygen consumed in the body produces an amount of energy which, expressed in heat units as an average, is quite close to 4.8 kilocalories—each of which is 1,000 small calories and is equal to about 4 British thermal units—for a person on the ordinary American diet. On a diet of pure fat it would be 4.69 kilocalories per liter of oxygen and on one wholly of carbohydrates, 5.05 kilocalories per liter. As no one lives on such a diet, the oxygen consumption and the energy expenditure of the body may be considered to be, at nearly all times, so nearly proportional that the correspondence may be treated as if it were invariable at the ratio of 1 liter of oxygen to 4.8 kilocalories. Every physical exertion, however slight or great, involves a corresponding increase of energy expenditure, increase of oxygen consumption and carbon dioxide production, and a closely proportional increase in the volume of breathing. Even rising from a sitting to a standing position costs nearly 1 kilocalorie; sitting up in bed, about half a kilocalorie, and even lifting a hand costs an appreciable amount. An athlete in a Marathon race, or an equivalent prolonged exertion, may maintain an expenditure of 10 or more times his resting rate. The maximum for a few minutes of most intense exertion is about 20 times the resting rate and, for a few seconds, perhaps even 30 or 40. But such intense exertions involve a temporary deficit of oxygen which is repaid during the succeeding period of rest.

The energy expenditure, oxygen consumption and volume of breathing of an athletic man of about 70 kg. (154 lbs.) weight under different conditions are roughly as shown in Table 1.

TABLE 1.

	Calories per minute	Oxygen Consumption (liters per minute) at 0° C. and 760 mm.	Volume of Air Breathed (liters per min.) at 20° C.
Rest in bed, fasting	1.15	0.240	6
Sitting	1.44	0.300	7
Standing	1.72	0.360	8
Walking 2 miles per hour	3.12	0.650	14
Walking 4 miles per hour	5.76	1.200	26
Slow run	9.60	2.000	43
Maximum exertion	14–20+	3.000–4.000	65–100

The energy expenditures of the body are most easily conceived as chargeable under two main items. One is the so-called "basal metabolism," the expenditure for the mere maintenance

of life during rest: the work of the heart, movements of the respiratory muscles, a minimal activity of the digestive apparatus, muscle tonus, and the resting heat production. This basal expenditure is, for practical purposes, calculated from measurements of the oxygen consumption during rest in bed several hours after a meal. The other item includes all the expenditures incidental to bodily activity. The normal basal rate for adult men and women of 20 to 40 years varies roughly with their weights and quite accurately in proportion to their skin areas. In children, the basal expenditure per unit of body surface is larger than in adults, and the ratio of surface to mass (weight) is greater, as geometry requires in bodies of similar shape but different sizes. The volume of blood, on the contrary, is proportional to body weight. For all these reasons the respiratory exchange of oxygen and carbon dioxide and the volume of air breathed by children are proportionally greater than in adults, and the rate at which a child absorbs any poisonous gas is correspondingly more rapid. Practical advantage is taken of this fact in mine rescue operations. Small animals, such as mice and canary birds, are carried with the rescue parties and are used as indicators of bad air. Owing to their relatively greater surface, metabolism and breathing, they are affected much more quickly than the men carrying them, who are thus warned of their danger.

Five volumes of oxygen are consumed in the body for approximately 4 volumes of carbon dioxide produced. This relation is due to the fact that about one-fifth of the oxygen is usually expended in oxidizing elements other than carbon, especially the hydrogen of fats and the sulfur of proteins. The relation of the volume of carbon dioxide produced to the volume of oxygen consumed, that is CO_2/O_2, is called the "respiratory quotient" and is indicated by the letters R.Q. It is often used as an index of the foodstuffs which are being consumed as fuel in the body. Carbohydrates, such as starch $(C_6H_{10}O_5)_x$, or cane sugar $(C_{12}H_{22}O_{11})$, which are converted in the body to dextrose $(C_6H_{12}O_6)$, produce as many molecules of carbon dioxide as the molecules of oxygen consumed in the oxidation of their carbon and have, therefore, an R.Q. of 1.00. Proteins consumed in the body give an R.Q. of 0.78 to 0.81, and may be distinguished from a mixture of carbohydrate and fat by determining the amount

of the nitrogen excreted in the urine, chiefly in the form of urea. Each gram of nitrogen comes from the decomposition of about 6.3 g. of protein. The fats of the food, if they alone were burned, would have an R.Q. of about 0.7. On a mixed diet, after the rise following a meal has passed off, the R.Q. generally approximates 0.8. The temporary rise after a meal is due to the fact that the carbohydrates of the meal are utilized at that time more extensively than the fats.

The R.Q. is, however, often quite misleading as an index of the character of the combustion at the moment. The evidence afforded by the R.Q. is reliable only under resting conditions, and in subjects trained for experimental work, or when the subjects are observed over considerable periods of time. Any excitement, such as that of being the subject of an experiment, may cause overbreathing and thus temporarily increase the elimination of carbon dioxide without affecting the oxygen consumption. During very hard work the oxygen consumption in the tissues may, for a time, exceed the amount that the circulation can supply. This induces such vigorous overbreathing—heavy panting—that excessive elimination of carbon dioxide results. These temporary deficits, both of oxygen and carbon dioxide, are made up during the subsequent rest. But until equilibrium is restored the R.Q. is, for the time being, abnormally high and may then, for a time, fall abnormally low. A true index of the fuel consumed—the proportions of fat and carbohydrate—is obtainable from the R.Q. only when the period of observation is sufficiently prolonged.

Combustion in the Tissues

From the foregoing discussion it would be natural to infer that when the body does mechanical work, the order of events is, first, an increased oxidation of carbonaceous substances and then, as in a steam engine, the conversion of a part of the energy so liberated into mechanical work. But in fact the order of events is almost exactly the opposite: first, the work is started—as, for instance, in running upstairs—and then only when the work is under way are respiration and the consumption of oxygen increased. From this it might be supposed that in the tissues, particularly in the muscles, some substances rich in oxygen, like gunpowder or nitroglycerin, are stored, and that when

a nerve impulse stimulates a muscle to contract, such substances, so to speak, explode. But again such an idea is erroneous: there are no such oxygen-rich substances in the body. Instead, the chemical processes in the tissues appear to be initially anaerobic. They are largely due to the action of enzymes, such as cytochrome, an oxidative ferment containing iron. In this respect they are essentially like those by which yeast produces fermentation.

For many years it was supposed that in the work of muscular contraction the principal reaction consisted in the splitting of dextrose ($C_6H_{12}O_6$) into twice as many molecules of lactic acid ($C_3H_6O_3$). Now, however, a more complex series of reactions is probable; they involve phosphoric acid in compounds with such nitrogen-containing substances as creatin, to form phosphagene with adenylic acid, and perhaps with others, which break down during the contraction of the muscle; and also with hexose ($C_6H_{10}O_5$) in combination with phosphoric acid, which is oxidized during the recovery period after a contraction to resynthesize phosphagene. The first of these reactions is anaerobic. It is only, or at least mainly, during the second—that of restitution—that oxygen is consumed and carbon dioxide is produced.

Structure of the Lungs

For a complete description of the lungs, and the thorax or chest in which they lie, reference should be made to a textbook of anatomy, but the structure is best understood from examination of a freshly killed animal. Those features of the lungs which particularly concern us here are as follows:

The lungs (see Fig. 1) are composed of a great number of minute chambers, the saccules, which are further divided by delicate partitions into the ultimate air spaces termed alveoli. These saccules form the terminal dilations of very small elastic air tubes called bronchioles. The bronchioles are branches of larger tubes, the bronchi, which open into the trachea, or windpipe, at the medial surface of the lungs directly behind the heart. The trachea, whose walls are stiffened by incomplete rings of cartilage, extends upward and terminates in the pharynx, or upper part of the throat, into which the mouth and nostrils also open. Thus there is free access for atmospheric air to the lungs through the nose, mouth and trachea, except momentarily when

the glottis is closed during the act of swallowing. The bronchi are provided with muscular walls and irritation may cause them to contract and prevent the passage of air into the bronchioles, saccules and alveoli. The trachea, bronchi and bronchioles are lined with mucous membrane which secretes a mucous fluid upon the walls of these airways. The entire system of tubes takes very little part in the exchange of gases; it merely affords passage to and from the terminal air sacs where the gaseous exchanges occur.

Fig. 1. Anatomical Relations of the Respiratory Tract.

The alveoli have exceedingly thin walls almost completely filled with a network of capillary blood vessels, set in an elastic framework of connective tissue and covered only by an extremely thin membrane. It is between the blood in these vessels and the air in the alveoli that the gaseous exchanges take place. Owing to the thinness of their walls and to the enormous total surface of the capillaries—estimated at 90 square meters in the lungs of man—the diffusion of gases is so rapid that a virtual equilibrium of the partial pressure of every gas is almost instantly established between the blood in the capillaries and the air in

the alveoli. It is an amazingly effective apparatus for equilibrating the gases in the blood with those in the atmosphere of the lungs.

The blood is supplied to the lungs through arteries from the right heart which follow along the bronchi. From this point the vessels divide and subdivide until they form the alveolar capillaries. From the capillaries onward the blood vessels again unite into increasingly larger vessels, and these pulmonary veins finally emerge near the point of entrance of the bronchi and pass to the left heart. The lungs have normally only one attachment in the body, which is that on the medial surface where the bronchi and blood vessels enter. At all other points the lungs are freely movable within the chest cavity.

The entire structure of the lungs is elastic. In a lung which has been removed from the body the saccules contract until they are almost collapsed and contain only a very small amount of air. In the body this collapse is prevented by the fact that the lungs are encased in the airtight and comparatively rigid-walled cavity of the thorax and by the fact that during life the diaphragm, which separates the thorax from the abdomen, is never entirely relaxed. There is no air in the potential space between the chest wall and the lungs and only a film of fluid by which the walls are moistened sufficiently for lubrication. Since the interior of the lungs is in communication with the outside air through the trachea, the elasticity of the saccules is overcome by the pressure of the atmosphere, and the lungs are inflated so that they completely fill the thoracic cavity and are held tightly against the chest walls and diaphragm. By the same mechanism any movement of these walls, which increases or decreases the size of the thorax, results in a like change in the volume of the lungs, which are thus expanded or contracted in exact conformity to the size and shape of the chest cavity. As a result, air passes in and out of the air sacs and alveoli and through the bronchi and trachea and thus produces the tidal movements of the air in and out of the nose and mouth.

As all the air sacs of the lungs open freely through the bronchioles and bronchi into the trachea and are of equal elasticity, the inspired air is generally shared nearly equally by all parts of the lungs. Were the alveoli of some parts of the lungs to receive more air than others they would be put under a greater

elastic stretch, and the strains would then tend to equalize, as in any physical system. The only unequal distribution of air in the lungs results from the friction of the air in passing to those saccules which are supplied by the longer tubes. For this reason the areas nearest the stalk of the lung where a bronchus enters expand first and the more distant areas only an instant later. The lungs thus open out somewhat after the manner of a fan, but in ordinary full, slow breathing there is sufficient time for a general equalization of the air throughout the lungs.

The surface of the lungs is covered with a thin layer of smooth tissue, the pleura. Similar tissue lines the inner surface of the chest walls. These two pleural surfaces, which together form a closed sac, slide over each other during the inflation and deflation of the lungs by the expansion and contraction of the thorax. The surface of the lungs may slide upon the chest wall as much as 7 or 8 cm., or even more, at some points distant from the lung stem, when a deep breath is drawn and then deeply exhaled.

Nervous Control of Breathing

To a limited extent, breathing is under the control of the will: otherwise, we could not talk or sing. One can voluntarily breathe deeply for a short time and stop entirely for half a minute, or, under some experimental conditions, even for several minutes; but by no possible exertion of the will can one "hold his breath" for longer. For the most part, breathing goes on automatically without our even being aware of it. Yet experimental studies show that the volume of air with which the lungs are ventilated by breathing is rigorously controlled and adjusted. By this adjustment, the volume of air breathed by a vigorous man may vary from 5 or 6 liters a minute during bodily rest up to 80, or even 100, liters per minute under vigorous muscular exertion. Within this wide range the ventilation of the lungs in liters of air per minute is increased and decreased in close proportion to the energy expenditure, amount of oxidation and interchange of oxygen and carbon dioxide between the blood and the tissues of the body. In the adjustment of breathing to these needs, many factors take part. But in the main the controls by which the adjustment is effected are afforded by the chemical influences of carbon dioxide and oxygen of the blood

upon the respiratory nerve center in the medulla oblongata at the base of the brain. The influence of carbon dioxide is exerted —probably through the pH of the blood (see p. 44)—directly upon this center. That of oxygen is effected reflexly through sensitive nerve endings in the sinus caroticus, a small bulb on the carotid artery in the neck, from which nerve fibers pass to the respiratory center. From the respiratory center nervous impulses are discharged along fibers in the spinal cord to motor centers in the spinal cord; and from these spinal centers the impulses are relayed over motor nerves to the diaphragm and other muscles involved in the movements of breathing.

As the lungs are nearly perfect organs for the almost instantaneous diffusion of gases between the air within them and the blood flowing through them, the tension of carbon dioxide is always exactly the same in the arterial blood as in the alveolar air. The flow of blood from the lungs to the brain requires but a moment. Consequently any increase or decrease in the tension of the carbon dioxide in the lungs acts through the blood almost instantly upon the respiratory center to increase or decrease the movements of breathing and the ventilation of the lungs. Similarly, when any foreign gas, such as nitrous oxide or the vapor of ethyl ether, is drawn into the lungs and there mixed and diluted in the alveolar air, the blood flowing through the lungs immediately comes into gaseous equilibrium with it and carries it to the brain; and within a short time, usually a matter of seconds, the tension (partial pressure) of that gas in the brain becomes nearly the same as that in the blood and lungs. It is because of this relation between the lungs, blood and brain that the volatile anesthetics administered through the lungs act so much more rapidly than do drugs administered through the stomach, or subcutaneously: more rapidly even than those injected intravenously.

That the main center of control over breathing is placed in the medulla oblongata at the base of the brain is demonstrated by a celebrated experiment, which demonstrates also that the chief influence exerted directly upon this center is that of the carbon dioxide in the blood. This experiment is that of the so-called "crossed circulation" in which Leon Fredericq attached the carotid artery of dog A to the head of dog B so that the brain of B was supplied with blood that had passed, not through

its own lungs, but through the lungs of dog A. And he found that B then breathed more deeply when carbon dioxide was administered, not to its own lungs, but to the lungs of dog A.

That the influence of oxygen, or rather that of want of oxygen, is exerted reflexly through the sinus caroticus, rather than directly upon the respiratory center, is demonstrated by the fact that a sudden inhalation of nearly pure nitrogen induces a vigorous, even violent, increase of breathing; but that if—in an animal—the nervous fibers from the sinus to the respiratory center have been cut, no increase of breathing is induced by the anoxia. On the contrary, if the inhalation is continued, the center is soon paralyzed by the lack of oxygen and death by asphyxia results.

In the flow of air in and out of the lungs, the lungs themselves are quite passive. Their movements are induced by the rhythmic contraction and relaxation of the diaphragm and the muscles attached to the ribs. The diaphragm is a sheet of muscle convex toward the thorax and separating that cavity from the abdomen. Its contraction increases the length, or height, of the cavity; while an upward movement of the ribs, owing to the direction in which they are hinged on the spine, increases the cross-section of the chest, especially transversely. Inspiration is due to contraction of the diaphragm and thoracic muscles. Expiration is a less active process for, when the muscles relax, the elasticity of the lungs themselves tends to drive out the air previously inhaled. This action is assisted by the weight of the thorax in the standing and sitting positions and by the weight of the liver and stomach upon the diaphragm when the person is lying upon his back.

Owing to the fact that the respiratory muscles normally do work in overcoming the elastic pull of the lungs during inspiration, but not during expiration, it is found that in the use of gas masks and other respiratory apparatus a resistance to inspiration amounting to a negative pressure of 3 or 4, or even 5 or 6 cm. of water column, can be tolerated for some time; but a resistance to expiration of a positive pressure of more than 2 cm. of water column soon becomes distressing. When the resistance arises from irritation and inflammation, with consequent narrowing of the air tubes of the respiratory tract, expiration is likely to be much more noticeably impeded than inspiration. The lungs

become stretched and a chronic condition, termed emphysema, may result.

When the volume of breathing is increased by physical exertion, many accessary muscles, chiefly those of the back and shoulders, are called into action to assist in inspiration, and expiration then involves also vigorous contraction of the abdominal muscles.

Atmosphere of the Lungs

The lungs do not contain atmospheric air, but instead a special atmosphere in which oxygen and carbon dioxide are present in proportions quite different from those in the outside air; and these proportions are accurately maintained. If each inspiration filled the lungs with atmospheric air and each expiration blew it all out, the blood would be alternately over- and underventilated. At one moment the oxygen in the air of the lungs would be high and the carbon dioxide low and, at the next moment, the oxygen low and the carbon dioxide high. The lungs are, on the contrary, particularly adapted and managed to prevent such variations and to keep the alveolar air—that with which the blood comes into gaseous equilibrium as it flows through the lungs—very nearly uniform.

During life, the lungs are never emptied of air; the tonus of the diaphragm and thoracic muscles prevents this. Even after the deepest forced expiration they still contain about 1.5 liters of residual air. After an ordinary expiration they contain an additional 1.5 liters of supplemental air. To the sum of the residual and supplemental airs, which together constitute the so-called stationary air of about 3.0 liters, the ordinary inspiration during quiet breathing adds 0.3 to 0.6 liter of tidal air. Of this tidal air only about two-thirds reaches the lungs, where it is mixed instantly and completely with the stationary air to add oxygen and slightly dilute the carbon dioxide. The other third of the tidal air stops momentarily in the so-called respiratory dead space—the mouth, nose, windpipe and bronchi—and takes virtually no part in the exchange of oxygen and carbon dioxide. It is swept out of the dead space by the next inspiration. Expired air is therefore a mixture of about two-thirds alveolar air and one-third air from the dead space from which little or

no oxygen has been absorbed, and only a little carbon dioxide added, plus water vapor.

Vital Capacity and Dead Space

In addition to the tidal air the deepest inspiration may draw in about 1.5 liters more of complemental air. The sum of the supplemental, tidal and complemental volumes is the so-called "vital capacity," and is determined from the individual's maximum expiration into a graduated spirometer after a maximum inspiration. The amount of the vital capacity in normal persons is a function of their size or weight; it has been used as an index of physical efficiency. It is decreased in some diseases, particularly of the heart, in which the volume of blood in the lungs is abnormally increased. During heavy breathing after physical exertion, the tidal air may be increased to include much of the supplemental and nearly all the complemental air.

The dead space of breathing might be supposed to be a fixed quantity for the individual—the same for deep as for shallow breathing—and if only the larger airways were involved such would, of course, be the case. But, when the volume of the virtual dead space is calculated from analyses of samples of alveolar air and of mixed expired air, it is generally found that, alike during the quiet breathing of bodily rest and during the far larger breathing of vigorous physical exertion, the percentage of carbon dioxide in the expired air is quite close to a figure which is two-thirds that for the alveolar air. As the expired air is a mixture of alveolar air with air from the dead space, this figure indicates that two-thirds of the expired air has come from the lungs and one-third from the dead space. It shows that in deep breathing the bronchioles are expanded and add an appreciable volume to the virtual, or functional, dead space.

These features of breathing may be summed up in the statement that, instead of being operated merely to absorb oxygen and eliminate carbon dioxide, the lungs are ventilated in such a manner as to maintain the alveolar air at a nearly constant composition. For individuals adjusted to sea level conditions this composition is 5.5 per cent of carbon dioxide and 15.0 per cent of oxygen, instead of the 0.03 per cent of carbon dioxide and 21.0 per cent of oxygen in atmospheric air.

In the volume of breathing, measured in liters of air per

minute, two elements are involved: they are the size of the breaths and their number, or the rate per minute. It is mainly upon the volume of the breaths that the chemical influence of the blood gases—particularly that of carbon dioxide—is exerted. In common with all the other muscles of the body, those concerned in breathing have a property called tonus, which determines the length and elasticity of each muscle. The tonus of the diaphragm and thoracic muscles is controlled by the respiratory center largely under the influence of carbon dioxide. It increases with each inspiration and decreases with expiration; and the extent of these variations of tonus largely determines the volume of the breaths.

Not only is the volume of the breaths in normal breathing determined by the influence of the blood gases upon muscle tonus; muscle tonus is still present to some degree even in an unconscious and non-breathing man, but it decreases as asphyxia passes into death. Resuscitation from drowning and electric shock is possible only as long as the body still has some degree of tonic elasticity; for the volume of lung ventilation that can be induced by artificial respiration is determined by the residual tonus of the diaphragm and the muscles of the thorax. It is for this reason that inhalation of a mixture of carbon dioxide and oxygen greatly increases the efficiency of artificial respiration. In drowning and other forms of acute asphyxia, irreparable damage to the higher centers in the brain is induced by even a few minutes—at most about 5—of complete deprivation of oxygen and among the earliest results of this damage is abolition of muscle tonus. The muscles of respiration, in common with the entire body, then become flaccid and manual artificial respiration is ineffective. In this condition ventilation of the lungs with a pump or bellows is, however, even less effective, since it does not aid the circulation as manual artificial respiration does. At death, tonus is abolished; it is therefore a distinctly vital property under reflex and chemical control through the nervous system. In this respect the elasticity of tonus is quite different from the elasticity of a spring or rubber band.

The Rhythm of Breathing

For effective and uniform ventilation of the lungs it is necessary that air should be drawn in and again discharged by a

rhythmic alternation of contractions and relaxations of the respiratory muscles. The mechanism involved is of the type that an engineer calls "reciprocating." It is similar to that employed in such acts as walking, chewing and, in some animals, wagging the tail. For such actions the bones are utilized as levers in a multiplicity of forms and are moved by muscles under the control of the nervous system.

In the movements of breathing the ribs serve as levers to lift and expand the chest. As always in such physiological mechanisms, two antagonistic sets of muscles are involved. In order to flex and then extend a joint, or to inspire air and then expire it, it is necessary that one of these sets of muscles shall relax while the other contracts, and then that the first shall contract while the second relaxes. The relaxation is almost as essential as the contraction and the accurate timing of the alternation is essential for rhythm and efficiency. The alternation of inspiration and expiration does not depend upon any mechanical arrangement of the bones and muscles, or of any other mechanical parts as in a steam engine; it is rather like the ignition of a gasoline motor which fires the cylinders in a recurring sequence. The respiratory center is, like the heart, inherently rhythmic and its rhythmicity is reinforced by the so-called proprioceptive reflexes of the respiratory muscles and their nerves. Each nerve to a muscle contains a double set of fibers. One set carries the motor impulses from the nerve center in the spinal cord to the muscle and induces contraction. The other set carries impulses in the opposite direction—that is, from the muscle to its own and other nerve centers in the spinal cord. Each time the muscle contracts, the contraction itself sends an impulse up these afferent fibers and, for an instant, inhibits further motor discharges to that muscle. At the same time these afferent impulses influence the centers of the antagonistic muscles to discharge motor impulses to their muscles. On this account, all parts of the body would have a tendency—once they were set in motion—to swing back and forth rhythmically like the pendulum of a clock were their spinal centers not dominated by higher centers in the brain.

The rhythmic movements of breathing are further maintained and regulated by two special pairs of nerves: one the phrenics, which are the motor nerves to the diaphragm; the other the vagi, which are the afferent nerves of the lungs. It is largely because

of these nerves that the alternation and timing of inspiration and expiration are so accurately maintained. Whenever an inspiration has occurred and the lungs are stretched, the vagal endings in the lungs are stimulated to transmit nervous impulses to the respiratory center, and these impulses inhibit the inspiratory contraction of the diaphragm and induce expiration. Conversely, the partial deflation of the lungs by expiration induces inspiration. When either phase is opposed by obstruction to the flow of air—as with some gas masks and other breathing apparatus—that phase tends to be prolonged and its muscular effort intensified.

The impulse to inspiration is much stronger than that to expiration and for this reason it is much more difficult for a man to hold his breath with his lungs empty than with them full. An uncontrollable impulse to inspire sometimes costs the life of a miner wearing a self-contained breathing apparatus. If the breathing bag of the apparatus is compressed and emptied, as happens sometimes in rescue work while a man is crawling through a low passage, he is prevented from inspiring. The vagal nerve endings are then so strongly stimulated by the emptied state of the lungs that the man may tear off the apparatus in order to fill his lungs again, even though he knows the atmosphere about him is deadly.

The influence of the vagi upon breathing is also of great importance whenever any continuing irritation in the lungs occurs, as in pneumonia or from an irritant gas. The irritation then tends to induce a rapid alternation of inspiration and expiration, and a correspondingly shallow form of breathing, by which only a part of the lungs is ventilated (see p. 26). Through the unventilated parts the blood passes with little or no gain of oxygen or decrease of carbon dioxide, while the blood flowing through the ventilated area is overaerated and its carbon dioxide content thus reduced below normal. The mixed arterial blood flowing onward to the body is the average of the two fractions and may have a normal, or even slightly subnormal, content of carbon dioxide. The mixed arterial blood is, however, incompletely oxygenated because of the fact that the overventilated fraction of the blood cannot take up more than its hemoglobin content allows, while the other fraction is not oxygenated.

The patient is therefore cyanotic (blue), although gasping for breath, and may exhibit other symptoms of oxygen deficiency.

Chemical Regulation of Breathing

Oxygen is the most immediately essential of all the substances required for the vital combustion, but it is not a stimulant. If a normal man is made to inhale pure oxygen instead of air, neither his breathing nor his consumption of oxygen is appreciably increased. If the tension of oxygen in the air is progressively decreased, the volume of breathing increases, but the amount of oxygen consumed is not decreased appreciably until respiration fails. Generally, where a candle will burn, a man can live, but there are conditions where a candle will burn and a man may die. The vital combustion does not flare up and die down under the influence of oxygen as does an ordinary fire: the control is quite different.

Even a slight want of oxygen induces profound disturbances, both physical and mental. Complete deprivation of oxygen for as long as 5 minutes, as in drowning, induces irreparable damage, particularly to the brain. The reason lies chiefly in the fact that the total reserve supply of oxygen in the body—the sum of that in the air of the lungs and that in the blood and tissues—amounts to only 1,500 to 1,800 cc., or barely enough to cover the consumption for 5 minutes.

Against any considerable deficiency of oxygen, the nerve endings in the sinus caroticus and their connection to the respiratory centers afford efficient protection. These nerve endings, although not very sensitive to slight and temporary decrease in the tension of oxygen in the blood, are powerfully stimulated by such acute deprivation of oxygen as may be induced experimentally in the laboratory by the inhalation of pure nitrogen or hydrogen, or methane in a coal mine, or by such anoxic atmospheres as sometimes occur in the holds of ships. Under the ordinary conditions of life, the supply of oxygen afforded by pure air is adequate for all the needs of the body and the nerve endings in the sinus caroticus are not excited. The protection afforded by the sinus caroticus comes into play only when, under vigorous physical exertion, oxygen is temporarily consumed faster than the circulation of the blood can transport it from the lungs to the tissues.

In contrast to its relative insensitiveness to oxygen, the respiratory center is exquisitely sensitive to even slight variations in the carbon dioxide in the blood flowing to the center from the lungs. This adjustment is so precise that the slightest increase or decrease of carbon dioxide production in the body immediately induces an almost proportional increase or decrease of the volume of breathing. The volume of air breathed almost exactly compensates for any tendency of the concentration of carbon dioxide in the lungs to rise or fall more than a minute amount above or below the normal. The result and, in a physiological sense, the purpose of this regulation is that a nearly uniform concentration of 5.5 per cent, or 40 mm. of carbon dioxide, shall be maintained in the lungs and arterial blood. The adjustment is so flexible that even under wide variations of bodily activity it maintains the normal quantitative relations between energy expenditure, tissue combustion, oxygen supply and volume of breathing. An ample supply of oxygen is thus assured. As expressed by Miescher, who first clearly recognized the regulation of breathing by carbon dioxide, "Over the oxygen supply of the body, carbon dioxide spreads its protecting wings."

It is of great advantage toward the smoothness of breathing that the immediate control is vested in carbon dioxide rather than in oxygen. The blood normally contains, chiefly in the form of bicarbonates, 50 volumes per cent of carbon dioxide, or even a little more, and the tissues also hold considerable amounts. Thus the mass of carbon dioxide normally present in the body is large as compared with that of oxygen, which is held in the blood only to the amount of 18 to 20 volumes per cent, and even less in the tissues. And this has the additional importance that carbon dioxide is now known to be, not merely a waste product, but in the form of carbonic acid a primary factor in balancing the bicarbonates of the blood and thereby maintaining the normal hydrogen-ion concentration, or pH, of the fluids and tissues of the body.

The distinction between the influence of oxygen and that of carbon dioxide may be expressed in a statement which is oversimplified but practically useful. It is that the activity of the respiratory center is determined, not by one influence or factor, but by two factors which act in opposite directions. One of these factors is the chemical stimulus of the carbon dioxide in

the blood. The other factor is the influence of oxygen, or lack of oxygen, upon the excitability of the center. The rule, then, is that the higher the tension of oxygen, the lower the excitability of the center and the higher the tension of carbon dioxide required, therefore, to stimulate the center; and, on the other hand, the lower the tension of oxygen, the higher the excitability and the lower the required tension of carbon dioxide. These relations work in such fashion that, under a lowered tension of oxygen, breathing is increased and the amounts of carbon dioxide held in the alveolar air and arterial blood are decreased.

The relation of these two factors to each other in respiration may be illustrated by comparing the regulation of the interior atmosphere of the body to the regulation of the temperature of the air in a house with central heating controlled by a thermostat. In mild weather, the thermostat induces only a slight activity in the furnace; in cold weather, the slight cooling of the house acts as a stimulus to the thermostat which then increases the activity of the furnace. Similarly, the production of a small amount of carbon dioxide, as during bodily rest, affords only a small stimulus and induces only gentle breathing; but the production of a large amount of carbon dioxide during muscular activity induces a correspondingly strong stimulus and a correspondingly greater activity in respiration.

The analogy can be carried further. On every thermostat there is an adjusting dial by which the instrument may be set to maintain any desired temperature in the house: it may be 60, 65, 70, or even 80° F. And it is this feature of thermostatic control that furnishes an enlightening analogy to the excitability of the respiratory center. It is the excitability of this center that determines whether respiration shall maintain the air in the lungs at 6 per cent (45 mm.) of carbon dioxide, or 5 per cent (38 mm.), or 4 per cent (30 mm.), or even at some lower tension, as it does in healthy people acclimatized to altitudes many thousands of feet above sea level. And the factor which is mainly effective in adjusting and setting the excitability of the respiratory center to carbon dioxide is the tension of oxygen in the atmosphere, which is always close to 21 per cent of the barometric pressure at the locality where the people so adjusted live.

The distinction between stimulus and excitability is not

merely theoretical; it is extremely practical. A man sitting still at sea level produces some 250 cc. of carbon dioxide per minute and ventilates his lungs so that the air within them contains 5 per cent (38 mm.) of carbon dioxide. The volume of air reaching his lungs will be $250 \times \frac{100}{5} = 5{,}000$ cc. (the actual volume of air breathed will be some 50 per cent greater because of the 33 per cent dead space). Suppose now that he walks about at a fair pace and produces 500 cc. of carbon dioxide and ventilates his lungs so that the air within them still contains 5 per cent of carbon dioxide. The volume of air reaching his lungs will be $500 \times \frac{100}{5} = 10{,}000$ cc. Suppose now that he were to go and live at a great altitude and that after a few hours or days of mountain sickness—headache, nausea, bad temper, confusion, and even fainting—he becomes so completely acclimatized to the lower tension of oxygen that he feels quite fit. His respiration then automatically maintains the carbon dioxide in his lungs at only 2.5 per cent of a sea level atmosphere (19 mm.). As he still produces the same amount of carbon dioxide as at sea level, the volume of air reaching his lungs, even when he is sitting still, will be $250 \times \frac{100}{2.5} = 10{,}000$ cc. The first of these two adjustments involves a change in the amount of the stimulus without change of excitability. The second involves a change in the degree of excitability without change in amount of stimulus. Stimulus and excitability are thus independent variables. It is only when a man has made a vigorous exertion that for a time he is affected both by oxygen want and excess of carbon dioxide. In that condition, both the stimulus and excitability are increased, and he pants heavily. The details of these effects are still in dispute. Some investigators hold that carbon dioxide itself acts directly upon the respiratory center. Others believe that its influence is exerted through the hydrogen-ion concentration of the blood. The latter is the broader concept; for, from sea level up to the greatest altitudes (15,000 to 19,000 feet) at which a man may live, the higher his residence, the lower the content of bicarbonate in his blood, and the lower the tension of carbon dioxide which respiration maintains in his lungs. To this extent the influence of carbon dioxide varies; but at all altitudes

the proportion of carbon dioxide to the blood bicarbonate, $H_2CO_3/BHCO_3$, and therefore the hydrogen-ion concentration, are maintained nearly the same.

Oxygen want acts directly upon the nerve endings in the sinus caroticus and apparently indirectly through some chemical product of oxygen deficiency formed in the tissues. Such substances as cyanides, sulfides, iodoacetate and others, when introduced into the blood, have this effect also.

The most striking and instructive demonstration of the influence of oxygen, or deficiency of oxygen, upon respiration is afforded by the greatly increased, or even violent, breathing induced by inhalation of a few breaths of an inert gas such as nitrogen, hydrogen, or methane, with no admixture of oxygen whatever. The effect is nearly instantaneous. If normal air or oxygen is supplied immediately afterward, the excessive breathing continues for only a minute or two. Then, instead of returning at once to normal breathing, the subject exhibits a respiration of subnormal volume or even stops breathing altogether for a short period. The explanation of this fact is that during the hyperpnea, or overventilation, induced by the acute deficiency of oxygen, the elimination of carbon dioxide is augmented far above normal. When oxygen is again obtained, the temporary deficiency of carbon dioxide is such as to produce apnea, cessation of breathing, or at least subnormal breathing, until the normal amount of carbon dioxide reaccumulates in the blood and in the lungs. Thus, after a period of such anoxic hyperpnea, oxygen itself may act as a respiratory depressant and retard the elimination of some foreign or poisonous gas which has caused excessive breathing. Such is the case, for instance, in carbon monoxide asphyxia, particularly when induced by city gas rich in hydrocarbons. But this depressant influence of pure oxygen may be counteracted by using oxygen to which a small amount of carbon dioxide has been added. This is one of the reasons why a mixture of oxygen and carbon dioxide, instead of oxygen alone, is used for resuscitation from asphyxia.

When the deficiency of oxygen is slight, the increase of breathing is also slight or, for a short time, does not occur. Owing to the character of the combination which oxygen makes in the blood, the effect of a progressive decrease of the oxygen in the air does not become marked until the partial pressure has

fallen from the normal of 21 per cent to about 13 per cent of an atmosphere, which brings the oxygen in the alveolar air of the lungs down to about 8 or 9 per cent. From this point onward the volume of breathing increases progressively. Consciousness is lost when the inspired air (at normal barometric pressure) contains less than 11 per cent of oxygen; but respiration is not abolished and death is not quickly induced until the proportion of oxygen has fallen to 8 per cent or less. There are marked individual differences in the extent of decrease of oxygen pressure that can be endured before fainting or unconsciousness occurs.

The Time that the Breath can be Held

The distinction between stimulation by carbon dioxide and the increase of excitability induced by a lowered tension of oxygen can be easily demonstrated by anyone, even without ascending a mountain, or making a vigorous muscular exertion, or subjecting himself to temporary asphyxiation. He need only determine how long he can hold his breath under conditions that are varied in respect to carbon dioxide and oxygen, as in the following simple experiments.

A man in normal health can usually hold his breath for only 40 or 50 seconds. After breathing oxygen he can hold it no longer, or, in some cases, longer by only a few seconds. After breathing air containing 4 or 5 per cent of carbon dioxide, not only is his breathing increased, but he can hold his breath for only 10 or 20 seconds, if so long.

After forcing himself to breathe for 10 or 15 seconds as deeply as possible, but at a normal rate, so as to overventilate the blood passing through his lungs, he may hold his breath for a couple of minutes. After such forced breathing for 4 or 5 minutes he may hold his breath for 3 or 4 minutes, and even go "blue in the face" before the breaking point is reached. After forced breathing for 4 or 5 minutes, ending with 2 or 3 full breaths of oxygen, he may go considerably longer than 3 or 4 minutes and not turn blue. (The record for breath-holding after prolonged forced breathing ending with a few breaths of oxygen is now 18 minutes.)

The explanation of these experiments on so-called voluntary apnea is obtained by analysis of the alveolar air, by which it is

easy to determine the tensions of the carbon dioxide and oxygen in the blood flowing from the lungs to the respiratory center and carotid bulb. To obtain that air, the subject need only make a sudden deep expiration through a piece of rubber tubing 2 cm. in diameter and 100 to 150 cm. in length. He then holds his tongue against the end of the tube while a sample of the air in the tube close to his mouth is drawn off into a gas burette for analysis. Analyses of alveolar air obtained in this way show that the duration of breath-holding without preliminary over-ventilation is determined almost wholly by the accumulation of carbon dioxide. After a brief period of forced breathing, the amount of carbon dioxide in the blood is decreased and it takes longer for the accumulation to develop; but the tension of carbon dioxide in the alveolar air at the breaking point is the same as before. After more prolonged forced breathing, however, the tension of carbon dioxide at the breaking point is not the same; it is much lower. The reason is that the carbon dioxide is so much decreased, and the period of voluntary apnea may be so long, that a deficiency of oxygen also develops, and under this deficiency the respiratory center becomes abnormally sensitive to carbon dioxide. Less carbon dioxide is therefore required to force a return of breathing. It is only by means of a final inhalation of oxygen, leaving the lungs full of oxygen and preventing an anoxial increase of excitability after prolonged over-breathing, that it becomes possible to hold the breath for 10 or 15 minutes or more.

The Circulation as a Factor in Respiration

It is easy to measure the volume of air that flows in and out of the lungs in 1 minute. It is much more difficult to determine the volume of blood that is pumped by the heart through the lungs in 1 minute. Yet the latter measurement becomes possible also if it is borne in mind that the volume of oxygen which the air loses in the lungs is also the volume of oxygen that the blood gains. Four analyses are needed: two to determine the percentages of oxygen in the inspired and expired airs respectively, and two on the blood—one to determine the oxygen in the venous blood that has been through the lungs and the other on the arterial blood before it has been through the lungs. In order to make these relations definite, suppose that a man at rest is found

to breathe 8 liters, or 8,000 cc. of air per minute and that the inspired air is found, on analysis, to contain 21 per cent of oxygen and the expired air 17 per cent. As the difference is 4 per cent, the oxygen absorbed is $8{,}000 \times 0.04 = 320$ cc. Suppose, next, that a sample of blood drawn from the right side of the heart—as has been done even on a man—is found by analysis to contain 13 cc. of oxygen in each 100 cc. of the blood and that a sample drawn from an artery is found to contain 19 cc. of oxygen in each 100 cc. of blood. Then the blood stream that is pumped through the lungs in a minute is calculated to be $320/0.06 = 5{,}400$ cc. per minute.

From such analyses and calculations, the so-called minute-volume of the circulation is known to be roughly 60 to 70 per cent as large as the minute-volume of breathing, or almost as large as the ventilation minus the dead space. As the total volume of blood in the body is estimated to be approximately 8 per cent of the body weight, the body of a 70 kg. man (154 lbs.) contains approximately 5,240 cc. of blood, and the result of these calculations is that on an average a volume equal to all the blood in the body—but some of it a little more often and some a little less often—passes through the lungs and around through the tissues once each minute. (There are less radical methods of estimating the oxygen content of the blood than by puncture of the heart, but the principle involved is the same and the details of these methods do not concern the present discussion.)

Under physical exertion the heart beats faster and the stroke volumes are larger. By increase of both factors the minute-volume of the circulation may be increased 6, or even 8, times the volume during bodily rest. But as the volume of breathing may be increased 10 or 12 fold, or even more, it follows that the maximum exertion of the body is limited rather by the capacity of the heart to pump blood than by that of respiration to ventilate the lungs.

The two points of most importance to be noted here are: first, that owing to the rapidity and volume of the circulation of the blood through the lungs and tissues, all parts of the body are so well "ventilated," so to speak, that the tensions of oxygen and carbon dioxide in the tissues are kept close to those in the alveolar air of the lungs; and second, that although the increase

of breathing under moderate physical exertion is due almost solely to the production of carbon dioxide, oxygen want affords a large accessory stimulus in the heavy panting of intense exertion.

The relation of the circulation to respiration is seen most strikingly when, as a result of acute heart failure or a severe hemorrhage, arterial pressure and the flow of blood to the brain suddenly cease. The violent breathing thus induced is called "air hunger."

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Chapter 3

Respiratory Functions of the Blood and Their Laws

The blood is the principal agent for the transportation of substances from one part of the body to another. Of all the substances transported, oxygen and carbon dioxide are the most immediately important. The volume of these gases taken up and given off in the lungs and tissues is large and variable. During bodily rest the quantities in a man are about 0.2 to 0.3 liter of each gas per minute, during moderate work 1.0 to 2.0 liters per minute, and during intense exertion 3.0 to 4.0 liters.

Three Functions of Hemoglobin

Both oxygen and carbon dioxide dissolve in the blood in accordance with the law of Henry; but the amounts held in simple solution at the gas pressures prevailing in the lungs and tissues (3 volumes per cent of carbon dioxide and 0.4 volume per cent of oxygen) are too small to afford an effective mode of transportation. If the volumes taken up and given off by the blood depended merely upon the law of Henry, that is, on solubility, very large differences of pressure between the lungs and tissues would be required to enable the blood to transport the amounts of oxygen and carbon dioxide that it does. Actually, large volumes are transported with slight differences of pressure.

It has long been known that it is the special function of hemoglobin, the red coloring matter of the blood, to take up a large volume of oxygen in the lungs and to give it off in the tissues. It has now come to be recognized that hemoglobin plays an almost equally important part in the transportation of carbon dioxide, although in quite a different manner. The two functions are, in fact, performed by different atomic groups in the hemoglobin molecule. It is a common mistake, and very misleading, to think of hemoglobin as exchanging oxygen for carbon dioxide in the tissues and *vice versa* in the lungs. Actually the blood may transport maximum quantities of both gases at once. The

mechanisms of transportation are distinct; nevertheless, they exert a considerable reciprocal influence upon each other.

Carbon dioxide itself does not combine with hemoglobin. Among the numerous and complex properties of hemoglobin is its capacity to act as a weak acid. As such it is combined with the alkalies which are normally in slight excess in the blood. As the blood passes through the tissues, the carbon dioxide which they produce reacts with this alkali-hemoglobin to form alkali bicarbonates; and it is in the form of sodium bicarbonate, chiefly in the plasma, and to a less extent of other alkali bicarbonates within the corpuscles, that carbon dioxide is held and transported in the blood.

It is characteristic of the way things are managed in the living body that owing to these properties of hemoglobin the blood is enabled to transport large volumes of oxygen and carbon dioxide, not only with slight alterations of their partial pressure, but also with a correspondingly slight alteration of the balance of acid and alkaline elements in the blood. Hemoglobin thus performs three functions: (1) it combines with oxygen and gives it up again readily; (2) it provides the alkali to allow the formation of alkali bicarbonate for the transportation of carbon dioxide; and (3) it takes up and gives off alkali so readily, being itself a very weak acid, that it maintains the acid-alkali balance, that is, the hydrogen-ion concentration, of the blood within narrow limits of variation.

Transportation of Oxygen by Hemoglobin

Hemoglobin forms, apparently, a true stoichiometrical chemical compound with oxygen, although the union is loose. Hemoglobin is a complex compound protein with a very large molecule. It contains iron, which passes readily from a less to a more oxidized form and back again, 1 atom of iron combining with 2 atoms of oxygen. The controlling conditions are the partial pressures of oxygen to which the blood is exposed in the lungs and tissues and with which it is equilibrated. In blood containing the amount of hemoglobin within the limits of variation normal for healthy men, complete saturation of the hemoglobin with oxygen amounts to about 18 to 20 volumes of this gas per 100 volumes of blood. This is termed 100 per cent saturation. Arterial blood which is in gaseous equilibrium with the

atmosphere of the lungs (about 100 mm. partial pressure of oxygen) is about 97 per cent saturated. The average mixed venous blood returning from the body to the lungs in healthy men during rest has lost about 6 volumes per cent of oxygen and is therefore about 75 per cent saturated. During vigorous exercise with a large consumption of oxygen in the tissues, the degree of unsaturation in the venous blood may increase to 60 per cent or more, which is the same thing as a saturation of 40 per cent or less.

If these percentage saturations, and the partial pressures corresponding to them, were directly proportional, a 74 per cent and a 40 per cent saturation would correspond respectively to partial pressures of 74 mm. and 40 mm. Actually they correspond to partial pressures of about 43 mm. and 26 mm. respec-

FIG. 2. Oxyhemoglobin Dissociation Curve of Blood in the Presence of 40 mm. CO_2. Broken line, Oxygen Dissociation Curve in the Body.

tively. In other words, the oxyhemoglobin dissociation curve has a form which is neither a straight line nor a simple exponential expression. It has an S-shape rising from zero pressure and zero content of oxygen slowly at first at pressures below 10 mm.; then more rapidly so that it reaches 20 per cent saturation at 15 mm.; 40 per cent at 26 mm.; 60 per cent at 35 mm.; 80 per cent at 48 mm.; and 97 per cent at 100 mm. From these figures, and from the curves in Figure 2, it can be seen at a glance why a slight lowering of the oxygen pressure in the air breathed and in that of the lungs (normally about 100 mm.) has a compara-

tively slight effect; for until the pressure is considerably reduced the amount of oxygen taken up by the blood is only slightly decreased.

The subject of the relations of oxygen and hemoglobin is extensive and complex and need not be pursued here. But it is important to note that the affinity of hemoglobin for oxygen is influenced by many factors, although these factors and their resultant general effects on hemoglobin are held nearly constant during health. A pure or nearly pure solution of hemoglobin in water, when equilibrated with various pressures of oxygen, affords a dissociation curve which is a rectangular hyperbola. At comparatively low oxygen pressures such a solution takes up, relatively to the amount of hemoglobin, much more oxygen than does hemoglobin under the conditions existing in blood. This oxyhemoglobin dissociation curve is markedly affected by the presence of salts (KCl, etc.) which cause it to take the S form above referred to. This curve is also extremely sensitive to the hydrogen-ion concentration of the fluid; even a slight increase in this condition causes a marked decrease, not in the total amount of oxygen held at complete saturation, but in the amount combined at any partial pressure corresponding to less than complete saturation, as shown by the lower curve in Figure 2. In the blood, hemoglobin is held in the corpuscles, probably in a colloidal form. The concentration of the various salts is quite uniform and is kept at the normal values by the action of the kidneys.

Influence of Hydrogen-Ion Concentration upon Hemoglobin

The hydrogen-ion concentration of the blood is maintained nearly uniform by respiration. The small increase of carbon dioxide in the venous blood induces a slight increase of H ions, *i.e.*, decrease of pH, each time the blood goes around the circulation; but this effect is immediately compensated by the elimination of carbon dioxide in the lungs. Yet even this rhythmic variation in the reaction of the blood is sufficient so that the giving off of oxygen in the tissues is effected at a distinctly higher pressure, and the taking up of oxygen in the lungs may occur more readily than would be the case without this action of carbon dioxide and of the hydrogen-ion concentration upon the affinity of hemoglobin for oxygen.

It may be seen from these facts why blood which has been hemolyzed, its corpuscles broken up by some toxic substance and the hemoglobin thrown into solution in the plasma of the blood, has properties which are distinctly abnormal. In illustration of this one of the writers (H.W.H.) has found that the hemoglobin in normal blood combines with oxygen and gives it off again with practically no heat of reaction; and he finds also (in common with others) that hemoglobin in solution has a distinct heat of reaction for combination with oxygen.

Transportation of Carbon Dioxide by Blood

The hemoglobin molecule probably contains both carboxyl and amido—*i.e.*, acid and basic—groups and is, therefore, an amphoteric electrolyte. Its isoelectric point lies at a hydrogen-ion concentration a little above, that is, more acid than that of blood, the pH of which is 7.35. It therefore acts as an acid which is less dissociated and weaker than carbonic acid. In arterial blood the hemoglobin is largely combined with base, chiefly potassium, and potassium chloride is the principal salt in the corpuscles. The principal inorganic constituents in the plasma, on the contrary, are sodium chloride, 0.12 mol. and sodium bicarbonate, 0.02 mol.

The walls of the red corpuscles are nearly impermeable to cations, but fairly freely permeable to anions such as chlorine and HCO_3. Suppose now that arterial blood, whose plasma has the salt composition just stated, passes through an active muscle where, owing to a higher pressure of carbon dioxide, it takes up a normal load of this substance. In solution carbon dioxide acts as carbonic acid, H_2CO_3; and, depending upon the concentration of this carbonic acid, a redistribution of acids and bases occurs. Chlorine from sodium chloride passes into the corpuscles and combines with the potassium previously united to hemoglobin. The sodium thus liberated from sodium chloride in the plasma forms $NaHCO_3$. Within the corpuscles also, carbon dioxide, or rather H_2CO_3, probably forms $KHCO_3$ in analogous fashion, for the increase of carbon dioxide is usually distributed fairly equally between corpuscles and plasma, volume for volume. The plasma is, however, the larger volume, and therefore the principal medium of transportation. But it is the hemoglobin of the corpuscles which chiefly enables it to perform this function,

although the proteins of plasma play a similar but much smaller role.

The constantly varying distribution of the various ions between the corpuscles and plasma which occurs as the blood passes through the lungs and tissues, losing a little carbon dioxide in the one and gaining a little in the other, accords closely with the requirements of the theory of equilibruim across a semi-permeable membrane as formulated by Donnan. The main outlines of the system chemically considered are thus fairly clear, but the details are complex. The foregoing discussion, therefore, emphasizes only those factors which bear upon the volume of breathing. Mention should, however, be made here of a chemical effect which seems to contribute an element characteristically physiological to the sum total of these reactions and processes. This consists in the fact, demonstrated by Haldane, that homoglobin, when combined with oxygen, has distinctly stronger acid properties and is more dissociated in respect to the hydrogen of its carboxyl groups than when deoxygenated. Thus in the lungs the oxygenation of hemoglobin assists in displacing carbon dioxide from the blood, and in the tissues the loss of oxygen in itself renders the blood slightly more alkaline and thus better capable of taking up carbon dioxide. Observations by Van Slyke indicate that the giving off of 10 parts of oxygen, and the simultaneous taking up of 7 parts of carbon dioxide, leave the hydrogen-ion concentration of the blood unaltered. As the respiratory quotient is usually about 0.8, it is evident that, as Haldane was the first to show, the hydrogen-ion concentration of venous blood is only slightly higher than that of arterial blood.

Hydrogen-Ion Concentration of Blood

In the chemistry of blood, as in all modern chemical thought, the concept of equilibrium is fundamental. A condition such as acidity or alkalinity is defined as an equilibrium, and is measured by a figure indicating the amount of some element in a certain state when the atomic rearrangement due to the addition of some substance, such as an acid or an alkali, is complete. Thus all possible degrees, both of alkalinity and acidity, are expressed in terms of the number of hydrogen atoms or ions dissociated from water in the presence of acids or alkalies. In all watery solutions a minute part of the water exists thus dis-

sociated; and the product of the H × OH ions is constant alike in pure water, neutral solutions of salts and in acid and alkaline solutions of all strengths. Acids and alkalies influence this condition in proportion to their concentrations and to the degree of their dissociation; a weak acid, being less dissociated and maintaining fewer hydrogen ions is, therefore, weaker than a strong acid. Dissociated alkalies similarly maintain more OH ions in the solution and reduce the hydrogen ions correspondingly.

The expression generally employed to indicate the hydrogen-ion concentration, or C_H, is unfortunately and unnecessarily complex and recondite; it is pH, which is the negative logarithm of the number of hydrogen ions in 1 liter of the solution. As the pH increases, the acidity and C_H decrease; a pH of 7.0 indicates neutrality. Both H and OH ions are then present in the amounts 1×10^{-7} in the fluid, and being equal they balance as in water, and afford neutrality.

By the hydrogen-ion concentration of blood is generally meant that of the plasma when the blood has a normal content of gases. It has been shown to depend with remarkable precision upon the simple relation first formulated by L. J. Henderson:

$$C_H = K \times \frac{H_2CO_3}{NaHCO_3} \qquad (1)$$

In this expression K is a constant, apparently identical for all conditions of the plasma of the bloods. For all purposes here concerned we may therefore omit K and use the sign $\propto$, meaning proportional. Thus the concentration of hydrogen ions is proportional to the ratio of dissolved carbon dioxide to the alkali or combined carbon dioxide.

$$C_H \propto \frac{H_2CO_3}{NaHCO_3} \qquad (2)$$

The H_2CO_3 in the numerator of the fraction and in the ratio is simply the amount of carbon dioxide held in solution in the plasma according to the law of Henry. It varies always in direct proportion to the partial pressure of carbon dioxide. In other words, it is the alveolar pressure of carbon dioxide multiplied by the constant of solubility of carbon dioxide in blood at body temperature. The $NaHCO_3$ of plasma, which forms the

FIG. 3. **The CO_2 Diagram.** The point marked A indicates the condition of the arterial blood. It lies upon the CO_2 dissociation curve, the solid line, which expresses by the scale at the left the alkali available in the blood, its CO_2 combining power at the time. The point on the curve at which A is held is determined by the pressure of CO_2, according to the scale immediately below the abscissa. In the next scale below are given the volumes of breathing, and below that the number of liters of air per minute in the breathing, which would give each particular pressure of CO_2 and would hold the arterial blood, A, at corresponding points to the right or left on the dissociation curve. The mass of CO_2 produced is assumed to be constant.

The oblique lines express the H-ion concentration for the points at which each intersects the dissociation curve. Each line expresses a certain relation of $P_{CO_2} : V_{CO_2}$ and therefore a constant H-ion concentration throughout its length.

If the volume of breathing, here indicated as six liters per minute, is increased to eight, because of a slight oxygen deficiency due to prolonged breathing of some asphyxiant, the A point is thereby shifted to the left. The blood is then abnormally alkaline; and as a compensation alkali passes out of the blood, and the dissociation curve is lowered, until the new arterial point A′ lies at the intersection of a new and lower dissociation curve and the normal H-ion diagonal. When, on the other hand, excess of oxygen is supplied, the breathing is gradually depressed; the A point moves to the right—and even more rapidly under inhalation of oxygen plus CO_2—and the blood is therefore abnormally rich in carbonic acid, and its H-ion concentration abnormally high. In compensation of this condition more alkali is called into the blood, and the dissociation curve is thus restored to a normal level. The dotted circle along which the A point moves counterclockwise indicates the course of such readjustments of the level of the CO_2 dissociation curve, under the influence of variations in the supply of oxygen and other fundamental conditions. The diagram as a whole shows how the volume of breathing, the amount of alkali in use in the blood, and the H-ion concentration interact to achieve normal relations.

denominator of the fraction, is usually termed the alkaline reserve. The term is, however, unfortunate, for the real alkaline reserve of the blood is the far larger amount of alkali combined with hemoglobin—chiefly as the potassium salt of hemoglobin—in the corpuscles. If the corpuscles are separated from the plasma by centrifugation, the plasma may be neutralized by means of dilute hydrochloric acid very much as if it were a solution of sodium bicarbonate. But if the corpuscles are present and the blood is in an atmosphere of air plus 5 or 6 per cent carbon dioxide, enormously more hydrochloric acid is required to neutralize it. Whole blood has a far greater power to neutralize acid and to maintain approximate neutrality than has mere plasma. The reason appears from the fact that if separated corpuscles are suspended in dilute neutral sodium chloride solutions, and exposed to an atmosphere of carbon dioxide and again centrifuged, a considerable part of the sodium is now found in the saline solution as bicarbonate. The chlorine ions have passed into the corpuscles and combined with potassium previously held by hemoglobin. This process of bicarbonate production may be repeated by transferring the corpuscles to fresh carbonated saline until a total of 200 or 300 volumes per cent of combined carbon dioxide or $NaHCO_3$ is thus produced. (The volume of the original blood from which the corpuscles were obtained is taken as 100.) In Figure 3 is reproduced the CO_2 diagram devised by the authors to show these relations.

Regulation of Respiration by the Blood

With these features of the blood as a physicochemical system before us, we may now describe, more precisely than was possible in the previous chapter, the physiological regulation of breathing. There are three controls of respiration: the immediate, the intermediate, and the fundamental. (1) The immediate control is exercised by the amount of carbon dioxide which the body produces and eliminates at the time. (2) The intermediate control is effected by the blood alkali which, in proportion to its amount, holds the dilution ratio of breathing at some nearly constant figure for the liters of air breathed per liter of carbon dioxide exhaled. It does this through the sensitiveness of the respiratory center to the hydrogen-ion concentration of the blood. (3) The fundamental control is the oxygen pressure to which the

individual is acclimatized. It determines, or on change of altitude (or barometric pressure) it readjusts, the amount of the blood alkali. It accomplishes this through the depressant influence on respiration exerted by each increase of oxygen pressure, or by the slowly developing stimulation of breathing which results from decrease of oxygen. This depression of breathing renders the blood relatively acid by accumulation of carbonic acid. On the other hand, the stimulation of breathing by low oxygen causes slight overbreathing with depletion of carbonic acid, and consequently a relatively too alkaline blood. In the normal body depressed breathing and acidosis (the only condition properly so-called outside of acute disease) tend to draw alkali into the blood from some undefined source. This process for increasing the blood alkali is used by the system in a manner characteristic of the purposefulness of biological mechanisms. Alkalosis, a low ratio of $H_2CO_3 : NaHCO_3$, no matter whether the blood alkali is absolutely high or low, is utilized by the organisms to reduce the blood alkali, partly through the urine and partly in still undefined ways.

There is some evidence that carbon dioxide exerts a specific influence upon the respiratory center, probably because of its high diffusibility through tissues; but it is probable that in general it is through the part which carbon dioxide plays in determining the hydrogen-ion concentration of the blood that it influences the respiratory center. This (in view of equation 2 given above) is equivalent to saying that respiration is regulated by the relation of the amount of the dissolved carbon dioxide, H_2CO_3, to the amount of combined carbon dioxide, $NaHCO_3$ in the plasma. Thus any increase of carbonic acid tends to increase respiration; on the contrary, any increase of the combined carbon dioxide or bicarbonate tends to decrease it; but it is their ratio, not their sum or difference, which regulates.

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Chapter 4

Practical Applications of the Laws of Gases and Vapors

The laws defining the behavior of gases are among the simplest of the principles of science and their formulas are easily learned. The mistakes, to which nearly anyone is liable in applying them to any but familiar types of problems, are equally simple and easy to make. What, for instance, is the lifting power of helium as compared with hydrogen in a balloon? (Molecular weights, 4 and 2 respectively.) Two of the most eminent of American scientists replied offhand, "One-half." The correct answer is, of course, "approximately twenty-four twenty-sixths, if we take air at a mean molecular weight of twenty-eight."

Similarly in respect to negative pressures the correct conception does not always come first. Suppose one side of the thorax has been punctured and the lung on that side has collapsed. (See Figure 1, page 22.) Will the heart, which with its connections forms a slightly flexible partition dividing the chest into two compartments, be pressed toward or away from the intact lung? And suppose an inspiration is drawn so that the intact lung is inflated further, will the heart be pressed more or less firmly in that direction? "Toward the intact lung," and "more firmly," are the mechanically correct answers, although the opposite answers are frequently given offhand. For an anatomical reason the heart is moved by inspiration toward the deflated lung, but the usual reason offered for the answer arises from a misapprehension of the mechanics of the chest. The way in which the lung is expanded by a negative pressure on its pleural surface prevents it from ever pushing against the heart.

A third common mistake occurs in calculating the respiratory quotient (see page 19). It is natural to divide the percentage of carbon dioxide in the expired air by the apparent oxygen deficit in the air, that is, by the figure by which its oxygen content falls short of 20.93 per cent. But this overlooks the fact

that the volume of the expired air at all respiratory quotients below 1.0 is less than that of the inspired air, and thus leads to an error which is sometimes important. It is corrected by use of the fact (or assumption) that the volumes of nitrogen in the inspired and expired airs are exactly the same. Many problems in this field present themselves, like these three samples, as elementary but tricky puzzles.

The laws of Boyle, Charles, and Henry, and the strict statement of the behavior of vapors, may be found in textbooks of physics and need not be repeated here. But an attempt will be made in this chapter to show the kind of use to which these fundamental principles are put in the field of respiration, and some of the easy and frequent mistakes that are likely to occur. No attempt will be made to state rigorously exact definitions or rules, but rather to place warnings near the various false turnings of the paths in this field. The important thing is to develop the instinct for seeing each problem from a correct and practical angle.

Modes of Expressing Concentration of Gas

There are commonly in use four forms of expression for the concentration of gases and vapors in air: (1) per cent by volume, (2) parts by volume, (3) partial pressure and (4) weight per volume (milligrams per liter) of air. Each has advantages for particular circumstances and is convertible into any of the other forms.

Partial pressure and per cent by volume are generally employed to express the concentration of the common respiratory gases, oxygen, nitrogen and carbon dioxide, and for the relatively inert gases, such as methane and hydrogen, which must be present in high concentration to exert any physiological effect.

The form parts by volume, or parts per thousand, per ten thousand, or per million parts of air, is employed to give the concentration of more actively toxic gases. Recently in this country the form "parts per million" has been generally adopted. This mode of expression is convenient in many cases, but it does not afford a true basis of comparison of the toxicity of the various volatile substances, except when they have nearly the same molecular weight. For instance, to compare the toxicity of equal volumes of ammonia gas (molecular weight 17) and of bromine

vapor (molecular weight 159.8) would be quite misleading, for one would contain by weight nearly 9.4 times as much of the active substance per unit volume of air respired as the other.

The expression of concentration by the weight of the volatile substance per unit volume of air, usually as milligrams per liter, affords not only a ready means of comparison of the toxicity of the various gases and vapors but also the best basis for estimating the rate at which air is vitiated by vapor from a volatilizing fluid and the rate at which a gas or vapor is absorbed in the lungs. A table for conversion of concentrations from parts by volume to milligrams per liter and *vice versa* is given here.

Weight of Gas Volumes

One gram molecule of every gas occupies the same volume as 1 gram molecule of every other gas when measured under the same conditions of pressure and temperature. This means that equal volumes contain the same number of molecules and that the weights in grams are in the same relation as the molecular weights of the substances. At 0° C. and 760 mm. this volume is 22.4 liters. The weight of 1 liter of any gas at 0° C. and 760 mm. therefore is the gram molecular weight divided by 22.4. The molecular weight of oxygen is 32; the weight of 1 liter of oxygen under standard conditions is $\frac{32}{22.4}$ or 1.428. At other temperatures and pressures the weight of 1 liter of oxygen is modified according to the laws of pressure and temperature, as given hereafter. Thus 1 liter of oxygen at 38° C., 740 mm. when wet (water vapor 50 mm.) will weigh:

$$1.428 \times \frac{(740 - 50) \times (273)}{760 \times (273 + 38)} = 1.138 \text{ g.} \qquad (3)$$

The weight of a unit volume is important in expressing the concentration of various gases in air. As stated above, the most convenient and precise mode of expression is in milligrams of the substance per liter of air. An expression of this type is readily converted into percentage or into parts (*i.e.*, volumes) of the gas in question per million volumes of air. To make this conversion the number of milligrams of the substance per liter of air is divided by the molecular weight of the substance and then multiplied by 0.0224 to find the number of cubic centimeters

Table 2. Conversion Table for Gases: Parts per Million Versus Milligrams per Liter.[1]

[25° C. and 760 mm. mercury, barometric pressure.]

M. W.	1 mg./l.-p.p.m.	1 p.p.m.-mg./l.	M. W.	1 mg./l.-p.p.m.	1 p.p.m.-mg./l.	M. W.	1 mg./l.-p.p.m.	1 p.p.m.-mg./l.
1	24,450	0.0000409	51	479	0.002086	101	242.1	0.00413
2	12,230	.0000818	52	470	.002127	102	239.7	.00417
3	8,150	.0001227	53	461	.002168	103	237.4	.00421
4	6,113	.0001636	54	453	.002209	104	235.1	.00425
5	4,890	.0002045	55	445	.002250	105	232.9	.00429
6	4,075	.0002454	56	437	.002290	106	230.7	.00434
7	3,493	.0002863	57	429	.002331	107	228.5	.00438
8	3,056	.000327	58	422	.002372	108	226.4	.00442
9	2,717	.000368	59	414	.002413	109	224.3	.00446
10	2,445	.000409	60	408	.002554	110	222.3	.00450
11	2,223	.000450	61	401	.002495	111	220.3	.00454
12	2,038	.000491	62	394	.00254	112	218.3	.00458
13	1,881	.000532	63	388	.00258	113	216.4	.00462
14	1,746	.000573	64	382	.00262	114	214.5	.00466
15	1,630	.000614	65	376	.00266	115	212.6	.00470
16	1,528	.000654	66	370	.00270	116	210.8	.00474
17	1,438	.000695	67	365	.00274	117	209.0	.00479
18	1,358	.000736	68	360	.00278	118	207.2	.00483
19	1,287	.000777	69	354	.00282	119	205.5	.00487
20	1,223	.000818	70	349	.00286	120	203.8	.00491
21	1,164	.000859	71	344	.00290	121	202.1	.00495
22	1,111	.000900	72	340	.00294	122	200.4	.00499
23	1,063	.000941	73	335	.00299	123	198.8	.00503
24	1,019	.000982	74	330	.00303	124	197.2	.00507
25	978	.001022	75	326	.00307	125	195.6	.00511
26	940	.001063	76	322	.00311	126	194.0	.00515
27	906	.001104	77	318	.00315	127	192.5	.00519
28	873	.001145	78	313	.00319	128	191.0	.00524
29	843	.001186	79	309	.00323	129	189.5	.00528
30	815	.001227	80	306	.00327	130	188.1	.00532
31	789	.001268	81	302	.00331	131	186.6	.00536
32	764	.001309	82	298	.00335	132	185.2	.00540
33	741	.001350	83	295	.00339	133	183.8	.00544
34	719	.001391	84	291	.00344	134	182.5	.00548
35	699	.001432	85	288	.00348	135	181.1	.00552
36	679	.001472	86	284	.00352	136	179.8	.00556
37	661	.001513	87	281	.00356	137	178.5	.00560
38	643	.001554	88	278	.00360	138	177.2	.00564
39	627	.001595	89	275	.00364	139	175.9	.00569
40	611	.001636	90	272	.00368	140	174.6	.00573
41	596	.001677	91	269	.00372	141	173.4	.00577
42	582	.001718	92	266	.00376	142	172.2	.00581
43	569	.001759	93	263	.00380	143	171.0	.00585
44	556	.001800	94	260	.00384	144	169.8	.00589
45	543	.001840	95	257	.00389	145	168.6	.00593
46	532	.001881	96	255	.00393	146	167.5	.00597
47	520	.001922	97	252	.00397	147	166.3	.00601
48	509	.001963	98	249.5	.00401	148	165.2	.00605
49	499	.002004	99	247.0	.00405	149	164.1	.00609
50	489	.002045	100	244.5	.00409	150	163.0	.00613

Factors for conversion of some units.

1. Mg. per l. × 28.32 = Mg. per cu. ft.
2. Mg. per l. × 1,000 = Mg. per cm.
3. Mg. per cu. ft. × 35.314 = Mg. per cm.
4. Mg. per cm. × 0.02832 = Mg. per cu. ft.

[1] U. S. Bureau of Mines, Technical Paper 248 (1921).

Table 2.—*Continued*

M. W.	1 mg./l.-p.p.m.	1 p.p.m.-mg./l.	M. W.	1 mg./l.-p.p.m.	1 p.p.m.-mg./l.	M. W.	1 mg./l.-p.p.m.	1 p.p.m.-mg./l.
151	161.9	0.00618	201	121.6	0.00822	251	97.4	0.01027
152	160.9	.00622	202	121.0	.00826	252	97.0	.01031
153	159.8	.00626	203	120.4	.00830	253	96.6	.01035
154	158.8	.00630	204	119.9	.00834	254	96.3	.01039
155	157.7	.00634	205	119.3	.00838	255	95.9	.01043
156	156.7	.00638	206	118.7	.00843	256	95.5	.01047
157	155.7	.00642	207	118.1	.00847	257	95.1	.01051
158	154.7	.00646	208	117.5	.00851	258	94.8	.01055
159	153.7	.00650	209	117.0	.00855	259	94.4	.01059
160	152.8	.00654	210	116.4	.00859	260	94.0	.01063
161	151.9	.00658	211	115.9	.00863	261	93.7	.01067
162	150.9	.00663	212	115.3	.00867	262	93.3	.01072
163	150.0	.00667	213	114.8	.00871	263	93.0	.01076
164	149.1	.00671	214	114.3	.00875	264	92.6	.01080
165	148.2	.00675	215	113.7	.00879	265	92.3	.01084
166	147.3	.00679	216	113.2	.00883	266	91.9	.01088
167	164.4	.00683	217	112.7	.00888	267	91.6	.01092
168	145.5	.00687	218	112.2	.00892	268	91.2	.01096
169	144.7	.00691	219	111.6	.00896	269	90.9	.01100
170	143.8	.00695	220	111.1	.00900	270	90.6	.01104
171	143.0	.00699	221	110.6	.00904	271	90.2	.01108
172	142.2	.00703	222	110.1	.00908	272	89.9	.01112
173	141.3	.00708	223	109.6	.00912	273	89.6	.01117
174	140.5	.00712	224	109.2	.00916	274	89.2	.01121
175	139.7	.00716	225	108.7	.00920	275	88.9	.01125
176	138.9	.00720	226	108.2	.00924	276	88.6	.01129
177	138.1	.00724	227	107.7	.00928	277	88.3	.01133
178	137.4	.00728	228	107.2	.00933	278	87.9	.01137
179	136.6	.00732	229	106.8	.00937	279	87.6	.01141
180	135.8	.00736	230	106.3	.00941	280	87.3	.01145
181	135.1	.00740	231	105.8	.00945	281	87.0	.01149
182	134.3	.00744	232	105.4	.00949	282	86.7	.01153
183	133.6	.00748	233	104.9	.00953	283	86.4	.01157
184	132.9	.00753	234	104.5	.00957	284	86.1	.01162
185	132.2	.00757	235	104.0	.00961	285	85.8	.01166
186	131.5	.00761	236	103.6	.00965	286	85.5	.01170
187	130.7	.00765	237	103.2	.00969	287	85.2	.01174
188	130.1	.00769	238	102.7	.00973	288	84.9	.01178
189	129.4	.00773	239	102.3	.00978	289	84.6	.01182
190	128.7	.00777	240	101.9	.00982	290	84.3	.01186
191	128.0	.00781	241	101.5	.00986	291	84.0	.01190
192	127.3	.00785	242	101.0	.00990	292	83.7	.01194
193	126.7	.00789	243	100.6	.00994	293	83.4	.01198
194	126.0	.00793	244	100.2	.00998	294	83.2	.01202
195	125.4	.00798	245	99.8	.01002	295	82.9	.01207
196	124.7	.00802	246	99.4	.01006	296	82.6	.01211
197	124.1	.00806	247	99.0	.01010	297	82.3	.01215
198	123.5	.00810	248	98.6	.01014	298	82.0	.01219
199	122.9	.00814	249	98.2	.01018	299	81.8	.01223
200	122.3	.00818	250	97.8	.01022	300	81.5	.01227

of the gas in question per liter of air; one-tenth of the number of cubic centimeters is the percentage; a thousand times the number of cubic centimeters per liter would be the parts per million.

Gauge Pressure and Absolute Pressure

The use of gauges for the measurement of gas or vapor pressures causes much confusion when the requisite distinction between absolute pressure and gauge pressure is disregarded. For work under compressed air, as in caissons and deep-sea diving, it is the absolute pressure which is the essential factor causing nitrogen to dissolve in the blood and thus, if the pressure is lowered too rapidly, induces caisson disease. But in this and many other practical matters it is customary and convenient, from an engineering standpoint, to express values in terms of gauge pressure. Gauge pressure is the difference between two absolute pressures. The ordinary steam gauge furnishes an illustration. With no fire under the boiler and with free connections to the outside air, the gauge rests at zero pressure, although the pressure within the boiler is actually 1 atmosphere or 15 lbs. on each square inch. Such also is the pressure surrounding the gauge. On closing the boiler and firing it, the pressure recorded on the gauge rises, let us say, to a reading of 15 lbs. The pressure within is thus 15 lbs. greater than the outside pressure, while the absolute pressure within the boiler is 30 lbs. That the reading of the gauge is purely relative is further illustrated by supposing the gauge reversed and placed inside of the boiler with its steam connection opening outside of the boiler. Under this condition the pressure recorded will be below zero of the gauge and each pound rise of steam will be read as a "pound of vacuum" in the surrounding air. The absurdity of this is at once apparent with 100 lbs. steam pressure in the boiler and a gauge reading of the surrounding air showing a vacuum of 100 lbs.—manifestly impossible, for an absolute vacuum is a negative pressure of only 15 lbs.

Although we do not commonly think of air as exerting any pressure against the inside of the flask which contains it, it is in reality exerting an outward pressure equal to the inward pressure exerted by the weight of air pressing against the outside of the flask. But if the air is sucked out by means of a pump, and the

outward propulsive force is thus removed, the flask may be collapsed by the inward pressure of the air surrounding it. The barometer is the instrument employed to measure the weight of the surrounding air. It is calibrated on a scale of absolute pressure which has as its zero a complete vacuum. But in ordinary life and in many conditions of chemistry and engineering, the zero referred to is atmospheric pressure. It is essential always to keep in mind which of the zeros is being used. At sea level the average absolute pressure of the surrounding air is 760 mm. of mercury; this varies slightly with the meteorological conditions and widely with the altitude above sea level at which the measurement is made. The normal absolute pressure at Pike's Peak, Colorado (altitude 14,100 ft.) is about 450 mm. of mercury. There is a decrease of approximately 22 mm. of mercury per thousand feet of elevation up to about 13,000 ft., after which the decrease is somewhat less rapid.

Misapprehension of the distinction between gauge and absolute pressure is not limited to the field of gas measurement. A particularly striking example is the common belief that nosebleed among those going to high altitudes is the result of the decrease in the external pressure of the air. It is true that the blood pressure (gauge pressure) is the same at high and low altitudes while the atmospheric pressure (absolute pressure) is decreased as we ascend. It is argued that the vessels are therefore under a greater strain and hence more likely to rupture. Reference to absolute pressure shows, however, that the absolute blood pressure has fallen by the exact amount that atmospheric pressure has decreased. The hemorrhage is, in reality, due to the drying and cracking of the nasal membrane as a result of the increased evaporation in the dry and rarefied air.

It might be thought that the pressure of the gases in the blood would play a part, for instance the pressure of nitrogen. There is, indeed, a pressure of nitrogen in the blood, but it soon becomes equal to that of the nitrogen in the air breathed. The same amount of nitrogen is held in solution in venous as in arterial blood, and therefore the pressure of nitrogen is the same in each. Similarly, the fact that arterial blood pressure is usually about 100 mm. of mercury higher than venous blood pressure does not at all affect the nitrogen pressure, nor does it make the pressures of oxygen or carbon dioxide at all higher in arterial

than in venous blood. Gas pressures in the blood and blood pressure have no direct relations.

Relations of Volume and Pressure

A gas is a substance existing in a low degree of aggregation and exhibiting therefore, a high degree of compressibility. The volume occupied by any mass of gas, the temperature remaining constant, is determined by the pressure exerted upon it. Furthermore, the change in volume is proportional to the change in absolute pressure, not the gauge pressure. The volumes (V and V') occupied by the same mass of gas at two pressures (P and P') will therefore vary in the ratio $V/V' = P'/P$ or concretely for a given mass of gas expanded or compressed to a certain extent (say one-half) $1V/2V = 2P/1P$. That is, the pressure increases as the space occupied decreases, and *vice versa*. In order to compare the amounts of gas in units of volume it is essential that the pressures at which they are measured should be known; otherwise, the comparison may be wholly misleading.

Partial Pressures

The pressure exerted by a mixture of gases in a bag or other collapsible container is equal to the pressure exerted upon it and is the sum of all the pressures of the component gases. Each acts separately according to the principle just stated, and the pressure exerted by each is known as its partial pressure. To illustrate this, suppose all the air were sucked out of a 1-liter flask; the pressure within the flask would then be zero. The pressure exerted upon the outside of the flask would be that of the prevailing barometer, B. Into this flask is now run an amount of oxygen which, measured at the prevailing barometer, would be a half liter. A pressure reading shows that the pressure within the flask is $B/2$. A similar half liter of nitrogen is now run into the flask and the pressure rises to B. Although the total pressure is that of the prevailing barometer, the partial pressure exerted by the oxygen and by the nitrogen in each case remains $B/2$. The partial pressure exerted by any gas, therefore, is that fraction of the total pressure which is equal to its proportion (the proportion of the number of its molecules, not its weight) in the whole mixture.

Partial pressure is frequently given in terms of per cent. An

analysis of air shows it to contain approximately 21 per cent of oxygen and 79 per cent of nitrogen and other inert gases. At sea level the partial pressure exerted by these two gases (dry) would be respectively:

21 per cent of 760 mm. = 160 mm. partial pressure oxygen.
79 per cent of 760 mm. = 600 mm. partial pressure nitrogen, etc.

At higher altitudes the same percentages hold, but the barometric pressure is reduced and the partial pressure of each gas is proportionately decreased. For example, with a barometer of 750 the partial pressure of oxygen is 151 mm. and of nitrogen 569.

From these considerations it might appear that, as gas composition expressed in per cent is independent of barometric variation, it is superfluous to consider partial pressures which fluctuate with the barometer. In physiological work, however, it is partial pressure which is of critical importance. As will be seen in a subsequent section, the solution of gases in liquids is determined by the partial pressure, and not by the percentage of each gas in a mixture. The body gets its oxygen supply by diffusion through the moist membranes of the lungs, and is therefore dependent upon the partial pressure of oxygen, and largely independent of the amount of nitrogen with which it is mixed. This point is illustrated by the difference in behavior of a man and a burning candle under alteration in air composition. A candle is a well-known and usually practical test for sufficient oxygen in the air to permit a man to breathe safely in such places as a well or a silo. But man and candle are profoundly different. The burning candle is dependent upon the percentage composition of the air and is largely independent of the partial pressure of oxygen. A candle can be made to burn at almost any altitude, and only becomes extinguished when the size of the flame increases to such an extent that most of it is too far from the wick to maintain an ignition temperature. A man, on the other hand, is in danger when he reaches an altitude where the partial pressure of oxygen is insufficient for his blood to take up enough oxygen for his needs. The reverse of this behavior of man and candle is seen in an atmosphere partially depleted of oxygen but at normal pressure. The candle becomes extinguished when the oxygen falls to 15 or 16 per cent, or about 114 mm.

partial pressure, equivalent to the oxygen pressure at an altitude of 5,500 ft. above sea level, approximately that of Denver, Colorado, where people live healthy lives and candles also burn normally. A man is only slightly affected by an hour or two in 15 per cent of oxygen at sea level and collapses only when the oxygen percentage decreases to a partial pressure of 76 mm., which is about half that at sea level.

This comparison may be carried even further. An atmosphere containing 5 per cent of oxygen and compressed to 4 atmospheres' pressure (the partial pressure of oxygen will then be nearly normal, or 152 mm.) will maintain a man perfectly in respect to oxygen, but a candle cannot be lighted. Likewise in an atmosphere of pure oxygen of a pressure of only 152 mm. a man is entirely normal, whereas a candle burns with much more than ordinary rapidity.

Influence of Temperature on Volume

Gases, if restrained only by barometric pressure, increase in volume as the temperature rises. The rate of expansion is the same for all gases, and for each degree rise of temperature the increase is 1/273 of the volume at 0° C. The general formula for the relative volumes is

$$\frac{V}{V'} = \frac{273 + t}{273 + t'},$$

in which V and t are the initial volume and temperature and V' and t' the final conditions. Thus, in passing from 20° C. (ordinary room temperature) to 38° C. (lung temperature), a gas increases in volume in proportion to $\frac{273 + 38}{273 + 20}$ or 106 : 100, and in passing from 38° C. to 20° C. the decrease in volume is expressed by $\frac{273 + 20}{273 + 38}$ or 94 : 100. As the gas expands with rise of temperature but without change of pressure, as in a heated room, the weight of the amount in unit volume falls correspondingly.

Role of Water Vapor

In the lungs the pressure of water vapor is an important factor and must always be taken into account. It is the more

necessary to keep this in mind because in gas analysis percentage readings are ordinarily made upon the basis of dry gas, although actually the gases are completely saturated with water vapor; and, strange as it seems, no correction for water vapor is necessary in the analytical calculation. The reason no correction is needed is that in a wet gas burette all the measurements are made with the gases saturated with water vapor. The absorbing reagent (*e.g.*, alkali) takes out one of the constituent gases (*e.g.*, carbon dioxide) and part of the water vapor; but when the remaining gas is drawn back into the burette it is again saturated with water vapor. The volume of vapor in this second reading is less than in the previous reading in exactly the same proportion that the absorbed gas bore to the other gases, estimated dry. Thus a correct percentage of the absorbed gas to the total gases of the sample, apart from water vapor, is obtained.

In converting the percentage of the absorbed gas into terms of millimeters of partial pressure, however, the water vapor present in the original gas mixture under analysis must be taken into consideration. The water vapor in it exerts a partial pressure and, as the sum total of all the partial pressures of all the gases plus the pressure of water vapor only equals the barometric, the pressure of water vapor thus reduces the partial pressure of every other constituent. When the gas mixture is fully saturated with water vapor at a certain temperature, as air in the lungs is saturated at body temperature, the correction for vapor pressure is wholly a function of the temperature and is entirely independent of the barometer. It is necessary merely to subtract the water vapor pressure from that of the prevailing barometer and to consider the resultant value as the total dry gas pressure. The partial pressure of water vapor at 20° C. is 17.4 mm.; thus wet air at 760 mm. and 20° C. will have the oxygen partial pressure given by:

$$0.21 \times (760 - 17.4) = 155.9 \text{ mm. of oxygen.}$$

The same air when dry contains:

$$0.21 \times 760 = 159.6 \text{ mm. of oxygen.}$$

Fortunately in physiological work it is seldom necessary to consider partial saturations with water vapor, since gases inhaled

into the lungs become fully saturated with water vapor at the temperature of the body, and correction can be made on that basis. In men ascending to great altitudes the water vapor in the lungs plays a particularly important part, for as this factor remains constant at 50 mm., it becomes an increasingly large percentage of the total pulmonary contents. The constancy of the water vapor thus reduces the pressure of oxygen in the lungs more rapidly than it is reduced in the atmosphere, as the ascent rises to greater and greater heights. At a barometer of 50 mm., if such a height were attainable, the lungs would contain no air, but only water vapor or steam.

Standard Conditions

For comparison of gas volumes it is essential that they be referred to standard conditions of temperature, pressure, and moisture, that is, as they would be at 0° C., 760 mm. pressure, and dry. If the temperature and prevailing barometer are observed, the volume of gas under any conditions can readily be converted to standard conditions. For this conversion the general formula used is:

$$\text{Vol. of (dry) gas at } 0^\circ \text{ C., } 760 \text{ mm.} = \text{Vol. observed} \times \frac{(B - W) \times 273}{760 \times (273 + t)}$$

B = prevailing barometer
W = partial pressure of water vapor
t = observed pressure

Solution of Gases in Fluids

In order to operate fully and rapidly, the principle next to be discussed, that of defining the solution of gases in liquids, requires very large surfaces. The form in which this principle is usually stated applies only to equilibrium; but equilibrium is actually approached very slowly and is difficult to produce experimentally. It is best approximated by shaking the gas and fluid together so as to expose the large surfaces and small masses of bubbles, drops and foam, or by rolling the vessel so that a film of liquid is exposed on the wall of the vessel and continually renewed.

In the lungs, however, the blood is spread into extremely fine

streams in the capillaries, which are so numerous that the total surface is enormous; and yet, as the total cross-section of the stream is very large, the rate of flow is correspondingly slow. A virtually complete equilibrium of gas pressures between the alveolar air and arterial blood is thus attained, and this is accomplished almost instantaneously. Practical use of this quick and complete equilibration of gases is made for the purpose of determining the concentration of any foreign volatile substance in the blood. A small volume of air in a rubber bag or spirometer is rebreathed four or five times and an equilibrium between this air and the gas pressures of the venous blood (subject to certain limitations) is thus attained. The figures obtained from such determinations of the pressure of any foreign gas in the blood are multiplied by either the coefficient of solubility or the more convenient coefficient of distribution of the gas; and the results show the concentration of the substance in the blood. These results, when multiplied by the body weight, indicate the approximate total amount in the body.

Law of Henry and Dalton

This law defines the influence of pressure upon the solution of gases in fluids at equilibrium. It states that the amount of each gas that is dissolved in a fluid at any given temperature is directly proportional to the partial pressure of that gas acting upon the fluid and is totally independent of all other pressures. By means of this principle we can find, for example, the answer to the question raised in the next section: What amount of carbon dioxide will dissolve in water at 60° C. when the total pressure of carbon dioxide is 611 mm.? The law tells us that the water will reach 611/760 of the amount defined by the coefficient of solubility, which is 359 cc. of CO_2 per liter of water, when the gas is separated, dried, cooled to 0° C. and measured under 760 mm. pressure.

Conversely, if a certain sample of water contains 100 cc. of dissolved carbon dioxide per liter at 60° C., we can calculate the partial pressure. The water contains 100/359 of the amount that it would dissolve at this temperature and 760 mm. partial pressure of this gas; and by applying Henry's law, $100/359 \times 760 = 212$ mm. It does not matter at all what other gases are in solution in the fluid, nor their amounts or pressures. Nor does

any hydrostatic pressure to which the liquid may be subjected have any influence upon the partial pressure of the dissolved gas.

There are three forms of expression for the solubility of gases: (1) coefficient of solubility, (2) solubility by weight, and (3) coefficient of distribution.

Coefficient of Solubility

A gas in contact with a fluid dissolves until the partial pressure of the gas in solution equals the partial pressure of the remaining undissolved gas. The amount of gas which it is necessary to dissolve in any fluid to balance a given partial pressure of the gas varies with the nature of the fluid and the temperature. Although it is a general rule that with rise in temperature less gas must be dissolved to produce any given pressure, the influence upon the amount dissolved which is exerted by temperature is subject to no simple rule, but is specific for each gas and each liquid. It is therefore necessary to determine experimentally the solubility of each gas in each fluid at various temperatures. This value is known as the coefficient of solubility for the particular condition.

It is customary to express the coefficient of solubility for any given temperature as the amount of the gas in a unit volume of fluid which is in complete equilibrium with the gas at a partial pressure of 760 mm. and the given temperature. But this amount of dissolved gas is not stated at the volume that it would have as a free gas at the given temperature, but at 0° C. and 760 mm. Thus, to say that the coefficient of solubility of a certain gas in water at 38° C. is 0.05 means that water at that temperature dissolves 5 volumes per cent of the gas, and that if all the gas is then pumped out of 100 cc. of the water, dried, cooled to 0° C. and measured at 760 mm., it will be 5 cc.

Not only the total gas pressure acting upon a fluid at 760 mm., but also the vapor pressure of the fluid itself at the given temperature must be taken into account. Passing a gas through a flask of water until no more is taken up does not give the solubility at the pressure at which the gas stream is supplied. Thus, for example, the coefficient of solubility of carbon dioxide in water at 60° C. is given as 0.359. This does not mean that if the total gas and vapor pressure upon the water is 760 mm., the

amount of gas dissolved in 1 liter will be 350 cc. The partial pressure of carbon dioxide acting upon the water under the conditions here defined is, in fact, not 760 mm., but 760 minus the water vapor pressure at 60° C., which is 149 mm. The partial pressure of the carbon dioxide is therefore 611 mm. In order to produce a pressure of 760 mm. of carbon dioxide in water at 60° C., it would be necessary to force CO_2 into the flask under a total pressure of 760 plus 149 mm., or 809 mm. absolute, or 149 mm. gauge pressure.

Solubility by Weight

The solubility of gases in fluids is sometimes expressed in terms of the weight of gas in solution in unit volume of the fluid at a given temperature and normal atmospheric pressure. It is customary to give the weight of the gas found in unit volume when the fluid is exposed to 760 mm. of total pressure, that is, gas and water vapor, and not as in the case of the solubility coefficient with the partial pressure of the gas itself at 760 mm. The shift in base is somewhat confusing, but suitable correction is readily made. Thus a table contained in books of reference gives the solubility of carbon dioxide at 60° C. with a coefficient of volume solution of 0.359 or 359 cc. per liter, while the weight of the gas dissolved at this same temperature is given as 0.0577 per 100 cc. of water, or 0.577 g. per liter. These two amounts do not agree, for 1 cc. of carbon dioxide weighs 0.002 g. and 0.577 g. of carbon dioxide corresponds to 288 cc. of the gas. The latter figure corresponds, however, to a partial pressure of 611 mm. which (see above) is equivalent to 760 mm. minus the pressure of water vapor at 60° C.

Coefficient of Distribution

Still a third mode of expression has been found more convenient by the authors than either of the two preceding conventional forms for the solubility of gases in fluids. It is the coefficient of distribution. By this term is meant the relative weights of gas in equal volumes of the gas mixture and of the fluid which are in gaseous equilibrium. In expressing the ratio of distribution it is customary to take the concentration of the gas phase as the unit. Thus in a system in which each liter of air contains 3 mg. of the substance, and the fluid in equilibrium

with it contains 12 mg. per liter, the ratio is 3 : 12, and the coefficient of distribution would be given as 1 : 4, or merely as 4.

The use of the coefficient of distribution is particularly convenient in dealing with the absorption of gases through the lungs into the blood. As stated here the term "coefficient of distribution" is very similar to the "proportionality constant" (K) used in the thermodynamic presentation of Henry's law, in which the partial pressure (p) of any volatile substance present in small amounts in a solution is proportional to its molar concentration, (C). That is,

$$p = KC, \text{ or } \frac{C}{p} = K$$

The value of K is, of course, dependent upon the nature of the substance dissolved and the solvent fluid, and upon the temperature. The distinction between the proportionality constant and the coefficient of distribution (D) lies in the fact that the latter is given in the same terms of molar concentration for both the solution and the vapor. Thus

$$\frac{C}{C'} = D$$

Here C is the concentration in the fluid and C' the concentration in the vapor phase; and both are expressed in mols., or both in grams per liter.

Behavior of Vapors

A vapor differs from a gas in the fact that, while the latter under ordinary conditions exists only in the gaseous state, the former is the gaseous phase of a substance which (as in the case of water vapor above discussed) can exist also in the form of liquid at common temperatures and pressures. Thus, for example, at room temperature a flask partially filled with ethyl ether may contain both liquid ether and ether vapor; while on the contrary hydrogen, nitrogen, carbon dioxide, etc., are encountered under these conditions only as gases. At very low temperatures and high pressures these typical gases are partially condensed to liquid form and may then be present as vapors.

The distinction between gases and vapors is necessary because of the difference in behavior of these two classes of substances in respect to alterations of temperature and pressure. The

behavior of a vapor mixed with air is in fairly close accord with the gas laws and can be so treated, providing none of the substance is present in liquid form, and that there is no passage from the gaseous phase to the liquid. The more dilute the mixture of a vapor in air the more nearly does it conform to the gas laws. But alterations of phase introduce special considerations for vapors.

When a volatile fluid is exposed to the air, a portion evaporates and exists mixed with the gases of the air as the gaseous or vapor phase of the substance. If the air and fluid are enclosed in a vessel, a point will finally be reached at which equilibrium is established between the fluid and vapor and no further volatilization occurs. A pressure gauge connected with the vessel shows that, in consequence of the addition of the vapor to the air, the pressure has risen. If the flask is closed while containing air and liquid, but before the liquid has evaporated appreciably, the increase in pressure resulting from the volatilization of the fluid at the existing temperature is known as the vapor pressure. The vapor pressure of a liquid in equilibrium with the pure substance increases with rise in temperature much more rapidly than does the pressure of a true gas; when separated from its liquid, however, it follows the law of Charles. Different liquids have different vapor pressures for the same temperature; but at the boiling point of any fluid the vapor pressure equals the barometric pressure prevailing upon the fluid. The lower the barometer the lower the boiling point. Thus water at 40° C. has a vapor pressure of 55 mm., and when the atmospheric pressure is reduced to 55 mm., it therefore boils.

Thus the treatment of vapors in terms of the gas laws reaches a limit at the vapor pressure. To state the matter broadly and in practical terms: a vapor ceases to behave as a gas and tends to condense into the liquid form whenever the weight per volume of air, or the partial pressure of vapor measured at the existing temperature and barometric pressure, equals the maximum weight or partial pressure of the vapor which can be developed by volatilization in a closed vessel at the given temperature. To illustrate, let as assume that we are dealing with a liter of air at 760 mm. and 30° C. containing 2 g. of ether vapor. The ether in this mixture will behave essentially as a true gas during any decrease of pressure, due to enlarging the space, or any increase

of temperature. If, on the contrary, the space were contracted at the same time that the temperature was decreased to 20° C., so that the pressure remained 760 mm., the air at that temperature would contain an amount of ether corresponding to 2.08 g. per liter. Condensation must then take place, for at 20° C. the vapor pressure, or maximum possible partial pressure of ether, is 442 mm., which is equivalent to 1.9 g. per liter. Therefore, 0.18 g. per liter will condense and pass into the liquid state. On the other hand, if the same mixture were made up at 30° C. and were maintained at this temperature, but compressed to half its volume (a pressure of 1,520 mm. of mercury), the partial pressure of ether would be doubled, so that 4 g. would be contained in 1 liter. But this condition cannot persist, since the limit of partial pressure of ether at 30° C. is 648 mm., which is equivalent to 2.58 g. per liter. On this account 1.42 g. will be condensed out as liquid ether. Subject to these limitations, however, the weight of a liter of vapor is calculated by dividing the gram molecule of the substance by the gas constant and treating it in the manner described for gases.

Solubility of Vapors

The solubility which particularly concerns us here is that of vapors in blood at body temperature, in other words, the coefficient of distribution under the conditions existing in the lungs and determining the absorption of vapor when it is inhaled. The solubility in blood has been determined directly for very few substances. In general it is slightly less (about 10 per cent) than in water; it is decreased in about the proportion that the water in blood is diluted by its solid constituents. This statement regarding the solubility of volatile substances in blood is based on the experience of the authors; it contradicts a belief common among physiologists and biochemists that the lipoids in blood add considerably to its solvent power for volatile substances. The purpose of the discussion here is to point out how such data as exist for the solubility of volatile substances in water may be so applied as to afford approximate values for blood. When they react with hemoglobin or some other constituent of the blood, another factor enters.

Substances which can exist both in liquid and vapor form at ordinary temperatures vary in the extent to which the vapor

pressures of solutions of the substances in water are decreased below those of the pure liquids. There are wide differences in behavior between those substances whose liquids are miscible with water in all proportions and those whose liquids are very slightly soluble in water; and there are all gradations between these extremes. No single simple formula applies to all. In order to be of practical use here and not erroneously applied, Raoult's law, which is more general than the law of Henry, and other theoretical matters, would require, not only full discussion, but careful limitation. A textbook of physical chemistry may be consulted: but even in the case of substances suitable for direct application of Raoult's law, accurate data are often lacking. Even the solubilities in water of volatile substances in liquid form are in many cases undetermined; and such data as are available are, for the most part, rather rough approximations. Very few solubilities have been determined directly for vapors in water.

The solubility of a water in vapor at a certain temperature can usually be estimated however by combining the data from two tables in books of reference: the table showing the vapor pressure of the pure liquid and the table showing the solubility of the liquid in water. For solutions in water of substances which do not themselves dissolve in water to any great extent, a rough approximation of the coefficient of distribution between the vapor phase and the dissolved phase is obtained by assuming that the amount of the substance that would be dissolved under a pressure equal to the vapor pressure of the pure liquid is the same as the amount dissolved when the substance in liquid form has been freely exposed to water. Below this pressure the concentration and pressure vary proportionally in accord with the law of Henry.

The general principle of Raoult's law applying to this matter is that the vapor pressure of a volatile substance in solution is the same as that of the substance in liquid form in which a certain amount of water is dissolved and in which the molar concentration of the volatile substance is thus reduced. As the molar concentration is decreased the vapor pressure is decreased proportionally. Thus if two dishes, one (A) containing water, and the other (B) containing the pure liquid substance, are put together under a bell jar and left until equilibrium has been

reached by the passage of both water vapor and the vapor of the other volatile substance between the contents of the dishes, the concentration of the latter substance in solution in the water in A will be that which is in equilibrium with a vapor pressure less than that of the pure liquid, which was originally in B, in proportion as this liquid in B has itself become diluted by dissolving water.

The next chapter will show how large and important is the part which solubility plays in the absorption, distribution and elimination of volatile substances through the lungs and in the body.

Chapter 5

Principles Determining Absorption, Distribution and Elimination of Volatile Substances

Noxious gases and vapors, other than irritants and simple asphyxiants, exert their action only after absorption into the blood. The body is poisoned by the absorbed substance in the same way, and to the same extent, as it would be if a like amount entered the body through any other channel of absorption—*i.e.*, if it were swallowed* or were given intravenously or per rectum. The toxic effects of noxious substances are determined by the amount accumulated in the body—*i.e.*, by the total dosage. The idea of total dosage is universally understood in respect to poisons which are swallowed or which are given by injection. It is less well understood in respect to substances absorbed through the lungs. But the fact remains that, with qualifications in respect to the immediate anesthetic effects of volatile hydrocarbons, to be discussed later in this chapter, it is total dosage—the number of milligrams per kilogram of body weight—of the noxious substance, volatile or otherwise, taken into the body which determines the effect produced.

The obvious, basic feature of total dosage relates the toxicology of noxious gases and vapors to that of all other noxious substances. But it is a feature often overlooked because of the practice of expressing physiological response to gases and vapors only in terms of concentration of the gas or vapor in the air breathed and length of exposure. These values are practical in setting up working standards for ventilation but in them is involved not only total dosage but also the physical characteristics of the gas or vapor, particularly its solubility, its molecular weight, if the concentration is expressed in volume relation of

* In occasional instances there is an exception to this statement in that substances which are absorbed from the alimentary tract pass through the liver before entering the general circulation. The liver may act upon the absorbed material to modify a portion of it before any is distributed to the body; as noted later, this is presumed to occur with mercury (see p. 233).

vapor, and the peculiarities of absorption through the lungs. The concentration and length of exposure which lead to the accumulation of a certain amount of one gas or vapor in the body may lead to the accumulation of a widely different amount of another gas or vapor. Representations of effect in terms of concentration and exposure have therefore only empirical significance unless the variables involved and their relation to each other are understood. The present chapter deals with these relations.

Maximum Possible Absorption

There are two obvious general facts in regard to the absorption of any volatile substance through the lungs: (1) No more of the substance can be absorbed than is taken into the lungs in the air breathed; and (2) absorption ceases when an equilibrium is reached between the amounts in the body and in the air. The second of these will be dealt with on page 75. The first—the maximum possible absorption—will be considered here only as it affords a rule of thumb which is useful in making approximations of the physiological response to be expected from various concentrations of a gas or vapor in the air breathed.

The amount of any vapor brought to the lungs for absorption is determined by the product of three factors: (1) the volume of pulmonary ventilation per minute; (2) the concentration of the vapor in the air expressed in milligrams per liter; and (3) the length of exposure. The pulmonary ventilation of a man of average size performing work requiring moderate exertion may be taken as 8 liters per minute, or, in round numbers, 4,000 liters in an 8-hour working day.

If the air breathed contains 1 mg. per liter of some volatile substance the amount brought to his lungs, and hence the maximum amount that can be absorbed, is 4 g. The same maximum dose would be accumulated in an exposure of 1 hour to a concentration in the air 8 times as high as that given.

The next question would be that of the pharmacological effect of such a dosage. It is often possible to obtain from medical literature some idea of the toxic and non-toxic doses for single and repeated administrations of many of the volatile substances used in industry. The relation of dosage and physiological effect has a much more definite meaning than does that of concentration in the air and physiological effect.

General Process of Absorption

Figure 4 represents diagrammatically the physiological factors concerned in the absorption of gases and vapors: the circulation of the blood, respiration, and the body tissues. In this diagram the upper chamber represents the lungs. For convenience the ventilation is considered as a continuous flow of air—the inspired air entering at the right and the expired air passing out

FIG. 4. Diagram of the Respiratory Tract to Show the Relations of the Dead Space, Lung Ventilation, Blood Circulation and Body Tissue.

at the left. The partition across the chamber divides the stream of air so that the portion above the partition does not come into contact with the blood. This represents the virtual dead space; through it the air passes from inspiration into expiration without appreciable diffusion of any gas it may contain into the blood (see page 28). The remainder of the air is the effective pulmonary ventilation and it comes into free diffusion with the pulmonary blood. Virtually complete equilibrium in respect to all gases is almost instantly established between the air and blood in the lungs and is continually and accurately maintained.

At the commencement of inhalation of any gas or vapor, that portion which is taken up by the blood is carried in the arterial stream to the capillaries where exchange of the gas or vapor

takes place by diffusion between the blood and tissues. Here, as in the lungs, a nearly complete equilibrium is reached almost instantaneously. The venous blood, therefore, leaves the tissues with a concentration of gas or vapor practically identical with that developed in the tissues through which it has passed. The blood, with a reduced amount of the gas or vapor, then returns to the lungs, where it is again brought into equilibrium with the concentration of gas or vapor in the lungs. As the process continues, the amount of gas or vapor, and hence the tension, constantly rises in the tissues. The amount in the venous blood also rises correspondingly and tends gradually to approach that in the arterial blood. More and more of the gas or vapor is thus carried back to the lungs by the venous blood; consequently a decreasing amount is taken up by the blood from the air in the lungs and by the tissues from the blood. The limit approached is a state of saturation—equilibrium—at which absorption ceases (except to replace the small amounts eliminated in urine and sweat) and the body is saturated with the particular gas or vapor at the concentration existing in the air breathed. At this saturation the body will contain an amount of gas or vapor equal to the product of three factors: (1) the weight of the body; (2) the concentration of the gas or vapor in the air in the lungs; and (3) the coefficient of solubility of the gas or vapor in the body tissues at body temperature.

The Course of Absorption

The general course of absorption may be expressed as follows: If, during any time, t, the body becomes saturated to x per cent of full saturation for the tension inhaled, it will, in the next equal period, increase in saturation by x per cent of the remaining unsaturation. Thus after 2 and 3 times this amount of time we shall have:

$$x + x(1 - x) = 2x - x^2 = \text{saturation after } 2t, \text{ and}$$
$$2x - x^2 + x(1 - 2x - x^2) = 3x - 3x^2 + x^3 = \text{saturation after } 3t, \text{ and so on.}$$

This type of mathematical expression gives rise to a curve approaching the logarithmic in shape, as illustrated in Figure 5. The ordinates of the curve express the percentage saturation of the body with the gas or vapor. The abscissa represents time,

but has different values for different gases; its scale, if all the physiological conditions (such as respiration, circulation and body weight) are constant, depends upon the coefficient of solubility of the gas. In other words, the absorption of any and all non-reactive gases and at all concentrations follows this curve. The ordinates are always percentages of complete saturation of a body of a particular weight, by a gas of a particular solubility and for a particular concentration in the air. For twice the con-

Fig. 5.

Curve of Absorption of a Non-reacting Gas. The Value for 100 per cent Saturation is that of Full Equilibrium between the Body and the Surrounding Atmosphere.

centration the ordinates, when translated into terms of milligrams per liter or per kilogram, would indicate twice the amounts, but in terms of percentage saturation the ordinates are the same for all concentrations.

Equilibrium Value

What we have called here the equilibrium value—the full saturation of the body for any one concentration of gas or vapor—is of great practical importance: it expresses completion of absorption and therefore does away with all further consideration of time of exposure in relation to concentration of the gas or vapor in the air. If the total amount of gas or vapor that can have been absorbed into the body at equilibrium with any given concentration in the air causes no harm, then that concentration may be inhaled indefinitely, since at equilibrium no more of the gas or vapor can accumulate in the body. In this respect absorp-

tion by way of the lungs differs from absorption through any other channel. When a noxious substance is repeatedly swallowed, it continues to enter the body as long as it is taken; when a gas or vapor is inhaled, the absorption stops when the tension of the gas in the body corresponds to that outside of the body. Both the amount in the body and the concentration in the blood are then stationary at their maximum for the particular concentration in the air.

The equilibrium value thus establishes a limit for maximum possible absorption. With highly soluble gases or vapors, absorption may continue throughout an entire working day, but with those of low solubility, equilibrium is reached within a period of less than 8 hours and absorption is terminated.

In discussing maximum possible absorption an example was given in which a man was exposed to air containing 1 mg. per liter of vapor; he breathed 4,000 liters in 8 hours and his maximum possible absorption was 4 g. The saturation or equilibrium value for any gas or vapor—that is, the maximum amount that can be absorbed at any concentration—is determined as the product of the weight of the body, the concentration of the gas or vapor in the lungs, and its coefficient of solubility. A man of average size weighs about 70 kg.; he will be assumed here to breathe an atmosphere containing ether vapor; the coefficient of solubility of ether is 15. The saturation value for such a man breathing an atmosphere containing 1 mg. of ether vapor per liter of air would be 1.05 g. He could not accumulate a greater amount in any length of exposure, no matter how long. The saturation value in a gas or vapor of this solubility and lower becomes, therefore, a primary consideration in determining the maximum possible absorption.

The calculations made here are valid only for vapors which are essentially non-reactive in the body, as are the great majority encountered in industry. With reactive vapors, such as ethyl alcohol, the continual oxidation would keep the dose much lower than that calculated as above and saturation could not be attained. Such reactivity is a distinct advantage when the products of oxidation are, as with ethyl alcohol, non-toxic. However, it is a disadvantage when, as with aniline, the oxidation products are toxic. The continual oxidation prevents attainment of saturation and hence of cessation of absorption; the continued

absorption leads to progressive accumulation of the toxic products of oxidation.

Half Saturation Value

The maximum amount of a gas or vapor that can be absorbed is not a fixed absolute quantity, but is proportional to the concentration of that particular gas or vapor in the air and proportional also to its solubility. When respiration and circulation remain uniform, the rate of absorption is such that, if a certain percentage of the saturation is attained in 1 minute, the same percentage of the remaining unsaturation will be reached in the second minute, and so on thereafter. Thus if saturation is taken as 100, and if 1 per cent of this amount is absorbed in 1 minute, 1 per cent of 99 will be absorbed in the second minute; 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 or some other percentage of saturation.

The time required to reach a certain percentage saturation, x, may be derived as follows: Let A be the amount absorbed in the time, t. Then, since the maximum amount that can be absorbed, the equilibrium value, is CKW (in which C is concentration, K, coefficient of solubility, and W, body weight), and since

$$\frac{dA}{dt} \propto (CKW - A), \text{ therefore } \frac{dA}{dt} = k(CKW - A).$$

Integrating with θ as the constant of integration:

$$\ln [\theta(CKW - A)] = -kt, \text{ and } \theta(CKW - A) = e^{-kt}.$$

$$A = CKW - \frac{e^{-kt}}{\theta}; \text{ but when } t = 0, A = 0, \text{ and therefore } \theta = \frac{1}{CKW}.$$

Accordingly,

$$A = CKW\,(1 - e^{-kt}). \tag{1}$$

Now if x equals the percentage of saturation reached in time, tx,

$$x\,(CKW) = CKW\,(1 - e^{-ktx}).$$

$$\frac{1}{1-x} = e^{-kt}x, \text{ or } kt_x = \ln \frac{1}{1-x}$$

$$t_x = \frac{2.3}{k} \log \frac{1}{1-x} \qquad (2)$$

Since at the start $A = 0$, therefore $\frac{dA}{dt} = k(CKW)$; and from general consideration initially $\frac{dA}{dt} = \frac{LCKB}{BK + L}$; combining these two expressions we have $k = \frac{LB}{(BK + L)W}$ which can be substituted in (1) and (2).

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, as 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 adult at rest with a normal volume of respiration and circulation, the time of half saturation for a gas or vapor of $K = 15$, such as ethyl ether, is about 2.5 hours, while for one of $K = 0.014$, nitrogen, it is about 7 minutes, and for 90 per cent of saturation about 22 minutes. For a child, owing to its 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, by the pharmacological action of the gas itself, or in any other way.

The absorption of any absolute amount of gas, for example, the anesthetic amount of ether, is effected very slowly when a low concentration of the gas is inhaled, but with 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 concentration. An absolute amount,

therefore, may be only a relatively low percentage of the saturation limit (*CKW*) of a high concentration, but it may be a high percentage of the limit, or even exceed the limit, for a low concentration.

Mathematical Expression of the Process of Absorption

In order to express mathematically the part played in absorption by variations in blood flow, respiration, concentration of the gas and its solubility, these factors may be assigned the following symbols.

L—Effective pulmonary ventilation in liters per minute. This is the amount of air breathed minus the amount which enters the dead space and takes no part in gaseous exchange (see Chapter 2). The effective pulmonary ventilation is usually about two-thirds of the volume of breathing.

C—Concentration of gas or vapor in the air breathed. For mathematical consideration this is most conveniently expressed as milligrams per liter of air when warmed to body temperature, 38° C. and saturated with moisture as it is in the lungs (see Chapter 4).

K—Solubility of the gas or vapor expressed as the amount dissolved in the blood when the amount of the gas or vapor in an equal amount of air in gaseous equilibrium with the blood is 1. Thus if the solubility of a gas or vapor in blood at body temperature is 10, the value signifies that in the arterial blood leaving the lungs, or in blood brought into equilibrium outside of the body with an atmosphere containing the gas, there will be 10 times as much of the gas or vapor in 1 liter of blood as in 1 liter of alveolar air.

k—Relative solubility of the gas or vapor in the tissues of the body as a whole when that in the blood is taken as 1. Gases and vapors are more soluble in some tissues than in others, but for the majority the solubility in the tissues as a whole is nearly the same as in the blood. To this general rule ethyl and methyl alcohols, and other substances highly soluble in water, are an exception. Their solubility in any tissue is determined by the amount of water present, and is therefore higher for blood than for the tissues as a whole. The solubility in the tissues as a whole is approximately 0.8 of that in the blood.

G—Liters or kilograms of blood in active circulation in the

body. In man the volume of blood ranges between 7 and 9 per cent of the body weight; a man of average size would have about 6.5 liters of blood.

B—Circulation defined as the number of liters or kilograms of blood flowing through the lungs in 1 minute. This rate, like the volume of breathing, varies with bodily activity. In a man of average size at rest the volume of circulation will approximately equal the volume of pulmonary ventilation, 4 to 8 liters per minute. Under exertion both the volume of breathing and of circulation increase, but not proportionally. The volume of breathing increases out of proportion to that of the circulation. In the exertion of vigorous walking the circulation may double, but the volume of breathing triples.

Ac—the concentration of the gas or vapor in milligrams per liter of the arterial blood.

Vc—the concentration of the gas or vapor in milligrams per liter in the mixed venous blood in the heart—*i.e.*, the blood returning from all the tissues, but not yet exposed to the air in the lungs for equilibrium with the gas or vapor in the alveolar air.

W—body weight in kilograms.

Using these symbols and definitions, the following simple and useful expressions follow logically.

LC – amount of gas or vapor inhaled into the lungs per minute. (3)

During the first minute of absorption, and before the blood has had time to make a complete circuit and return to the lungs, the amount of gas or vapor brought to the lungs is equilibrated between the air brought to the lungs, L, and the volume of blood flowing through the lungs, B, in the proportion expressed by the solubility, K.

The equations expressing this equilibration are

$$LC \times \frac{BK}{BK + L} = \text{amount of gas entering the blood } i.e., \text{ absorbed} \quad (4)$$

$$LC \times \frac{L}{BK + L} = \text{amount of gas exhaled from the lungs, } i.e., \text{ unabsorbed} \quad (5)$$

$$\frac{K}{BK + L} = \text{concentration of gas or vapor developed in the arterial blood, } Ac \quad (6)$$

It will be observed that the concentration in the arterial blood does not rise gradually from zero at the beginning of absorption, but instead rises abruptly to the value established by equation (6). The subsequent rise in concentration, provided the factors of this equation remain constant, depends upon the return of venous blood containing some of the gas or vapor. In dealing with this feature the convenient interval of 1 minute, as used in equations (4) to (6) inclusive, cannot serve; the actual intervals are those of rounds of the circulation as expressed by $\frac{G}{B}$, which, during bodily rest, approximate but may be less than 1 minute.

During the second round of the circulation some gas or vapor would return in the venous blood and be added to that brought to the lungs in the inspired air. This total amount of gas or vapor would be equilibrated between the air in the lungs and the blood passing through the lungs. Slightly less of the gas or vapor would therefore be absorbed during the second minute than during the first, and slightly more would leave the lungs in the expired air.

If it is assumed here that the circulation to all tissues is approximately uniform (the exception to this feature will be discussed subsequently), and that therefore the blood leaving the lungs during the first minute will distribute its content of gas or vapor uniformly to the tissues as a whole, the amount of gas or vapor brought back to the lungs during the second round of the circulation will therefore be

$$\frac{LCKG}{BK + L} \times \frac{G}{W} \tag{7}$$

The concentration in the venous blood, Vc, returning to the lungs will be this amount divided by the volume of circulation, B. The amount or dose of the gas or vapor accumulated in the tissues at the end of the first round of the circulation will be the amount absorbed, and this corresponds to the concentration in the venous blood times the coefficient of distribution of the gas or vapor between blood and tissues, k, times the weight of the body, W.

The amount of gas or vapor which will be present in the body at full saturation—equilibrium with the concentration of

the gas or vapor in the air inhaled—does not depend upon any physiological process but solely upon the physical properties of the gas or vapor: its solubility and the concentration in which it is inhaled.

The concentration of the gas or vapor in the blood at equilibrium is expressed by the equation:

$$Ac \text{ (or } Vc) = CK \tag{8}$$

The amount of gas or vapor in the body per kilogram is,

$$Ac \text{ (or } Vc) \times k \tag{9}$$

or

$$CK\,kw \tag{10}$$

And the total amount of the gas or vapor in the body at this time is

$$Ac \text{ (or } Vc) \times k + W \tag{11}$$

The influence of volume of breathing and of circulation on the rate of absorption is best expressed by the time required to reach 50, or any other percentage of saturation as expressed by the formula:

$$\frac{t_x}{t'_x} = \frac{\dfrac{BK + L}{LB}}{\dfrac{B'K' + L'}{L'B'}} \tag{12}$$

Using this formula and substituting various values of K, so as to see the effect of solubility, 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

Table 3.

	$B=B'=1$		$L=L'=1$	
	$L = 1$	$L' = 2$	$B = 1$	$B' = 2$
$K = 0.01$	1.01	1.005	1.01	0.51
$K' = 10.0$	11.0	6.0	11.0	10.5

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 rates of absorption

and elimination. On the other hand, with a gas of solubility 10.0, 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. The relative amounts of time in hours or fractions of an hour required to effect, for instance, 50 per cent saturation are shown in Table 3.

Concentrations of Gas or Vapor in Blood, Urine and Expired Air

The concentrations of vapor in the blood, urine and alveolar air bear definite relations to one another and to the amount of vapor absorbed in the body. But to use these concentrations for more than an approximate estimation of the amount absorbed, or to compare physiological effects, the factors affecting these relations must be taken into consideration. It is only when absorption has ceased, or is at an extremely slow rate and a virtual equilibrium of the vapor throughout the body has been reached, that the concentrations in the blood, urine or alveolar air become precise indices of the amount in the body. Short of this equilibrium, and while absorption is continuing actively, the concentration in the arterial blood is at a continually higher level than that in the venous blood. Furthermore, the blood drawn from veins in different parts of the body during this time may show widely different concentrations. With slow absorption from low concentrations of vapor inhaled, these differences are slight; with rapid absorption from high concentrations, they may be large.

The maximum amount of the inhaled gas which any organ or tissue can absorb at a given tension is determined by the solubility of the gas in that tissue. The rate at which the gas accumulates in the particular tissue depends both upon the solubility of the gas in that tissue and also upon the amount of the gas brought to the tissue in any period of time. The latter factor is determined by the blood supply in relation to the bulk of the tissue. Thus a tissue with a comparatively low solubility for the gas and a large blood flow approaches saturation rapidly, whereas a tissue of high solubility and small blood flow approaches saturation much more slowly.

During bodily rest it may be estimated that approximately 80 per cent of the blood passes through 20 per cent of the tissues

in each round of the circulation; the remaining 80 per cent of the tissues receive only 20 per cent of the blood. Bone and fat, which together constitute a large part of the tissues of the body, receive a comparatively small blood flow. The flow to the brain, viscera and glands is large. This latter group of organs therefore approaches saturation at a much more rapid rate than do the bone and fat. The same relation holds true of elimination.

The rate of saturation of tissues with a large blood supply follows closely the concentration of a gas or vapor in the arterial blood. The concentration in these tissues therefore rises at first much more rapidly than in the tissues with a smaller blood supply, but the less rapidly saturating tissues act as a buffer to prevent immediate and complete equilibrium. This is the case both during absorption and elimination of the gas. During absorption the tension of a gas in any tissue cannot rise above the tension of gas in the arterial blood, nor can it fall below this limit during elimination. The tissues of small circulation and slow saturation and desaturation influence the concentration in the venous blood and consequently that in the lungs and arterial blood also.

Certain gases and vapors, particularly the anesthetic hydrocarbons, exert their acute action specifically upon one organ—the brain—and are largely inert in regard to others. The brain has an extremely large blood supply; the anesthetic action therefore tends to follow closely the concentration in the arterial blood and is little influenced by the total amount absorbed. The concentration in the peripheral venous blood indicates only the degree of saturation in the particular organ from which the blood is returning. Because of the large circulation to the brain the concentration in the brain builds up rapidly and the concentration in the blood from the jugular vein follows closely that in the arterial blood. Because of these relations the momentary inhalation of a high concentration of an anesthetic hydrocarbon, *e.g.*, ethyl ether, may cause marked symptoms before any large amount has been absorbed into the other parts of the body. On breathing fresh air the effects pass off equally rapidly since, when the inhalation of the vapor ceases, there is an immediate fall in the concentration in the arterial blood and correspondingly in the brain. If the inhalation has been prolonged with the accumulation of a large amount of the vapor in the body, this rapid fall

does not occur, since the concentration in the arterial blood is maintained by the vapor returned in the venous blood; a much longer time is then required for recovery.

The concentration of any vapor in the alveolar air corresponds to that in the arterial blood leaving the lungs at the time the alveolar air is collected. The relation of the concentrations in the air and blood is that of the coefficient of distribution for the particular vapor.

The concentration of the vapor in the urine corresponds closely to that in the arterial blood passing through the kidneys at the moment the urine is secreted. It must be borne in mind that the urine which has collected in the bladder does not show this relation for any one time; it is instead a composite of the urine secreted during the entire period in which it has collected and the varying concentrations in the blood at these times. The relation between the concentrations in the blood and urine—secreted at one time—is in the same relation as the solubility of the vapor in the two fluids; the difference in these solubilities is usually slight.

Elimination of Gases and Vapors

Gases and vapors are eliminated largely through the lungs and to a much less extent through the urine. Elimination through the lungs follows definite principles which are similar to those of absorption in reverse.

At the termination of absorption the body contains an amount of the gas which is equivalent to full equilibrium with some tension of the gas, although this may be much lower than the inhaled concentration. If none of the gas is eliminated, the body forms a closed and static system in which the gas is distributed to the various tissues and to the air in the lungs in proportion to their capacity to dissolve the gas. The concentrations in the arterial and venous bloods, under these circumstances, are the same. When elimination begins and part of the air in the lungs is replaced by fresh air, a part of the gas is carried away in the expired air and the concentration of the gas in the arterial blood leaving the lungs is reduced below that in the venous blood coming to the lungs.

The following expressions give the relations of the factors concerned in elimination:

$$V_cB \times \frac{L}{BK + L} = \text{amount of the gas or vapor in milligrams eliminated in 1 minute} \quad (13)$$

$$V_cG \times \frac{L}{BK + L} = \text{amount of the gas or vapor in milligrams eliminated in 1 round of the circulation} \quad (14)$$

Since the body is 100 per cent saturated to a degree corresponding to some tension of the gas at the beginning of elimination (namely that developed in the pulmonary air under the static equilibrium above mentioned), the loss of the amount of gas expressed by equations (13) and (14) decreases this percentage saturation to an extent expressed by the fraction:

$$\frac{\text{Gas or vapor eliminated in first period}}{\text{Total gas or vapor previously absorbed}} = \text{Rate of elimination in \% of body content} \quad (15)$$

During a second period of the same duration a further but slightly less amount of the gas or vapor will be eliminated, and this amount is the same percentage of the gas remaining in the body. Obviously, this is the same type of mathematical expression as that for the rate of absorption in equations (1) and (2) (page 74) and the curve would be the reverse of that given in Figure 5 (page 75). The elimination is, therefore, rapid in the beginning and becomes more gradual until the curve is nearly horizontal, which indicates that the final rate of elimination is very slow.

The solubility of the vapor is a primary factor in determining the rate of elimination; the more soluble the vapor the slower the elimination. As with absorption, the rate of circulation is the predominant influence for the rate of elimination of vapors of low solubility, but volume of respiration has little influence. These relations are reversed with soluble vapors; rate of circulation has little effect on rate of elimination, and volume of respiration has a marked influence.

Solubility is the controlling influence in the proportion of the amounts of absorbed vapor which will be eliminated in the expired air and urine. The amounts eliminated in the urine and expired air are in the relation

$$Ut \times K' \times K : Lt$$

in which U is the amount of urine secreted in 1 minute; t, the total time of elimination in minutes; K' the coefficient of distribution of the vapor between blood and urine (not far from 1); and K and L, as in previous equations, the coefficient of distribution for blood and the per minute volume of pulmonary ventilation. From this ratio it is evident that for vapors of high solubility a much greater percentage is eliminated in the urine than for those of low solubility.

Accumulation of Gases and Vapors

Under industrial conditions exposure to a gas or vapor is limited to the working hours. The time spent away from work is usually more than adequate to permit complete elimination of the gas or vapor and consequently none is present in the body at the beginning of the next daily exposure. There is therefore no accumulation of gases and vapors from daily exposure. The only possible exception to this general statement would be with highly soluble and non-reactive substances, such as methyl alcohol, or with reactive gases or vapors whose decomposition products were eliminated slowly.

Absorption of Volatile Substances Through Channels Other Than the Respiratory Tract

Volatile substances may be absorbed through channels other than the respiratory tract. The ingestion of alcohol, the administration of ether by way of the colon, and the absorption of aniline through the skin are examples. Under these circumstances the volatile substances enter the venous blood instead of the arterial; and this is different in principle from absorption through the respiratory tract. The venous blood from the place of entrance carries the dissolved gas or vapor to the right heart, where it is diluted by the entire venous stream and then passed through the lungs. The volume of breathing and rate of blood flow then determine the distribution of the substance between the air to be expired and the arterial blood to be distributed to the tissues of the body. The process is not unlike that of elimination, as discussed above, with this exception: the concentration of the gas or vapor in the mixed venous blood does not express the average of the concentrations in all the tissues of the body. Furthermore, although the substance is being eliminated,

the concentrations in the tissues rise instead of fall, for the absorption under these circumstances is in the nature of a redistribution. With these modifications the equations given under the discussion of absorption and elimination apply to absorption through channels other than the respiratory tract. The factors are the same, namely, the circulation, respiration and coefficient of distribution of the gas between blood and air in the lungs; but they interact in different associations when absorption occurs through channels other than the pulmonary tract.

Reactive and Non-reactive Gases and Vapors

The gases and vapors which exert their action after absorption into the blood may be divided into two classes according to whether they are reactive or non-reactive.

Reactive gases and vapors are altered within the body and are eliminated to a large extent in forms other than those in which they are absorbed. The toxicological action may be exerted either by the substance in its original form or by the product of such reaction. Ethyl alcohol is an example of a reactive vapor which exerts its action before its destruction has taken place; aniline is an example of a vapor which exerts its main action in the product arising from its reactions in the body.

Non-reactive gases and vapors are not altered to any appreciable extent in the body and are eliminated in the same form in which they are absorbed. The aliphatic hydrocarbons are examples of non-reactive gases and vapors.

Absorption and Elimination of Reactive Gases and Vapors

The character of the process concerned in the absorption of reactive gases is in general like that for non-reactive gases but with this difference: the reaction and consequent destruction of the gas prevent the attainment of equilibrium. The venous blood does not return to the lungs carrying the amount that would be anticipated from the equations given for the absorption of non-reactive gases and vapors. The course of absorption is influenced by the rate of alteration of the gas or vapor within the body; this rate has been determined only in the case of a few substances, notably ethyl alcohol and ethyl iodide, and in these cases only approximately. Neither of these approximations, in the one case an oxidation, in the other probably a hydration, is

sufficiently precise for mathematical analysis; nor do the values determined apply to other substances.

The elimination of reactive substances is likewise influenced by their alterations within the body. The amount of the substance eliminated is less than the amount absorbed. The mathematical analysis of elimination, presented in the previous section, applies to reactive substances only in regard to the exhalation through the lungs of a certain portion of the amount brought to them by the venous blood and not to the total quantity in the body. The curves of absorption and elimination of reactive substances do not correspond to that given in Figure 5 (page 75).

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Chapter 6

The Significance of Standards for Physiological Response to Various Concentrations of Gases and Vapors

Throughout later chapters the physiological effects of the various gases and vapors discussed will be given in relation to the concentrations in the air breathed. Such information is of primary importance to the chemist and engineer in those industries where volatile substances may occur. And of this information the most important is that concerning the maximum concentration of the gas or vapor which causes no ill effects, and is therefore safe and allowable for daily exposures throughout the entire working period. But before this information is accepted and applied, it is important to have a clear understanding of how the values for such concentrations are obtained and what they actually signify.

It is obvious that figures given for the physiological responses to various concentrations are not to be regarded as being as exact as such physical constants as boiling point and vapor pressure. In all matters affecting the human and animal bodies and their operation there are normal physiological variations; two men do not respond in precisely the same way to identical doses of a drug taken by mouth or to identical concentrations of a gas or vapor in the air breathed. In part, these differences may be due to the factors influencing absorption, distribution and equilibrium of gas and vapor as discussed in the previous chapter: body weight, degree of activity, volume of breathing and rate of circulation. But, in part also, they may be due to factors which are inherent in the constitution of the man and as yet not fully understood; these factors result in variation in tolerance or susceptibility beyond that of the average individual.

In setting up industrial standards for permissible concentrations of gas or vapor in the air breathed, reasonable allowances can usually be made for these normal physiological variations, or the standard can be phrased to indicate the susceptibility and

therefore to advise the exclusion of some group of individuals as by sex or age. The most difficult feature in establishing allowable concentrations is the determination of a basic figure applicable to the average man. Such determination requires a full knowledge of all immediate and remote physiological effects of the gas or vapor and some method of determining quantitatively the limits of these effects in terms of the concentrations inhaled. For most gases and vapors this knowledge is difficult to obtain, and for many it has not yet even been attempted. The maximum allowable concentration can usually be obtained only indirectly. As a consequence, there may be differences of opinion as to what constitutes a permissible concentration of any gas or vapor for prolonged exposure. The standards adopted in industries or set by law vary accordingly. Moreover, standards now in effect are subject to revision as additional information is obtained from research in laboratory and field.

In later chapters the concentrations of gases and vapors given as producing definite effects within a short time may appear as a range of figures. In these instances such a range does not indicate disagreement as to the findings of different investigators; it indicates mainly normal variations as between different men (or experimental animals) as discussed above. For many gases and vapors a range will also be found for the concentration given as permissible for prolonged exposure. In these instances the differences in concentrations reported indicate mainly disagreement in opinion.

Determination of Physiological Response

Four general procedures are used in attempting to establish the physiological response to various concentrations of gases and vapors:

1. **Experiments on Animals.** Such experiments consist of exposing animals to various concentrations of gases and vapors for lengths of time ranging from a few minutes to months and observing the ill effects suffered by the animals. This procedure is a primary step toward determining the physiological response to any gas or vapor. Great caution must be exercised, however, in drawing conclusions applicable to man, except as showing that certain concentrations are unquestionably fatal for short exposure, or that the gas is virtually non-toxic even in very high

concentrations. There are two main limiting factors to any broader application: the first of these factors is that of the qualitative effect on certain species—does the gas affect man in the same way that it does the experimental animal? The second factor is that of quantitative effect—if it does affect man in the same way, does it affect him to the same degree?

2. **Experiments on Man.** Experiments on man are made only when sufficient knowledge has been obtained of the full pharmacological action of the gas as to render such experiments safe. The data obtained are free from the objection raised in the previous section, but they are limited to concentrations which produce no serious disturbance. It is difficult, however, to evaluate maximum allowable concentrations unless the concentrations are raised to that at which disturbances are produced. It is, moreover, usually extremely difficult, and always expensive, to carry out prolonged and controlled experiments on a sufficient number of men to give results which have statistical validity.

3. **Field Experiments.** Data of great practical importance as to the maximum allowable concentration of any gas or vapor can be obtained from studies made under actual working conditions. The concentration of gas or vapor in the air is determined by frequent analyses and the health of the employees is followed by means of frequent medical examinations. One of the greatest difficulties in such studies is accurate determination of the concentrations of the gases or vapors inhaled by the men and women. The concentration varies with the proximity to the source and it usually fluctuates. Much care and study must be given to obtain truly representative samples.* For some vapors valuable additional information as to the amount absorbed may be obtained from the concentration of the vapor or its oxidation products in the urine, blood or expired air.

4. **Estimation from Dosage.** For many substances which exert their action after absorption, there is extensive medical knowledge of the relation of this action to dosage taken by stomach. The data given in the previous chapter serve to correlate concentration in the air with dosage in the body.

* A thorough and authoritative presentation of the principles and practices in determining the concentration of gases and vapors in air will be found in Jacobs' "Analytical Chemistry of Industrial Poisons, Hazards and Solvents," New York, 1941.

The limitations of the various methods of correlating concentrations and physiological response for gases and vapors, as classified in later chapters, are discussed below.

Group I. **Irritants.** The action of irritants in producing inflammation is fundamentally the same in all experimental animals and in man. The concentrations causing death on short exposures and those which are definitely dangerous to breathe for any length of time, as determined on experimental animals, may generally be taken as applicable to man. Below the concentration inducing acute injury, the results obtained on experimental animals, although valuable as a guide, cannot be applied quantitatively to man. Prolonged daily exposures to certain irritants in concentrations which do not cause any immediate disablement may in time result in a chronic respiratory disease. Reliable quantitative information on this point cannot be obtained from experimental animals.

Lack of knowledge as to the effects of low concentrations of gases and vapors is frequently reflected in wide variations in the maximum concentrations considered safe for prolonged daily exposure. With the common primary irritants there is close agreement as to safe concentrations, with the exception of nitrous fumes. This agreement is due to the simplicity of the physiological action of the irritants as compared to other noxious gases and from the wide and long industrial experience with these substances.

The inflammation caused by irritant gases and vapors occurs only on surface tissues; the principles of physiological effect in relation to the amount accumulated in the body, as discussed in Chapter 5, do not, therefore, operate for the irritants. This is a point of considerable importance in regard to the relations between time of exposure and the concentration of the gas or vapor. When a non-reactive gas or vapor exerts its action after absorption, the duration of exposure and the concentration inhaled are of equal importance. That is, if the inhalation of a certain concentration for 1 hour results in the accumulation of a certain amount in the body, approximately the same amount will be accumulated in half the time on doubling the concentration, or twice the time on halving it. The physiological effects experienced will be approximately the same, with some qualifications to be discussed later in this chapter in respect to the

anesthetic hydrocarbons. This direct relation does not hold with the irritants. Time of exposure is an important factor in determining the extent of the injury to the surface tissues; but the destructive action of the irritant is increased out of proportion to rise in concentration. The action of an irritant in causing inflammation is direct, and is essentially the same as that of heat in causing burns on the skin. It is well recognized that if exposure to a certain temperature for a certain time produces a mild burn, a much more severe burn will be produced at twice the temperature in half the time.

If the concentration of an irritant is sufficiently low—and the level depends upon the strength and locus of action of the individual irritant—the tissues of the respiratory tract are not injured and inflammation does not result, even from the most prolonged exposures. This fact is illustrated by oxygen, which is an irritant only under exceptional circumstances. Normal air contains approximately 21 per cent of oxygen; at this concentration under ordinary barometric pressure it is obvious that no inflammation is produced. When, however, oxygen is breathed for many hours at a concentration approaching 100 per cent at normal atmospheric pressure, or in lower percentages at higher pressures, inflammation of the lungs may result. No evident inflammation follows the inhalation of pure oxygen at normal pressure (760 mm.) for a few hours, as with a self-contained breathing apparatus used for rescue work (see Chapter 18), but inflammation may result if this concentration is inhaled for more than 24 hours, as might occur in a therapeutic oxygen chamber. In such chambers the concentration of oxygen is now generally maintained below 70 per cent.

Group II. **Asphyxiants.** Asphyxiation occurs under many conditions other than inhalation of noxious gases, as in strangulation, in breathing rarefied air at high altitudes, and during heart failure. The physiological changes associated with these conditions have been extensively studied and a wide knowledge has been gained. The action of the asphyxiant gases is well understood and can be stated quantitatively. With the simple asphyxiants, such as nitrogen and methane, the physiological responses obtained with animals can, with little modification, be applied to man. So also for the acute effects from cyanide but not wholly for carbon monoxide. This gas, in contrast to cyan-

ide, exerts its specific action in low concentrations only in animals which have hemoglobin or similar compounds in their blood for the transportation of oxygen: on insects, carbon monoxide behaves essentially as a simple asphyxiant, *i.e.*, only in high concentrations. Furthermore, in studying the acute response to carbon monoxide in experimental animals, suitable allowance must be made for body size, blood volume and respiratory volume before the results can be applied to man.

The main uncertainties in respect to the asphyxiants do not lie in the response or lack of response to various concentrations; there is a full knowledge on these points. The uncertainty lies in the possible organic disturbances resulting from prolonged and severe carbon monoxide poisoning involving many hours of unconsciousness. It lies also in the question of alleged chronic functional disturbances from repeated exposures to concentrations too low to cause unconsciousness.

Groups III and IV. **Volatile Drugs and Drug-like Substances and Inorganic Gases.** Aside from the irritation which some of these gases and vapors induce, their action occurs after absorption. Each must be considered individually in respect to its fate in the body and its pharmacological peculiarities.

Many of the volatile drug-like substances, when inhaled in sufficient concentrations, exert an anesthetic action. This action is the same in all experimental animals and in man. Information on acute anesthetic effects gained from animals can be applied directly to man, but not when the anesthetic effects are slight.

Intoxication by anesthetics too mild to interfere seriously with coördination, as shown by staggering, may nevertheless affect judgment—a function impossible to evaluate in experimental animals. Such mild intoxication, while not endangering health, may, under the conditions in which men work in factories, greatly increase the frequency of accidents. This feature is one of primary importance in respect to anesthetic action.

A second feature of importance in respect to gases and vapors with an anesthetic action concerns variations in the concentrations inhaled. It was pointed out in the previous chapter that the anesthetics act primarily on the brain and that the concentration in that organ follows closely the concentration in the arterial blood. The inhalation of a high concentration of an anesthetic, even for a short time, therefore induces marked

physiological effects, although the total amount absorbed may be small. The effects pass off rapidly when the inhalation ceases, since the concentration in the arterial blood is not, under these circumstances, supported by any large amount accumulated in the tissues. The brief intoxication, however, may seriously predispose to accidents. So far as actual amount absorbed is concerned, it makes little difference whether a high concentration is inhaled for a short time or a low concentration for a longer time, but the rapidity with which intoxication develops is distinctly different. Any allowable concentration for anesthetic gases or vapors, therefore, should not be based on the average concentration, but should include a second maximum beyond which the concentration should not be permitted to rise, even for brief exposure.

The most specific effects of the volatile drug-like substances result from secondary toxic action which may appear only after prolonged or repeated exposures. Here amount absorbed rather than fluctuation in concentration is the important feature. Experiments on animals may give valuable information concerning the nature of these chronic effects, but attention must be given to differences in species. Thus cats respond to exposure to aniline vapors by the formation of methemoglobin with great sensitivity; dogs moderately so; and rats and rabbits only slightly. There may be similar differences in the response to the action of benzene on the blood-forming organs and of carbon disulfide and methyl alcohol on the nervous system. Information as to the chronic effects of volatile drug-like substances gained on experimental animals must be interpreted with especial caution before being applied to man. It is virtually impossible to make any direct quantitative application.

Some of the substances that fall into Groups III and IV have been long and widely used in industry, and experience has led to the setting of reliable standards for safe concentrations. Such experience is not available for other substances in these groups, and new substances are continually appearing. Consequently there may be considerable uncertainty as to the concentrations which are safe for prolonged and repeated exposures. This point will be discussed further in relation to the halogenated hydrocarbons, Chapter 14.

Chapter 7

Classification of Noxious Gases and Vapors

In the introductory chapter a convenient classification of the noxious gases is given. In the present chapter and its accompanying table the names, chemical formulas and physical characters of the gases which occur most often in modern industry are set down along with the general nature of their physiological action. In this table they are listed in their chemical sequence so that they may be easily found. But in order that the reader who consults this table may see immediately the nature of the action of each gas on men and animals, a column has been placed at the right of the table showing to which of the various toxicological classes each gas must be assigned in accord with its physiological action; and a reference is also given to the chapter where this action is described.

In succeeding chapters the chemical order will be largely neglected and the particular gases will be dealt with under the different classes of physiological action. To save space and the reader's time, general descriptions of the various types of physiological action will be given with lists of the substances producing these effects, instead of the endless detail and repetition which would be involved in following the chemical order and treating each gas separately. A few gases must be treated separately, because their special physiological characteristics differentiate them from all others. With these few exceptions, each gas will be described only in association with its physiological relatives in the family of gases.

There are many other noxious gases besides those here listed. An indication of the probable pharmacological action of these little known or rarely occurring gases may usually be obtained by noting the toxicological character of related and analogous substances in the chemical order.

Table of Noxious Gases Listed According to Chemical Composition and Classified According to Their Action

Name	Formula	Molecular Weight	Boiling Point (°C.)	Ordinary condition	Nature of physiological action: classification
		Elements			
Fluorine	F_2	38.00	−187.0	Gas	Group I Primary Irritants. Chapters 8 and 9.
Chlorine	Cl_2	70.92	−34.6	Gas	
Bromine	Br_2	159.84	58.8	Liquid	
Iodine	I_2	253.84	183.0	Solid	
Ozone	O_3	48.00	−112.0	Gas	
Oxygen	O_2	32.00	−183.0	Gas	Irritant only at high partial pressures.
Nitrogen	N_2	28.02	−195.8	Gas	Group I Simple Asphyxiants. Chapter 10.
Helium	He	4.00	−268.9	Gas	
Hydrogen	H_2	2.02	−252.8	Gas	
Neon	Ne	20.18	−245.9	Gas	
Argon	A	39.94	−185.7	Gas	
Mercury	Hg	200.61	356.9	Liquid	Group IV. Inorganic Vapors. Chapter 16.
Phosphorus	P	30.98	280.0	Solid	
		Acids, Bases and Oxides			
Hydrochloric acid	HCl	36.47	−83.7	Gas	Group I. Primary Irritants. Chapters 8 and 9.
Chlorine monoxide	Cl_2O	86.91	———	Gas	
Chlorine dioxide	ClO_2	67.46	———	Gas	
Hydrofluoric acid	HF	20.01	19.4	Liquid	

Sulfuric acid	H_2SO_4	98.08	330.0	Liquid	
Nitrogen dioxide	NO_2–N_2O_4	46.01	21.3	Gas	
Ammonia	NH_3	17.03	−33.4	Gas	
Sulfur dioxide	SO_2	64.06	−10.0	Gas	
Nitrous oxide	N_2O	44.02	−89.5	Gas	Group II. Simple Asphyxiants. Chapter 10.
Carbon dioxide	CO_2	44.01	−78.5	Gas	
Carbon monoxide	CO	28.01	−192.0	Gas	Group II. Chemical Asphyxiants. Chapter 11.
Hydrogen sulfide	H_2S	34.08	−61.8	Gas	Group IV. Inorganic Gases and Vapors. Chapter 16. Irritants. Chapter 9.
Carbon Disulfide					
Carbon disulfide	CS_2	76.13	46.3	Liquid	Group III. Volatile Drugs and Drug-like Substances. Chapter 14.
Salts and Non-Metallic Halides					
Phosphorus trichloride	PCl_3	137.39	75.5	Liquid	Group I. Irritants. Chapters 8 and 9.
Phosphorus pentachloride	PCl_5	208.31	———	Solid	
Arsenic trichloride	$AsCl_3$	181.28	130.2	Liquid	
Sulfuryl chloride	SO_2Cl_2	134.97	69.1	Liquid	
Sulfur monochloride	S_2Cl_2	135.03	135.6	Liquid	
Thionyl chloride	$SOCl_2$	118.97	78.8	Liquid	
Silicon tetrachloride	$SiCl_4$	169.89	57.6	Liquid	Probably resembles carbon tetrachloride. Chapter 14.

Table of Noxious Gases Listed According to Chemical Composition and Classified According to Their Action—*Continued*

Name	Formula	Molecular Weight	Boiling Point (°C.)	Ordinary condition	Nature of physiological action: classification
		Organometallic Compounds and Hydrides			
Hydrogen arsenide	AsH_3	77.93	−55.0	Gas	Group IV. Organometallic Compounds. Chapter 15.
Hydrogen antimoniate	SbH_3	124.78	−17.0	Gas	
Cacodyl oxide	$(CH_3)_4As_2O$	225.96	149–151	Liquid	
Methyl arsine	CH_3AsH_2	91.96	2.0	Gas	
Dimethyl arsine	$(CH_3)_2AsH$	105.99	35.6	Liquid	
Trimethyl arsine	$As(CH_3)_3$	120.01	52.8	Liquid	
Diethyl mercury	$Hg(C_2H_5)_2$	258.73	159.0	Liquid	
Dimethyl mercury	$Hg(CH_3)_2$	230.68	95.0	Liquid	
Tetraethyl lead	$Pb(C_2H_5)_4$	323.45	200.0	Liquid	
Tetramethyl lead	$Pb(CH_3)_4$	267.35	110.0	Liquid	
Triethyl antimony	$Sb(C_2H_5)_3$	208.94	159.5	Liquid	
Trimethyl antimony	$Sb(CH_3)_3$	166.86	80.6	Liquid	
Methyldichloroarsine	CH_3AsCl_2	160.86	133–136	Liquid	Groups I and IV. Irritants and Organometallic Compounds. Chapters 9 and 16.
Ethyldichloroarsine	$C_2H_5AsCl_2$	174.90	156.0	Liquid	
Phenyldichloroarsine	$C_6H_5AsCl_2$	222.98	252.0	Liquid	
Chlorovinyldichloroarsine	$ClCH{:}CHAsCl_2$	207.30	190.0	Liquid	
		Hydrocarbons of the Aliphatic Series			
Methane	CH_4	16.04	−161.5	Gas	Group III. Volatile Drugs and Drug-like Substances. Chapter 13.
Ethane	CH_3CH_3	30.07	−88.3	Gas	
Propane	$CH_3CH_2CH_3$	44.09	−42.2	Gas	
Butane	$CH_3(CH_2)_2CH_3$	58.12	−0.6	Gas	
Pentane	$CH_3(CH_2)_3CH_3$	72.15	36.2	Liquid	
Hexane	$CH_3(CH_2)_4CH_3$	86.17	69.0	Liquid	

Heptane	$CH_3(CH_2)_5CH_3$	100.20	98.5	Liquid	
Octane	$CH_3(CH_2)_6CH_3$	114.23	125.8	Liquid	
Nonane	$CH_3(CH_2)_7CH_3$	128.25	150.7	Liquid	
Decane	$CH_3(CH_2)_8CH_3$	142.28	174.0	Liquid	
(The low volatility and low solubility of the higher homologs prevent their absorption in quantities sufficient to induce physiological effects.)					
Ethene (Ethylene)	CH_2CH_2	28.05	−130.9	Gas	Group III. Volatile Drugs and Drug-like Substances. Chapter 13. Lower members of the series, also simple asphyxiants. Chapter 10.
Propene (Propylene)	CH_2CHCH_3	42.08	−47.0	Gas	
Butene (Butylene)	$CH_2CHCH_2CH_3$	56.10	−0.5	Gas	
Hexene (Hexylene)	$CH_2CH(CH_2)_3CH_3$	84.16	64.1	Liquid	
Heptene (Heptylene)	$CH_2CH(CH_2)_4CH_3$	98.18	94.9	Liquid	
Ethyne (Acetylene)	$CHCH$	26.04	−88.5	Gas	
Propyne (Allylene)	$CHCCH_3$	40.06	−23.3	Gas	
Hydrocarbons of the Aromatic Series					
Benzene	C_6H_6	78.11	80.1	Liquid	Group III. Volatile Drugs and Drug-like Substances. Chapter 14.
Toluene	$C_6H_5CH_3$	92.13	110.8	Liquid	
Xylene	$C_6H_4(CH_3)_2$	106.16	144.0	Liquid	
Halogenated Hydrocarbons					
Chloromethane (Methyl Chloride)	CH_3Cl	50.49	−23.7	Gas	Group III. Volatile Drugs and Drug - like Substances. Chapter 14.
Bromomethane (Methyl Bromide)	CH_3Br	94.95	4.6	Gas	
Iodomethane (Methyl Iodide)	CH_3I	141.95	42.5	Liquid	
Dichloromethane (Methylene Chloride)	CH_2Cl_2	84.94	40.1	Liquid	
Trichloromethane (Chloroform)	$CHCl_3$	119.39	61.3	Liquid	Some are irritating in moderate degree and many decompose in flame or on contact with hot metal to give off irritant fumes. Chapter 9.
Tribromomethane (Bromoform)	$CHBr_3$	252.77	149.5	Liquid	
Trifluoromethane (Fluoroform)	CHF_3	70.02	−82.2	Gas	
Tetrachloromethane (Carbon Tetrachloride)	CCl_4	153.84	76.0	Liquid	
Tetrabromomethane (Carbon Tetrabromide)	CBr_4	331.67	189.5	Liquid	

Table of Noxious Gases Listed According to Chemical Composition and Classified According to Their Action—*Continued*

Name	Formula	Molecular Weight	Boiling Point (°C.)	Ordinary condition	Nature of physiological action: classification
Halogenated Hydrocarbons—Continued					
Monofluorotrichloromethane	CCl_3F	137.38	24.1	Liquid	
Dichlorodifluoromethane	CCl_2F_2	120.92	−28.0	Gas	
Chloroethane (Ethyl Chloride)	CH_3CH_2Cl	64.52	12.2	Gas	
Bromoethane (Ethyl Bromide)	CH_3CH_2Br	108.98	38.0	Liquid	
Iodoethane (Ethyl Iodide)	CH_3CH_2I	155.98	72.2	Liquid	
Dibromoethane(Ethylidene Bromide)	CH_3CHBr_2	187.88	110.0	Liquid	
Trichloroethane(Methyl Chloroform)	CH_3CCl_3	133.42	74.0	Liquid	
Tetrachloroethane	$CHCl_2CHCl_2$	167.86	146.3	Liquid	
Pentachloroethane	$CHCl_2CCl_3$	202.31	162.0	Liquid	
Dichlorotetrafluoroethane	$C_2Cl_2F_4$	170.93	4.0	Gas	
Chloroethene (Vinyl Chloride)	CH_2CHCl	62.50	−13.9	Gas	
Bromoethene (Vinyl Bromide)	CH_2CHBr	106.96	15.8	Gas	
Iodoethene (Vinyl Iodide)	CH_2CHI	153.96	56.0	Liquid	
Chloropropene (Allyl Chloride)	CH_2CHCH_2Cl	76.53	44.6	Liquid	
Bromopropene (Allyl Bromide)	CH_2CHCH_2Br	120.99	71.3	Liquid	
Iodopropene (Allyl Iodide)	CH_2CHCH_2I	167.99	103.1	Liquid	
Dichloroethylene	CH_2CCl_2	96.95	37.0	Liquid	
Trichloroethylene	$CHClCCl_2$	131.40	87.0	Liquid	
Tetrachloroethylene	CCl_2CCl_2	165.85	121.2	Liquid	
Chloropropane (Propyl Chloride)	$CH_3CH_2CH_2Cl$	78.54	47.2	Liquid	
Bromopropane (Propyl Bromide)	$CH_3CH_2CH_2Br$	123.00	70.9	Liquid	
Trichloropropane (Allyl Trichloride)	$CH_2ClCHClCH_2Cl$	147.44	156.8	Liquid	
Chloroprene (Chloro-butadiene)	$CH_2CHCClCH_2$	88.54	59.4	Liquid	Irritant action predominant. Secondary Irritants. Chapter 9.
Chlorotoluene (Benzyl Chloride)	$C_6H_5CH_2Cl$	126.58	179.0	Liquid	
Bromotoluene (Benzyl Bromide)	$C_6H_5CH_2Br$	171.04	198.0	Liquid	
Chlorobenzene	C_6H_5Cl	112.56	132.0	Liquid	
Bromobenzene	C_6H_5Br	157.02	155–156	Liquid	
Chloroxylene (Xylyl Chloride)	$CH_3C_6H_4CH_2Cl$	140.61	199.0	Liquid	
Bromoxylene (Xylyl Bromide)	$CH_3C_6H_4CH_2Br$	185.07	217.7	Liquid	

Alcohols, Ethers, Aldehydes and Ketones					
Methanol (Methyl Alcohol)	CH_3OH	32.04	64.6	Liquid	Group III. Volatile Drugs and Drug-like Substances. Chapter 14.
Ethanol (Ethyl Alcohol)	CH_3CH_2OH	46.07	78.5	Liquid	
Propanol (Propyl Alcohol)	$CH_3CH_2CH_2OH$	60.09	97.2	Liquid	
Butanol (Butyl Alcohol)	$CH_3(CH_2)_2CH_2OH$	74.12	117.7	Liquid	
Pentanol (Amyl Alcohol)	$CH_3(CH_2)_3CH_2OH$	88.15	138.0	Liquid	
Propenol (Allyl Alcohol)	CH_2CHCH_2OH	58.08	96–97	Liquid	
Ethylene glycol	CH_2OHCH_2OH	62.07	197.2	Liquid	
Diethylene glycol	$HOCH_2CH_2OCH_2CH_2OH$	106.12	244.5	Liquid	
Ethylene glycol monomethyl ether	$HOCH_2CH_2OCH_3$	76.09	124.0	Liquid	
Ethylene glycol monomethyl ether	$HOCH_2CH_2OC_2H_5$	74.12	134.8	Liquid	
Diethylene glycol monoethyl ether	$HOCH_2CH_2OCH_2CH_2OC_2H_5$	150.17	202.0	Liquid	
Methyl ether	$(CH_3)_2O$	46.07	−23.7	Gas	
Ethyl ether	$C_2H_5OC_2H_5$	74.12	34.6	Liquid	
Propyl ether	$(CH_3CH_2CH_2)_2O$	102.17	91.0	Liquid	
Butyl ether	$CH_3(CH_2)_3O(CH_2)_3CH_3$	103.23	142.0	Liquid	
Allyl ether	$(CH_2CHCH_2)_2O$	98.14	94.3	Liquid	
Ethylene oxide	$(CH_2)_2O$	44.05	10.7	Gas	
Methanal (Formaldehyde)	$HCHO$	30.03	−21.0	Gas	Irritant action predominant. Chapter 9.
Ethanal (Acetaldehyde)	CH_3CHO	44.05	21.0	Liquid	
Propenal (Acrolein)	CH_2CHCHO	56.06	52.5	Liquid	
2-Propanone (Acetone)	CH_3COCH_3	58.08	56.5	Liquid	Group III. Volatile Drug and Drug-like Substances. Chapter 14.
2-Butanone (Ethyl Methyl Ketone)	$CH_3COC_2H_5$	72.10	79.6	Liquid	
2-Pentanone (Methyl Propyl Ketone)	$CH_3CO(CH_2)_2CH_3$	86.13	101.7	Liquid	
2-Hexanone (Butyl Methyl Ketone)	$CH_3CO(CH_2)_3CH_3$	100.16	127.2	Liquid	
Thio Ethers, Halogenated Ethers and Ketones					
Dichloromethyl ether	CH_2ClOCH_2Cl	114.95	160.0	Liquid	Group I. Irritants. Chapter 9.
Dichloroethyl sulfide (mustard gas)	$(ClCH_2CH_2)_2S$	159.08	215–217	Liquid	
Chloropropanone (Chloroacetone)	CH_3COCH_2Cl	92.53	119.0	Liquid	
Bromopropanone (Bromoacetone)	$CH_2BrCOCH_3$	136.99	136.5	Liquid	

Table of Noxious Gases Listed According to Chemical Composition and Classified According to Their Action—*Continued*

Name	Formula	Molecular Weight	Boiling Point (°C.)	Ordinary condition	Nature of physiological action: classification
		Esters			
Methyl formate	$HCOOCH_3$	60.05	31.5	Liquid	Group III. Volatile Drugs and Drug-like Substances. Chapter 14.
Methyl acetate	CH_3COOCH_3	74.08	57.1	Liquid	
Methyl butyrate	$CH_3CH_2CH_2COOCH_3$	102.13	102.3	Liquid	
Ethyl formate	$HCOOC_2H_5$	74.08	54.3	Liquid	Some irritant action. Chapter 9. The formates are strongly irritating.
Ethyl acetate	$CH_3COOC_2H_5$	88.10	77.2	Liquid	
Ethyl butyrate	$CH_3CH_2CH_2COOC_2H_5$	116.16	121.3	Liquid	
Propyl formate	$HCOOC_3H_7$	88.10	81.3	Liquid	
Propyl acetate	$CH_3COOC_3H_7$	102.12	101.6	Liquid	
Propyl butyrate	$CH_3CH_2CH_2COOC_3H_7$	130.18	143.0	Liquid	
Butyl formate	$HCOOC_4H_9$	102.13	106.8	Liquid	
Butyl acetate	$CH_3COO(CH_2)_3CH_3$	116.16	126.5	Liquid	
Butyl butyrate	$CH_3CH_2CH_2COOC_4H_9$	144.21	166.4	Liquid	
Amyl formate	$HCOO(CH_2)_4CH_3$	116.16	130.4	Liquid	
Amyl acetate	$CH_3COO(CH_2)_4CH_3$	130.18	145–147	Liquid	
Amyl butyrate	$C_3H_7COO(CH_2)_4CH_3$	158.24	185.0	Liquid	
Methyl nitrate	CH_3ONO_2	77.04		Liquid	
Ethyl nitrate	$C_2H_5ONO_2$	91.07	88.7	Liquid	
Methyl nitrite	CH_3ONO	61.04	−12.0	Gas	Group III. Volatile Drugs and Drug-like Substances. Nitrite effects. Chapter 15.
Ethyl nitrite	C_2H_5ONO	75.07	17.0	Liquid	
Propyl nitrite	$CH_3CH_2CH_2ONO$	89.09	57.0	Liquid	
Butyl nitrite	$CH_3(CH_2)_3ONO$	103.12	77–79	Liquid	
Amyl nitrite	$CH_3(CH_2)_4NO_2$	117.15	104.0	Liquid	
Dimethyl sulfate	$(CH_3)_2SO_4$	110.13	188.0	Liquid	Irritant action predominates. Chapter 9.
Diethyl sulfate	$(C_2H_5)_2SO_4$	154.18	208.0	Liquid	

Halogenated Esters					
Methylchloroformate	$ClCOOCH_3$	94.50	71.4	Liquid	Group I. Irritants. Chapter 9.
Ethylchloroacetate	$CH_2ClCOOC_2H_5$	122.55	144.2	Liquid	
Trichloromethylchloroformate (diphosgene)	$ClCOOCCl_3$	197.85	127.5	Liquid	
Nitro Compounds					
Nitromethane	CH_3NO_2	61.04	101.0	Liquid	Group III. Volatile Drugs and Drug-like Substances. Chapter 15.
Nitroethane	$C_2H_5NO_2$	75.07	114.8	Liquid	
Nitrobenzene	$C_6H_5NO_2$	123.11	210.9	Liquid	
Trichloronitromethane (Chloropicrin)	CCl_3NO_2	164.39	112.0	Liquid	Group I. Irritants. Chapter 9.
Amines					
Methylamine	CH_3NH_2	31.06	−6.5	Gas	Group II. Irritants. Chapter 9. Also Volatile Drugs and Drug-like Substances. Chapter 14.
Dimethylamine	$(CH_3)_2NH$	45.08	7.4	Gas	
Trimethylamine	$(CH_3)_3N$	59.11	3.5	Gas	
Ethylamine	$C_2H_5NH_2$	45.08	16.6	Liquid	
Diethylamine	$(C_2H_5)_2NH$	73.14	55.5	Liquid	
Triethylamine	$(C_2H_5)_3N$	101.19	89.5	Liquid	
Benzylamine	$C_6H_5CH_2NH_2$	107.15	185.0	Liquid	
Aniline	$C_6H_5NH_2$	93.12	184.4	Liquid	
Toluidine	$CH_3C_6H_4NH_2$	107.15	199.8	Liquid	

Table of Noxious Gases Listed According to Chemical Composition and Classified According to Their Action—*Continued*

Name	Formula	Molecular Weight	Boiling Point (°C.)	Ordinary condition	Nature of physiological action: classification
		Cyanogen Compounds			
Cyanogen	NCCN	52.04	−20.5	Gas	Group II. Asphyxiants. Chapter 11. Halogenated members, irritants. Chapter 9.
Hydrogen cyanide (Hydrocyanic acid)	HCN	27.03	26.0	Liquid	
Cyanogen chloride	CNCl	61.48	13.8	Gas	
Cyanogen bromide	CNBr	105.93	61.6	Liquid	
		Acyl Halides			
Phosgene	$COCl_2$	98.92	8.3	Gas	Group I. Irritants. Chapter 9.
Thiophosgene	$CSCl_2$	114.98	73.5	Liquid	
Benzoyl chloride	C_6H_5COCl	140.57	197.0	Liquid	

Character of Substances Included

The list of noxious substances here presented is limited to those which are volatile, either gases or vapors. Dusts are not included. Thus mercury finds a place in the table because its vapor pressure at ordinary temperatures is sufficiently high for the substance in gaseous form to induce poisoning. Lead, on the other hand, is listed here only as the alkyl compound. That compound is truly volatile; but metallic lead at ordinary temperatures does not exist as a gas. Poisoning from the inhalation of the fumes of the metal, or of its inorganic salts, results, not from the gas or vapor, but from the substance in the form of dust. Such dust may indeed arise from the condensation of lead vaporized at high temperatures; but a line must be drawn somewhere as to inclusions in this book, and dusts have been ruled out. We feel justified in this for the reason that the hygienic aspects of dusts are, in many respects, quite different from those of gases, and have their own extensive literature.[1-4]

Physiological Classification of Gases and Vapors

The classification of gases according to their physiological actions divides them into four main groups and several subgroups, which will be described here somewhat more fully than in the first chapter.

Group I. Irritants. The gases of this class are, for the most part, substances which, from the standpoint of chemistry, would be regarded as corrosive. They injure the surface tissues of the respiratory tract and thus induce inflammation of the air passages and of the lungs themselves. While the effects of the various irritant gases differ considerably one from another, these differences depend in part upon the solubilities of the substances, and on this basis gases of this class are more easily arranged in a scale than in a succession of subclasses. Subclassification is, however, made on the basis of what will be termed primary and secondary irritants. Primary irritants are those which have little or no systemic toxic effect in the concentrations which cause death. The secondary irritants produce systemic toxic effects in addition to surface irritation.

Group II. Asphyxiants. This group includes volatile substances which induce anoxemia, or an equivalent condition, in that they interfere with the supply or utilization of oxygen in

the body. It is characteristic of such gases that they bring about this result without any direct interference with the mechanics of respiration. They do no direct injury to the lungs.

This group is further subdivided: (A) *Simple Asphyxiants.* These are inert gases, that is, inert physiologically, although they may be, from the standpoint of chemistry, quite active substances. They act by excluding oxygen from the lungs. (B) *Chemical Asphyxiants.* These are gases which possess some specific property which renders them asphyxiants even when they are present in very minute amounts in the air. Their action is therefore not that of excluding oxygen from the lungs. They exert an action either upon the blood, which prevents it from transporting oxygen, although the lungs are well aerated, or upon the tissues to prevent them from using oxygen, although it may be brought to them in ample amount by the blood.

Group III. Volatile Drugs and Drug-like Substances. This group includes those gases which exert a drug-like action after they have been absorbed through the lungs into the blood. They consist largely of hydrocarbons and the action common to all of them is that of inducing anesthesia. This general anesthetic action may, however, be accompanied by other and more injurious effects or even obscured entirely by some special action. The subgrouping here is made on the basis of the presence or absence of these features and of their nature. Subgroup *a* includes those volatile drugs whose irritant action on the respiratory tract largely obscures the systemic action; *b* includes those which have little action beyond causing functional disturbances such as anesthesia and respiratory failure, and are here classed as primary anesthetics; *c, d,* and *e,* those which in addition to their anesthetic action cause organic injury, respectively, to visceral organs, the hematopoietic system and the nervous system; and *f,* those whose anesthetic action is largely obscured by other systemic effects particularly upon the hemoglobin and the arterial pressure.

Group IV. Inorganic and Organometallic Gases. The gases and vapors containing phosphorus, mercury, lead, and so on, are not asphyxiants or pulmonary irritants (at least in their chief action), but are true poisons acting only after absorption into the blood. They are volatile poisons in the strictly toxicological sense. Each has its own specific physiological action.

Introductory Bibliography on Dusts

1. Drinker and Hatch: "Industrial Dust," New York, 1938. Extensive bibliography.
2. "Fourth Saranac Symposium on Silicosis" (1939) edited by L. W. Gardner, Saranac, N. Y.
3. Lanza: "Silicosis and Asbestosis." Article by Pendergrass and Gardner. Oxford Medical Publications, N. Y., 1938.
4. National Silicosis Conference, U. S. Dept. of Labor Bull. 21 (4 parts) Govt. Print. Office, 1938.

Chapter 8

Group I. Irritant Gases

The gases and vapors classed as irritants differ widely in chemical and physical properties. They have, however, one physiological property in common: they induce inflammation in tissues with which they come in direct contact. This inflammation is manifest, therefore, almost solely in surface tissues: the skin, the conjunctiva of the eyes, and particularly the membranes of the respiratory tract.

Inflammation

It must be clearly understood that the inflammation caused by an irritant, even when of the most intense character with destruction and sloughing of the tissues, is a process totally distinct from a simple chemical corrosion. The inflammation develops from the disturbance in the normal vital processes in the tissue, such as coagulation, liquefaction, dehydration or some other injury. The type of direct injury caused by the gas or vapor is often too slight to be seen and depends upon the chemical nature of the irritant. But the inflammation which follows is independent of the nature of the initial injury. It is a vital process, and is essentially the same for all irritant gases and vapors.

The initial reaction of tissues to the irritants with which they come in contact is chemical or physical. It can be demonstrated *in vitro* as a chemical reaction of the irritant with protein and tissue fluids. But *in vivo* these effects are usually not sufficiently intense to be visible. What is seen and felt is the vital reaction which is made by the tissues in response to the irritation. In other words, inflammation is a physiological reaction and not merely a direct chemical change. When hydrochloric acid acts upon zinc, the metal is dissolved with the evolution of hydrogen gas. When hydrochloric acid gas acts upon living tissue, the comparable direct effect is usually slight and almost or entirely invisible. Soon, however, the disturbed vital process of the affected tissues manifests itself physiologically as inflammation.

If the tissues were already dead, as in a corpse, high concentrations of the gas, even far above those causing death, would induce no visible effect. The effect of an irritant gas or vapor, except in the most exceptional instances of overwhelming concentration, is not simple and direct corrosion. The irritant gases and vapors act in such extreme dilution that such gross effects are not usually involved. When actual chemical corrosion does occur to any considerable extent, the shock may cause almost immediate death.

The general process of inflammation as induced by an irritant is familiar from sunburn. Here the irritation is due to the actinic rays of the sun the initial injury to the skin is invisible and the "burn" appears subsequently as the vital reaction of inflammation and in a degree determined by the extent of the initial injury.

Similarity of Action but Dissimilarity of Symptoms

Although fundamentally the reaction to all irritants is the same except in degree, widely different symptoms result from the action of different irritant gases and vapors. These differences are mainly due to differences in the localities on which the irritants act. The characteristic symptomatology of any irritant is therefore an expression of the particular structure in which inflammation is induced, rather than of any fundamental dissimilarity in the action of the irritants. Some irritant gases act primarily upon the upper respiratory tract and induce rhinitis, pharyngitis and laryngitis. Others extend their action to the bronchi and cause bronchitis and bronchopneumonia. Still others act chiefly on the lungs and cause pulmonary edema and pneumonia. The symptoms of laryngitis induced by an irritant gas are quite different from those of pulmonary edema; but so also, for example, are the symptoms arising from a burn upon the palm of the hand and one on the eyeball. The burns in these two localities have a different symptomatology, not because of any differences in the physiological process of inflammation in these two localities but only because of the differences in the structures affected by the inflammation.

Similarly, the location exposed to an irritant gas or vapor influences the symptomatology and pathology. For example, exposure to ammonia gas in high concentration is followed by

intense congestion and swelling of the upper respiratory passages and possibly rapid death from spasm or edema of the larynx. If the immediate effects are survived, there may be little serious consequence, since the deeper structures of the respiratory tract are not reached and therefore are not injured. On the other hand, phosgene and nitrogen peroxide, even in concentrations which may later be lethal, cause comparatively little immediate irritation, but induce pneumonia or pulmonary edema through their action on the alveoli of the lungs. Chlorine is intermediate in its action between ammonia on the one hand and phosgene and nitrogen peroxide on the other. Such distinctions in the action of irritant gases are due to the differences in the locality in the respiratory tract upon which they act and this, in turn, upon solubility.

In very high concentrations any irritant gas or vapor, even one for which the action is ordinarily slow in developing, as nitrous fumes, may cause such intense irritation over a wide area in the respiratory tract that the immediate reaction is that of shock as might occur after a large burn on the skin. Death may then result in a short time.

Characteristics of Gases and Vapors and Locus of Action

The points of action for the various irritants are the result, not so much of the differences in their chemical properties as of differences in their physical properties, particularly solubility, boiling point and volatility.

To exert its action, an irritant must be taken up by the surface tissues, and be dissolved in the fluid which bathes them. The severity of the effect is greatest upon those surfaces which are most easily penetrated and particularly upon those which are moist. Therefore, the epithelium and mucous membrane of the respiratory passages and the surface tissues of the eyes are the areas first attacked. A concentration of ammonia gas which is intolerable to the eyes and throat may cause no appreciable irritation of the skin when it is dry. When the eyes and respiratory tract are protected with a gas mask, high concentrations of ammonia can be tolerated but the skin may be attacked, especially in regions where it is moist, as about the armpits and groin.

The physical states of the various irritants at ordinary tem-

peratures vary widely; some have a boiling point below these temperatures and, as encountered, behave essentially as gases; others are liquids, often with a boiling point above that of water from which vapors are evolved into the air. The locus of action on the respiratory tract is influenced by these differences in physical state. The selective action of the gaseous irritants is determined primarily by their solubility. Solubility, however, plays a far less important part in determining the locus of action of irritants with boiling points above ordinary temperatures.

Any gaseous irritant which is highly soluble in water is absorbed from the inspired air by contact with the first moist tissue which it reaches in the respiratory passages. As a consequence, the upper respiratory tract bears the brunt of the action; the lungs are relatively little affected, since the concentration of the irritant which reaches them is greatly reduced by absorption in the upper passages. With those gases which have a low solubility, the upper respiratory passages suffer little, for little is absorbed, and the main damage is deep in the lungs. A gas of moderate solubility exerts its action more or less uniformly throughout the entire respiratory tract. Thus, as a general rule, the irritant gases are dangerous inversely as their solubility; the less soluble any one of them is the more insidious is its action.

A simple experiment illustrates how the solubility of the particular gas determines its selective action as between the various parts of the respiratory tract. Each of the various gases, such as ammonia, chlorine and phosgene, in turn is diluted with a large volume of air in a suitable vessel, and is then passed slowly through a long glass tube, the full length of the inside of which is lined with filter paper moistened with water. If the gas is acid or alkaline in character, litmus paper may be substituted for the filter paper. The amount of each gas which is absorbed in the water held by the filter paper in different parts of the tube is chiefly determined by the solubility of the gas. The nearer end is saturated first. For a readily soluble gas the amount absorbed in that locality is large, the amount further on is comparatively small, while the air which passes from the effluent end of the tube is practically free from gas. On the other hand, the amount of a slightly soluble gas absorbed during the passage through the tube is small, and the concentration which passes out of the effluent end is high. In this experiment the tube through

which the gas passes is analogous to the respiratory passages: the nose, throat, trachea and bronchi. The effluent gas is that which would pass into the lungs.

In this artificial system the continued passage of the gas results in an increase in the concentration of the dissolved substances in the fluid until further absorption of the gas from the air finally ceases; at this equilibrium the effluent air then has the same concentration as the affluent. With the exception of certain vapors of hydrocarbons, which are absorbed unchanged, this equilibrium is not reached in the living body with the irritant gases.

The severity of the action of an irritant gas does not vary in proportion to the product of the amount of the gas in the air multiplied by the duration of exposure to it, as is the case with an asphyxiant gas such as carbon monoxide. A high concentration for even a short time has an intense effect. A reduction of one-half would allow it to be withstood for much more than twice as long and with less effect. Consequently any reduction in the concentration of an irritant during its passage through the upper respiratory tract results in a more than proportionate sparing of the tissues of the lungs.

The principles defined here as to the locus of action in relation to solubility do not apply to irritants which are absorbed without alteration, such as the vapors of ethyl ether. The greater part of the irritant action occurs in the upper respiratory passages, bronchi and bronchioles, while the lung alveoli and atria are relatively little affected. Such amounts of gas as reach the lungs themselves are absorbed and are the cause of systemic but not of pulmonary symptoms. The sparing of the deeper portions of the lungs is due to the active absorption into the blood which prevents the accumulation of the irritant in the alveoli and so maintains there a lower concentration than in the upper respiratory passages.

A still further exception to the rule of solubility as a determinant of locus of action occurs with vapors from liquids which have a boiling point well above ordinary temperatures. Thus many of the substances which, even in low concentrations, are intensely irritating to the eyes and nose and are used in chemical warfare as lachrymators, have a low solubility. For example, bromobenzyl cyanide, one of the most effective lachrymators, has

its melting point at 24° C., its boiling point at 225° C. and is only slightly soluble in water. The vapor of such an irritant is taken up by the skin, the eyes, and the surface of the respiratory tract as if it existed as a mist of droplets rather than as a vapor which persists in the air. Its initial action is, therefore, on the upper respiratory tract; but if the inhalation is continued all the respiratory passages are finally affected.

Injury at Different Levels of the Respiratory Tract

The selective action of the irritant gases in the respiratory tract determines the relative danger of death from them. The delicacy of the respiratory membranes, their susceptibility to injury, and the seriousness of the damage which results, are very different in the upper and lower respiratory tracts. This same also holds for inflammation resulting from bacterial infection. Infection of the nose and throat leads only to a head cold and pharyngitis which in themselves are not serious; infection of the bronchial tubes leads to bronchitis and bronchopneumonia; and infection in the lungs themselves leads to pneumonia. Similarly, the action of irritant gases and vapors in the nose and pharynx may render them raw by the inflammation without immediate danger or permanent damage. It is a more serious matter when the trachea and bronchi are injured. Not only are the local effects painful, but general systemic effects develop as in acute trachitis and bronchitis from bacterial infection. The most serious, but the least painful results of inhalation of an irritant gas or vapor occur when the lungs themselves are acted upon. The damage then gives rise to an acute edema leading to suffocation or, if this danger is escaped, to pneumonia with prostration and circulatory impairment. The outcome of either process may be fatal.

Inflammation of the Upper Respiratory Tract and Bronchi

The first visible reaction to irritation is redness due to the dilatation of the small vessels in the irritated area. In such mucous membranes as those which cover the surface of the respiratory tract, except in the air sacs of the lungs, the initial redness is accompanied by increased activity of the mucous glands. A profuse flow of mucus is secreted over the irritated

surface. After moderate exposure to irritant gases and vapors which affect primarily the upper respiratory tract, the inflammation may not extend beyond this stage; the symptoms then are those of pharyngitis, laryngitis, and trachitis—pain, some swelling, redness and flow of mucus.

If the irritation is severe, the inflammation does not stop with redness and increased flow of mucus. Plasma exudes from the walls of the engorged blood vessels, thus producing marked swelling, separation of the tissues and their consequent destruction, or it exudes into the respiratory passages and spaces and blocks them. In the upper respiratory passages and bronchi these changes appear first as a loss of normal gloss and translucency together with some swelling. The plasma which exudes to the surface clots there and is frequently streaked with extravasated blood. The tenacious layer thus formed may appear as a false membrane. In severe cases the mucosa may be stripped from the submucosa and lifted by the fluid in much the same manner that a blister is formed on the skin after a burn. This tissue sloughs off, leaving raw and oozing surfaces covered with mucopurulent material.

The symptoms of severe membranous trachitis and bronchitis accompany these inflammatory changes and may persist for several days. In non-fatal cases the mucous membrane then begins to regenerate from the patches of relatively uninjured epithelium where folds in the mucosa have protected it. In the large bronchi the repair is usually effected with little permanent scarring; the smaller bronchial tubes may, however, show some thickening. Before the regeneration of the mucosa can occur, however, infection of the bronchi generally develops, since the normal barrier to bacterial invasion is removed. The infectious organisms are those ordinarily found in the mouth and upper respiratory tract. The symptoms resemble mild or severe head cold, laryngitis, bronchitis, or bronchopneumonia, depending upon the severity and depth of the inflammation.

In exceptionally severe inflammation of the upper respiratory tract the soft tissues about the larynx may become so swollen from the fluid extravasated into the tissues that the opening of the trachea is occluded; death then occurs from acute suffocation. Laryngeal edema is the common cause of rapid fatality during or soon after exceptionally severe exposure to those irri-

tant gases and vapors, particularly ammonia, which act upon the upper respiratory tract.

Inflammation of the Lungs

The outstanding feature of inflammation in the lungs resulting from the action of irritant gases is pulmonary edema. The condition reaches its height in from 4 to 24 hours after the exposure. If death does not occur, it tends to regress within 48 hours.

The edema results from inflammatory changes similar to those which occur in the upper respiratory passages. The tissue of the finer air sacs in the lungs, both of the atria and alveoli, is damaged by the irritant. Fluid extravasates from the capillaries and accumulates between the cells. Fluid also escapes into the alveolar spaces, coagulates and fills them with fibrin, thus seriously interfering with the respiratory exchange of oxygen and carbon dioxide between the air and the blood. At the same time the flow of blood through the lungs is obstructed and a severe strain is placed upon the right side of the heart. The loss of fluid from the blood in the form of exudate may be of a quantity sufficiently serious to deplete the body of water and to result in a decrease in the volume of the blood and an increase in its viscosity.

The edema induced by irritant gases differs from that of non-irritant origin in that the latter is usually particularly marked in the deeper parts of the lungs, whereas the edema arising from irritation is not greatly affected by gravity or the posture of the patient. Not all parts of the lungs, however, are equally involved in the inflammatory changes arising from the action of irritant gases. The irritant action upon the smaller bronchial tubes may cause some of them to constrict so that the portions of the lungs to which they lead escape the action of the gas. Owing to this bronchoconstriction, as well as to the plugging of the bronchi with sloughed mucosa and fibrin, areas of atelectasis and emphysema may occur in the edematous lung.

Irritation of the lungs does not give rise to severe pain as does inflammation of the upper passages. The principal symptoms are those of asphyxia. This asphyxia, however, is of a peculiar character in that its early stages are not associated with marked air hunger. The patient may present only an ashy gray

color, no dyspnea, and yet slight exertion may cause immediate death. The state of gray cyanosis without marked dyspnea is due to anoxemia unattended by increased carbon dioxide in the blood. In a later stage purple cyanosis and intense air hunger characterize the clinical picture. In this condition the edema is so severe that it interferes with the elimination of carbon dioxide as well as the absorption of oxygen; accordingly the classic symptoms of suffocation develop.

The peculiar feature of early pulmonary edema, the stage of gray cyanosis, is due to the unequal ventilation of the blood with respect to carbon dioxide and oxygen. Carbon dioxide is much more soluble than oxygen in the plasma which covers the surface of the alveoli. Oxygen diffuses through the pulmonary membrane less readily than carbon dioxide and its absorption is much more readily impaired than is the elimination of carbon dioxide. In this respect the anoxemia of early pulmonary edema is similar to that of mountain sickness. At first, therefore, the exchange of oxygen is hindered to a greater degree than is that of carbon dioxide, and the oxygen of the blood is decreased without any appreciable rise of carbon dioxide. There may even be a decrease of carbon dioxide owing to some degree of overbreathing, for oxygen deficiency is a stimulant to respiration, although relatively slow in developing. Thus the signs of asphyxia at this stage are not striking, although the condition is acutely dangerous.

With the progress of the edematous condition, some of the alveoli become filled with frothy fluid and the terminal bronchioles become plugged. Such areas then take little part in the gas exchanges of the lungs, and the air occluded within them comes to have the same gas pressure as the venous blood. At the same time areas which are less involved in the edema are hyperaerated and the carbon dioxide in the blood passing through them is reduced below the normal level. Hyperaeration cannot, however, raise the oxygen content of the blood passing through these parts of the lungs above the amount which the hemoglobin normally holds. The characteristics of the oxyhemoglobin dissociation curve permit no more. Under these conditions the blood which reaches the left side of the heart is a mixture; one portion has the same content of gases as the venous blood, while the other approaches the normal arterial blood in its content of oxy-

gen but is lower than normal in carbon dioxide. The mixture of over- and under-aerated blood which is pumped into the arteries is thus low in oxygen; but during the early stages it is not far from normal, or even below normal, in respect to carbon dioxide.

As the edema progresses, the diffusion of carbon dioxide, as well as that of oxygen, is interfered with to an increasing extent. The pressure of carbon dioxide in the arterial blood rises, probably the blood alkali also increases, while anoxemia becomes more and more intense; all three conditions contribute to the intense air hunger. The more marked symptoms depend upon the excessive pressure of carbon dioxide in the arterial blood, but the more serious damage results from the deficiency of oxygen. The asphyxia of lung edema arising from irritant gases, therefore, is more dangerous than the superficial signs indicate. Consequently it frequently happens that a man who appears to be only slightly affected is allowed, or told, to make some movement, such as sitting up in bed so that a physician may listen to the rales in his lungs; and as the result of this slight exertion he falls back dead. This is probably the failure of an overworked and asphyxiated heart.

Treatment of Pulmonary Edema

Severe edema of the lungs usually terminates fatally. In non-fatal cases the acute symptoms of the gassing usually diminish within 48, or at most 72, hours and are followed by symptoms of bacterial infection. Medicinal measures contribute little to the relief of pulmonary edema. It is doubtful if any benefit is derived from the intravenous administration of saline solution, and such administration may do harm. Inhalation of oxygen tends to relieve the anoxemia and cyanosis and should always be commenced as early as possible in the stage of gray cyanosis. As in the case of pneumonia, it is important to begin the inhalation while the symptoms are slight, instead of waiting, as is usually done, until the patient has suffered loss of strength and functional impairment from anoxemia. It is not sufficient merely to discharge oxygen from a funnel held over the face, for only a negligible amount is then inhaled. For the inhalation to be effective, an efficient inhalator and a close and comfortably fitting mask must be used. With such an inhalator it is best not

to administer pure oxygen, but a mixture of oxygen and air just sufficiently rich to counteract the cyanosis. By far the most important feature of treatment in such cases is absolute quiet and rest.

Infection as a Sequel to Inflammation

Inflammation of the respiratory tract induced by the irritant gases lessens or removes the normal barriers to bacterial invasion. Consequently infection is a common sequel to the action of this class of gases. The organisms involved in this infection are usually those which normally inhabit the mouth and upper respiratory tract. The symptoms are identical with those of infections of non-irritant initiation.

Exposure to an irritant gas insufficient to affect the lungs directly may lead to the development of bronchopneumonia. The disease then develops as a sequel to a bronchitis or trachitis caused by the action of the irritant on the higher respiratory structures. The infections following exposure to irritant gases probably constitute a far greater cause of death than does primary pulmonary edema. It is probable that prolonged inhalation of irritant gases or vapors, even in high dilution, may predispose to the development of infections of the respiratory tract. Thus the sulfur dioxide from coal smoke of cities and irritant vapors from the exhausts of automobiles on city streets probably contribute to the frequency of respiratory infection in urban districts. These infections are primarily of the upper respiratory tract, but they may nevertheless, when neglected, cause bronchopneumonia as a sequel.

In contrast to pneumonia, tuberculosis probably does not arise as a direct sequel to the action of irritant gases. The statistics of the subsequent health of soldiers gassed during war indicate that when the lungs have once healed they are not appreciably more liable to tuberculosis than they would have been otherwise. Nevertheless when the man who has been gassed has suffered a period of decreased vitality or ill health as a consequence of the action of an irritant gas upon the respiratory tract, or as a result of the subsequent infection, then tuberculosis may develop actively in a preëxisting lesion, just as it may follow decreased vitality and ill health from any other cause. In considering tuberculosis, it is necessary to assume that even a healthy person

may carry a dormant infection and that the disease may become clinically evident whenever the resistance of the body is lowered sufficiently. Thus severe gassing may lead to the exacerbation of preëxisting tuberculosis, but it cannot properly be regarded as the cause of tuberculosis developing at some time subsequent to recovery from the gassing itself. The question in any particular instance is whether or not the gassing has undermined the individual's general health to an extent sufficient to allow the active development of preëxisting tuberculosis.

Chronic Effects of Exposure to Irritant Gases

Long-continued derangement of health may arise in two distinct ways from exposure to irritant gases: (1) As a chronic inflammation following a single very severe exposure to the gas; and (2) as a chronic inflammation caused and maintained by continued exposure to low concentrations of the irritant.

After a severe irritation of the bronchi and lungs with subsequent bacterial invasion, the infection sometimes persists as a chronic condition and causes a protracted period of ill health. The most characteristic features are chronic bronchitis, cicatrization of the lungs (fibrosis), and obliteration of a portion of their deeper structure, sometimes with abscess formation.

The second type of chronic inflammation arises from prolonged exposure to sublethal concentrations of irritant gases. The distinguishing feature is a catarrhal inflammation of the upper respiratory tract.

Often there are repeated attacks of respiratory infections appearing as severe head colds or bronchitis. If the exposure is more or less a regular part of the man's working condition, the sharp cough present in the beginning of the inflammation becomes less marked. The man then appears to have acquired a partial tolerance to the gas. No true tolerance exists, however, toward any irritant gas. The appearance of tolerance arises from the fact that the protective reflexes, especially coughing, are less active because the surface of the upper respiratory tract is covered with tenacious mucus, and thus is partially shielded from the action of the gas. The catarrhal exudate does not, however, afford any protection to the deeper respiratory structures. It rather exposes them the more to the action of the gas because of the partial abolition of the respiratory reflexes. In

addition, the inflammation diminishes the normal protection against bacterial infection. The condition is detrimental to the general health.

Protective Reflexes

The so-called protective reflexes do not in reality actually protect the respiratory tract from the action of irritant gases. They nevertheless play an important role in funishing a warning of the presence of irritants in the inspired air, particularly those irritants which attack the upper respiratory tract. One of the features which renders especially dangerous any exposure to those gases which primarily attack the lungs is the fact that they do not greatly irritate the upper respiratory tract; phosgene and nitrogen peroxide are especially notable in this respect. Lethal concentrations of these gases can be inhaled with less warning from irritation of the throat and from coughing than would be elicited by a concentration of ammonia, for example, well below an immediately dangerous level.

The protective respiratory reflexes consist in coughing, constriction of the larynx and bronchi, closure of the glottis, and inhibition of respiration. Coughing is excited by even slight irritation of the larynx; it consists of a series of expiratory blasts which tend to expel the stimulating material. Coughing obviously does not prevent the passage of irritant gases, but it warns of the presence of these substances. When higher concentrations of irritants act upon the larynx, the superior laryngeal nerve is stimulated and respiration is inhibited with the chest in the position of expiration. The breathing is almost equally disturbed by stimulation of the sensory fibers of the trigeminal nerve in the nasal passages; this causes sneezing. With severe irritation, the glottis is closed reflexly by constriction of the adductor muscles and the bronchial musculature is constricted so that the passages to the lungs are partially closed. The inhibition of respiration is usually only temporary and is broken through by the increasing excitement of the respiratory center because of the lack of ventilation and the increasing venosity of the blood. Occasionally the spasm of the glottis may persist so long that symptoms of acute asphyxia are induced. The constriction of the bronchi, particularly of the smaller tubes, may be sufficient to prevent the entrance of the gas into some portions

of the lungs, even under the most acute conditions, and, as stated previously, areas of atelectasis and emphysema may result.

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Chapter 9

Group I (cont'd). Special Characteristics of Various Irritant Gases

It was shown in the preceding chapter that irritant gases and vapors differ mainly in the locus of their action. On this basis the present chapter will deal with the more common irritants and with some exceptional characteristics of particular irritants.

Classification of Irritants

The irritant gases and vapors fall into two general groups: (a) those whose action is limited to irritation and (b) those whose action extends to a systemic effect.

Subgroup A. Primary Irritants

The primary irritants exert no systemic toxic effects (1) because the products formed by them on tissues of the respiratory tract are non-irritant; and (2) because their irritant effects are so violent as to obscure any systemic toxic action. Thus the inhalation of hydrochloric acid gas leads to the formation of sodium chloride, which is non-toxic. Similarly, nitrous fumes produce nitrites which are toxic, but the irritant action of the fumes is far more serious than any effect from the nitrites. Likewise many of the organic halogen compounds listed as irritants would be toxic on absorption, but before absorption in appreciable amounts could occur, death would result from the irritation.

The primary irritants may be further classified according to their locus of action:

(1) Those affecting mainly the upper respiratory tract.

(2) Those affecting the upper respiratory tract and also the deeper structures such as the bronchi.

(3) Those acting primarily upon the lungs and, to a much less extent, upon the upper respiratory tract.

(4) Organic vapors which do not follow the general rule as to solubility in relation to locus of action.

Subgroup B. Secondary Irritants

The irritant action of the secondary irritants may be less marked, particularly in high concentrations, than are their systemic toxic effects resulting from absorption.

Subgroup A, 1

Ammonia Gas. Ammonia is a colorless gas with a specific gravity 0.597 that of air. It is easily liquefied and is extremely soluble in water, with which it forms ammonium hydroxide. Strong ammonia water contains 28 to 29 per cent of ammonia and at 25° C. has a specific gravity 0.90 that of water.

Ammonia is one of the products of the putrefaction of nitrogenous substances. Near putrefying substances, the amount of ammonia may be of the order of 15 to 1,500 parts per million of air. Except in the immediate neighborhood of the decomposing material, however, ammonia does not exist in the air in the free state, but is combined usually as the carbonate.

Ammonia results from the destructive distillation of bones and also from that of coal in the manufacture of coal gas; the latter is the ordinary commercial source. Ammonia is usually transported either in liquefied form in steel cylinders, or dissolved in water as the hydrate. The aqueous solution yields the gas on exposure to air.

Liquid ammonia is extensively employed as a refrigerant in cold-storage plants and for the manufacture of artificial ice. To some extent it is being replaced in these uses by other refrigerants. If a pipe or joint breaks or leaks, ammonia gas escapes into the air and quickly becomes intolerable to everyone in the vicinity who is not wearing a gas mask. Contamination of the air may occur also from the bursting or leaking of a cylinder of the liquid in filling, storage, or transit. The aqueous solution of ammonia has a wide application in the arts. Accidents are fairly frequent, but are rarely serious. Ammonia acts so violently upon the upper respiratory tract and eyes as to give ample warning of its presence in the air. Serious gassing from ammonia may occur, however, when the liquefied gas is sprayed into the face of a man unprotected by a mask during the repairing of refrigerating machinery. Accidents may also occur among those temporarily blinded by ammonia vapors while attempting to escape from a workroom where ammonia water has been spilled.

Injury from ammonia may occur from the use of this substance in attempts to resuscitate unconscious persons by inhalation of ammonia. Ammonia should not be used for this purpose; it has no real value. The influence of ammonia on respiration and the heart is due to reflexes from the upper respiratory tract. If the concentration is high, respiration may be stopped.

Table 4. Physiological Response to Various Concentrations of Ammonia.[1,2]

	Parts of ammonia per million parts of air
Least detectable odor	53
Least amount causing immediate irritation of the throat	408
Least amount causing irritation of the eyes	698
Least amount causing coughing	1,720
Maximum concentration allowable for prolonged exposure	85 to 100
Maximum concentration allowable for short exposure (½ to 1 hour)	50 to 100 300 to 500
Dangerous for even short exposure (½ hour)	2,500 to 6,500
Rapidly fatal for short exposure	5,000 to 10,000

Hydrochloric Acid (Hydrogen Chloride). Hydrogen chloride is a colorless gas with a specific gravity 1.269 times that of air. On exposure to air this gas forms dense white fumes from the condensation of atmospheric moisture and the formation of hydrochloric acid in minute droplets like steam. The gas is rarely encountered in the anhydrous state and the irritation is caused by these droplets.

Hydrochloric acid is prepared mainly by the action of sulfuric acid upon sodium chloride as a by-product in the manufacture of soda ash. The solution of the acid is used extensively in industry, but usually in small amounts except during the manufacture of the acid and in the "pickling" of iron. In the latter process the iron to be cleaned is immersed in the acid. A copious evolution of hydrogen results, and each bubble escaping is coated with a film of acid which is carried into the air. Fumes from hydrochloric acid are occasionally encountered in large quantities by firemen in burning buildings, particularly storage depots and chemical factories containing supplies of the bottled acid.

The toxicity of hydrochloric acid as droplets is less than that of anhydrous hydrogen chloride since the droplets have lost their dehydrating action. Unusual conditions of heat and absence of

moisture may explain the occasional increase of toxicity which hydrochloric acid vapors are sometimes said to exhibit.

Table 5. Physiological Response to Various Concentrations of Hydrochloric Acid Gas.[2-9]

	Parts of hydrogen chloride per million parts of air
Causes irritation of throat on short exposures	35
Maximum concentration allowable for prolonged exposure	10
Maximum concentration tolerable for a few hours	10 to 50
Maximum concentration tolerable for 1 hour	50 to 100
Dangerous for even short exposures	1,000 to 2,000

Sulfuric Acid. Sulfuric acid is a liquid at ordinary temperatures. As its boiling point is 330° C., it gives off no appreciable fumes. So-called fuming sulfuric acid contains 30 to 50 per cent of dissolved sulfuric anhydride, which does come off as fumes. When, however, the ordinary concentrated sulfuric acid is heated, it gives off dense and intensely irritating fumes. When dilute sulfuric acid is heated, very little vapor is evolved until after most of the water has been evaporated.

When hydrogen is evolved from a sulfuric acid solution acting on a metal, the bubbles of gas carry a finely divided spray of the acid into the air. The air may become contaminated with this thin mist of sulfuric acid during the charging of lead storage cells, or in the "pickling" of metals with dilute sulfuric acid.

The concentration at which sulfuric acid mist becomes irritating has not been recorded. Although it is more corrosive than hydrochloric acid, there is probably little difference in the toxic concentrations as expressed in parts per million of air. The concentrations as expressed in milligrams per liter of air are not, however, comparable because of the greater molecular weight of sulfuric acid.

Hydrofluoric Acid (Hydrogen Fluoride). Hydrogen fluoride is a colorless fluid. As with hydrogen chloride, the vapor combines with moisture in the air to form a mist. Hydrogen fluoride diluted with water to a specific gravity of 1.15 distills unchanged at 120° C. and is handled in this form commercially.

The acid was formerly extensively used to etch glass, but this use is now diminishing. It is employed in the extraction of silicates and phosphorus in the refining of gold and in the electrolytic production of aluminum. It is said to be formed when the

organic fluorine compounds, dichlorodifluoromethane (Freon, F-12), trichlorofluoromethane (F-11) and dichlorotetrafluoroethane (F-114), which are used as refrigerants, come into contact with a flame or hot metal surface, as in burning buildings. Chlorine, phosgene and hydrochloric acid may also result from this reaction.

Physiologically hydrofluoric acid is a much more active substance than is hydrochloric acid. Aside from the irritation induced by its acid properties, both hydrofluoric acid and its neutralization products, such as sodium fluoride, are direct protoplasmic poisons. Its inhalation may cause deep ulcers in the upper respiratory tract. These ulcers heal slowly. Hydrofluoric acid is intensely caustic to the skin and conjunctiva. It may cause many troublesome but usually slight accidents wherever it is used, even in small amounts.

Table 6. Physiological Response to Various Concentrations of Hydrofluoric Acid Gas.[4, 6–10]

	Parts of hydrogen fluoride per million parts of air
Maximum concentration allowable for prolonged exposure	3
Maximum concentration allowable for short exposure (½ to 1 hour)	10
Dangerous for even short exposure	50 to 250

Formaldehyde. Formaldehyde is a colorless gas. At temperatures of 20° C. and above, it polymerizes to paraformaldehyde or polyoxymethylene $(HCHO)_x$. This polymerization is retarded by water and for this reason formaldehyde is used commercially as a solution of the gas in water. The name formalin is applied to a solution of a strength of 37 per cent.

Formaldehyde is used in the manufacture of plastics, in the preparation of dyes, as a preservative, and extensively as a disinfectant. In the last use formaldehyde is employed both in solution and in the gaseous state.

The powerful irritant action of formaldehyde upon mucous membranes is due to its forming an irreversible combination with the protein of the surface cells. In contact with living tissues some of the formaldehyde is also changed into formic acid and methyl alcohol.

Formic acid is irritating, but the neutralization product, sodium formate, is not particularly toxic. Methyl alcohol, how-

ever, and possibly other methyl compounds formed by the breakdown of formaldehyde, have a marked toxic action when absorbed in sufficient quantities. To some solutions of formaldehyde 10 to 15 per cent of methyl alcohol is added to prevent polymerization to paraformaldehyde. A number of fatalities have been recorded from the swallowing of solutions of formalin. In each of these cases the amount taken was more than 0.09 liter, 33 g. of formaldehyde. Recovery has been observed after a dose of 0.06 liter of formalin, or 22 g. of formaldehyde. From these amounts it appears that the systemic action of formaldehyde is not very intense. The serious symptoms following inhalation are induced by the local irritation. Its products—formic acid and methyl alcohol—play a negligible part in acute poisoning. It is uncertain whether or not a systemic effect is produced by prolonged inhalation of low concentrations of formaldehyde. Brunnthaler [12] believes that the decomposition products have a cumulative action, but the amount absorbed from exposure to any concentration of formaldehyde which can be tolerated must be slight. The outstanding feature of both acute and chronic poisoning is inflammation of the respiratory passages.

Formaldehyde has an irritating action upon the skin, but different individuals show a marked difference in susceptibility to the irritation. After severe inflammation, a skin which has previously been resistant may become acutely sensitive. Brunnthaler [12] believes that similar increase in susceptibility may develop after inhalation of the gas.

Table 7. Physiological Response to Various Concentrations of Formaldehyde.[4, 6-9, 21]

	Parts of formaldehyde per million parts of air
Maximum concentration allowable for prolonged exposure	20

Acetic Acid and Acetic Anhydride. Acetic acid is extensively employed in industry and the arts. Its vapor is irritating to the upper respiratory tract. No figures have been published for the physiological response to various concentrations.

Acetic anhydride is used in the manufacture of artificial silk, photographic films, and as a solvent. In contact with water or water vapor it is hydrolyzed to acetic acid. It is uncertain whether the irritating properties of acetic anhydride are exer-

cised wholly by the acetic acid formed with the moisture of the air or by acetic acid formed in the moisture on the tissue of the respiratory tract with which it is brought into contact. If hydrolysis were complete in the air, the action would be entirely that of acetic acid vapor and would be largely limited to the nose, throat, and eyes; if the hydrolysis were incomplete, the action might extend deeper into the respiratory tract.

Sulfur Monochloride, Thionyl Chloride and Sulfuryl Chloride. Sulfur monochloride is a reddish yellow liquid used as a solvent, as a fumigant, and in the manufacture of organic chemicals. Thionyl chloride and sulfuryl chloride are colorless liquids used in the manufacture of organic chemicals.

The vapors of these three substances decompose on contact with moist air with formation of dense fumes. Sulfur monochloride decomposes to sulfur dioxide, sulfur and hydrochloric acid; thionyl chloride to hydrochloric and sulfuric acids. The irritation from the fumes is due to these decomposition products. Under ordinary conditions the decomposition appears to be nearly complete before the vapors are inhaled. The effects, consequently, are mainly on the upper part of the respiratory tract. It is possible, however, that under some conditions, especially in dry air, undecomposed vapors may be inhaled, and under such conditions they would affect the deeper parts of the respiratory tract. The toxicity would then be considerably increased.

Mice are said to die after an exposure of 1 minute to 150 parts per million of sulfur monochloride and cats to die after exposure of 15 minutes to 48 parts per million.[4] In such determinations, however, it is uncertain to what extent the vapors had decomposed before inhalation.

Sulfuryl chloride has a limited use in industry. On exposure to the moisture in air it is hydrolyzed with the formation of hydrochloric and sulfuric acids. Its irritant properties are due to these products. No figures have been published for the physiological response to various concentrations.

The toxicity of sulfuryl chloride as a war gas is said to be one-sixth that of chlorine.[4]

Subgroup A, 2

Sulfur Dioxide. Sulfur dioxide is a colorless gas with a specific gravity 2.23 times that of air. It arises from the com-

bustion of sulfur. It occurs in the gases issuing from volcanoes and is constantly discharged into the air of cities by the burning of coal containing sulfur. In the presence of moisture the dioxide is oxidized and forms sulfuric acid. Sulfur dioxide and sulfuric acid are notable constituents of the black and yellow fogs of London.

Sulfur dioxide under pressure in the liquefied state is used as a refrigerant, usually on a small scale. It is also used as a fumigant and bleach. The gas is made in large quantities as a step in the manufacture of sulfuric acid and occurs in the gases arising from the smelting of ores containing pyrites. It is the main irritant (but not for men and animals the chief toxic substance, which is carbon monoxide) among the gases produced by the burning of coal. It is the constituent of coal smoke which is mainly injurious to vegetation, particularly to the conifers.

Table 8. Physiological Response to Various Concentrations of Sulfur Dioxide.[1, 8–9, 12, 22]

	Parts of sulfur dioxide per million parts of air
Least detectable odor	3 to 5
Least amount causing immediate irritation to the throat	8 to 12
Maximum concentration allowable for prolonged exposure	10
Least amount causing immediate irritation to the eyes	20
Least amount causing coughing	20
Maximum concentration allowable for short exposure (½ to 1 hour)	50 to 100
Dangerous for even short exposure	400 to 500

Chlorine. Chlorine is a greenish yellow gas with a specific gravity 2.47 times that of air. It is readily liquefied and it is handled commercially in the form of liquid in steel cylinders or special tank cars. Chlorine is obtained during the electrolysis of sodium chloride for the manufacture of sodium hydroxide.

Liquid chlorine is used extensively to disinfect the water and sewage of cities, for recovering tin from scrap plate, for bleaching cotton, paper and flour, and for the manufacture of disinfecting agents, such as chloride of lime and other chemicals. Extensive contamination of the air with chlorine occurs occasionally during fires in buildings where cylinders containing it are stored. The cylinders are tested to 3,000 pounds pressure, but are equipped with safety plugs which release the gas slowly before the pressure has reached this point and thus prevent the bursting

of the cylinders. The pressure developed in the cylinders during fires leads to the escape and rapid volatilization of the chlorine.

It is commonly supposed that chlorine reacts with the moisture on the tissues to form hydrochloric acid, and that its detrimental effects arise from the action of this acid. The similarity between the action of chlorine and hydrochloric acid is pointed out in support of this view. The similarity, however, is more apparent than real. Chlorine is nearly 20 times as toxic as hydrochloric acid and, because of its relatively low solubility, its locus of action in the respiratory tract is much more extensive than is that of hydrochloric acid. A more probable theory of the action of chlorine is that it affects moist tissues in the same way that it does other moist organic material, namely, by the abstraction of hydrogen from the water present, the liberation of nascent oxygen and then the formation of hydrochloric acid. Oxidation is thus the major factor which, together with the action of the acid, induces irritation of the tissues.

In plants where chlorine is used there is a general belief that traces of the gas in the air exert a prophylactic action against diseases of the respiratory tract, possibly by keeping the bacterial count in the air at a low level.

High concentrations of chlorine have an irritating action upon the skin, but such irritation occurs only when exposure to the high concentrations is rendered tolerable by the use of a gas mask. Chlorine rash, an irritative dermatitis, has been reported as occurring in German factories where chlorine is made by electrolysis. This dermatitis does not result directly from the chlorine, but is produced by a chlorinated tar product arising from the action of the gas upon the tar cement at the anode of the cell.

Table 9. Physiological Response to Various Concentrations of Chlorine.[1, 3–9, 13]

	Parts of chlorine per million parts of air
Maximum concentration allowable for prolonged exposure	0.35 to 1.0
Least detectable odor	3.5
Maximum concentration allowable for short exposure (½ to 1 hour)	4
Least amount causing immediate irritation to the throat	15
Dangerous for even short exposure	40 to 60
Rapidly fatal for short exposure	1,000

Bromine. Bromine is a dark red liquid and its vapors are the same color. Bromine vapor has a specific gravity 5.5 times that of air. Because of improved methods of production, largely from sea water, the use of bromine has increased widely in the chemical industry.

The physiological action of bromine is essentially the same as that of chlorine. By the action of bromine on surface tissues, bromides are formed. In sufficient doses such bromides have a physiological effect as depressants. But even with the most prolonged and extensive exposure to bromine this effect is insignificant.

Table 10. Physiological Response to Various Concentrations of Bromine.[1-4, 7]

	Parts of bromine per million parts of air
Maximum concentration allowable for prolonged exposure	0.1 to 0.15
Maximum concentration allowable for short exposure (½ to 1 hour)	4
Dangerous for short exposure	40 to 60
Rapidly fatal for short exposure	1,000

Iodine. Iodine is a solid which volatilizes slightly at room temperatures. As the temperature is increased, purple fumes are evolved. The action of iodine is similar to that of chlorine and bromine, but it is more irritating to the lungs.

Table 11. Physiological Response to Various Concentrations of Iodine.[3, 4]

	Parts of iodine per million parts of air
Maximum concentration allowable for prolonged exposure	0.1
Maximum concentration allowable for short exposure (½ to 1 hour)	0.5 to 1.0

Arsenic Trichloride. Arsenic trichloride is a colorless liquid. Its vapors decompose in the presence of moisture with the liberation of hydrochloric acid and arsenous oxide. The action of the fumes is primarily irritant, but so far as is known, systemic poisoning from absorption of arsenic is not a considerable factor in the toxicity of arsenic trichloride. The possibility should, however, be kept in mind.

The toxicity of arsenic trichloride as a war gas is said to be one and a half times as great as that of chlorine.[4] This fact

suggests that some undecomposed trichloride reaches the deeper respiratory tract before the decomposition is complete, and that in addition to the marked irritation of the upper respiratory tract the deeper structures are affected with consequently more serious results.

Phosphorus Trichloride and Pentachloride. The vapors of phosphorus trichloride and pentachloride decompose in the presence of moisture with the liberation of hydrochloric and phosphoric acids. However, under ordinary conditions this decomposition may not be complete at the time the vapors are inhaled. Consequently, in addition to the marked irritation of the nose and throat, there may be irritation of the deeper respiratory structure, including the lungs, from the acids liberated on the surface of these structures.

Phosphorus pentachloride, in a concentration of 120 parts per million of air, is said to kill mice after an exposure of 10 minutes.[4] The toxic concentration of phosphorus trichloride, which has a wider industrial application, has been determined more fully.

Table 12. Physiological Response to Various Concentrations of Phosphorus Trichloride.[3, 13]

	Parts of phosphorus trichloride per million parts of air
Maximum concentration allowable for prolonged exposure less than	0.7
Maximum concentration allowable for short exposure (½ to 1 hour) less than	2 to 4
Dangerous for even short exposure	50 to 90
Rapidly fatal for short exposure	600

Subgroup A, 3

Ozone. Ozone is a gas of low solubility but of intensely irritating action. The upper respiratory tract is affected, but the main locus of action appears to be in the lungs. The toxic and allowable concentrations of ozone are not well established, possibly because of differences in the purity of the ozone as liberated by electric discharges. The figures given for the maximum allowable concentration for prolonged exposure vary between 0.15 [7] and 1.0 [8] part per million of air.

Nitrogen Dioxide, "Nitrous Fumes."[24] There are three common oxides of nitrogen: nitrous oxide (N_2O); nitric oxide (NO); and two forms of the dioxide (NO_2 and N_2O_4).

Nitrous oxide has no irritating action and is used extensively as an anesthetic for surgical operations and dental extractions. Its anesthetic action is rather weak and appears only when the gas is inhaled in high concentration. For prolonged anesthesia it must be mixed with oxygen instead of air. When inhaled without oxygen, nitrous oxide is a simple asphyxiant.

Nitric oxide does not exist in atmospheric air, for in the presence of moisture and oxygen it is converted into the dioxide.

Nitrogen dioxide in the form of N_2O_4 is a yellow or colorless solid which has a boiling point of 21.3° C. Nitrogen dioxide in the form of NO_2 is a gas, which is dark brown in color. The molecular form of the oxide is determined by the temperature. Thus on heating, the colorless N_2O_4 is first changed to a pale yellow; this color becomes deeper until at 15° C. it is orange, and at 20° C. a reddish brown vapor. The color of this vapor becomes deeper, until at 40° C. it is a dark chocolate brown. The change of state consists in the relative preponderance of one or the other of the two forms of the dioxide.

In whatever molecular form the dioxide is inhaled, it is at once altered to that corresponding to body temperature. At 40°C. approximately 30 per cent of the dioxide is in the form of NO_2 and 70 per cent as N_2O_4. It is in this proportion that the gases act upon the respiratory tract.

Nitrogen dioxide in the form of N_2O_4 reacts with water to form nitric and nitrous acids. The dioxide in the form NO_2 reacts with water and oxygen from the air to form nitric acid and nitric oxide. The nitric oxide formed is oxidized and converted into nitric acid.

The decomposition of 1 mg. of nitrogen peroxide reaching the respiratory tract yields 0.55 mg. of nitrous oxide and 0.98 mg. of nitric acid. These acids react with the alkali in the tissues of the respiratory tract and in so doing exert their irritating action. The neutralization results in the formation of nitrates and nitrites, chiefly the sodium salts. The former has no physiological significance, but the nitrite, when absorbed, exerts a systemic action. For each milligram of the dioxide acting upon the respiratory tract, 0.75 mg. of sodium nitrite is formed. The inhalation of nitrogen dioxide in a concentration of 10 parts per million parts of air over a period of 8 hours would result in the absorption of approximately 40 mg. of sodium nitrite. (This

is figured on an effective pulmonary ventilation of 6 liters and complete absorption. Higher or lower concentrations in the inspired gas would result in the absorption of proportionately greater or less amounts of the nitrite.)

The sodium nitrite formed from nitrous fumes, and then absorbed from the surface of the respiratory tract, produces the same systemic action as when sodium nitrite is swallowed. The arteries are dilated, the blood pressure falls and vertigo and headache follow; the nitrite also alters the hemoglobin to methemoglobin. The systemic action of the nitrites does not, however, play an important part in poisoning by nitrous fumes, for after exposure to high concentrations the irritation of the respiratory tract is so intense that it obscures the systemic action. In men frequently exposed to low concentrations of nitrous fumes habituation to sodium nitrite is rapidly acquired and prevents the development of systemic effects. Habituation in this respect does not, however, render their lungs less sensitive to irritation.

Nitrogen dioxide is evolved when nitric acid acts upon organic material; this occurs particularly when the acid is spilled during storage or shipment, for it then attacks wooden floors, sawdust, refuse, or any organic material with which it comes in contact, with evolution of the red fumes. Nitric acid is also decomposed into the dioxide by heat even in the absence of organic material. Numerous organic substances containing the nitrous radical give off nitrogen dioxide when burned. Celluloid and related products, guncotton and dynamite are important examples of this class of material. Only small amounts of the oxide result from the explosion of dynamite, but considerable quantities are produced when it is burned without exploding. Nitrogen dioxide also occurs as a waste or intermediary in numerous processes of chemical manufacture employing nitric acid. Nitrous fumes are evolved during the process of electric arc welding. They may also be present in the exhaust of Diesel engines.

The nitrous fumes are by no means the most toxic of the irritant gases, but they are among the most insidious. The inflammation of the lungs gives rise to little pain, but is out of all proportion to the irritation of the upper respiratory tract. These fumes, therefore, give little warning; a man may, without serious

discomfort, breathe an atmosphere containing a concentration of nitrous fumes sufficient to cause death some hours later.[14]

After the burning or incomplete explosion of dynamite in a tunnel, or the spilling of nitric acid on a wooden floor, or some similar slight mishap, a workman inhales some of the fumes for a time but is little inconvenienced. He goes home and eats his supper suffering no ill effects. During the night edema of the lungs may develop and before noon, or even before morning, he may be dead, drowned in the volume of fluid poured out in his lungs.

Table 13. Physiological Response to Various Concentrations of Nitrous Fumes.[3-9, 14-16, 20]

	Parts of nitrogen dioxide per million parts of air
Maximum concentration allowable for prolonged exposure	10 to 40
Least amount causing immediate irritation to the throat	62
Least amount causing coughing	100
Dangerous for even short exposure (½ to 1 hour)	100 to 150
Rapidly fatal for short exposure	200 to 700

Phosgene. Phosgene is a colorless gas of specific gravity 1.38 times that of air. The gas is used to some extent in the chemical industry; it has been extensively employed as a war gas, and it may be developed from the decomposition of chlorinated hydrocarbons on contact with flames or heated metal surfaces.

The danger of using chloroform in the presence of an open fire or gas flame has long been recognized by anesthetists; but the use of indirect heating and electric illumination and, even better, the disuse of chloroform as an anesthetic, have largely removed the dangers of phosgene from this source. Carbon tetrachloride, however, has come into extensive use as a fire-extinguishing agent. When it is sprayed upon heated metal or open flames, appreciable amounts of phosgene may be formed; the dangers are, of course, limited to enclosed spaces where this type of extinguishing fluid should not be used.[1, 23-25]

In the presence of moisture, phosgene decomposes with the liberation of hydrochloric acid. The small amount of acid formed by the moisture of the air may cause irritation of the upper respiratory tract and thus give some warning of the presence of phosgene. In dry, heated air this warning may be slight. The

decomposition of the inhaled phosgene takes place mainly in the lungs.

In its slight immediate effects and subsequent virulent results, phosgene resembles the nitrous fumes.

Table 14. Physiological Response to Various Concentrations of Phosgene.[1-5, 7, 9]

	Parts of phosgene per million parts of air
Maximum concentration allowable for prolonged exposure	1.0 or less
Least amount required to cause immediate irritation of the throat	3.1
Least amount required to cause immediate irritation of the eyes	4.0
Least amount required to cause coughing	4.8
Least detectable odor	5.6
Dangerous for even short exposure (½ to 1 hour)	25.0
Rapidly fatal for short exposure	50.0 or over

Subgroup A, 4

Acrolein. Acrolein, or acrylic aldehyde, is a colorless or slightly yellow fluid. When kept at room temperature it is polymerized with the formation of disacryl, which is a solid and does not have the irritating characteristics of acrolein. The polymerization can be inhibited by adding hydroquinone or benzoic acid. Acrolein has been used as a war gas and it finds some employment in synthetic chemistry, but its most common occurrence is from heating fats, oils or glycerin to high temperatures. It is the main irritant in the exhaust gas from internal combustion engines; it comes from the incomplete oxidation of lubricating oils.

The vapor has only slight solubility in water, but its main locus of action is on the eyes and upper respiratory tract. It is intensely irritating and so gives adequate warning of its presence. Inhalation of the vapor in high concentration is said to induce edema of the lungs.

Table 15. Physiological Response to Various Concentrations of Acrolein.[3, 17-18]

	Parts of acrolein per million parts of air
Immediately detectable	1.0
Intense irritation	5.5
Lethal in a short time	10.0 and over
Unbearable	24.0

Dimethyl Sulfate. Dimethyl sulfate is a colorless liquid. Its vapors have a specific gravity 4.4 times that of air. The vapors are only slightly soluble in water and decompose slowly into a number of products, among which are sulfuric acid, dimethyl ether, methyl alcohol and formaldehyde. Dimethyl sulfate is used in the manufacture of organic chemicals.

The vapors of dimethyl sulfate, although of low solubility, have a powerful irritant action on the conjunctiva and upper respiratory tract. It has been used in chemical warfare as a lachrymator.

It is improbable that this action on the upper respiratory tract, which is especially characteristic of irritants of high solubility, is in this instance due to any extensive decomposition of dimethyl sulfate in moist air. The undecomposed substance is more irritating than its products in the concentration that would be developed. If the concentration is sufficiently high, the action of dimethyl sulfate extends to the lungs with development of edema.

Dimethyl ether is said to be more toxic than phosgene.[19]

Halogenated Organic Compounds. The selection of gases and vapors for the brief descriptions given in this chapter has been dictated mainly by industrial occurrence. The list by no means exhausts the substances. Studies made in the interest of chemical warfare have disclosed a large number of substances which would come under this classification. The great majority are halogenated organic compounds.

Most of these compounds are only slightly soluble in water; many decompose on contact with water with the formation of halogen acids, formaldehyde or other irritant substances. In general, the action of these halogenated organic compounds is similar to that of dimethyl sulfate as described above; they cause intense irritation of the eyes, nose and throat and thus give warning of their presence in concentrations which, in most instances, are below those causing death; but if they are inhaled in higher concentrations the deeper respiratory passages and lungs are irritated. There is one important limiting factor to the lethal action of these substances: some with high boiling points, and correspondingly low vapor pressures, do not volatilize sufficiently under ordinary conditions to produce a lethal concentration in the air.

A partial list of irritant organic halogen compounds is given here and arranged in order of toxicity based on the concentration required to kill an animal after 10 minutes of exposure. For comparison, the similar values of toxicity are given for phosgene and chlorine.*

Table 16. Irritant Organic Halogen Compounds.

Name	Boiling point (° C.)	Toxicity as minimum concentration, lethal, 10 min. exposure
Chlorine		*1,926*
Phosgene		*123*
Dichloroethyl sulfide	228	23
Dibromomethyl ether		48
Dibromomethyl sulfide		99
Dichloromethyl ether	106	100
Ethylchlorosulfonate	153	169
Ethyliodoacetate	178 to 180	171
Iodoacetone		252*
Chloropicrin	112	297
Bromomethylethyl ketone	145 to 146	324*
Benzyl iodide		337
Ethylbromoacetate	168	337
Methylchlorosulfonate		375
Bromoacetone	135 to 136	573†
Chloroacetone		607*
Benzyl bromide	201	634*
Xylyl bromide	210 to 220	740*

* Main irritation under ordinary atmospheric conditions limited to upper respiratory tract.

† Main irritation of upper respiratory tract but some irritation of lower.

Subgroup B, Secondary Irritants

Hydrogen Sulfide. Hydrogen sulfide is a general poison and as such will be dealt with in Chapter 16. In concentrations lower than those causing marked systemic effects it exerts an irritant action on the respiratory tract which resembles that of chlorine, but is less intense. Immediate death from hydrogen sulfide is due to its systemic action, for the gas has an immediate lethal effect not far below hydrogen cyanide. The occasional delayed death, occurring one or two days after exposure, may be the result of its irritant action on the respiratory passages.

Hydrogen sulfide, even in low concentrations, exerts a marked irritant action upon the cornea of the eye. The surface epithelium is eroded, presumably by the sodium sulfide formed from hydrogen sulfide. There is usually marked photophobia.

* A detailed discussion of these irritants and of war gases in general will be found in Prentiss, "Chemicals in Warfare," New York, 1937.

The eyes feel as though grains of sand were on the conjunctivae. The action of the gas upon the eyes is limited to irritation of the surface and does not arise, as is sometimes supposed, from the absorption of the gas from the respiratory tract.

Volatile Hydrocarbons. There are a large number of vapors which exert both a systemic and an irritant action but which are not altered during absorption. Into this class fall a number of aldehydes, ketones, ethers, alcohols and esters, which will be discussed in Chapters 13, 14 and 15 and also pyridine and turpentine. The predominant irritant action of these substances is upon the upper respiratory tract and bronchi.

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Chapter 10

Group IIA. Asphyxiation and Simple Asphyxiants

Asphyxiation is a perversion of the chemical life processes of the tissues under deficiency of oxygen. The damage resulting from this perversion under complete anoxia for as long as 8 minutes produces immediate death. But if a full supply of oxygen to the tissues is renewed within 6 minutes, rapid recovery generally occurs, the perversion is reversed, and there are generally no postasphyxial sequelae. These statements are best illustrated by drowning and by resuscitation with artificial respiration and inhalation of oxygen. But they apply equally to the effects of sudden exposures to an atmosphere entirely devoid of oxygen, such as sometimes occur in mines ("black damp"), silos, and the holds of ships.

Different in important features are the effects of prolonged exposure to conditions involving a partial deficiency of oxygen in the arterial blood. Such exposure and its effects occur in slowly induced carbon monoxide asphyxia and under nitrous oxide anesthesia when the admixture of oxygen is allowed to fall below 10 per cent. Under these and similar conditions profound damage to the tissues develops. Although death may not occur immediately, recovery is slow and may be so incomplete that death may follow hours, or even days, later: death which no amount of oxygen can prevent. The tissues chiefly affected are those of the nervous system; but any considerable physical exertion during a partial shortage of oxygen may injure the heart, and after prolonged asphyxia other organs also are occasionally damaged.

It was formerly supposed that not only deficiency of oxygen but also an excessive accumulation of carbon dioxide must be involved in asphyxia. The point was overlooked that, if the supply of oxygen to the tissues is stopped or decreased, the production of carbon dioxide is thereby also stopped or decreased.

In most forms of asphyxia—perhaps in all—the amount of carbon dioxide in the blood, instead of being increased is, in fact, greatly decreased. Except when submerged in water, buried under sand, or suffocated under a pillow, a man undergoing asphyxiation breathes so as to produce, not less, but far more than his normal volume of lung ventilation. The deficiency of oxygen in the blood acts upon the sinus caroticus (see p. 32) to induce an excessive respiration; the blood is thereby overventilated and the content of carbon dioxide is decreased. In this way anoxia induces acapnia, and the acapnia, by depressing respiration, later renders the restoration of the supply of oxygen even more difficult than would otherwise be the case. Overbreathing, as in severe carbon monoxide poisoning, is not, however, the only cause of the decrease of carbon dioxide in the blood in asphyxia. Both in the victims of drowning (Lougheed, *et al.*) and in babies born in asphyxia, the amount of carbon dioxide in the blood is decreased much below normal. It may be that the lactic acid produced in the tissues under deficiency of oxygen reacts with the bicarbonates of the blood, in which most of the carbon dioxide is held. But how the tissues are able to absorb the carbon dioxide so liberated is at present unexplained. We only know that in all forms of asphyxia, acapnia accompanies anoxia and that for the most rapid and complete restoration of the normal chemical processes in the tissues both oxygen and carbon dioxide are needed.

The deficiency of oxygen inducing asphyxia may be caused by at least five general types of external conditions: (1) by mechanical conditions that prevent breathing, such as submersion in water, or under earth, or by a cord around the neck, or by a bolus of food caught in the throat; (2) by narcotic and anesthetic drugs which depress the respiratory center to the point of failure; (3) by physiologically neutral gases, such as nitrogen, methane, hydrogen, etc. which exclude oxygen, or by great altitudes where barometric pressures fall so low that the partial pressure of oxygen is insufficient to support life; (4) by carbon monoxide which, even when present in small amounts in otherwise normal air, may combine with the hemoglobin of the blood and thereby decrease correspondingly its capacity to transport oxygen from the lungs to the tissues; (5) by cyanides which, by combining with the oxidative ferment in the tissues, deprive

them of the capacity to use oxygen for the maintenance of their vital combustion.

In addition, there are many internal conditions that have asphyxial effects, or at least tendencies. Hemorrhage, by depriving the blood of its red corpuscles, decreases its power to transport oxygen, even when the volume of the blood is restored by infusion of plasma or saline solution. Valvular heart disease manifests itself chiefly by more or less marked asphyxial symptoms. Other organic diseases also may impair the capacity of the body to utilize oxygen and thereby increase susceptibility to asphyxial gases. The capacity of the body to liberate energy and do work, or even to maintain a minimal activity, is essentially determined by its capacity to obtain oxygen from the air, transport it to the tissues and there consume it. Decrease of this capacity is the outstanding feature of old age. In most deaths, whatever the preliminary stages, the final events are asphyxial through failure of respiration, circulation or some other related function.

A question sometimes arises as to the length of time that a man can survive in an airtight enclosure, such as the safety deposit vault of a bank, or a sunken submarine. If the cubic capacity of the enclosure is known, the answer may be calculated from the fact (see p. 18) that a man at rest consumes 1 liter of oxygen in 3 to 4 minutes, but more if he makes any physical exertion. During rest, therefore, he would consume about half the oxygen in 1 cu.m. of air in 5 to 6 hours. By that time, in so small a chamber, the accumulation of carbon dioxide would cause heavy panting, although death would not occur until the depletion of oxygen had gone considerably below 10 per cent. If the accumulation of carbon dioxide is prevented by absorption with alkali, as in self-contained mine rescue apparatus and in the rebreathing apparatus used to determine the "ceiling" of aviators, most men rebreathing a small volume of air will reduce the oxygen to about 13 per cent before any notable effect is induced so long as they remain at rest. But at that figure, or even above it, they may collapse on any physical exertion.

Symptoms of Asphyxia

Even slight degrees of deficiency of oxygen impair the coördinating capacity of the nervous system; the subject can neither

think clearly nor control his limbs accurately. The development of symptoms depends upon the degree and the duration of the oxygen want and also upon the rapidity with which the want is developed. In sudden and acute asphyxia, such as that from inhalation of pure nitrogen, or of a high concentration of carbon monoxide or hydrocyanic acid gas, unconsciousness is immediate. The man falls as if struck down by a blow on the head, and he may die in a few minutes.

When, on the contrary, asphyxia develops gradually, the victim passes through a succession of stages ranging from the first barely perceptible impairment of behavior and self-control up to death under failure of respiration and fibrillation, or standstill and dilatation of the heart. When the asphyxiation develops slowly enough to allow the symptoms of each stage to appear, the full series presents the following succession of clinical pictures:

First Stage. When the oxygen of the inspired air is diminished from the normal 21 per cent of the atmosphere at sea level —a partial pressure of about 160 mm. of oxygen—to values between 16 and 12 per cent, that is, somewhat beyond the point at which a candle is extinguished (17 per cent), the first perceptible signs of anoxemia develop. The volume of breathing is increased and the pulse rate is accelerated. (Both of these conditions actually begin earlier, but not noticeably.) The ability to maintain attention and to think clearly is diminished but can be restored with effort. Muscular coördination for the finer skilled movements, such as writing, is somewhat disturbed. Respiration is increased and the amount of carbon dioxide in the body is correspondingly decreased.

Second Stage. When the oxygen is diminished to values between 14 and 10 per cent the higher centers of the brain are affected. Consciousness continues, but judgment becomes faulty. Severe injuries, such as burns, bruises and even broken bones, may cause no pain. Emotions, particularly ill temper and pugnacity, and less often hilarity, or an alternation of moods, are aroused with abnormal readiness. Muscular efforts lead to rapid fatigue and may permanently injure the heart. As they intensify the anoxemia, they may induce fainting. The respiration is frequently of the intermittent or Cheyne-Stokes type.

Third Stage. When the oxygen is diminished to values

between 10 and 6 per cent, nausea and vomiting may appear. The subject loses the ability to perform any vigorous muscular movements, or even to move at all. Bewilderment and loss of consciousness follow, either with fainting or a rigid, glassy-eyed coma. If revived, the subject may have no recollection of this state, or an entirely erroneous belief as to what has happened. Up to this stage, or even in it, he may be wholly unaware that anything is wrong. Then his legs give way, leaving him unable to stand, walk, or even crawl. This is often the first and only warning, and it comes too late. He may realize that he is dying, but he does not greatly care. It is all quite painless.

Fourth Stage. When the oxygen is diminished below 6 per cent, respiration consists of gasps separated by apneas of increasing duration. Convulsive movements may occur. Then the breathing stops, but the heart may continue to beat for a few minutes and then develop ventricular fibrillation, or stand still in extreme dilatation.

Sequelae of Asphyxia

If the asphyxia is stopped before it has continued for more than a short time at the fourth stage, most of the symptoms clear up in a few hours. The most frequent after-effect is a headache, often associated with nausea and general malaise, which may increase in intensity for several hours and last even into the next day. This post-asphyxial headache is due, in part at least, to the edematous condition which develops in the tissues of the brain and produces an increased intracranial pressure. The intravenous administration of hypertonic saline, or even a saline cathartic, tends to withdraw the excess of water from the brain and thus to relieve the edema and headache.

When the asphyxial stage has been both severe and prolonged, organic changes of a degenerative type may subsequently develop in the nervous tissue. Cases of this type include a variety of paralyses, amnesias and other nervous derangements, with rare (alleged) cases of degeneration in other organs. These injuries are not due to any special action of carbon monoxide upon nervous tissue, for it has none; they are due to the prolonged subfatal asphyxia which this gas may induce. The number of cases in which permanent organic changes in the brain resulted from severe and prolonged carbon monoxide asphyxia,

although never numerous, was formerly considerably greater than at present with the use of the inhalational method of resuscitation; few even of those who have been severely asphyxiated, and who have not died during the asphyxiation, fail to make complete recoveries after receiving this inhalation.

Pulmonary sequelae are common in untreated cases after prolonged and severe asphyxia. Clinically these changes are indicated by rales and areas of dullness; in fatal cases extensive areas of congestion are often found in the lungs. These pulmonary effects are probably due to atelectasis, either massive or patchy, because of low tonus in the diaphragm, and not to any direct irritant action upon the lungs. Formerly, in untreated cases, pneumonia was a frequent sequel of prolonged asphyxia. The asphyxiants, with the sole exception of cyanogen chloride, have no direct irritant action upon the tissues of the respiratory tract.

Symptoms Resulting from Chronic Anoxemia

The reaction of the body to chronic anoxemia depends upon the duration and frequency of the periods of oxygen deficiency. Prolonged slight anoxemia, such as results from change of residence or an expedition to a high altitude—so-called "mountain sickness"—leads to a definite series of compensatory changes classed together under the term "acclimatization." The number of red cells in the blood is increased, first by mere concentration due to the abstraction of water from the blood, and second, and more slowly, by a greater production of red cells. The first process occurs in a few hours; the second requires weeks or months. The polycythemia increases the amount of oxygen that the blood can carry.

The breathing is somewhat increased in volume as a result of the acclimatization. In some persons this occurs in a few hours; in others only in the course of some days, or possibly weeks: the more slowly it occurs, the more severe and prolonged is the mountain sickness. The anoxemic increase of pulmonary ventilation lowers the pressure of carbon dioxide in the blood and displaces the normal balance of alkali and carbonic acid, and consequently, the hydrogen-ion concentration, so that the blood becomes, for a time, abnormally alkaline. A complex of symptoms develops as a result of the anoxemia and its conse-

quent acapnia—a complex characterized by physical and mental depression, nausea, severe headache and even fainting. Continuation of the anoxemia and its accompanying acapnia results in a gradual diminution of the alkali of the blood to balance the diminished carbonic acid; and a normal hydrogen-ion concentration is thus ultimately restored. The increased volume of respiration is then maintained in this new adjustment by the same processes as at sea level; after a variable period, lasting from 1 or 2 days to a week or two, the symptoms of mountain sickness pass off and acclimatization is established. In fully acclimatized individuals the increase in volume of breathing and of red cells in the blood, the diminution of alkali in the blood and of carbon dioxide in the alveolar air, are all proportional to the altitude. In these effects of barometric pressure the oxygen partial pressure is the essential factor. Each altitude from sea level to 14,000 ft. has its own nicely adjusted degree of functional readjustment, and this holds true also, although with increasing strain upon the system, up to 23,000 ft. Because of the necessity for an increased volume of respiration, muscular exertion becomes increasingly difficult as the altitude increases, even for those who are fully acclimatized. If, for example, a certain exertion at sea level increases respiration 4 fold (*i.e.*, from 7 liters per minute at rest to 28 liters), it increases the respiration in an acclimatized man also 4 fold, *i.e.*, from 14 liters during rest to 56 when he makes the same exertion.

When the periods of anoxemia are irregular and relatively brief, as occurs in repeated airplane flights to great altitudes, the mechanism of compensation is alternately started and reversed. Under these conditions little or no acclimatization may develop. Instead, an ill-defined condition of nervousness, irritability and weakness results, which is designated as "air staleness" and is similar to the state of "over-training" or "out-of-condition" in athletes.

Two Subgroups of Asphyxiants

Asphyxiants may be conveniently defined as substances which induce a deficiency in the supply of oxygen to the tissues through some means other than interference with the mechanics of respiration. They do not directly obstruct breathing. They merely make it ineffective as a means of obtaining oxygen. There are

two subgroups of this class of gases: simple asphyxiants (Group IIA) and chemical asphyxiants (Group IIB). The simple asphyxiants are numerous and may be further divided into two types. Those of one type are entirely inert physiologically; they are such gases as hydrogen and nitrogen. Those of the other type have some slight specific action, but when they are inhaled in high concentrations they cause asphyxia before this drug action is manifest. The second type of this subgroup includes the lighter hydrocarbons of the aliphatic series, such as methane and ethane, and some of the gases which, when administered with oxygen, are now used as anesthetics.

The simple asphyxiants of both types induce asphyxia entirely by excluding oxygen from the lungs; their effect is proportional to the extent to which their presence diminishes the percentage, or rather the partial pressure, of oxygen in the expired air. They all act identically, therefore, when present in equal molecular concentrations. Moreover, they must be present in considerable amounts before they exert any appreciable effect.

Table 17. Simple Asphyxiants.

Name	Formula	Boiling Point (° C.)	Occurrence
Nitrogen	N_2	−195.8	Constituent of "black damp" found in mines (87% nitrogen, 13% carbon dioxide).
Hydrogen	H_2	−252.8	
Helium	He	−268.9	Used for filling balloons.
Methane	CH_4	−161.5	Marsh gas; "fire damp" of mines. (Explosive.)
Ethane	CH_3CH_3	− 88.3	For description, see Anesthetic Hydrocarbons. Chapter 13.
Propane	$CH_3CH_2CH_3$	− 42.2	These substances have anesthetic properties when administered with oxygen, but when mixed with air act chiefly as simple asphyxiants.
Nitrous oxide	N_2O	− 89.5	
Ethylene	C_2H_4	−103.9	
Acetylene	CHCH	− 88.5	

They may decrease the oxygen of the air to two-thirds of its normal percentage—13 per cent of an atmosphere—before noticeable symptoms of anoxemia develop. A reduction of the oxygen to this degree necessitates the presence of the simple asphyxiants in a concentration of 33 per cent in the mixture of air and gas. When the gas is present to the extent of 50 per cent, and the oxygen is reduced by one-half, a man is soon rendered incapable

of making a vigorous effort to escape. About 75 per cent is quickly fatal.

Altitude Sickness

The expression "altitude sickness" was introduced by E. C. Schneider in 1918 to designate the condition induced by anoxia during airplane flights to great altitudes, and to differentiate it from the more slowly developed, and usually less acute, mountain sickness.

Aside from the fact that mountain climbing involves vigorous and prolonged physical exertion, while flight does not, the factors involved in the anoxic sickness of the aviator are essentially the same as those in the sickness of the mountaineer. In both conditions the four stages of asphyxia, described earlier in this chapter, occur. The only significant difference arises from the fact that, while the mountaineer passes from near sea level to a great altitude only in the course of hours, days, or even weeks, the aviator may make an equal, or even greater, ascent in a few minutes. In the aviator there is often too little time for that readjustment of respiration by which acclimatization is initiated in the mountaineer. Men of apparently equally vigorous physique, as was found by Schneider, may differ enormously in the rapidity or tardiness with which their respiration makes this readjustment. The difference depends, as Christensen and Krogh have found, upon the sensitivity of the nerve endings in the sinus caroticus to stimulation by anoxemia. One man at 10,000 ft. may experience no appreciable increase in his lung ventilation above that at sea level. The partial pressure of oxygen in his lungs is therefore greatly decreased and he may collapse. Another man, as he rises past 10,000 ft. and on up even to much greater altitudes, exhibits an increased volume of breathing which, in considerable part, compensates for the lowered partial pressure of the oxygen in the external air: he collapses only at a great altitude. Yet at the point at which each of two such types of men collapse, the one at 10,000, the other at 19,000 or even 20,000 ft., they have the same partial pressure of oxygen in their lungs.

Military aviation lies outside the limits of this book. But the increasing commercial use of air transportation involves conditions which resemble those of mild degrees of gas asphyxiation. The cause lies wholly in the decreased pressure of oxygen

in proportion to the decreased air pressure, as measured by the barometer, as the altitude increases.

Up to about 5,000 ft. no one, except persons with severe heart disease, is appreciably affected by deficiency of oxygen. But at 10,000 ft., and increasingly at all higher altitudes, even quite healthy persons suffer from breathlessness, heart palpitation and sometimes even fainting. To counteract these effects, they should remain as still as possible, or lie down and inhale oxygen. After return to the ground, persons who have been at all severely affected by the oxygen lack may suffer from a headache.

Compressed Air Illness

Although this disease is not strictly a form of asphyxia, the fact that it is induced by nitrogen renders it suitable for consideration here.

Compressed air illness or caisson disease occurs in men who, after being subjected to total air pressures of more than two atmospheres, are then rapidly decompressed. It is important to realize that the illness does not occur while the man is under increased pressure, but only during and after decompression. In the worst cases the man collapses and, in a few minutes, is dead. In severe but not fatal cases his legs become paralyzed—so-called "diver's paralysis." More often there is severe pain in the limbs, especially the joints, and in the abdomen—the condition known among the workmen as the "bends." In still other cases the only discomfort may consist of a temporary pruritus.

The Causes of Compressed Air Illness. The living body is permeated by the atmosphere in which it lives. This atmosphere consists of two classes of gases: (1) the biological gases, oxygen and carbon dioxide, and (2) the inert gases which constitute 79 per cent of normal air, but which take no part in vital processes.

The amounts of these two classes contained in the body are determined by quite different principles. The amount of oxygen in the blood is more, and in the tissues less, than would be held in simple solution at atmospheric pressure, while the amount of carbon dioxide in both blood and tissues is considerably more than simple physical principles would maintain.

The amounts of the inert gases which the body contains are, on the contrary, determined wholly by their pressure in the air

breathed. These gases form no chemical combinations with hemoglobin or the alkali of the blood. They are held in simple solution. Entering by way of the lungs and transported by the blood, these gases diffuse through all the fluids and tissues of the body. Each particular gas has a specific solubility peculiar to itself; some are relatively more soluble in the fats than in the water of the tissues, as is the case with nitrogen. But, subject to this peculiarity, the amount of each gas that goes into solution is directly proportional to its pressure in the atmosphere, as mere physical law requires. If the pressure of the atmosphere or that of any of its constituent gases is increased or decreased, the gas or gases pass in or out of the fluids and tissues of the body until a new equilibrium is attained. The gases involved are nitrogen, argon, neon, krypton and xenon; and if any other non-reactive gas, such as helium, is inhaled, it behaves similarly.

Whenever the fluids and tissues of the body, after being for a time under a certain pressure of a given gas, are then exposed to a lower pressure of that gas, the escape of the now excessive amount of the gas in solution may occur in either or both of two different ways. It may diffuse from the tissues into the blood and from the blood into the air in the lungs; or, if the pressure is lowered too rapidly for such diffusion, it may form bubbles in the tissues and even foam in the blood. When a man who has been under a high pressure is decompressed too rapidly for the dissolved gas to escape by diffusion it is the formation of bubbles in the tissues and blood that causes the pain and injuries of compressed air illness. The mechanism is essentially like that observed in carbonated water when the pressure is released. But as nitrogen is the largest constituent of air, and this gas, although not very soluble in water, is quite soluble in fatty substances, the bubbles that produce the disease consist mainly of nitrogen and are likely to occur in adipose and nervous tissue.

Conditions Under Which Compressed Air Illness Occurs. Men are exposed to high atmospheric pressure in diving and in engineering work carried out under water in caissons and submarine tunnels. The highest pressures are encountered in deep diving and may reach 10 atmospheres, or 135 lbs. gauge pressure —9 atmospheres more than in normal air. Danger begins at 1 atmosphere gauge pressure, or 2 atmospheres total pressure.

The dress of the diver consists of a copper helmet which is clamped water-tight to a stout suit of rubber covering the whole body except the hands, which project through sleeves with water-tight cuffs. Air is pumped down to the diver through a hose attached to the helmet. At the side of the helmet there is a spring valve which is adjusted by the diver to regulate the escape of air and thereby to maintain the air within the helmet at a pressure slightly above that of the surrounding water.

For every 32 ft. of fresh water or 31 ft. of salt water, the pressure increases by 1 atmosphere, or nearly 15 lbs. to the square inch. It is absolutely necessary that the diver shall be continually supplied with compressed air so as to maintain the same pressure within his lungs as that of the water about his body. If the air pressure fails at a great depth, his breathing is first stopped by the weight of the water against his abdomen and chest, and the blood is then squeezed up to his head in the inelastic helmet and pours from his nose and mouth, causing immediate death.

It is essential also that the volume of air supplied shall be increased to correspond to the pressure. If the supply is sufficient to keep the air in the helmet pure, the only gases that come into consideration are nitrogen and oxygen. If, however, the supply is deficient and the air in the helmet is vitiated by breathing, carbon dioxide accumulates and prevents vigorous work. With a constant percentage of carbon dioxide in the air in the helmet, the partial pressure of that gas rises in proportion to the degree to which the air is compressed, and the physiological effects of the gas are determined solely by its partial pressure. Thus contamination of the air in the helmet with 2 per cent of carbon dioxide (15 mm. partial pressure) before the descent into the water would cause only a moderate increase of breathing and would not greatly decrease the capacity for work. But the same percentage under 5 atmospheres would be equivalent to 75 mm. partial pressure of carbon dioxide and would incapacitate the man for any exertion.

At great depths the high pressure of oxygen also becomes important. Under 10 atmospheres' pressure the partial pressure of oxygen, which at sea level is 150 mm. (20 per cent of 750), rises to 1,500 mm., and exposure to such a concentration of oxygen for more than a short period may induce inflammation in

the lungs. This hazard, and to a large extent that due to the pressure of nitrogen also, is now counteracted by the use of mixtures of helium and oxygen instead of air. By this substitution, which was developed in the United States Navy, excessive partial pressures of oxygen are avoided; and as helium is more readily diffusible than nitrogen, and much less soluble in fats, greater depths may be reached with decreased risk of subsequent compressed air illness or of oxygen poisoning.

Work in a Caisson. A caisson is a chamber sunk under water with walls and roof but no floor. As the caisson rests on the bottom, it allows the men within it to excavate the dirt or rock and lay the foundation for the pier of a bridge. In the top of the caisson there is an air lock, or chamber, or vertical passage closed by two air-tight doors. Air is pumped down into the caisson under sufficient pressure to force back the water, sand and mud which would otherwise enter from the bottom. The workmen enter and leave the caisson through the air lock, remaining in it only long enough for the pressure to be raised to that of the air in the caisson during entrance, but spending a much longer time during their exit.

For a tunnel under a river the excavation usually starts from a shaft well back from the shore. In the tunnel near the foot of this shaft is built a bulkhead sufficiently strong to bear a pressure equivalent to the weight of the river at the greatest depth to which the tunnel will go. In this bulkhead is installed the air lock through which the workmen must pass to and from the working face of the tunnel.

When a group of workmen enter the lock, the door to the outer air is closed and compressed air is blown in until the pressure is equal to that in the tunnel. The inner door is then opened and the men go to the points at which the work is to be done. This compression has no effect, good or bad, upon any function or organ other than the middle ear. As the pressure rises, the discomfort felt in the ears may be counteracted by swallowing, which tends to open the Eustachian tubes, or by holding the nose and blowing air through these tubes to counterbalance the external pressure on the eardrums. If neither effort is effective, the tympanic membrane may be ruptured.

The Absorption and Elimination of Nitrogen. As nitrogen enters and leaves the tissues only by way of the blood, both the

absorption and elimination under any increase or decrease of pressure are determined by the rate at which the blood circulates. In this respect the illness induced by nitrogen differs from that caused by carbon monoxide, and its treatment differs correspondingly. While the elimination of carbon monoxide may be greatly accelerated by increasing the volume of breathing by inhalation of carbon dioxide, this treatment does not greatly increase the circulation of the blood and is not effective for the elimination of nitrogen.

Because of the mode of absorption of nitrogen, it takes many hours for the body to become saturated to full equilibrium with any considerably increased pressure, and correspondingly long for any large amount of nitrogen to be completely eliminated. The times required to reach full saturation are approximately the same for all pressures, but the total amount which would finally be absorbed in each case is proportional to the pressure. That is, it takes an equal length of time to become adjusted to the nitrogen at 2 atmospheres and at 4 atmospheres; but at the end of equal periods the body will have absorbed twice as much nitrogen under 4 pressures as under 2.

When the man returns to normal pressure, the tendency for the nitrogen to diffuse outward will also be twice as great in the one case as in the other. But, if the decompression is rapid, the blood and tissues will remain for a considerable time more or less supersaturated with nitrogen and the gas may separate as bubbles. If these bubbles are formed in the blood they produce emboli that may block the circulation. In the synovial fluid of a joint they cause acute pain, and if formed in and about the nerves, paralysis, temporary or permanent, may result.

Decompression. The prevention of compressed air illness requires that the rate of decompression shall be sufficiently slow to permit diffusion and prevent the formation of bubbles in the tissues and blood. There are two methods by which this may be accomplished: *uniform decompression* and *stage decompression.* The first consists in a constant rate of diminution of the pressure, starting at that to which the man has been exposed and ending at atmospheric pressure. After exposure to high pressures much time is consumed in the gradual lowering of the pressure, particularly after long exposures. In stage decompression the pressure is lowered, not uniformly but in steps. These steps are

so regulated that the supersaturation of the nitrogen in the blood is kept below, but not too far below, the point of bubble formation. Men rarely, if ever, continue under pressure long enough to become fully saturated with nitrogen to that pressure. Therefore, during the first part of the period of uniform decompression, they are absorbing and not eliminating nitrogen, while during the second part of the period the difference of pressure in their tissues and that in the air may be dangerously great. It has been observed that it is safe for men who have worked at a pressure of 2 atmospheres, or 15 pounds gauge pressure, to pass immediately from this into normal pressure—a decrease of one-half; and in stage decompression, as developed by Haldane, a rapid decompression by approximately one-half is also found to be safe. Thus men who have worked in 8 atmospheres can be dropped rapidly to 4 atmospheres without danger. After remaining at 4 atmospheres for a time the pressure is lowered by small steps until atmospheric pressure is reached. Compressed air illness is much less likely to develop after such stage decompression than after continuous decompression, and the time consumed is considerably shortened. By neither method, however, is the entire excess of nitrogen in the body ordinarily removed; and it rather frequently happens that after a man has left the air lock, bubbles start to form in some part, such as a joint or the skin, in which there is still a considerable excess of nitrogen.

In order to reduce the incidence of such cases to a minimum, and to prevent more serious effects, schedules have been adopted for the duration of decompression according to the degree of pressure under which men may work and the duration of their exposure. Such schedules are now generally embodied in law, or are laid down by state industrial commissions or the public health authorities. Provision is also required for the treatment of any cases of compressed air illness that, in spite of all precautions, may occur.

Recompression. All forms of the disease are treated immediately by recompressing the man sufficiently to cause the separated nitrogen to redissolve in his blood and tissues. The ease with which this reabsorption can be effected depends upon the size of the bubbles which have separated: the smaller the bubbles the more readily they redissolve. Therefore, the sooner the treatment is applied, the more likely it is to give relief.

Recompression chambers, or medical air locks, are steel chambers large enough to hold the patient and a physician or an orderly, and are essential parts of the equipment necessary for safety in deep diving and caisson work. At the appearance of the first symptoms of the disease, the man is placed in one of these chambers, which is at once sealed, and compressed air is admitted up to approximately the pressure at which the man has been working. The pressure is afterward allowed to fall very slowly, while the affected part is massaged and such medication as may be needed to diminish pain and support vitality is administered by the physician, who generally enters the medical lock with the patient.

The one disadvantage of this treatment by recompression is, that while it immediately relieves the acute symptoms due to the formation of bubbles in the tissues, it does not diminish the amount of nitrogen in the body. On the contrary, it tends to increase the amount and thereby to lengthen the time before the patient can safely be restored to the outside air. This disadvantage may, however, be overcome by administering to the patient in the air lock, an inhalation of a mixture of 20 per cent oxygen and 80 per cent helium. To fill the lock with this mixture would be expensive and would require some arrangement for absorbing the heat and carbon dioxide given off by the patient and physician and recirculating the artificial atmosphere. More practical and more effective would be the use of the inhalator now generally employed in the treatment of the victims of carbon monoxide asphyxiation, but with the substitution of oxygen and helium for oxygen and carbon dioxide. This inhalation will hasten the elimination of nitrogen, but it cannot safely be substituted for recompression. It should be used with recompression.

As attacks of compressed air illness may occur as much as an hour or even several hours after decompression, the men in this trade should be lodged near their work, so that they may be "recompressed" at the first sign of illness. Before being employed they should be subjected to a thorough physical examination.

Fatalities in the Use of Submarine Escape Apparatus. An apparatus has been developed in the United States Navy (Behnke) to enable the crew of a damaged and sunken submarine to escape. It consists of a bag containing oxygen for

each man, into which he breathes while floating to the surface of the water. All members of the crews are now trained in the use of this Momsen "lung." During their training they are particularly instructed to continue to breathe during the ascent to the surface, and on no account to hold the breath. When this warning is disregarded the difference in pressure that develops between the air in the man's lungs and that outside his body as he comes to the surface, even from a quite moderate depth, causes minute tears in the pulmonary tissue through which air enters the circulation. The resulting air embolism is immediately fatal.

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Chapter 11

Group IIB. Chemical Asphyxiants

The chemical asphyxiants are few in number; they include only carbon monoxide and the cyanides, particularly hydrocyanic acid. Nevertheless, owing to the frequency of asphyxiation by carbon monoxide, this group is by far the most important of all the classes of noxious gases. Carbon monoxide is an asphyxiant because of its property of combining with the hemoglobin of the blood to the exclusion of oxygen. Cyanides, on the other hand, act upon the tissues and temporarily deprive them of the capacity to use the oxygen which the blood brings to them. In their modes of action carbon monoxide and the cyanides offer an interesting contrast to the substances which act merely as simple asphyxiants. Those inert gases exert their action in the lungs merely by keeping oxygen from reaching the blood. Carbon monoxide, even in lethal amounts, exerts no such action. Throughout an asphyxiation, oxygen is present in the lungs and is there in contact with the blood in ample amounts, but the blood cannot absorb or transport it. Cyanides neither prevent oxygen from reaching the blood nor from being absorbed into the blood and transported to the tissues. Instead, they act in the tissues and prevent them from using the oxygen which is brought to them.

Carbon Monoxide

Carbon monoxide, CO, is a gas at ordinary temperatures. It has a slight garlic-like odor, but this is seldom noticed. Its boiling point is $-190°$ C. and its specific gravity is 0.967. At 40° C. its solubility in water by volume is 0.0178.

Only in rare conditions does carbon monoxide appear in nature; it is, however, almost universally present wherever man lives and uses fire. It usually originates from the incomplete combustion of carbonaceous material. Illuminating gas is one of the commonest sources of acute poisoning; many of these cases are suicides. Coal gas, which is made by the destructive distillation of coal, contains from 4 to 6 per cent of carbon monoxide. Water gas, which is made by passing steam over heated

coke, contains about 40 per cent of carbon monoxide. In England and on the European continent coal gas is chiefly used for illuminating gas. In American cities a mixture is usually supplied consisting largely of water gas enriched either with some coal gas or with petroleum products to afford luminosity and raise the thermal value. Illuminating gas in the United States contains from 6 to 30 per cent, or even more, of carbon monoxide.

City gas which is mixed with air before being burned shows only a blue flame. Practically all the carbon monoxide which it contains is consumed, producing carbon dioxide. If, however, the blue flame is brought against a cold body, such as a water pipe or cooking utensil, it is chilled. As a result, not only may the carbon monoxide in the gas escape combustion, but carbon monoxide may even be formed from other carbonaceous gases. In fact, such a production of carbon monoxide readily occurs, even from natural gas, which is chiefly methane and contains no carbon monoxide, when it is used in water heaters and in improperly arranged open gas fires in living rooms. A similar result is produced when any "Bunsen" type burner with any gas is lighted improperly or "snaps back" and burns at the base. When fatalities occur from a production of carbon monoxide in one of these ways the claim is sometimes made that the death was not caused by carbon monoxide, since no gas leak occurred, and that it must have been due to the consumption of all the oxygen in the room and to excess of carbon dioxide. But in fact, low oxygen would extinguish the fire long before it would seriously affect a man, and excess of carbon dioxide up to 10 or 12 per cent would merely stimulate respiration.

The Primus stove, used by Arctic explorers, by itself produces no carbon monoxide. But when its flame comes against the cold vessels of a Nansen cooker, dangerous amounts may result.

Under various trade names the more volatile components of petroleum, chiefly propane, are sold in cylinders of the compressed and liquefied gases, chiefly for domestic cooking. For this purpose such fuel is convenient and safe. It is also sometimes used in radiant heaters in bedrooms and particularly in automobile tourist camps and cottages. Owing to the fact that propane is itself virtually non-toxic, some states and towns now neglect to require, as they should, that all gas heaters in bed-

rooms must be connected with a chimney or a special flue to carry off the products of combustion. It is indeed true that investigation has shown that, if such a heater is fully turned on, combustion of the gas to carbon dioxide and water is usually complete. If, however, the supply of gas is turned down until one or more of the burners may go out, or be easily blown out, while some of the other burners continue to burn, the gas from the now unlighted burners may undergo a flameless and incomplete combustion and produce considerable amounts of aldehydes and carbon monoxide. The deaths of two persons so asphyxiated have recently been investigated in this laboratory.

The gas from blast furnaces contains from 24 to 30 per cent of carbon monoxide; producer gas from 22 to 26 per cent.

The smoke from a coal fire contains variable amounts of carbon monoxide, depending upon how free the draft is; the more the combustion is impeded, the higher is the percentage of carbon monoxide. Flue gas from boilers and house heaters has sometimes caused poisoning through a leak or a back draft in the heating apparatus, or from the smoke or fumes after leaving the flue. The gas from charcoal braziers and from coke-burning salamanders contains considerable quantities of carbon monoxide; when used without flues they frequently give rise to poisoning. The smoke in burning buildings, particularly if the fire is of the smouldering basement type, contains a considerable percentage of carbon monoxide, and poisoning by the smoke is mainly due to carbon monoxide. Fires in mines produce especially high percentages of carbon monoxide because of the confined space and deficiency of oxygen. The "after damp" produced by an explosion of coal dust, the cause of many deaths among miners, also owes its toxicity to carbon monoxide.

The exhaust gas from internal combustion engines contains carbon monoxide in percentages ranging from a fraction of 1 per cent to 7 per cent or even higher. The variation depends upon the proportions of air and gasoline in the mixture burned as determined by the adjustment of the carburetor; the richer the mixture, the higher the percentage of carbon monoxide in the exhaust gas. A rough estimate of the volume of carbon monoxide that an automobile may produce is 1 cu. ft. (28 liters) per minute per horse power. This is sufficient to render the atmosphere of a single car garage deadly within 5 minutes, if the engine is run

while the garage doors are closed. A man breathing such an atmosphere often falls helpless before he realizes that he is affected; hence, many fatalities occur. In streets where traffic is congested, the content of carbon monoxide rises to about 100 parts per million of air—1 per 10,000—enough to cause slight headache after long exposure.

Diesel engines are now widely used in buses, trucks and tractors. Although these engines can be operated to produce considerably less carbon monoxide than gasoline engines usually do, the carbon monoxide hazard is by no means eliminated. Recent investigations by the U. S. Bureau of Mines showed, in addition to carbon monoxide, both oxides of nitrogen and aldehydes in Diesel exhaust gas. Although aldehydes are not very poisonous, their odor is extremely disagreeable. When a Diesel engine was operated on a low fuel-air ratio, figures for carbon monoxide as low as 200 parts per million (*i.e.*, 2 per 10,000), were found without loss of power. With excess of fuel, 6 times as high a proportion resulted: figures comparable to those from a rich mixture in a gasoline engine.

Formation of Carbon Monoxide Hemoglobin. Carbon monoxide is, except for one reaction, a physiologically inert gas; it is not a protoplasmic, or tissue, poison. Were it not for its affinity for the hemoglobin of the blood, carbon monoxide would be classed with nitrogen and hydrogen as a simple asphyxiant. Nerve cells of the chick were found by Haggard to grow normally in an atmosphere of 80 per cent carbon monoxide and 20 per cent oxygen. A mouse can live in a high percentage of carbon monoxide provided the pressure of oxygen is also increased (Haldane), for the amount of oxygen which then enters the blood in simple solution eliminates the need for transportation by hemoglobin. Animals, such as insects, are entirely unaffected by carbon monoxide, even in high concentration. All the toxic action of carbon monoxide, therefore, is exercised through the anoxemia resulting from the conversion of oxyhemoglobin to carbon monoxide hemoglobin.

In the tissues there is indeed another substance containing iron and capable, like hemoglobin, of combining with carbon monoxide—the catalyst cytochrome which plays a part in tissue oxidation. Cyanides kill by combining with cytochrome. But the affinity of cytochrome for carbon monoxide is so low that a

concentration of carbon monoxide sufficient to induce a fatal degree of saturation of hemoglobin would have no appreciable effect through its reaction with cytochrome. Ignorance of this fact led to the introduction, for a time, of methylene blue as a counter-asphyxiant in carbon monoxide poisoning. But as this substance tends to convert hemoglobin into methemoglobin, instead of aiding in resuscitation, it further decreases the oxygen-carrying capacity of the blood.

The combination of hemoglobin with carbon monoxide is effected by means of the iron in the hemoglobin molecule exactly as is that with oxygen. On this account carbon monoxide displaces oxygen from hemoglobin and, in turn, oxygen may again displace carbon monoxide and restore to hemoglobin its oxygen-carrying capacity. These reversible reactions of oxygen and carbon monoxide with hemoglobin are expressed by the following equation, in which hemoglobin is designated by the symbol Hb:

$$HbO_2 + CO \rightleftarrows HbCO + O_2$$

This equation indicates that carbon monoxide does not form a permanent union with hemoglobin, but that, on the contrary, the red corpuscles of the blood, in which the hemoglobin has been, for a time, combined with carbon monoxide and has then been freed from that combination by means of oxygen, are not injured; they are as capable of transporting oxygen as if they had never been exposed to the other gas. But as long as the combination with carbon monoxide continues, they are incapable of fulfilling their respiratory function. The factors determining these reactions and reversals are the relative amounts of the two gases to which the blood is exposed in the lungs—that is, their mass actions and their relative affinities for hemoglobin.

According to Stadie and Martin, an increase of carbon dioxide in the blood—acting through a decrease of pH—decreases the affinity of hemoglobin for carbon monoxide compared with its affinity for oxygen and tends to aid in eliminating carbon monoxide from the blood. Presumably, also, the loss of carbon dioxide, which occurs during the excessive breathing while severe asphyxia is developing, tends to increase the relative force of attraction of hemoglobin for carbon monoxide in comparison to oxygen. But, apart from this minor influence, the distribution of hemoglobin between carbon monoxide and oxygen—that is, the

percentage of the hemoglobin that will be combined with carbon monoxide—is determined by the relative strength of the affinities of the two gases for hemoglobin, and particularly by their relative concentrations in any atmosphere to which blood is exposed.

The body of an adult man of average size and weight contains enough hemoglobin to hold about 1 liter of oxygen, approximately 4 minutes' supply. If completely saturated, the hemoglobin would hold the same amount of carbon monoxide, 1 molecule of carbon monoxide replacing 1 molecule of oxygen in the blood. The absorption of 10 cc. of carbon monoxide from the lungs produces, then, 1 per cent of saturation and abolishes 1 per cent of the oxygen capacity.

During bodily rest the tissues extract only about 6 cc. per 100 cc. of blood, or 30 per cent of the oxygen in the arterial blood, before it passes into the veins and so back to the heart with 70 per cent of its load unused: a large factor of safety. During muscular exertion, this factor of safety is drawn on to such an extent that 70 or 80 per cent of the arterial oxygen is consumed in the tissues and correspondingly less is carried on into the veins. For these reasons a man at rest can tolerate a temporary abolition of nearly 30 per cent of the oxygen capacity of his blood by carbon monoxide and experience thereafter nothing more than a headache. If, however, he makes any considerable exertion, the supply of oxygen to his tissues, and particularly to his brain, is inadequate and he faints.

The units in which noxious gases are commonly measured are so many volumes of the gas per million volumes of air. But in the case of carbon monoxide, convenience and custom have often led to the practice of expressing the concentration in "parts" of this gas mixed with 10,000 times as much air. A "part" of carbon monoxide" is thus one hundredth of 1 per cent, or one ten thousandth of an atmosphere. A man at rest may breathe a little more than 8 liters, or 8,000 cc., of air per minute, of which about 6 liters reach his lungs, or 60 liters in 10 minutes. If he is on a street with heavy traffic when the air contains 1 part of carbon monoxide in 10,000 of air (100 parts per million), or say 6 cc. per 60 liters, at first all this will be absorbed; his blood will become "saturated" at the rate of 1 per cent of its oxygen capacity about every 15 minutes. If the air in a garage or repair shop contains 10 parts of carbon monoxide in 10,000 of air (1,000 parts

per million) as it sometimes does, the rate of absorption will be 10 times as rapid. If the man walks at a moderate pace and doubles his volume of breathing, or if, while at work in a garage, he increases the volume of his breathing 4 fold or more, the rate of absorption will be correspondingly increased. Evidently, then, the concentration of the gas in the air breathed, the length of time it is breathed, and the volume of breathing during rest and work are all essential factors in determining the amount of carbon monoxide absorbed. But a short exposure to a low concentration is harmless, for a man cannot absorb more than he inhales.

When a man begins breathing any moderate concentration of carbon monoxide mixed with air, absorption occurs at very nearly such rates, but only at first. Then the rate becomes slower. Even if the exposure is prolonged, carbon monoxide merely displaces oxygen up to a point of equilibrium depending upon the relative amounts, or mass actions, of the carbon monoxide and oxygen in the air breathed, and upon the intensity of the affinities of the two gases for hemoglobin. If the amounts of either the carbon monoxide or the oxygen in the atmosphere breathed are altered, the system begins immediately to seek a new equilibrium.

More precisely expressed, the distribution of hemoglobin between oxygen and carbon monoxide always tends to an equilibrium determined by the products of the tensions and affinities of the two gases. Thus, if PO_2 and PCO are the tensions, or partial pressures, of oxygen and carbon monoxide, and HbO_2 and HbCO are the amounts of oxyhemoglobin and carbon monoxide hemoglobin in the blood, the relations are expressed by equations:

$$\frac{PO_2 \times 1}{PCO \times 300} = \frac{HbO_2}{HbCO}$$

$$\frac{PCO \times 300}{PO_2 + (PCO \times 300)} \times 100 = \text{Percentage HbCO}$$

In these equations, the figure to be used for the partial pressure of oxygen is not that of 21, which is the percentage of oxygen in pure air, but 15, which is the approximate tension in per cent of an atmosphere in the air of the lungs. On this basis it is possible to calculate the equilibrium percentage of carbon mon-

oxide in the blood for any concentration of carbon monoxide in the air and thus to obtain the carbon monoxide dissociation curve of the blood as determined first by Haldane.

As the mechanics in a garage often work for a time in atmospheres containing considerable amounts of carbon monoxide, the question of practical importance is: How long a time would be required, in any particular atmosphere, to attain any particular percentage of saturation? The equations given above and the carbon monoxide dissociation curve determined by Haldane define the ultimate equilibria. But to attain such equilibria many hours, or even days, would be required: indeed, the time

FIG. 6. Carbon Monoxide Equilibrium Curve of Blood, solid line, after Prolonged Exposures, as Determined by Haldane; and Curve for Maximum Degrees of Saturation Attainable in One Hour during Rest, as Determined by Henderson and Haggard, broken line.

is indeterminate. The figures so calculated have, therefore, little more than a theoretical value, and those needed for application to industrial conditions cannot be directly derived merely by theoretical calculation.

This problem, in its practical aspects, is somewhat like that involved in measuring the rate of radiation and decay in radium,

which is also indeterminate. In work to determine the standard of ventilation for the Holland vehicular tunnels under the Hudson River in New York City, Henderson and Haggard undertook to determine experimentally the length of time required for the blood to become half saturated for all concentrations of carbon monoxide in the air breathed up to concentrations of 10 parts in 10,000 parts of air. The results of their work are expressed in the broken line in the accompanying figure. The rule of safety which this curve expresses is that, if the air contains such an amount of carbon monoxide that the blood in full equilibrium with it would be combined with carbon monoxide to the extent indicated by a point on the upper curve in the figure, a man at rest may breathe that air for 1 hour before his blood will absorb more than half the equilibrium amount as indicated by a point on the lower curve directly below the upper point. And under any physical exertion which increases the volume of breathing, the time required to reach such a degree of saturation would be inversely decreased.

In using this rule of safety, it is important to keep in mind that it applies fully only to adults of about average size and weight. When two individuals, one of whom is much smaller than the other—particularly if the smaller is a child—are exposed to the same atmosphere, it is the smaller and younger—that is, the individual with the more active metabolism and relatively larger volume of respiration—who absorbs carbon monoxide and approaches saturation the more rapidly. This fact is applied practically in the use of small animals, such as mice and canaries, as indicators of dangerously vitiated air in mine rescue operations. When the mouse can no longer maintain its equilibrium, or the canary falls off its perch, men breathing the same atmosphere may estimate the time allowable for their escape as approximately inversely as their skin areas and volume of breathing are to those of the mouse and canary.

Effects of Various Durations of Exposure in Various Concentrations of Carbon Monoxide. When the time of exposure is measured in hours, and the concentrations of carbon monoxide are expressed in parts per million, the physiological effects may be roughly defined by the equations:

Time × concentration = 300: no perceptible effect

Time × concentration = 600: a just appreciable effect

Time × concentration = 900: headache and nausea

Time × concentration = 1,500: dangerous

The amounts of carbon monoxide that must be absorbed to give these effects and the effects themselves, somewhat more precisely defined, are as follows:

Table 18.

% Carbon monoxide hemoglobin	Physiological effects
10	No appreciable effect, except shortness of breath on vigorous muscular exertion.
20	No appreciable effect in most instances, except shortness of breath, even on moderate exertion; occasionally slight headache.
30	Decided headache; irritable; easily fatigued; judgment disturbed.
40 to 50	Headache; slight confusion; collapse and fainting on exertion.
60 to 70	Unconsciousness; respiratory failure and death if exposure is long continued.
80	Rapidly fatal.
Over 80	Immediately fatal.

From these data the following definitions of safety and danger are derived.

Table 19.

Parts of carbon monoxide per million parts of air	Physiological effects
100	Concentration allowable for an exposure of several hours.
400 to 500	Concentration which can be inhaled for 1 hour without appreciable effect.
600 to 700	Concentration causing a just appreciable effect after exposure of 1 hour.
1,000 to 1,200	Concentration causing unpleasant but not dangerous symptoms after exposure of 1 hour.
1,500 to 2,000	Dangerous concentration for exposure of 1 hour.
4,000 and above	Concentrations which are fatal in exposures of less than 1 hour.

Elimination of Carbon Monoxide. The anoxemia induced by carbon monoxide does not cease as soon as fresh air is inhaled, as is the case with the simple asphyxiants, but persists in diminishing degree until all the gas has been eliminated from the blood. Even with the simple asphyxiants the after-effects of anoxemia—headache, disturbance of judgment, etc.—persist for some time after an ample supply of oxygen is restored. With carbon monoxide there is the additional disadvantage that in untreated cases the period of slow elimination is often much longer than the

period of actual exposure in the atmosphere containing the gas. Carbon monoxide is not burned to carbon dioxide nor otherwise destroyed in the body, and in untreated cases it is only gradually eliminated through the lungs when air free from carbon monoxide is inhaled. The mechanism is the reverse of that of absorption. The carbon monoxide does not separate from hemoglobin spontaneously, but is displaced only by the mass action of oxygen. Experience has shown that during the first hour after moderate degrees of gassing, with no treatment other than fresh air, little more than half the carbon monoxide is eliminated, and that the elimination is not complete for many hours. After brief exposures to high concentrations of the gas with rapid absorption, the anoxemia is therefore suffered mainly after the man has been removed from the contaminated atmosphere. It is extremely important, therefore, to hasten the elimination and thus abbreviate this period of post-gassing asphyxia. Of two workmen exposed for a short time to a high concentration of carbon monoxide—as in a trench in the street or a sewer or manhole—and equally gassed, one who is allowed to recover spontaneously merely in fresh air may remain unconscious for an hour or more and be ill for a day or two, while the other, who is treated immediately with an inhalation of carbon dioxide and oxygen, recovers promptly and usually with little after-effect.

Treatment of Asphyxia. The treatment of asphyxia by inhalation of a mixture of oxygen and 7 to 10 per cent of carbon dioxide was developed by the authors of this book primarily to deal with asphyxia caused by carbon monoxide—the commonest of all forms of poisoning by gases. The treatment is, however, applicable to other asphyxiants without modification. It applies equally well to the anesthetic hydrocarbons and hydrogen sulfide, although less effectively to cyanides. But it does not apply, and is quite unsuitable, to the treatment of cases poisoned by irritant gases.

In respect to resuscitation from carbon monoxide asphyxiation, four main stages occur. (1) The man becomes unconscious, but he continues to breathe and his heart still beats; (2) he has stopped breathing but his heart still beats for some seconds or minutes; (3) both breathing and the heart have stopped, but some tonus remains in the muscles for a few minutes; (4) death occurs and *rigor mortis* develops.

The first step in treating a man in any of the first three stages is to remove him immediately to fresh, but not cold, air. He is laid on his stomach with his face turned to one side. If he is breathing, he is given an inhalation of oxygen containing 7 to 10 per cent of carbon dioxide. If he is not breathing, manual artificial respiration should be started at once, and the inhalation of oxygen plus carbon dioxide administered simultaneously. The inhalation of oxygen and carbon dioxide is continued for 15 to 30 minutes after spontaneous respiration returns. The after-treatment consists of general measures designed to prevent the development of pneumonia. Drugs have little value in the treatment of asphyxia. Alcohol is contra-indicated, but coffee may be given after the patient is able to hold a cup.

It should be clearly understood that the essential condition in carbon monoxide asphyxia consists, not in the cessation of the movements of breathing, for respiration continues almost to death, but in the interruption of the supply of oxygen to the tissues of the body, and especially to the brain, because of the inability of the blood to carry oxygen. In this respect asphyxia by gases contrasts with drowning and electric shock. In both of the latter conditions spontaneous respiration is stopped and artificial respiration is the supremely important measure of assistance, although in those conditions also inhalation of oxygen and carbon dioxide is a valuable accessory.

Even after a prolonged and severe asphyxia by carbon monoxide, the victim, unless irretrievable, is generally breathing spontaneously, although poorly. The administration of oxygen alone is then not very effective, for the reason that it is not inhaled in sufficient volume. The carbon dioxide mixed with the oxygen acts, however, as a powerful respiratory and cardiac stimulant. It both replaces the carbon dioxide that the body has lost and, by the increase of respiration, it induces a deep and full inhalation of the oxygen with which the carbon dioxide is mixed. It increases muscle tonus and thus aids the venous return of the blood to the heart.

Drugs, such as lobeline and coramine, which stimulate respiration when administered hypodermically, are inadvisable because they do not replace, but may even further deplete, the body's needed supply of carbon dioxide. Before inhalation of carbon dioxide with oxygen was introduced as a respiratory stimulant,

such drugs as atropine, caffeine, strychnine, camphor, cocaine, apomorphine, adrenalin, and even ether, were sometimes administered subcutaneously. Methylene blue was, for a time, advocated as a counter-asphyxiant; but by converting hemoglobin into methemoglobin it actually further decreases the oxygen-carrying capacity of the blood. In brief, all hypodermic and intravenous medications—and particularly intracardiac injections—are not only valueless but even harmful in this field. Transfusion of blood free from carbon monoxide, once practiced, has been discarded.

Alleged Chronic Poisoning. Daily exposure to small amounts of carbon monoxide may lead to either of the types of response to repeated partial deficiency of oxygen described in the previous chapter. Workers about blast furnaces and in some automobile repair shops where there is frequent exposure to low concentrations of carbon monoxide may develop a considerable degree of true acclimatization, as indicated by an increase in the red cell count. On the other hand, when, as is generally the case, the exposure is less regular but more severe, symptoms similar to overtraining in athletes and to air staleness in aviators may develop (see p. 148).

Carbon monoxide is not a cumulative poison. There is, therefore, no such condition as the expression "chronic carbon monoxide poisoning" would imply. In pure air and with a sufficient volume of breathing, small amounts of this gas are readily ventilated out of the blood. Unlike lead or silica dust, it cannot accumulate in the body progressively over long periods. Repeated exposures, as of garage mechanics, blast-furnace workers and cooks may temporarily, but only temporarily, impair health. More often a compensatory polycythemia develops like that in acclimatization to altitude.

After severe asphyxia followed by prolonged coma the victim generally dies within 36 hours without regaining consciousness. Otherwise he usually recovers completely in a few days. The belief in "chronic carbon monoxide poisoning" arises from the fact that in occasional instances prolonged asphyxia damages the brain too deeply for complete restoration, but not quite enough to kill. The patient then survives with impaired mind, particularly loss of memory and paralysis or sensory defects. These sequelae are due, not to retention of carbon monoxide, but

to degeneration of the nerve centers. The determining factor in their production is the physical condition of the individual and the length of time that the tissues have been subjected to oxygen lack. The strain put on bodily functions by asphyxia is, in many respects, similar to that of exercise. Individuals who are old, in frail health or suffering from cardiovascular disease, do not stand the strain of asphyxia as well as do robust individuals.

Claims of impaired health from exposure to carbon monoxide are now common as the basis of law suits. In the majority of cases these claims are unjustified. They should not be accepted as valid unless all of three conditions can be established: (1) at least a 50 per cent saturation of the blood or a concentration of carbon monoxide in the air sufficient to induce at least 50 per cent saturation; (2) an exposure of at least 3 hours; and (3) continuous complete unconsciousness lasting for at least 6 hours after return to fresh air. Short of conditions of such severity, recovery is practically always complete.

Cyanogen Compounds

The following table presents the more important volatile cyanogen compounds with their general physical and physiological data as far as they are known.

Table 20. Volatile Cyanogen Compounds.

Name	Formula	Boiling Point (° C.)	Physiological Action
Cyanogen	NCCN	−20.5	Arrest oxidation in the tissues and thus produce asphyxia.
Hydrocyanic acid	HCN	26.0	
Acetonitrile	CH_3CN	82.0	
Propionitrile	CH_3CH_2CN	97.1	
Methyl isonitrile	CH_3NC	59.6	
Ethyl isonitrile	C_2H_5NC	79.0	
Benzonitrile	C_6H_5CN	190.7	
Cyanogen chloride	CNCl	13.8	As above, but also strongly irritating to the respiratory tract.

In industry the important toxic cyanogen compound is hydrocyanic acid. It is used extensively as a fumigant; it kills all insects—and all higher animals—but is not a bactericide. As a salt it is used in extracting gold from ore and in the manufacture of dyestuffs and synthetic chemicals. Small amounts occur in coal gas and in the gases from blast furnaces and coke ovens.

It is evolved when Celluloid is burned and constitutes a considerable danger to city firemen. It is also evolved from its alkali salts on contact with air.

Action of Cyanides. The cyanogen compounds are true protoplasmic poisons in the sense that they arrest the activity of all forms of animal life, but not of bacteria. They are not disinfectants. They exert an inhibiting action upon tissue oxidation by combining with the catalysts in the living cells of the body tissues containing iron or sulfur. The tissues manifest life by heat and movement and the continual oxidation of foodstuffs. Cyanides stop this oxidation, and the vital functions are thereby suspended. The suspension is maintained only during the presence of the cyanide; its removal allows the return of normal function, if death has not occurred during the period of oxygen starvation. Cyanide poisoning is a form of asphyxia caused by the arrest of internal respiration.

Hydrocyanic acid combines with difficulty with hemoglobin, but readily with methemoglobin to form cyanmethemoglobin. The combination of cyanide with hemoglobin occurs in the body only in the presence of methemoglobin, and hence is a post-mortem change. The bright red color of the venous blood in cyanide poisoning is due to the fact that oxygen is not abstracted from the blood in the tissues and the blood therefore returns in the veins still in the arterial condition.

Cyanides are powerful respiratory stimulants. Their action is exerted on the nerve endings in the sinus caroticus. But their effect is brief, as they are rapidly destroyed in the body, combining with sulfur to form non-toxic sulfocyanides.

Cyanogen has the same physiological action as hydrocyanic acid gas and may also occur in coal gas. Acetonitrile, propionitrile, benzonitrile and methyl and ethyl isocyanides also exhibit the same effects in various degrees, but are less toxic than hydrocyanic acid. The halogen-bearing compounds of cyanogen, such as cyanogen chloride and bromide and phenylcarbylamine chloride, have pronounced irritating properties.

Symptoms of Cyanide Poisoning. Acute cyanide asphyxia is one of the most rapid modes of death. In the ordinary case of acute poisoning the man falls after a few breaths, or even a single breath, of the contaminated atmosphere. Breathing may

continue for a brief period and during this time it is greatly increased in volume; but death often follows almost immediately.

In less acute cases the sequence of events is less rapid and symptoms typical of ordinary asphyxia are more clearly seen. Mild cases and non-fatal cases of poisoning result in headache and a feeling of suffocation and nausea which may last for some hours.

Table 21. Physiological Response to Various Concentrations of Hydrocyanic Acid Gas.[9-15]

	Parts of hydrogen cyanide per million parts of air
Maximum concentration allowable for prolonged exposure	20
Slight symptoms after exposure of several hours	20 to 40
Maximum concentration that can be inhaled for 1 hour without serious consequences	50 to 60
Dangerous after exposure of 30 minutes to 1 hour	100 to 240
Fatal after exposure of 30 minutes	200 to 480
Rapidly fatal	3,000

Cyanide Poisoning from Fumigation. Potassium cyanide and other salts of hydrocyanic acid have long been recognized as among the most rapid and intense poisons, but they have caused few deaths except by suicide. It is only since hydrocyanic acid gas has come into wide use as a fumigant to rid houses of insect vermin and the holds of ships of rats and plague-infested fleas that accidental deaths from inhalation of the gas have become common. Apart from its extreme hazardousness in case of any carelessness, inadvertence or ignorance in its use, this gas is an altogether ideal fumigant. Even in low concentrations it kills all forms of animal life, and not merely red-blooded creatures as carbon monoxide does.

The most convenient means of using the fumigant is as liquid hydrocyanic acid (HCN) in steel cylinders from which it is forced by air pressure as a fine spray which volatilizes immediately. The gas may also be generated by adding sodium cyanide to sulfuric acid, or to sodium chlorate and 50 per cent hydrochloric acid. Somewhat safer—if so intense a poison can ever be said to be safe—is the use of one of several solid preparations in fuller's earth or wood fiber, or as calcium cyanide which, if left for a time in a closed space, gives off enough of the gas to be effective. To kill rats 2 oz. of hydrocyanic acid gas per 1,000 cu. ft. of air are needed.

As the molecular weight of HCN is low—only 27, less even than the average of the gases of air—this gas has a remarkably high capacity to penetrate bedding and other household furnishings and merchandise and grain in the holds of ships. Unless fully aired, such material may later give off enough of the gas to render the air in a confined space dangerous. Foodstuffs should be aired for at least 24 hours, but are then free from injurious effects. In the practice of fumigation the operators must take the utmost care not to get caught in the building or the hold of a ship after the liberation of the gas has begun, or to return until all spaces have been thoroughly aired. A gas mask with a canister of activated carbon affords effective protection against inhalation, but the gas may possibly be absorbed through the skin, although very slowly.

Treatment of Cyanide Poisoning. When cyanides have been taken into the stomach, from which absorption is much less rapid but more prolonged than from the lungs, the now standard antidotes are sodium nitrite and sodium thiosulfate, administered by subcutaneous injection one after the other rather than together. Methylene blue is now rarely used.

In cases of poisoning by inhalation, subcutaneous or even intravenous treatment is, however, too slow to be effective. On the contrary, the patient should receive an immediate inhalation of amyl nitrite. Glass "pearls" containing this substance should be on hand and their contents liberated by breaking one or more into a handkerchief, which is then held over the patient's face while manual artificial respiration is applied, if the breathing threatens to fail.

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Chapter 12

Group III. Volatile Drugs and Drug-like Substances

The gases and vapors classified here as volatile drugs and drug-like substances include a wide variety of organic chemicals —and one non-carbonaceous gas—many of which have an extensive industrial and domestic use, especially as solvents and fuels. The essential feature of the grouping here is that all these substances exert their major physiological action after they have been absorbed into the blood. It is to them that the principles of absorption, distribution and elimination, as defined in Chapter 5, particularly apply.

The one physiological property common to these substances, although it is in some cases obscured by intense action in some other direction, is that of inducing the symptoms of anesthesia when inhaled in sufficient quantities. Some of the volatile drugs have virtually no other action on the body. This anesthetic action varies in intensity: with some of the volatile drugs it is strong, but with others it is so mild that they behave more as simple asphyxiants. Some of the volatile drugs, in addition to their anesthetic action, cause organic disturbances in various structures of the body. These toxic effects may be manifest after a single severe exposure; but, what is more important, they may develop from the long-continued exposure to concentrations which do not induce anesthesia to any appreciable degree.

Some of the volatile drugs and drug-like substances are irritating to surface tissues. When this irritation is less marked than the systemic effect after absorption (cf. secondary irritants, Chapter 9), they are included in the description here. But when the irritation is so intense as to prevent the absorption of an appreciable amount of the substance, they are considered as primary irritants (Chapter 9) and, although classified here, they are described in that chapter.

Classification

The gases and vapors dealt with here as drugs and drug-like substances may be classified under six subgroups according to their characteristic chemical, physical, and especially physiological properties.

Subgroup A. Primary Irritants. Substances having an irritant action on the respiratory tract sufficiently intense to prevent the absorption of any appreciable amount or largely to obscure the effect from any absorbed. This subgroup is discussed in Chapter 9.

Subgroup B. Primary Anesthetics. Substances which produce no marked effect other than anesthesia or cause any serious systemic effect from prolonged exposure to subanesthetic concentrations: nitrous oxide, hydrocarbons of the paraffin, olefin and acetylene series, ethers and aldehydes.

Subgroup C. Anesthetic vapors which injure visceral organs: chlorinated hydrocarbons.

Subgroup D. Anesthetic vapors which injure the hematopoietic system: benzene and its homologs.

Subgroup E. Anesthetic vapors which injure the nervous system: methyl alcohol, carbon disulfide and esters of organic acids.

Subgroup F. Volatile drugs and drug-like substances in which the anesthetic action is obscured by other and more profound systemic effects, especially on the hemoglobin of the blood and on arterial pressure: organic nitro compounds.

Action of Anesthetic Gases and Vapors

The anesthetic gases and vapors are characterized primarily by their depressant effects upon the central nervous system, particularly the brain. On inhalation they are carried to the brain in the blood and to all other tissues of the body. The volume of blood flow through the brain is so large, however, as compared to most other tissues, that the partial pressure of any gas or vapor dissolved in the blood rises almost immediately to the same pressure in the brain as in the lungs. As shown in Chapter 5, the pressure of each gas in the arterial blood as it leaves the lungs is in equilibrium with the pressure of that gas in the air of the lungs. Thus for all gases of this class the partial pressure of the gas in the brain almost immediately becomes the same as that

in the lungs. The concentration in the brain depends upon the solubility of the gas in its tissues and upon the partial pressure; the concentration varies, therefore, in proportion to the partial pressure of the gas in the lungs. The effective concentration is probably that in the lipoids of the nervous tissue rather than in the brain as a whole; but the vapor pressures would be the same and the concentrations therefore proportional to the solvent capacity.

The degree of the anesthetic effect of each gas depends both upon the (effective) concentration in the brain and upon its own specific pharmacological action. According to the Meyer-Overton theory (see below), the specific action is the same for all anesthetics: the degree of effect would then be proportional simply to the molecular concentration. Thus for substances of high solubility in lipoids, low partial pressures would be anesthetic.

With all anesthetic gases and vapors the effects pass through a series of stages as the partial pressure of the gas in the lungs is increased from a low to a high intensity. The following stages may be observed.

Stages of Anesthesia

In what may be termed the preliminary stage of anesthesia, the low pressure of the gas in the lungs and blood, and the proportionally low concentration in the central nervous system disturb judgment slightly and decrease the accuracy of the coördination of the finer movements. Skilled work is performed more slowly and more errors occur than when the individual is in a normal condition.

In the next stage, somewhat higher concentrations in the blood cause confusion of ideas and bewilderment. Muscular coördination is seriously disturbed; the man is somewhat "drunk." In this stage, and to a somewhat less extent in the previous stages, there is serious danger of accidents.

In the third stage (termed the first stage of surgical anesthesia) higher pressures in the lungs and higher concentrations in the brain generally induce excitement; but the degree of excitement is variable and with some anesthetics may be almost entirely absent. With those anesthetics which induce excitement the condition is largely the result of loss of functional control, and particularly loss of inhibition, so that the centers of motion

are set free and act more strongly than when they are under their normal regulation. Excitement from this cause varies widely from one man to another. In addition to this excitement some anesthetic gases, notably the higher members of both the methane and aromatic series, stimulate the cortex of the brain and induce convulsive muscular movements, twitchings and writhings.

In the fourth stage (corresponding to the second stage of surgical anesthesia) still higher concentrations of the anesthetic gases induce complete unconsciousness and immobility. In the lowest concentrations sufficient to induce unconsciousness the muscles maintain their tonicity and, with some anesthetics, even exhibit a hypertonicity, but as the concentration rises, they relax. The face then assumes a calm, death-like appearance. The reflexes disappear; one of the last to go is the closure of the eyelid when the cornea is touched.

The final stage is reached when the concentration of the anesthetic in the blood abolishes the activity of the respiratory center. The extent to which the concentration in the blood can be raised above that necessary to induce unconsciousness without danger of respiratory failure varies with the different anesthetics. With some, the margin is wide, but with others, death results from even a slight increase in the concentration beyond that of unconsciousness. Death is due to the paralysis of the respiratory center. The heart generally continues to beat for some minutes after breathing stops. Exceptions to this order of events occur only in a few special cases, particularly with chloroform and related substances, when the heart may stop first or go into fibrillation.

Pharmacological Activity

The pharmacological activity of the various anesthetic drugs is inversely proportional to the concentrations in the blood necessary to elicit any particular degree of effect, such as unconsciousness. Wide differences are found. For example, a concentration of approximately 0.25 g. of chloroform per liter of blood causes unconsciousness; while 1.0 g. of ether, or 3.0 to 4.0 g. of ethyl alcohol, is required to produce the same degree of effect. It is important not to lose sight of the fact that the comparison of anesthetics is usually made upon the basis of the concentration

in the blood and not of that in the air breathed, nor even of the partial pressure of the gas in the air of the lungs. Solubility and volatility are both important factors in the action of the anesthetic hydrocarbons.

Volatility and Solubility

A substance of low volatility produces at most only a low partial pressure of vapor and for this reason inhalation of it may have little physiological effect. A substance of low solubility is absorbed into the blood only in correspondingly low concentrations. Thus unless the pharmacological activity of the substance is high, its low volatility and low solubility may deprive it of appreciable physiological effect. Contrariwise, high volatility and high solubility may afford a high physiological effectiveness even for a substance of low inherent pharmacological action.

Any anesthetic substance present in the blood in sufficient quantity will produce a high, or even fatal, degree of anesthesia; many of the anesthetics, however, because of their low solubility, are unable to enter the blood in its passage through the lungs in a quantity sufficient to elicit more than a feeble response. For example, decane is, by all indications, a more powerful substance pharmacologically than is pentane; decane has, however, an extremely low solubility in blood, whereas pentane is much more soluble. Therefore, when the two gases are inhaled in equal amounts, the feebler pentane induces the greater anesthetic effect because its solubility allows the concentration in the blood to rise to a point which more than compensates for its weaker pharmacological activity as compared to decane. The higher members of the paraffin series are inert by reason of their insolubility.

Solubility not only plays a part in limiting the action of an anesthetic, but contributes as well to the character of its action. Soluble anesthetics are absorbed rapidly (when the amounts are expressed by dose and not as percentages of saturation of the body) and eliminated slowly; their action is therefore prolonged, as in the case of methyl alcohol. Relatively insoluble anesthetics are eliminated rapidly, for a high pressure of the vapor in the air is necessary to hold them in solution. The part played by

solubility in the absorption and elimination of gases and vapors has been discussed in Chapter 5.

The volatility of a fluid limits the concentration which its vapor can attain in the air and therefore limits its physiological action. Decane, used in the illustration above, has a vapor pressure of 2.7 mm. at 20° C.; the maximum concentration of the vapor which can exist in the air at this temperature is 3,550 parts per million, while at body temperature the maximum concentration in the air is 10,000 parts per million. Neither of these concentrations would cause death.

Chemical Structure and Pharmacological Activity

Present knowledge of the chemistry of the living body is not sufficient to permit complete formulation of the relations of chemical structure to pharmacological action; but certain generalizations can be made in respect to anesthetics and their pharmacological activity.

As a rule, in any homologous series of hydrocarbons, the higher members have a greater pharmacological action than the lower. Thus propane and butane produce unconsciousness when present in the blood in a lower concentration than methane or ethane; amylene is more active than ethylene. This relation applies likewise to their alcohols; thus the anesthetic potency of the simple alcohols rises from methyl alcohol through ethyl, propyl and butyl to amyl alcohol, which is the most powerful of the series. On the other hand, when the hydroxyl groups of the alcohols are increased, as in the series ethyl alcohol, glycol and glycerol, the action is progressively diminished.

The presence of the carboxyl group generally prevents any anesthetic activity. Replacing the H of the carboxyl group with a radical of one of the fatty hydrocarbons to form an ester restores the anesthetic action, but only slightly. Acetic acid has no anesthetic properties, but ethyl acetate is mildly anesthetic.

The substitution of a halogen for a hydrogen of the fatty hydrocarbons greatly increases the anesthetic action. Furthermore, the compound becomes less specific in its action and affects other tissues besides those of the nervous system. In many instances it alters and injures them organically. Chloroform (trichloromethane) is much more active pharmacologically than

methane and, in addition, has toxic properties which may cause degeneration of the liver, heart muscle and kidneys.

The aldehydes of the fatty hydrocarbons are anesthetic in their action, but the lower members of the series are irritating to the surface tissues of the respiratory tract to such an extent that their anesthetic action is largely obscured.

Many of the esters of the fatty hydrocarbons fail to exhibit their anesthetic action because they contain more active radicals. Thus ethane (C_2H_6) is an anesthetic, but ethyl nitrite, ($C_2H_5NO_2$) cannot be so classed because the NO_2 radical has a powerful and entirely different effect which forces the narcotic action into the background.

Theories of Anesthetic Action

The action of the anesthetic hydrocarbons is exerted directly upon the nervous tissues; the phenomena of anesthesia are induced through this specific action and do not arise secondarily from alteration in such bodily functions as respiration or circulation. Beyond this point the fundamental action of the anesthetics is a matter of speculation. Numerous theories have been advanced, but probably no one of them affords a complete explanation of the action. These theories, nevertheless, indicate the trend of present ideas upon the subject and for that reason the more important are given here.

(1) Claude Bernard, and later Verworn, pointed out the similarity of the symptoms of anoxemia and anesthesia. It was suggested that anesthesia was due to the inhibition of oxidative activity of the nerve cells. More recently this theory has been extended to the idea that the primary action is upon the respiratory enzyme system of nerve cells. According to some exponents of this theory, the inhibiting effect is particularly marked on the pyruvic acid oxidizing system. It has been suggested that there is a dehydrogenase in the brain which acts as a hydrogen carrier in this oxidation system and which is highly sensitive to anesthetics.

(2) Meyer and Overton have suggested that the anesthetics act upon the lipoids in the membranes of nerve cells and alter their permeability and the electrical polarization of nerve cells. This theory rests mainly on the fact that when the anesthetics are arranged according to their solubilities in oil and water the

series accords with their potency as anesthetics. As there are some exceptions to the rule, it may indicate only an interesting observation and not a cause of anesthesia.

(3) Höber and Lillie have suggested that the essential feature of anesthesia is physical, and that it consists in a diminished permeability of the cell membrane to ions; when ions can no longer penetrate, vital activity ceases.

(4) Moore and Roaf have concluded that the action of anesthetics is chemical in that the anesthetic agents form unstable compounds with the protein of the nerve cells. Anesthesia, they believe, is due to a paralysis of the chemical activity of the protoplasm resulting from this combination.

(5) Claude Bernard, and later Barcroft and Richter, have advanced the conception that anesthesia is associated with an aggregation of cell colloids.

(6) Traube, Lillie and Warburg hold that the potency of anesthetics is correlated with their ability to lower surface tension. They assume that the anesthetics alter the surface properties of the nerve cells and hence change their permeability or interfere with their vital activities.

(7) Still another view is based on the electrical phenomena of the nervous system. It has been suggested that anesthesia is due to a decreased negative potential in certain parts of the brain and to lessened conductivity through other parts.

This much is clear: the anesthetics exert their action particularly upon those tissues in which sensitivity is greatest. But the manner in which they interfere with the functions of these tissues is still undetermined. It is a fact, whether or not of fundamental significance, that the abolition of functions follows in reverse order the evolutionary development of the various classes or levels of centers in the nervous system. Thus the higher centers, those concerned with consciousness, judgment, voluntary motions, and sensations, are affected first and most intensely; the basal centers controlling respiration, heart rate and other involuntary functions are affected last. The sequence is essentially the same as in asphyxiation.

Chronic Poisoning

Ordinarily the removal of the anesthetic from the blood soon restores the nervous system to its original state of health. For

only a short time some reaction persists and is felt as a "hang-over" as after alcoholic intoxication and surgical anesthesia.

Probably any anesthetic substance acting sufficiently often and with sufficient severity will eventually induce chronic poisoning and some organic changes in the body. But there is no evidence that exposure to primary anesthetics in subanesthetic concentrations will cause such damage, and some evidence that they do not. Ethyl alcohol, although ordinarily taken by way of the alimentary tract instead of the lungs, affords the most common example of functional derangement, passing in time into organic derangement. Alcohol is a typical primary anesthetic, but drunkenness usually does not pass the second stage of anesthesia as the stages are defined here. After such degree of anesthesia there is recovery with no apparent damage. When, however, the ingestion of alcohol is frequent and in large quantities, and some degree of anesthesia is maintained over long periods of time, organic changes do usually develop in the nervous system and the liver. The quantity of alcohol required to produce such changes is, however, large, probably in excess of a half pint of whisky a day. Moderate consumption of alcohol without sustained anesthesia does not, even after many years, produce any organic changes in the nervous system.

The situation is different for the anesthetics of Subgroups C, D, and E. These substances exert actions beyond that of simple anesthesia; they have definite toxic properties. The hydrocarbons of the aromatic series induce changes in the hematopoietic (blood-forming) system which, after prolonged exposure to even subanesthetic concentrations, may result in anemia, hemorrhages and loss of white cells. Such changes, as a rule, do not occur after a single severe exposure to these hydrocarbons. The halogen derivatives of the fatty hydrocarbons exert their toxic action on the visceral organs, particularly the liver and heart. These organic effects may result even after a short exposure to anesthetic concentrations; a single anesthesia by means of chloroform is sometimes followed by death from degeneration of the liver. Some alcohols, notably methyl, cause organic changes in the nervous system; carbon disulfide exerts this action upon the nervous system to a high degree. The action of the anesthetic hydrocarbons as protoplasmic poisons is the basis of the classification in the first section of this chapter.

Treatment of Acute Poisoning

The essential points in the treatment of acute poisoning by the anesthetic gases are: first, to keep the patient alive until the anesthetic is eliminated from the blood, and second, to promote its rapid elimination. Death usually results from paralysis of the respiratory center; with a few exceptions—chiefly the halogen compounds—the heart continues to beat for several minutes after breathing has stopped. The course of treatment is the same as that for carbon monoxide poisoning as described in Chapter 11. It consists in the administration of oxygen and 7 to 10 per cent carbon dioxide. If natural breathing has ceased, manual artificial respiration by the prone pressure method should be administered. The patient should be kept warm and absolutely quiet for several hours after return of consciousness. Nothing should be administered by mouth until the patient is fully conscious. No hypodermic medication should be given except when some physical injury requires morphine to overcome pain.

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Chapter 13

Group III (cont'd). Volatile Drugs and Drug-like Substances

Subgroup B. Primary Anesthetics

This subgroup includes both the surgical anesthetics and also a large number of related substances which are used in industry. The surgical anesthetics have their own extensive literature, but it deals mainly with the acute physiological responses to high concentrations. Conditions in the factory, on the contrary, involve not only unintentional anesthesia as a factor in accidents, but also prolonged daily exposure to low non-anesthetic concentrations.

Hydrocarbons of the Paraffin Series. The hydrocarbons of the paraffin series occur almost exclusively as products of petroleum. Except methane, the "fire-damp" of coal mines, these hydrocarbons are rarely found singly, but occur as mixtures. They are the lighter petroleum distillates.

Fuel oil and lubricating oil, which are essentially petroleum from which the volatile constituents have been removed by fractional distillation, do not require consideration here, for only the lighter constituents are sufficiently volatile to give rise to toxic contamination of the air at ordinary temperatures. The vapors arising from crude petroleum at these temperatures consist of these more volatile substances.

The gas coming from oil or gas wells consists chiefly of methane and ethane but may also contain small amounts of propane and butane. The crude oil pumped from the wells contains some ethane and, in addition, all the volatile hydrocarbons of the methane series. When petroleum is distilled, the ethane, propane, and butane pass off first and are collected and liquefied by compression, either separately or in mixtures. Propane and butane are used as refrigerants, and ethane and propane as fuels. Methane and ethane are essentially simple asphyxiants; propane and butane in high concentrations have some anesthetic proper-

ties. Except for the hazard of explosion there are apparently no ill effects from remaining for several hours in an atmosphere containing these gases in concentrations as high as 3 to 5 per cent, or from repeated exposures. It must be borne in mind, however, that the combustion of these hydrocarbons, as well as the higher homologs as fuels, with an inadequate supply of air will lead to the formation of carbon monoxide and risk of asphyxia.

Table 22. Hydrocarbons of the Methane Series.

Name	Formula	Boiling Point of Normal Isomers (°C.)	Physiological Action
Methane	CH_4	−161.5	Simple asphyxiants
Ethane	CH_3CH_3	−88.3	
Propane	$CH_3CH_2CH_3$	−42.2	Anesthetic
Butane	$CH_3(CH_2)_2CH_3$	−0.6	
Pentane	$CH_3(CH_2)_3CH_3$	36.2	Anesthetic and irritant
Hexane	$CH_3(CH_2)_4CH_3$	69.0	
Heptane	$CH_3(CH_2)_5CH_3$	98.5	
Octane	$CH_3(CH_2)_6CH_3$	125.8	
Nonane	$CH_3(CH_2)_7CH_3$	150.7	
Decane	$CH_3(CH_2)_8CH_3$	174.0	

The homologs higher than decane are not sufficiently volatile to permit a concentration in the air, under ordinary conditions, which can exert any physiological action. The members of the series from $C_{16}H_{34}$ upward are solids at body temperature.

Some crude oils contain sulfur compounds; these liberate hydrogen sulfide which may cause poisoning.

As originally applied, the name "gasoline" was synonymous with "petroleum ether" and "first-run gasoline." Prior to the employment of internal combustion engines, gasoline was an undesirable product which it was necessary to separate from the higher distillates to render them safe to use for illuminating purposes. The great demand for gasoline for motor cars now makes it the most valuable product of petroleum distillation. In order to supply the demand for gasoline, petroleum ether has been replaced by a less volatile product containing, in addition to petroleum ether, considerable amounts of naphtha and benzine.

In an increasing proportion of the gasoline now sold the products of petroleum distillation are blended with light hydrocarbons from other sources. For this purpose the distillation products from coal, from oil shale and from cracked petroleum are

used. These products contain cyclic compounds, substances with delayed toxic effects, in addition to those of the paraffin series. In order to increase the volatility of such mixtures, "casing head" gasoline is added; this consists principally of butane, and is obtained by condensation from natural gas.

Thus there are wide variations in the components of commercial gasoline. Naphtha and benzine may be classed physiologically with gasoline, but are less varied in composition. They are inherently more toxic than the lighter fraction of gasoline, but as they are also less volatile, they are not so readily inhaled. They are largely used for dry cleaning, grease extraction, and in paint as a substitute for turpentine. Benzine should not be confused with the cyclic compound benzene.

The principal fractions obtained from petroleum on distillation are as follows:

Table 23. Fractions of Petroleum.

Name of Product	Boiling Point (°C.)	Main Constituents
Petroleum ether	20 to 60	Butane, pentanes and hexanes
Petroleum benzine	40 to 90	Pentanes, hexanes and heptanes
Naphtha	65 to 120	Hexanes, heptanes and octanes
Benzine	110 to 150	Octanes and nonanes
Gasoline	10% below 65 90% below 200	Pentanes, hexanes, heptanes, octanes, nonanes, decanes and some higher homologs.
Kerosene	150 to 300	Nonanes, decanes and mainly higher homologs.
Lubricating oils	above 300	

The distillation products of coal are used to some extent in blending gasolines and present a toxicity quite distinct from that of the petroleum hydrocarbons (see Chapter 14). Besides benzene, other organic substances have been added to various gasolines as anti-detonants to prevent so-called "knocking" in high-compression motors. The most important of these components are lead tetraethyl (see page 239), aniline, and nitrobenzene.

For motorists, poisoning by gasoline rarely constitutes a hazard, although, as a result of incomplete combustion in the engine, gasoline vapor may appear in the exhaust gas. This results from a too rich mixture of gasoline with too little air because of a faulty adjustment of the carburetor or from failure of the gasoline vapor to ignite. The idea that the toxicity of motor exhaust is due to unburned gasoline is entirely fallacious, for the gasoline concentration in the exhaust gas, even at the highest point attain-

able, never approaches in toxicity the carbon monoxide present, even when this substance is at the lowest amount. It is carbon monoxide, almost alone, which gives exhaust gas its poisonous character. The mistake has probably arisen from the common observation that the exhaust gases are most toxic during the warming up of the engine, or when a very rich mixture is used, at which times the exhaust smells strongly of unburned gasoline. The point is overlooked that under such conditions the carbon monoxide content is also at its highest. It is possible also for the exhaust to be rich in carbon monoxide, but with little odor of gasoline. The unburned gasoline in exhaust gas is neither the cause, nor even a reliable index, of its poisonous character. Neither is the amount of smoke, for it is usually due to the partial volatilization and partial combustion of an excessive supply of the lubricating oil. The exhaust from Diesel engines may contain unburned and partially burned oil and, in addition, oxides of nitrogen and aldehydes; it contains relatively little carbon monoxide (see Chapter 11).

Men employed in the care and repair of automobiles are exposed to gasoline fumes to a greater extent than are the drivers. Gasoline spilled in confined quarters or in low places, such as the pit in a repair shop floor, during the draining of a gasoline tank, occasionally reaches a toxic concentration. The washing of automobile engines with gasoline, sometimes employed as a spray, in confined buildings may likewise occasionally cause poisoning. This is particularly true if the engine is cleaned while warm. The danger from fire during this procedure, however, greatly outweighs the chance of poisoning.

Toxic concentrations of gasoline vapors are occasionally encountered in confined quarters, as when gasoline leaks from storage tanks and pumping machinery, or is accidentally spilled in the underground pipe rooms of gasoline storage and dispensing stations. These conditions, however, involve an economic loss and for that reason are prevented or soon corrected.

Men employed in cleaning the interiors of tank cars or storage tanks which have contained gasoline or crude oil are particularly liable to poisoning, unless precautions are taken to remove, as nearly as possible, all the volatile matter and to insure a supply of uncontaminated air to the men. To remove all the liquid and vapor from such tanks, even with the use of

steam, is difficult and uncertain. When this precaution is neglected, fatalities may result and the rescuer also is often overcome. In such work, hose masks should be compulsory (see Chapter 18).

Establishments engaged in so-called "dry cleaning" of clothing may use considerable amounts of gasoline, naphtha or benzine to extract grease from the fabrics. The hydrocarbon is used hot and is later purified by redistillation. Unless precautions are taken to prevent the vapors escaping from the heated liquid, they may give rise to poisoning. This may also occur in the distillation of naphtha, which is used for the extraction of oleaginous matter from garbage and other industrial residues. Poisoning by petroleum vapors also occurs occasionally in men entering sewers into which gasoline, benzine or naphtha has been run as waste from garages, or from cleaning or extracting plants. Plants of this sort should be required to install well-vented traps to catch all such liquids and prevent them from reaching the common sewer.

Petroleum distillates, notably benzine, have an increasing application as substitutes for turpentine in paints. Instances of fatal anesthesia have occurred when such paints have been used in close and ill-ventilated quarters, especially when applied to heated metal surfaces. Anesthesia and death may also result from a few hours spent in painting the inside of a large water tank with such paint, yet the victim may have had only headache, muscular incoördination and nausea as a warning of his danger. Fortunately, if he is removed to fresh air before respiratory failure, the chances for his recovery without any serious after-effects are excellent—as with the surgical anesthetics. Benzine and naphtha are used as solvents in the manufacture of rubber goods; some chronic intoxication may develop unless adequate ventilation is provided. These solvents are used in many industrial procedures, such as removing grease and oil from machinery and cleaning type; intoxication under such conditions is rare.

The striking feature of acute gasoline poisoning is the severe muscular jactitation occurring during the stage of excitement. In some cases the muscular movements are as violent as in an epileptic convulsion; they are particularly marked during the recovery in fresh air. With vapors of this type there is only a

narrow margin between the concentration which produces anesthesia and that which causes death.

It is said that there is considerable individual tolerance to gasoline vapors as far as such mild effects as dizziness are concerned.[1]

Table 24. Physiological Reponse to Various Concentrations of Pentane, Hexane, Heptane, and Gasoline.[1–12]

	Parts of vapor per million parts of air
Pentane	
Exposure 10 min., no symptoms	5,000
Hexane	
Exposure 10 min., no symptoms	2,000
Exposure 10 min., dizziness	5,000
Heptane	
Exposure 6 min., slight dizziness	1,000
Exposure 4 min., dizziness	2,000 to 3,500
Exposure 4 min., marked dizziness, muscular incoördination, emotional disturbances	5,000
Exposure 15 min., similar symptoms as after 4 min. exposure but persisting for 30 min. following exposure	5,000
Gasoline	
Maximum concentration allowable for prolonged exposure	1,000 to 1,500
Slight symptoms after several hours	1,250 to 2,500
Maximum concentration tolerable for 1 hr.	4,000 to 7,000
Dangerous for short exposure	10,000 to 20,000
Fatal for short exposure	20,000 to 30,000

In considering the physiological responses to the various hydrocarbons it is significant that the vapors have a low solubility in water and blood. The amount which can accumulate in the body at any concentration in the air is correspondingly limited (see Chapter 5). In addition, equilibrium at any tolerable concentration would be reached within a period considerably less than that of the working day. Therefore, if symptoms do not develop after an exposure of 1 to 2 hours, none of serious nature are to be anticipated after 8 or 10 hours of exposure. Moreover, because of this low solubility the hydrocarbons are rapidly eliminated from the body when inhalation is discontinued. No accumulation occurs.

Hydrocarbons of the Olefin Series. The lower members of the olefin series are present, or are added in small amounts, in manufactured and natural gas to serve as illuminants, but they have no toxicological significance in such low concentrations. Ethylene is used extensively in the treatment of fruits and vegetables to mature the coloring. It is also used in welding.

Ethylene and propylene are used to induce surgical anesthesia, but they are effective only in high concentrations, 60 per cent or more, and for that reason should always be administered with oxygen. Both of these substances, when mixed with air, act rather as simple asphyxiants than as anesthetics. The high concentrations necessary to induce a marked physiological effect dilute the oxygen of the air to a level which will not support life; thus 60 per cent in air reduces the oxygen to 8.4 per cent. When mixed with oxygen, or even with air in certain proportions, these gases are highly inflammable and explosive.

The higher members of the series have a much stronger anesthetic action than ethylene and propylene, as is the case with the paraffins, but at present they are little used, although amylene has been employed for surgical anesthesia. The principal substances in this series are given in Table 25.

Table 25. Hydrocarbons of the Olefin Series.

Name	Formula	Boiling Point of Normal Isomers (°C.)	Physiological Action
Ethylene (ethene)	CH_2CH_2	−103.9	Simple asphyxiant and anesthetic
Propylene (propene)	CH_2CHCH_3	−47.0	
Butylene (butene)	$CH_2CHCH_2CH_3$	−5.0	
Amylene (pentene)	$CH_3CH_2CH_2CHCH_2$	40.0	
Hexylene (hexene)	$CH_2CH(CH_2)_3CH_3$	64.1	
Heptylene (heptene)	$CH_2CH(CH_2)_4CH_3$	94.9	

Hydrocarbons of the Acetylene Series. Acetylene gas is the only hydrocarbon of the acetylene series of industrial importance. The higher members of the series occur in small quantities in coal gas. Acetylene is extensively employed in welding and, to a less extent, for illumination in localities not equipped with coal gas or electricity. The gas is generated by the action of water on calcium carbide, and is made either at the place of use or supplied from central stations in steel cylinders in which the compressed gas is held in solution in acetone. Acetylene is extensively employed in the manufacture of synthetic chemicals.

Acetylene has been employed for surgical anesthesia. Forty per cent or more of the gas mixed with oxygen is used for this purpose. But, as with ethylene and propylene, it must be administered with oxygen; otherwise, it acts as an asphyxiant.

Commercial calcium carbide frequently contains calcium phosphide as an impurity and, as a result, the acetylene generated

may be contaminated with as much as 0.06 per cent of phosphene (see page 242).

Table 26. Hydrocarbons of the Acetylene Series.

Name	Formula	Boiling Point (°C.)	Physiological Action
Acetylene (ethyne)	CHCH	−88.5	Simple anesthetic and asphyxiant
Allylene (propyne)	CH_3CCH	−23.3	
Crotonylene (butyne)	CH_3CCCH_3	27.2	

Ethyl and Isopropyl Ethers. The only ether of industrial importance to come with certainty under the classification of primary anesthetics is ethyl ether; isopropyl ether may, however, be included, since, although suggested, no certain evidence is available that it causes injury on repeated exposure.

In two ethers of wide industrial use, diethylene dioxide (dioxane) and ethylene oxide, the irritant properties are more marked than the anesthetic. The alcohol ethers, such as ethylene glycol monoethyl ether, diethylene glycol monoethyl ether and ethylene glycol monobutyl ether, have little, if any, anesthetic action.

Ethyl ether in the high concentrations used for surgical anesthesia is somewhat irritating to the respiratory tract. The flow of mucus is increased and occasionally pneumonia follows ether anesthesia. However, it is uncertain whether irritation from the anesthetic is a factor, since massive collapse and pneumonia may occur after anesthesia with nitrous oxide, which is not irritating, and even after spinal anesthesia. It is probable that depression of breathing, atelectasis, and loss of the cough reflex during anesthesia may be the main causative factors rather than irritation of the airways. It is sometimes stated that the ether in the blood during surgical anesthesia may irritate the kidneys, but organic degeneration is rarely, if ever, caused by ether.

Inhalation of a concentration of 35,000 parts of ether per million of air, if continued for 30 to 40 minutes, induces unconsciousness. Higher concentrations produce unconsciousness in a shorter time, and very high concentrations, if the inhalation is at all prolonged, cause death by failure of respiration. The concentration requisite in the arterial blood for the production of surgical anesthesia is between 1.5 and 3.0 g. per liter. The coefficient of distribution for ether between the air of the lungs and the blood is 1:15.

The toxicity of ethyl ether is low; there have been few reports

of ill effects in anesthetists exposed daily to the vapors in concentrations below those producing intoxication. The allowable concentration for prolonged exposure has not yet been determined precisely under industrial conditions. Two approximations have been recorded in the literature as 165 [12] and 400 [10-11] parts of ether per million parts of air. It is said that concentrations as high as 2,000 or 3,000 parts per million may occur in the air during the manufacture of smokeless powder and that the only ill effect is an occasional slight intoxication. Use of the coefficient of distribution of ether permits calculation of the amount in the blood of men exposed to and in equilibrium with the concentration in the air. Since ether is only moderately soluble, equilibrium between blood and the atmosphere would be reached in less than the 8 hours of a working day. At a concentration of the vapor in the air of 165 parts per million (0.4 mg. per liter) the maximum amount absorbed by a man of average weight, 70 kg., would be 0.52 g. and the concentration in the blood, irrespective of weight, 0.0074 g. per liter; for a concentration in the air of 400 parts per million (1.2 mg. per liter) the corresponding values would be 1.25 and 0.018 g. A concentration of 0.018 g. per liter of blood is not associated with any signs of intoxication and the daily administration of 1.25 g. of ether does not, so far as known, cause any ill effects. The inhalation of a concentration of 2,000 parts of ether per million of air, if continued to equilibrium, would result in the absorption of some 6.25 g. of ether and a concentration of 0.09 g. per liter of blood. This concentration would probably induce dizziness in some individuals with increased likelihood of industrial accidents. Some tolerance is probably developed to ether, as with alcohol, on repeated exposures so that concentrations which at first induce very mild intoxication may later cease to do so.

Aldehydes. The aldehydes have anesthetic properties, but their action in this respect is largely masked by the more intense irritant effect upon the surface tissues of the respiratory tract. The lower members of the aldehyde series are highly soluble in water and for that reason act primarily upon the upper respiratory tract; the higher members of the series, especially acrolein, are less soluble and act rather in the deeper parts of the respiratory tract. The aldehydes are discussed in more detail with the irritants (Chapters 8 and 9).

Table 27. Aldehydes.

Name	Formula	Boiling Point (°C.)	Physiological Action
Formaldehyde (methanal)	$HCHO$	−21.0	
Acetaldehyde (ethanal)	CH_3CHO	21.0	
Propionaldehyde (propanal)	CH_3CH_2CHO	48.8	Primarily irritant but also anesthetic
Butyraldehyde (butanal)	$CH_3(CH_2)_2CHO$	75.7	
Acrolein (propenal)	CH_2CHCHO	52.5	

The polymer of formaldehyde, paraldehyde $(C_2H_4O)_3$, boiling point 124°C., has virtually no irritating properties and is widely used in medicine as a safe sedative and a mild anesthetic; it is ordinarily taken by mouth and its administration may be continued over long periods of time without any ill effect except a possible habituation. Methylal $CH_2(OCH_3)_2$, boiling point 44° C., also possesses anesthetic properties without marked irritation.

Ketones. Acetone, dimethyl ketone, is extensively used in industry as a solvent, extractive, intermediary in chemical synthesis, and as a constituent of varnish, lacquer, and paint remover. It is mildly irritant and definitely anesthetic in action. Acetone is one of the very few substances, classed among noxious vapors, of which small amounts may be formed in the body. It occurs as an intermediary product in metabolism, and appears in the blood, expired air, and urine in considerable quantities when metabolism is disturbed by fasting and in diabetes. A normal man, after fasting for 3 days, may have more than 0.05 g. of acetone per liter of blood,[13] and one with severe and uncontrolled diabetes, more than 0.2 g. per liter and, in addition, much greater amounts of so-called "acetone bodies." So far as is known, none of the ill effects of fasting or of diabetes are due to the acetone; its appearance in large quantities is a symptom of a more fundamental disturbance. The coefficient of distribution of acetone between air and blood at body temperature is approximately 1:350.[13] Therefore a concentration of 0.05 g. of acetone per liter of blood (as in fasting) corresponds to a concentration in the alveolar air of the lungs of 1.4 mg. per liter, or approximately 600 parts per million parts of air. A man breathing acetone vapors in this concentration would, at equi-

librium, develop in his blood approximately 0.05 g. of acetone per liter.

An uncertain factor in regard to acetone as a noxious gas is its fate in the body; it does not appear from the current literature to what extent, and under what conditions, inhaled acetone is burned in the body and therefore to what extent it may be treated as a partially reactive vapor. The widely varying concentrations estimated as allowable for prolonged exposure reflect some of the present uncertainty in regard to acetone: these values are 200,[11] 422 [12] and 1,265 to 2,110 [13] parts of acetone vapor per million parts of air.

It appears reasonably certain that acetone, in concentrations below those which are anesthetic, does not cause any organic injury to the body. As judged from the concentration in the inhaled air causing anesthesia, acetone is a somewhat more active anesthetic than is ethyl ether; but as judged from the concentration developed in the blood (because of the wide difference in solubilities of acetone and ether) it is a much less powerful anesthetic.

Table 28. Ketones.

Name	Formula	Boiling Point (°C.)	Physiological Action
Dimethyl ketone (acetone)	CH_3COCH_3	56.5	Anesthetic
Methyl ethyl ketone (butanone)	$CH_3COC_2H_5$	79.6	Irritant and anesthetic
Methyl propyl ketone (pentanone)	$CH_3CO(CH_2)_2CH_3$	101.7	
Methyl butyl ketone (hexanone)	$CH_3CO(CH_2)_3CH_3$	127.2	
Methyl isobutyl ketone	$CH_3COCH_2CH(CH_3)_2$	119.0	

Methyl ethyl ketone, methyl propyl ketone, methyl butyl ketone and methyl isobutyl ketone are used for purposes similar to those for acetone. In most series of volatile organic substances the toxicity increases as the series rises; and this is probably true for the ketones. This toxicity, however, is not directly referable to concentrations of the vapors in the air, but is based on the amount of the substance actually absorbed into the body. This dose is related to the concentration in the air by the solubility of the vapor in blood (see Chapter 5). A rising toxicity (on the basis of amount absorbed) may be more than compensated by decrease in solubility. Dimethyl ketone is highly soluble; but in the higher members of the ketone series the solubility falls off rapidly. Methyl ethyl ketone is moderately soluble, methyl

Table 29. Physiological Response to Various Concentrations of Ketones[8,14–16]

	Parts of vapor per million parts of air
Methyl ethyl ketone	
Maximum concentration allowable for prolonged exposure	Below 3,000
Slight symptoms after exposure of several hours	3,000
Maximum concentration safe for short exposure	10,000
Dangerous for short exposure	50,000 to 100,000
Methyl propyl ketone	
Maximum concentration allowable for prolonged exposure	Below 1,500
Slight symptoms after exposure of several hours	1,500
Maximum concentration safe for short exposure	5,000
Dangerous for short exposure	30,000 to 50,000
Methyl butyl ketone	
Maximum concentration allowable for prolonged exposure	Below 1,000
Slight symptoms after exposure of several hours	1,000
Maximum concentration safe for short exposure	3,000
Dangerous for short exposure	10,000 to 20,000

propyl ketone and methyl butyl ketone are only slightly soluble, and methyl isobutyl ketone is nearly insoluble.

The irritant actions of methyl ethyl ketone, methyl propyl ketone, methyl butyl ketone and methyl isobutyl ketone are more marked in relation to their anesthetic effects than is the case with acetone.

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Chapter 14

Group III (cont'd). Volatile Drugs and Drug-like Substances

Subgroup C. Anesthetic Gases and Vapors Which May Cause Organic Changes Mainly in Visceral Organs: Halogenated Hydrocarbons

Deep anesthesia, irrespective of the agent by which it is induced, if maintained for several hours, is accompanied by derangement of bodily functions and even some organic changes. With the primary anesthetics discussed in the previous chapter these organic changes are so slight, even after severe exposure, as to constitute no serious hazard. After deep anesthesia, the symptoms may resemble those after alcoholic intoxication. With the primary anesthetics any slight organic changes are rapidly repaired so that no serious or permanent damage results. The narcotic properties of this group of anesthetics are high in relation to any toxic action they may possess. This fact is of industrial importance. Deep anesthesia is rarely produced in industrial exposure except as the result of accident. Exposure to concentrations which do not produce any degree of anesthesia—or intoxication—is not followed by toxic effects or by symptoms.

This fortunate relation, however, does not hold with the subgroups of anesthetics next to be considered. They are not only more active than the primary anesthetics in causing organic damage in the body during anesthesia, but they even produce such damage from the inhalation of concentrations which do not cause anesthetic effects. Of equal importance is the occurrence of wide individual differences in susceptibility to the toxic effects of some of these anesthetics. Thus, whereas the concentrations which will cause deep anesthesia and death for all individuals fall within narrow limits and can readily be established, the concentrations which, on prolonged exposure, may produce chronic toxic effects vary widely as between different individuals and are correspondingly difficult to establish.

The discussion of the halogenated hydrocarbons is sometimes confused by attempts to consider simultaneously their anesthetic action and their more subtle toxic action. Which action predominates is determined by the conditions of exposure.

Acute Effects from a Single Exposure to a High Concentration. In deep anesthesia death may occur as the result of respiratory failure just as with primary anesthetics.

Death under light anesthesia may occur from fibrillation of the heart, which does not occur with primary anesthetics.

Death may occur one or more days after the anesthesia due to organic damage to the liver. The kidneys, the nervous system, and other organs may also be damaged. The damage to the liver is due to degenerative changes; if the degeneration is not sufficient to cause death from interference with liver function, full restoration of the liver tissue usually occurs.

Chronic Effects from Prolonged and Repeated Exposures to Concentrations Which do not Produce Anesthesia. Under these conditions the action is entirely from the inherent toxicity. If the concentration is sufficiently low, or the exposure short, any organic damage that may occur is repaired subsequent to the exposure without the appearance of symptoms. When, however, the concentration and length of exposure are such that full restoration cannot take place between exposures to the vapor, the rate of damage then exceeds the rate of restoration; progressively greater damage results and symptoms eventually develop. As stated above, there may be wide individual differences in susceptibility to the inherent toxic action of these substances; this is particularly true for damage to the liver. The extent of damage to the liver by chloroform is influenced by the nutritional state at the time of exposure; the damage is least when the liver is well supplied with carbohydrate and protein.

The toxicity of the halogenated hydrocarbons can readily be determined on animals. But this evidence from animals is not reliable for chronic poisoning from low concentrations in man. Some of the halogenated hydrocarbons which kill animals after only 1 hour in very high concentrations may have far lower permissible concentrations for the prolonged exposure of men than do others which cause acute fatal poisoning in comparatively low concentrations. These relations, so far as knowledge of them is available, are shown in Table 30. The figures given,

Table 30. Physiological Response to Various Concentrations of Halogenated Hydrocarbons. Concentration in parts of vapor per million parts of air.[1–10]

	Kills animals in a short time	Deep narcosis, 30 minutes	Slight symptoms, 8 hours	Estimated allowable concentration, prolonged exposure [12]	[4,9–10]
Methyl chloride	225,000	150,000	750	242	500
Methyl bromide	30,000	———	110	——	50
Dichloromethane	———	20,000	———	288	——
Chloroform	53,000	13,000	4,000	40	100
Carbon tetrachloride	65,000	22,000	1,600	32	100
Ethyl chloride	225,000	66,000	20,000	——	2,000
Ethyl bromide	150,000	———	2,300	——	1,700
Dichloroethane	150,000	12,000	1,000	494	100
Trichloroethane		8,000		183	——
Tetrachloroethane	7,300	3,200		1.5	10
Pentachloroethane	9,600	3,200		2.4	——
Vinyl chloride	300,000	———	7,500	——	——
Trichloroethylene	37,000	13,500		186	200
Tetrachloroethylene	———	8,000		147	200

with exceptions noted, are midway between the high and low values previously reported.

For any comparisons made here it should be borne in mind that the concentration of the vapor in air by volume is not a true measure of the amount absorbed; between the concentration, on the one hand, and the amount on the other, lie the weight of the vapor, which varies with molecular weight, and the solubility in the blood. This last feature has not been determined for the majority of the halogenated hydrocarbons. The comparison is therefore of necessity made here in the terms of concentration usually employed in industrial standards.

Table 31. Comparative Anesthetic Potency (Acute Lethal Action) of Halogenated Hydrocarbons, Carbon Tetrachloride = 1. Based on Concentrations by Volume in Air.

1.	Methyl chloride	0.29	0.15
2.	Vinyl chloride	0.22	
3.	Ethyl chloride	0.29	
4.	Ethyl bromide	0.40	
5.	Carbon tetrachloride	1.00	1.00
6.	Dichloromethane		1.10
7.	Chloroform	1.20	1.53
8.	Trichloroethylene	1.80	1.60
9.	Methyl bromide	2.20	
10.	Tetrachloroethylene		2.80
11.	Pentachloroethane	6.80	6.90
12.	Tetrachloroethane	8.90	6.90

When they are arranged in accordance with their anesthetic potencies, the order shown in Table 31 is obtained. The first

figure following each substance is derived from the concentrations killing experimental animals in a short time and the second from those causing deep narcosis in 30 minutes.

Table 32. Comparative Activity of Halogenated Hydrocarbons for Slight Symptoms After 8-hour Exposure. Carbon Tetrachloride Taken as 1. Based on Concentrations by Volume in Air.

1. Ethyl chloride	0.08
2. Vinyl chloride	0.21
3. Chloroform	0.40
4. Ethyl bromide	0.70
5. Carbon tetrachloride	1.00
6. Methyl chloride	2.10
7. Methyl bromide	14.50

In Table 32 the comparative toxicities are shown in respect to concentrations causing slight symptoms after an exposure of 8 hours. In Table 33 comparison is made on the basis of proposed allowable concentrations. The first column is derived from the figures given by Lehmann and Flury [12] and the second from

Table 33. Comparative Toxicity of Halogenated Hydrocarbons from Allowable Concentrations for Prolonged Exposure. Carbon Tetrachloride Taken as 1. Based on Concentration by Volume of Air.

Lehmann and Flury		More widely accepted American figures (1940)	
1. Dichloromethane	0.11	1. Ethyl chloride	0.05
2. Methyl chloride	0.13	2. Ethyl bromide	0.06
3. Trichloroethylene	0.17	3. Methyl chloride	0.20
4. Trichloroethane	0.18	4. Trichloroethylene	0.50
5. Tetrachloroethylene	0.22	5. Tetrachloroethylene	0.50
6. Chloroform	0.80	6. Chloroform	1.00
7. Carbon tetrachloride	1.00	7. Carbon tetrachloride	1.00
8. Pentachloroethane	13.50	8. Methyl bromide	2.00
9. Tetrachloroethane	21.50	9. Tetrachloroethane	10.00

various Americans since.[4, 9-10] There is a fair agreement as to order of toxicity, but there is a wide difference of opinion as to basic toxicity. In comparing toxicities as a basis for allowable concentrations, it must be borne in mind that the figures for concentrations are essentially estimates, as was explained in Chapter 6. Such comparisons, to be truly representative, require first, a valid base value, such as the concentration of carbon tetrachloride. The differences in the estimates of the allowable concentrations of carbon tetrachloride—32 and 100 parts per million parts of air—indicate the lack of precise information as to the proper allowable concentrations of the halogenated hydrocarbons.

Although the data here are far from complete, they are nevertheless suggestive as to at least one aspect of comparative toxicity. When the toxic effect is exercised primarily upon the nervous system, as with methyl bromide, the impairment of function is immediately evident. When, however, it is exercised upon the liver, as with chloroform or carbon tetrachloride, symptoms appear only when the reserve of this organ has been exceeded and considerable damage has already resulted. Consequently, deductions as to concentrations for prolonged exposure in the latter instance cannot be made from concentrations causing effects within a short time. Thus in producing slight effects after 8 hours of exposure methyl bromide is said to be 14.5 times as active as carbon tetrachloride, but from effects on repeated daily exposure it is judged as only twice as toxic.

Halogen Compounds of Methane

Methyl Chloride, Bromide and Iodide. The monohalogen compounds of methyl are largely broken down in the body into methyl alcohol and the halogen acids. The speed and extent of this decomposition are not known and it is therefore uncertain to what extent the undecomposed compounds exert any specific toxicity. The chloride formed from methyl chloride would have no toxic action, but the bromide formed from methyl bromide might contribute appreciably to the toxicity.

Compared on the basis of concentration in the air inhaled, the toxicity of methyl bromide is far greater than that of methyl chloride (see Table 30), and this in spite of the fact that the bromide is less soluble than the chloride and therefore less is absorbed at the same concentration in the air. The toxicity of methyl iodide is less than that of the bromide but higher than that of the chloride. These differences in toxicity, either acute or chronic, cannot be explained merely on the basis of poisoning by the methyl alcohol formed on decomposition. If the poisoning were entirely by methyl alcohol, the comparative toxicities of methyl chloride and bromide would be in relation to their molecular weights. Each gram of methyl chloride absorbed would yield 0.63 g. of methyl alcohol and 1.16 g. of sodium chloride; and each gram of methyl bromide 0.34 g. of methyl alcohol and 1.09 g. of sodium bromide.

Because of their decomposition, neither methyl chloride nor

methyl bromide can, of themselves, accumulate in the body to the point of equilibrium and consequent cessation of absorption, as with non-reactive vapors; instead, the absorption with formation of methyl alcohol and sodium chloride or bromide continues as long as exposure lasts. Accordingly, poisoning by methyl alcohol might result after prolonged exposure to low concentrations of the methyl monohalides. With methyl bromide there is, in addition, poisoning by bromides which, in chronic poisoning, are weight for weight more toxic than methyl alcohol. The absorption of 1, or possibly 2 g. of methyl bromide per day, if it were all decomposed, would cause an accumulation of bromide, but not an amount sufficient to cause serious symptoms; the absorption of 3 g. or more would, in time, lead to serious bromide intoxication. Under the rule of maxima (see Chapter 5) and the assumption of complete decomposition, the concentration of methyl bromide in the air for the absorption of 1 g. in 8 hours would be 0.33 mg. methyl bromide per liter of air, or approximately 100 parts of the vapor per million parts of air. The concentration suggested as the maximum for prolonged exposure is 50 parts per million.[10]

Irish, Adams, Spencer and Rowe[20] have shown that in rabbits symptoms comparable in severity to those caused by methyl bromide are not induced by the administration of methyl alcohol and sodium bromide in amounts estimated as corresponding to the methyl bromide. Their conclusion is that the toxicity is exercised in considerable part by the undecomposed methyl bromide. This may be true, but if so it gives no explanation for the slow recovery reported in the literature, unless it is assumed that serious organic damage to the nervous system occurred directly from the action of the methyl bromide in concentrations which are not immediately fatal. There is, however, a third possibility which is suggested here, not to controvert the findings of Irish, Adams, Spencer and Rowe, but only to point out that other possibilities still exist of explaining the peculiar toxic action of methyl and, to a less degree, ethyl bromides. When sodium bromide is administered, the dissociated bromide ion does not enter the intracellular water of the body and hence does not appear within the cells; it is limited entirely to the extracellular water and so acts only upon the outside of the cells of the nervous system. The possibility exists, however, that undecomposed methyl bromide,

like many hydrocarbons, may pass the cell membrane and enter the intracellular water. If decomposition occurred in that fluid, the bromide would be intracellular and might give not only more severe but also different symptoms from those of a like amount of bromide in the blood and other extracellular fluids. Likewise the bromide might be eliminated with especial slowness.

Poisoning by methyl bromide may be slow, but regardless of time of development, recovery is long delayed. There may be deep depression, bewilderment, and nervous impairment.

The concentrations suggested as probably safe for prolonged exposure to methyl chloride are higher than those for methyl bromide and range from 240 to 500 parts of the vapor per million of air.[2,10]

The methyl monohalides are used in the chemical industry for the preparation of various methyl compounds. Methyl bromide is used as a fumigant and methyl chloride as a refrigerant; when the latter is employed for this purpose in dwelling houses, and particularly in apartment houses with multiple installations, even small leaks may cause fatalities.

Dichloromethane. The di-, tri-, and tetra-halogen compounds of methyl are virtually non-reactive; their action is exerted by the undecomposed molecule.

Dichloromethane has a boiling point of 40 to 41° C. and is used as an industrial solvent, as a degreasing and cleaning fluid, and in paint removers. The vapors in contact with a flame decompose, as do those of chloroform and carbon tetrachloride, with the formation of phosgene and other irritant vapors (see Chapter 9). Dichloromethane is a less powerful anesthetic than chloroform (see Table 31); the range between narcosis and death is, however, narrow. Dichloromethane is less active in its secondary toxic effects on the liver than is chloroform or carbon tetrachloride, but it is by no means free from this action. A concentration of 288 parts per million of air has been suggested by Lehmann and Flury [12] as safe for prolonged exposure. No other estimates appear in the literature, and it is therefore necessary to point out here that these investigators are usually, but not always, more conservative in their statements of permissible concentration than are most others (see Table 33).

Chloroform. Chloroform has a boiling point of 61 to 62° C. and was formerly widely used as a surgical anesthetic, but is

now rarely used and only for brief anesthesias. It has a limited industrial use as a solvent and cleaning fluid. It is a more powerful anesthetic (see Table 31) than carbon tetrachloride, but appears to be slightly less active in its secondary toxic effects, which are exercised primarily on the liver. The suggested safe concentrations for prolonged exposure are estimated as 40 [12] and 100 [10] parts per million of air. On contact with a flame, or very hot surface, chloroform vapor decomposes with the formation of phosgene (see Chapter 9).

Carbon Tetrachloride. Carbon tetrachloride has a boiling point of 76.7° C.; it has a wide industrial use as a solvent and dry-cleaning fluid, and as a fire extinguisher. It is a less powerful anesthetic than chloroform, but appears to have greater secondary toxic effects, especially on the liver. The concentration estimated as safe for prolonged exposure, and widely accepted in the United States, is 100 parts per million of air; the estimate of Lehmann and Flury [12] is 32 parts per million.

With both chloroform and carbon tetrachloride there are wide individual differences in susceptibility to the toxic action on the liver; the state of nutrition at the time of exposure may influence the severity of these effects.

Fluorine Compounds of Methane. Dichlorodifluoromethane, boiling point −29.2° C. and trichlorofluoromethane, boiling point 23.7° C. are used as refrigerants. Dichlorodifluoromethane has little if any anesthetic or secondary toxic action. Trichlorofluoromethane has an intoxicating effect for animals in a concentration over 4 per cent in air for an exposure in excess of an hour, but so far as is known, no secondary toxic action. In contact with a flame or very hot surface, these substances are decomposed, with the formation of carbon monoxide and the irritants chlorine, phosgene, and hydrochloric and hydrofluoric acids (see Chapter 9).

Halogen Compounds of Ethane

Ethyl Chloride, Bromide and Iodide. Of the three monohalogen compounds of ethyl, *i.e.* ethyl chloride, boiling point 12.0 to 13.0° C.; ethyl bromide, boiling point 38.4° C.; and ethyl iodide, boiling point 73.4° C., only the chloride has extensive industrial application and that as a refrigerant. The monohalogen compounds of ethyl appear to be broken down somewhat

less rapidly in the body than those of methyl. The decomposition results in the formation of ethyl alcohol which, in the amounts produced, exerts virtually no action and is rapidly oxidized, and the halogen acids which combine with the alkalies of the blood to form chlorides, bromides and iodides.

Ethyl chloride has been used as a surgical anesthetic, usually for short periods only, and with little ill effect. It is a slightly more powerful anesthetic, judged on the basis of concentration in the air, than is methyl chloride, but the latter, presumably because of the formation of methyl alcohol, is more toxic for prolonged exposure. The estimated safe concentration for prolonged exposure is 2,000 parts per million,[10] some 4 to 8 times that taken for methyl chloride.

Ethyl bromide is more toxic than ethyl chloride. On prolonged exposure to sufficiently high concentrations it is said to cause serious symptoms without producing narcosis and appears to possess the peculiar toxic properties common to other bromide derivatives of the hydrocarbons.[13, 16-17]

Because of its limited industrial and medical use, few determinations have been made of the toxicity of ethyl iodide. Such as have been made indicate that it may have a higher toxicity than either the chloride or bromide and may be more active in causing degeneration of paracematous organs.[13] Further evidence is needed, however, before these statements are accepted.

Dichloroethane. Dichloroethane, boiling point 57.3° C., is used as an industrial solvent and insecticide. Its anesthetic action appears to be approximately the same as that of chloroform, but there is considerable difference of opinion as to the dangers of chronic poisoning. Until further knowledge is obtained, it may well be assumed to be similar to carbon tetrachloride in this respect. Fortunately it has a distinctive odor and irritant properties which give warning of its presence in relatively safe concentrations. For prolonged exposure a maximum concentration of 100 parts per million of air has been suggested in the United States.[9, 10] Lehmann and Flury,[12] however, suggest 495 parts per million, more than 10 times the concentrations given by them for chloroform and carbon tetrachloride.

Trichloroethane. Trichloroethane exists as two isomers: 1,1,1-trichloroethane, boiling point 74.1° C., and 1,1,2-trichloroethane, boiling point 113.5° C. The latter has the higher toxicity

and is apparently more irritating to the eyes and nose. Lehmann and Flury [12] suggest a concentration of 183 parts per million of air as safe for prolonged exposure.

Tetrachloroethane. Tetrachloroethane, boiling point 146.3° C. has a wide industrial use as a solvent in paint and varnish removers, lacquers and floor waxes, and as a dry-cleaning agent, insecticide, and fire extinguisher. It is, as judged on the basis of concentration of vapor in the air, a much more powerful anesthetic than chloroform; it appears also to exercise a greater secondary toxic action, mainly on the liver. A number of fatal cases of tetrachloroethane poisoning have been reported.[21,22] There appears to be considerable individual susceptibility to its action on prolonged exposure, as with other halogenated hydrocarbons which affect the liver. This fact suggests that the primary step in prevention of poisoning from tetrachloroethane is the careful selection of those exposed to the vapors with exclusion of any in whom impairment of liver function is suspected. Further prophylactic steps for those exposed would be routine medical supervision to detect the first stages of poisoning and also a diet rich in carbohydrate and protein. The suggested safe concentrations for prolonged exposure range from 1.5 [12] to 10.0 [9,10] parts per million parts of air.

The first symptoms of poisoning from tetrachloroethane after prolonged exposure suggest an effect on the nervous system as well as on the liver. These are headache, dizziness, nausea and vomiting; subsequently there may be jaundice and cerebral disturbances. In fatal poisoning, degenerative changes may be found in the heart, liver, and kidneys.

Liquid tetrachloroethane brought into contact with the skin is said to be absorbed in appreciable amounts.

Pentachloroethane. Pentachloroethane, boiling point 162° C., is used as an industrial solvent and as a dry-cleaning agent. It appears to have much the same toxic action, and in approximately the same intensity, as tetrachloroethane. Lehmann and Flury [12] have suggested as concentrations for prolonged exposure 2.4 parts per million of air.

Ethylene Derivatives

Vinyl Chloride. Vinyl chloride, boiling point −14° C., is used in the manufacture of organic synthetic chemicals. It is

much less powerful as an anesthetic than chloroform, being in this respect of the order of ethyl chloride. There are no reports in the literature of chronic poisoning.

Dichloroethylene. Dichloroethylene exists in two forms, *cis*-dichloroethylene, boiling point 60.1° C., and *trans*-dichloroethylene, boiling point 48° C. The former has an industrial use as a solvent, dry-cleaning agent, and insecticide. The anesthetic action of dichloroethylene appears to be about the order of that of chloroform and carbon tetrachloride. Its secondary toxic effects, as far as they have been determined, appear also to be similar to those substances. On exposure to an open flame or very hot metal it decomposes with the development of irritant fumes.

Trichloroethylene. Trichloroethylene, boiling point 87.2° C., is used extensively as an industrial solvent, for degreasing and dry-cleaning, as an ingredient of paints and varnishes, and as an insecticide. Inhalation of trichloroethylene has been employed for the relief of pain in neuralgia, headache, and angina pectoris. It has been suggested that impurities in commercial trichloroethylene may be responsible for some of the ill effects on the nervous system. As an anesthetic it appears to be somewhat more powerful than carbon tetrachloride, but its specific toxic effects are believed to be less marked and to be directed more to the nervous system than to the liver. The concentration in the air suggested as safe for prolonged exposure is estimated as 186 [12] to 200 [9,10] parts per million parts of air.

On exposure to a flame or hot metal, trichloroethylene may decompose with the formation of irritant gases and vapors, including phosgene.

Tetrachloroethylene. Tetrachloroethylene, boiling point 120.8° C., is used industrially as a solvent for degreasing and dry cleaning, and has some use in medicine as a vermifuge. Its general action appears to be similar to that of trichloroethylene, although it has a more powerful anesthetic action as judged on the basis of concentration in the air. The concentrations suggested as safe for prolonged exposure, as for tetrachloroethylene, are 147 [12] and 200 [9,10] parts per million parts of air.

Propyl Chloride and Bromide. Propyl chloride, boiling point 47.2° C., and propyl bromide, boiling point 70.8° C., and trichloropropane, boiling point 156.8° C., have no extensive indus-

trial use. No instance of human poisoning has been reported. Of the three, propyl chloride appears to have the least anesthetic power and to be the least toxic; its action on the heart is said to be more pronounced than that of chloroform. Propyl bromide, as with other halogenated hydrocarbons, is more toxic than the chloride. Trichloropropane is a more powerful anesthetic than propyl chloride. No degenerative changes in the liver have been reported from experimental studies with these compounds.

Allyl Chloride. Allyl chloride, 3-chloropropene, b.p. 44.8° to 45.3° C., is used to some extent in synthetic chemistry. It is strongly irritating in concentrations below those causing anesthesia. Death of experimental animals has been caused by concentrations as low as 1 mg. per liter for an exposure of 4 hours.

Chloroprene. Chloroprene, 2-chloro-1,3-butadiene, boiling point 59.4° C., is used in the manufacture of synthetic rubber. The vapors are irritating but this action does not entirely obscure their anesthetic action. It appears to exert a definite systemic poisonous effect directed, in part, toward the liver.

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Chapter 15

Group III (cont'd). Volatile Drugs and Drug-like Substances

Subgroup D. Anesthetic Gases and Vapors which Injure Chiefly the Hematopoietic System: Aromatic Hydrocarbons

The hydrocarbons of the benzene series are usually derived from the destructive distillation of coal and are, therefore, by-products of the illuminating gas and coke industries. Crude coal tar is a black, viscid liquid of specific gravity 1.1 to 1.2 and is a mixture of many organic substances. The crude tar is used for waterproofing the foundations of buildings, for tarring streets, for impregnating roofing felt, and for many other purposes. Poisoning can be produced by inhalation of the vapors given off when the crude tar is heated; these vapors are chiefly the first distillation fractions.

Table 34. Distillation Fractions of Coal Tar.

1. "Light oil" or crude naphtha collected up to 170° C.	Principal constituents: benzene, xylene, toluene, pyridine, thiophene.	Sufficiently volatile under ordinary conditions to cause poisoning from inhalation of vapors. This fraction is redistilled into 90% benzol, 50% benzol and solvent naphtha.
2. "Middle oil" collected between 170° and 230° C.	Naphthalene and phenol.	Not sufficiently volatile under ordinary conditions to cause poisoning from inhalation of vapors.
3. "Heavy oil" collected between 230° and 270° C.	Phenol, cresol, anthracene (called creosote).	
4. "Anthracene oil" collected above 270° C.	Anthracene, phenanthrene, and hydrocarbons which are solid when cooled.	
5. Pitch remaining in still.		

Coal tar, after the watery "gas liquor" has been driven off, is separated into fractions, each of which is a mixture of several substances.

Often the distillation is not carried through to completion.

When only the light oils and a considerable part of the heavy oils have been distilled off, soft pitch remains; when the light oils and only a small portion of the heavy oils have been removed, the residue is known as asphaltum. The low volatility of the materials in soft pitch and asphaltum renders poisoning from their vapors unlikely at ordinary temperatures.

The "light oil," or first fraction of distillation, is redistilled into fractions coming over respectively between 80° and 110°, 110° and 140°, 140° and 170° C. These fractions consist principally of hydrocarbons, but they also contain basic substances such as pyridine and acid substances such as phenol, as well as other constituents. The basic and acid substances are removed by washing in turn with sulfuric acid and caustic soda and are subsequently recovered.

The fraction of the "light oil" separated between 80° and 110° C. consists principally of the hydrocarbons benzene and toluene and is handled commercially as "90 per cent benzol." The fraction obtained between 110° and 140° C. consists essentially of the same two hydrocarbons, but in different proportion, together with xylene, and passes under the trade name of "50 per cent benzol." The last fraction, 140° to 170° C. consists of xylene and higher homologs, together with unknown hydrocarbons, and is called "solvent naphtha."

The fractions termed "90 and 50 per cent benzol" contain respectively about 70 and 46 per cent of pure benzene; the trade terms refer to the proportion of the mixtures which distills over below a temperature of 100° C. Pure benzene is obtained by further purification of "90 per cent benzol." All but the most refined products contain small proportions of toluene, paraffins and carbon disulfide, as well as other impurities including thiophenes. Thiophenes resemble benzene closely in chemical and physical properties and can be separated only with difficulty.

Benzene. Benzene has an extensive industrial use in the blending of motor fuels, the manufacture of paints, varnishes and stains, and as a solvent. Under many of the conditions in which benzene is used, including its manufacture, there is opportunity for escape of vapor only as a result of accident. Any poisoning from benzene is then of the acute type. When, however, benzene is employed as a solvent, or dry cleaning fluid, or in a paint, the benzene is permitted to evaporate in the air of

the workroom. If the ventilation is inadequate, the repeated inhalation of benzene vapors may lead to chronic poisoning.

Acute poisoning from benzene, as observed clinically, is of three general types, depending upon its severity. In all three the anesthetic action is predominant. Inhalation of very high concentrations of benzene vapors may result in the rapid development of unconsciousness, followed in a short time by death from respiratory failure. With somewhat lower concentrations the sequence of events is less rapid and the display of symptoms correspondingly more extensive. There may be dizziness, weakness, apprehension, collapse, and unconsciousness. These symptoms, common to all anesthetics, may be replaced by violent excitement. Death may occur from respiratory failure during the inhalation of the vapors. With most anesthetics, removal from the vapors before death has occurred, and the application of suitable treatment, are followed by recovery. This may occur with benzene. But there may also be a third type of poisoning in which death occurs from several hours to several days after the exposure, usually without recovery from coma. Presumably this delayed death results from the specific toxic action of benzene which is discussed below under chronic poisoning.

Table 35. Acute Physiological Response to Various Concentrations of Benzene.* [1, 2, 3]

	Parts of benzene vapor per million parts of air
Slight symptoms after several hours	1,500 to 3,000
Maximum concentration that can be inhaled for 1 hour without serious disturbance	3,000 to 4,700
Dangerous to life in ½ to 1 hour	7,500
Rapidly fatal for even short exposure	19,000 to 20,000

* The concentrations given here are for immediate acute effects only; exposure of several hours or days to concentrations lower than those mentioned here may lead to chronic poisoning.

In its anesthetic action benzene is only slightly more powerful than gasoline. But this parallelism does not hold in regard to chronic effects. Prolonged inhalation of benzene and its homologs, in concentrations too low to produce any immediate intoxication, may lead to subacute and chronic poisoning directed particularly against the hemotopoietic system, although a similar condition does not follow from exposure to petroleum distillates.

Benzene, after being absorbed into the body, is chiefly eliminated through the lungs when fresh air is breathed. During the

time that it stays in the body, however, a portion of that present is oxidized. The oxidation products, combined with sulfuric and glycuronic acids, are eliminated in the urine. The ratio of organic to inorganic sulfate in the urine may be used to estimate the degree of exposure to benzene.[4,5,6]

In producing chronic poisoning, the action of benzene or its oxidation products, is mainly upon the red marrow of the bones. This tissue is concerned with the formation of important blood elements: red cells, white cells (leucocytes) and the platelets which are essential for the clotting of the blood. The benzene may first stimulate the marrow so that there is an increased number of white cells; but with continued exposure this stimulation, if it occurs, gives place to depression and these elements of the blood are diminished. The most constant diminution is in the red cells—anemia; that of the white cells may be somewhat less marked and more variable. The decrease of red cells, when severe, causes symptoms typical of anemia: weakness, dizziness, rapid pulse rate, pain over the heart and shortness of breath. The diminution in the number of white cells may be accompanied by decreased resistance to infection, weakness, and ulcers in the mouth and throat. The decrease in platelets results in a delay in the clotting time of the blood which may lead to bleeding from mucous membranes, hemorrhages under the skin and other signs of purpura.

There is considerable variation in susceptibility to chronic benzene poisoning; this variation would appear to depend upon the resistance of the red bone marrow and on the possible presence of other conditions which put a strain upon this tissue. The changes seen in chronic benzene poisoning may occur from disturbances of the bone marrow from many causes other than the action of benzene. Young people of both sexes, and particularly pregnant women, appear to have the greatest susceptibility to chronic benzene poisoning.

The maximum concentrations suggested as permissible for daily exposure to benzene vapors range from 31 [2] to 75 [7] and 100 [8,9,10] parts per million parts of air. Regardless of care taken to regulate the concentration of benzene in the air, it is desirable, in view of the wide individual susceptibilities to this substance, to have frequent medical examinations of all employees who are regularly exposed to benzene fumes; this examination

should include a determination of the organic sulfates in the urine and a count of the red and white blood cells.

Toluene

In their anesthetic action the homologs benzene, toluene and xylene, as judged on the basis of concentration in the air, do not show any marked differences. On theoretical grounds the expectation would be that the anesthetic powers of these three substances would increase in the order of their ascent in the series when comparison is made on the basis of concentration in the blood. The diminishing solubility on ascent in the series would, on the other hand, tend to counterbalance an increasing physiological activity if the comparison were made on the basis of concentration in the air. In contrast to benzene, prolonged exposure to toluene does not increase the ratio of inorganic sulfate in the urine [15] or greatly decrease the number of white cells in the blood. Some enlargement of the liver and mild anemia may result, but much less than with comparable concentrations of benzene.[16]

The maximum concentrations suggested as permissible for daily exposure to toluene range from 53 [1] to 100 [8] or 200 [7] parts per million parts of air, and for xylene 100 [8] to 200.[7] A concentration of 200 parts of toluene per million inhaled for 8 hours, or 600 to 800 parts per million for a few hours, is said to cause slight but definite impairment of coördination and reaction time which may predispose to accidents.[15]

Cyclohexane, boiling point 81.4° C., is used as a solvent and chemical intermediate. It is said to be similar in action but weaker than benzene, both as regards acute and chronic effects.

Subgroup E. Anesthetic Gases and Vapors Injuring Chiefly the Nervous System

Alcohols

The alcohols most extensively used in industry have a high solubility; methyl and ethyl alcohols are miscible with water in all proportions. In consequence, even low concentrations in the air inhaled would result, if equilibrium were reached with the blood, in the accumulation of a large amount within the body. Their high solubilities also cause them to be eliminated slowly through the lungs. With ethyl alcohol the slow elimination is

largely counterbalanced by the oxidation of that alcohol within the body. Oxidation, however, occurs only to a small extent with methyl alcohol. The alcohols are anesthetics and, as with all anesthetics, death in acute poisoning results from respiratory failure. Ethyl alcohol is more toxic (in causing respiratory failure) than methyl alcohol for equal concentrations in the body; but the rapid oxidation of ethyl alcohol to water and carbon dioxide prevents it from acting as a serious toxic agent when it is absorbed through the lungs from any ordinary concentration of its vapor in air. Methyl and ethyl alcohols differ in their secondary toxic actions.

In addition to their anesthetic action, the alcohols have some direct poisonous action; and this is particularly marked with methyl alcohol. Butyl, propyl and amyl alcohols have little practical importance as noxious vapors, for although the pharmacological activity rises in ascending the series, it is more than offset by the decreasing solubility and volatility.

Table 36. Monohydric Alcohols.

Name	Formula	Boiling Point (°C.)
Methyl alcohol (methanol)	CH_3OH	64.6
Ethyl alcohol (ethanol)	CH_3CH_2OH	78.5
n-Propyl alcohol (propanol-1)	$CH_3CH_2CH_2OH$	97.8
sec-Propyl alcohol (propanol-2)	$CH_3CH(OH)CH_3$	82.3
n-Butyl alcohol (butanol-1)	$CH_3(CH_2)_3OH$	117.7
sec-Butyl alcohol (butanol-2)	$CH_3CH_2CHOHCH_3$	99.5
tert-Butyl alcohol (2-methyl-propanol-2)	$(CH_3)_3COH$	82.8
n-Amyl alcohol (pentanol-1)	$CH_3(CH_2)_4OH$	138.0
iso(*act*) Amyl alcohol (2-methyl-butanol-1)	$CH_3(C_2H_5)CHCH_2OH$	128.0
iso-Amyl alcohol (2,2-dimethyl-propanol-1)	$(CH_3)_3CCH_2OH$	114.0
sec(*act*) Amyl alcohol (pentanol-2)	$CH_3CHOHC_3H_7$	119.3
sec(*act*) Amyl alcohol (3-methyl-butanol-2)	$CH_3CHOHCH(CH_3)_2$	114.0
sec-Amyl alcohol (petanol-3)	$(C_2H_5)_2CHOH$	115.6
tert-Amyl alcohol (2-methyl-butanol-2)	$C_2H_5C(OH)(CH_3)_2$	101.8

Methyl alcohol. Methyl alcohol (methanol) is widely used in synthetic chemistry as a solvent, particularly in the preparation of lacquers, plastics and stains, and as a denaturant for ethyl alcohol. Crude methyl alcohol contains acetone, ethyl methyl ketone, methyl and dimethyl acetates, purpural, allyl alcohol and other bodies which give it a disagreeable odor and

taste. There was at one time a common belief, quite without foundation, that the toxicity of methyl alcohol is due to the impurities it contains and that pure methyl alcohol is not toxic. In reality, it is methyl alcohol itself that is poisonous; the impurities do not contribute appreciably to its toxicity.

Impure methanol is used as a denaturant of ethyl alcohol and is added to the extent of about 10 per cent. A few instances of poisoning from the vapor of methanol in this mixture have occurred from its use in the radiators of motor cars as an anti-freezing agent. In these cases the fumes from the heated alcohol in the radiator have escaped into the enclosed cabs of trucks built with the radiator outlet discharging into the cab. Ordinarily, however, poisoning from inhalation of the vapor of methanol occurs as the result of applying shellac or other lacquers, or varnish remover, and inhaling the vapor in an enclosed space, as inside a wooden vat.

One feature which gives to methanol its particularly toxic character is the slowness of its elimination: hence its prolonged action on repeated exposures. The coma caused by large doses of methanol may last from 2 to 4 days or even longer. Because of its cumulative action, a toxic concentration may be gradually built up in the blood as a result of exposure to concentrations which cause no appreciable effect after a single exposure.

The poisonous action of methyl alcohol (aside from its anesthetic action) is exerted particularly upon the optic nerves, probably commencing in the retina. No reason is known for this action of methyl alcohol. Similar effects may be produced in susceptible individuals by quinine and salicyl. As a rule, the involvement of the eye is first indicated by blurred and clouded vision, then pain in the eyeball; partial or complete blindness follows. After a few days the vision generally improves. Occasionally the improvement is permanent, but more often there is a second gradual failure of vision leading to permanent blindness. While the effects upon the eye are particularly striking, the toxic action of methanol is not limited to the retina and optic nerve, for among other symptoms, severe colic may follow inhalation of the vapor.

The destructive action of methanol upon nervous tissue has been variously ascribed to formic acid and formaldehyde produced by the oxidation of the alcohol within the body. As

neither of these substances can exist in the alkaline media of the body, it seems more probable that the action is due to the unoxidized methanol itself.

The maximum concentrations of methyl alcohol suggested as permissible for prolonged exposure have been given as 100,[8,9] 200[7] and 382[11] parts per million parts of air. Expressed in milligrams per liter, these concentrations correspond to 0.145, 0.29 and 0.50 mg. per liter. When the rule of maximum absorption (see Chapter 5) is applied to these values, the amounts (the dose) absorbed into the body during a working day of 8 hours would be 0.435, 0.870 and 1.5 g. of methyl alcohol respectively. The equilibrium doses for the concentrations would be higher, since the distribution of methyl alcohol between air and blood is of the order of 1:1700. Continued exposure to the concentrations given would result in the accumulation and retention after exposure of very considerable amounts of methyl alcohol in the body. For a man of average size (70 kg.), these values would be, for 0.145 mg. per liter of air, 17.2 g.; for 0.29 mg., 34.4 g.; and for 0.5 mg., 59.5 g. Obviously many days and nights of continuous exposure would be required before these equilibrium values were reached. The far smaller amounts absorbed during a single working day, as given above, would not in themselves cause any harm whatever, provided that between the periods of exposure the methyl alcohol absorbed were eliminated. If it were not eliminated, accumulation would occur with repeated exposure. This accumulation would not, however, continue to the amount at full equilibrium. The rate of elimination would vary with the amount present in the body at the end of the working day. Thus if accumulation occurred, elimination during the time free from exposure would also be increased, although not proportionally. As a result, the accumulation would eventually cease at the amount at which elimination would equal absorption. There would remain in the body a minimum residual amount above which the amount in the body would rise during the working day and to which it would fall at the beginning of the next working day. The concentrations of methyl alcohol appearing in the blood, urine, or expired air, on repeated determinations, would be a better index of the safety of working conditions than a standard based on ventilation.

These calculations emphasize the peculiarities of methyl

alcohol which result from its high solubility and its essentially non-reactive character. On the basis of dose, methyl alcohol is not a highly toxic substance; it becomes highly toxic because of the large amounts which, with continued exposure, may accumulate and be retained in the body. This point is important also in relation to such substances as methyl chloride and bromide, which are used as refrigerants and which are broken down in the body with the formation of methyl alcohol. Domestic exposure, in contrast to industrial, may continue night and day, and may lead to the accumulation of dangerous amounts of methyl alcohol from concentrations which would not be harmful for an 8-hour working day.

Ethyl alcohol. Ethyl alcohol (ethanol) has a wide industrial application as a solvent, as a fuel, and in synthetic and pharmaceutical chemistry.

In contrast to methyl alcohol, ethyl alcohol in its industrial occurrence may be considered as a primary anesthetic with no accessory toxic action. The habitual excessive use of ethyl alcohol as a beverage may, after many years, result in damage to the brain and nervous system. Such damage, however, follows only from amounts of alcohol far in excess of any that could be absorbed through the lungs in daily exposure to the vapors under industrial conditions. In industry, the ill effects experienced from ethyl alcohol are mainly those of mild irritation of the eyes and upper respiratory tract. Under exceptional circumstances, exposure to very high concentrations of the vapor may induce slight intoxication.

Although ethyl alcohol has nearly as high a distribution between air and blood as methyl alcohol (1,300 as compared to 1,700), it is, in complete contrast to methyl alcohol, a highly reactive substance, being burned in the body to carbon dioxide and water. It is therefore to a high degree a non-cumulative substance.

The concentrations considered safe for exposure during the working day range from 250 [8] to 1,064 [11] parts of vapor per million parts of air. Applying the rule of maximum absorption, as with methyl alcohol, these concentrations would result in the absorption during 8 hours of 1.5 and 6.0 g. of ethyl alcohol respectively. Neither of these amounts would cause intoxication nor, on repeated exposure, any systemic effects, since they corre-

spond to only 1 to 3 teaspoonfuls of whisky taken in the same period of time. Although there would be no intoxicating effects from these amounts of alcohol, either taken by stomach or inhaled from the air, ethyl alcohol vapors, even in low concentrations, are severely iritating to the eyes and upper respiratory tract. This feature of ethyl alcohol is more important in setting the standards for exposure than the secondary toxic effects from the alcohol absorbed.

Propyl, Butyl and Amyl Alcohols. The propyl alcohols have few industrial uses and little is known of their effects on repeated and prolonged exposures. For single large doses they are approximately twice as toxic as ethyl alcohol. The extent to which they are oxidized in the body, a highly important factor in their toxicology, has not yet been determined.

The butyl alcohols are widely used in industry as solvents. As with the propyl alcohols, little certain knowledge has been obtained of their physiological action and their fate in the body. Butyl alcohol in a single large dose is approximately 3 times as toxic as ethyl alcohol. The vapors are more irritating than those of ethyl, but less so than those of amyl alcohol. A concentration of 100 [8,11] parts of vapor per million parts of air has been suggested as safe for exposure during the working day. The butyl alcohols are much less soluble than the lower homologs and therefore are absorbed more slowly and to a much lower maximum amount than ethyl or methyl alcohol.

The amyl alcohols, especially isobutyl carbinol, have a wide industrial use in lacquers and varnishes, as solvents, and in the manufacture of synthetic rubber. They have a bad reputation as being the particularly poisonous and undesirable ingredients in distilled spirits, since amyl alcohols are the main components of fusel oil. In reality, in the amounts present in beverage spirits, the amyl alcohols exert virtually no toxic action; the toxicity of beverage spirits is due to ethyl alcohol. As with propyl and butyl alcohols, there is little reliable information as to the nature of the toxic actions of the amyl alcohols or their fate in the body.

On the basis of the relative amounts required to produce death from a single large dose, the amyl alcohols are about 4 times as toxic as ethyl alcohol. They have, however, a low solubility and are therefore absorbed slowly and to a lower

maximum than are the lower homologs. The vapors of amyl alcohol are irritating to the eyes and upper respiratory tract.

A concentration of 56 parts per million parts of air has been suggested by Lehmann and Flury [11] as safe for daily exposure of 8 hours. The same authors give the concentrations for methyl and ethyl alcohols as 382 and 1,064 parts per million parts of air respectively. They conclude that the vapors of the amyl alcohols, for safe exposures, should be present in only one-seventh that of methyl alcohol and one-twentieth that of ethyl alcohol. This point is emphasized here since the concentrations given as safe for methyl and ethyl alcohols by these investigators are considerably higher than those recommended in American standards.

Esters of Organic Acids. The esters of organic acids are included here, not because they have any direct toxic action upon the nervous system, but because they are broken down in the body into alcohols.

The addition of the carboxyl group (COOH) to the radicals of the fatty hydrocarbons destroys their anesthetic power. The combination of the acids thus produced with hydrocarbons to form esters, restores this power to a very limited degree. The vapors on absorption, and probably to some extent on surface

Table 37. Esters of Organic Acids.

Name	Formula	Boiling Point (°C.)	Physiological Action
Methyl formate	$HCOOCH_3$	31.5	Irritating and some anesthetic effects.
Ethyl formate	$HCOOC_2H_5$	54.3	
n-Propyl formate	$HCOOC_3H_7$	81.3	
n-Butyl formate	$HCOOC_4H_9$	106.8	
n-Amyl formate	$HCOOC_5H_{11}$	130.4	
Methyl acetate	CH_3COOCH_3	57.0	Mildly irritating and some anesthetic effects.
Ethyl acetate	$CH_3COOC_2H_5$	77.0	
n-Propyl acetate	$CH_3COOC_3H_7$	101.6	
Butyl acetate (*n.*)	$CH_3COOC_4H_9$	126.4	
Amyl acetate (*iso.*)	$CH_3COO(CH_2)_2CH(CH_3)_2$	142.0	
Amyl acetate (*sec.*)	$CH_3COOCH(CH_3)CH_2CH_2CH_3$	133.5	Irritating and some anesthetic effects.

tissues as well, are largely hydrolyzed, with the liberation of the acid and the primary alcohol. Any anesthetic effects developed are due to the alcohol.

Some of the esters are mildly irritating and some highly so and are properly considered as primary irritants. The acid

radical in the ester may exert a preponderant physiological action. Thus the formates are far more irritating than the acetates.

The fact that the esters of organic acids may be broken down in the body into alcohols raises the point of chronic poisoning. This feature would apply particularly to the acetates (other than the isoamyl acetates), since they can be tolerated in comparatively high concentrations with slight irritation.

Ethyl acetate would yield ethyl alcohol; but chronic poisoning does not occur from inhalation of its vapors; ethyl acetate is, moreover, far less soluble than ethyl alcohol, so that at the same concentrations in air, much less would be absorbed. Methyl acetate is the most soluble of the series. Its hydrolysis in the body yields methyl alcohol. The concentration inhaled for pro-

Table 38. Physiological Response to Various Concentrations of Esters of Organic Acids[7,8,10,12,13]

		Parts of vapor per million parts of air.
Methyl formate		
Slight symptoms after several hours		1,500 to 2,000
Maximum concentration safe for short exposure		5,000
Dangerous for short exposure		15,000 to 25,000
Methyl acetate		
Maximum concentration allowable for prolonged exposure		83
Ethyl acetate		
Maximum concentration allowable for prolonged exposure		139
Dangerous for short exposure		10,000 to 20,000
Propyl acetate		
Maximum concentration allowable for prolonged exposure		83
Butyl acetate		
Maximum concentration allowable for prolonged exposure		100
Amyl acetate		
Maximum concentration allowable for prolonged exposure	*iso.*	47 to 400
	sec.	———
Slight symptoms after several hours	*iso.*	———
	sec.	2,000
Maximum concentration safe for short exposure	*iso.*	5,000 to 10,000
	sec.	5,000

longed periods should, therefore, be regulated with the toxicity of methyl alcohol in mind. Butyl and amyl acetates yield the corresponding alcohols; but the higher toxicity of these alcohols, as compared with ethyl, is to a large extent counteracted by the

low solubility of these esters and the corresponding slowness of absorption.

Carbon Disulfide. Carbon disulfide, boiling point 46° C., is now less widely used in industry than formerly. The low boiling point, the high toxicity and the serious fire hazard of carbon disulfide have led to its replacement with other substances whenever possible. It is, however, still employed as a solvent and fumigant and occurs as a by-product in the manufacture of coal gas, in the distillation of tar, and in the manufacture of certain chemicals.

In acute poisoning by carbon disulfide, the anesthetic action is predominant; death results from respiratory failure. Carbon disulfide is a much more powerful anesthetic than chloroform. Acute poisoning is rare in industry but, as with all anesthetic substances, mild intoxication may occur from brief inhalation of moderately high concentrations. Such intoxication is usually unrecognized by the man affected but, as has been pointed out, may add greatly to the possibility of industrial accidents.

In chronic poisoning by carbon disulfide the chief damage is to the nervous system. In habitual exposure, the polyneuritis may involve any part of the nervous system. The symptoms are therefore variable and depend upon the locus of the action and its severity. Chronic poisoning usually commences with general disturbances in sensation, such as headache, vertigo and parethesias. If the exposure is continued, evidence of the involvement of motor nerves appears, and there are tremors and muscular weakness. Neuritis may also accur in the sensory nerves and give rise to areas of anesthesia or cause blindness from its extension to the optic nerve. The toxic action is also exerted upon the cortical region and causes changes in temperament, transient excitement, periods of dullness and apathy, hallucinations, and even acute mania which may be permanent. Mild cases recover after discontinuing exposure to the vapor; but a long time may be required. Serious nervous disturbances are usually permanent.

The concentrations given in Table 39 are for acute effects; exposure for several hours a day to much lower concentrations may, in a short time, lead to chronic poisoning. The estimates as to the concentration safe for daily exposure during the full working period vary widely. In part, at least, this variation has

Table 39. Physiological Response to Various Concentrations of Carbon Disulfide.[1, 2, 11]

	Parts of carbon disulfide per million parts of air
Slight symptoms after several hours	300 to 400
Maximum concentrations that can be inhaled for 1 hour without serious disturbance	480 to 1,600
Dangerous after exposure of 30 minutes or 1 hour	1,000 to 3,850

resulted from a desire to be extremely cautious with a substance which, in many instances, has caused severe injury. In many of these instances there has been no certain knowledge of the concentration to which the men were exposed. The concentrations suggested range from 3 [11] to 15 [7,8] and even 20 [10] parts of vapor per million parts of air.

Subgroup F. Volatile Drugs and Drug-like Substances Acting Mainly upon the Blood and Circulation: Organic Nitro Compounds

The organic nitro compounds, which are volatile, belong to the anesthetic series of hydrocarbons, but their anesthetic properties may be obscured by a more powerful and entirely different action by the nitrite, nitroso, and amine radicals which they contain. These substances, or their products after absorption, have the property of altering the hemoglobin of the blood to methemoglobin. In addition, the alkyl compounds induce in high degree the so-called "nitrite effect"—a general arterial dilatation. Nitrous fumes have a similar action but are mainly characterized by their irritant effects in the lungs. (See Chapters 8 and 9.) In addition to these two effects, some of the organic nitro compounds have a marked toxic action on the nervous system and the liver.

Formation of Methemoglobin

Methemoglobin is an isomer of oxyhemoglobin; the two substances have the same chemical composition but their structures are different. Methemoglobin holds oxygen much more firmly than does hemoglobin; it is not dissociated even by a vacuum. This stability of methemoglobin prevents it from performing the normal function of hemoglobin, that of transporting oxygen in the body. For this reason the formation of large amounts of methemoglobin causes asphyxia of the tissues.

Small amounts of methemoglobin may be normally present in the blood. When the amount becomes large, the color of the blood is altered to chocolate brown. The skin may appear bluish, a condition called cyanosis.

After the substance producing methemoglobin has been eliminated from the body, the methemoglobin may be converted back to oxyhemoglobin. The serious consequences of poisoning by substances causing methemoglobin formation probably are not primarily from the asphyxia produced but from the more specific toxic effects of these substances upon the tissues. Methemoglobin, however, serves to some extent as an index of the severity of the intoxication.

One of those toxic actions may be exercised on the red corpuscles, causing laking with discharge of hemoglobin into the plasma. The hemoglobin in altered form is then eliminated through the kidneys. This destruction of red cells may result in anemia and, if severe, in injury to the kidneys and liver.

The formation of methemoglobin may be due, not to the intact nitro compound, but to the product into which it is broken down by the liver. Thus aniline, which may cause marked formation of methemoglobin in the body, does not do so when added to blood in a test tube. The intermediate products believed to be primarily responsible for the formation of methemoglobin are amino compounds such as para-aminophenol. It is probable also that these products are in some measure responsible for the other toxic effects induced by aniline and similar substances.

Nitrite Effect

The nitrites have a powerful action on the peripheral arteries, causing them to dilate. This effect is particularly marked in those compounds in which the radical —NO, is attached to the other group through an atom of oxygen as in R—O—NO. The alkyl nitrites, such as ethyl nitrite, C_2H_5—O—NO, show this combination. The closely allied group of nitrites in which the nitrogen has 5 valences and is attached to the radical by oxygen, as in R—O—NO_2, does not affect the blood vessels. Some of the nitric esters, however, such as nitroglycerin, are reduced by contact with organic material and nitrites are formed; these nitrites therefore produce such effects, but their action is slower. The nitro-substitution products, in which the nitrogen is attached

to the alkyl group directly and not through an atom of oxygen as in R—NO_2, have a slight action upon the blood vessels, due presumably to splitting off the NO_2 in the tissues.

Practically all the immediate symptoms occasioned by the inhalation of nitrites arise from the fall in blood pressure. The heart rate is accelerated, not directly by the action of the nitrite, but as the result of the fall in blood pressure. In large quantities, however, the nitrites extend their action to the heart muscle and the heart beats are weakened.

The decreased supply of blood to the brain induced by the lowering of blood pressure gives rise to headache, weakness and, in severe cases, to stupor. It also excites the respiratory center in a manner similar to oxygen want. Breathing is quickened and deepened, but in severe cases it eventually becomes slower and shallower and finally stops. Death then results from asphyxia.

Classification of this Subgroup

For convenience of description, the more important gases and vapors of this subgroup acting upon the blood and upon the circulation may be further divided into two classes as follows:

1. Substances whose predominant action is the "nitrite effect," but which, to some degree, convert oxyhemoglobin to methemoglobin. The specially important substances of this class are alkyl nitrites and alkyl nitro-substitution products.

2. Substances whose predominant action is the conversion of oxyhemoglobin to methemoglobin with relatively little "nitrite effect." The important substances of this class are amido compounds and aromatic nitro-substitution products.

Alkyl Nitrites and Nitro-Substitution Products. These substances have only a limited industrial use. Ethyl nitrite is present in the fumes arising during the manufacture of fulminate of mercury. Amyl nitrite is used in medicine to induce a fall in blood pressure, particularly in the treatment of angina pectoris and as an antidote to cyanide poisoning. They are all powerful drugs and, even in small quantities, rapidly induce their characteristic effect. But unless the exposure is protracted, the effects pass off quickly after the inhalation ceases. For example, inhalation of the vapors arising from 1 g. of amyl nitrite moistening a cloth held to the nostrils causes a fall of 10 to 15 mm.

in the arterial pressure, which reaches its maximum in 3 minutes and returns to normal in 7 minutes. Habituation to the alkyl nitrites can, to some extent, be acquired, but the partial immunity disappears within a few days after the exposure ceases.

The nitrite effect induced by the alkyl nitrites is much more marked than their action upon hemoglobin; methemoglobin is formed only after severe or prolonged exposure.

Aromatic Nitro-Substitution Products and Amido Compounds. These substances are extensively used in the dye industry and for the manufacture of explosives. Fortunately their boiling points are high and their volatility consequently low, so that their action in the vapor state is limited by the relatively low concentration in the air even at full saturation at room temperatures. The majority of cases of poisoning by these compounds occur from their absorption through the skin or from inhalation of the dust of the higher members of the series which are solid at ordinary temperatures.

As in the case of the anesthetic hydrocarbons, the chemical structure of the nitro derivatives of the aromatic series influences the intensity of their action. The attachment of the nitroso group (NO) and the nitro group (NO_2), either on a side chain or on the benzene ring, increases the toxicity of the cyclic hydrocarbons. Thus nitrobenzene is more toxic than benzene. The toxicity, however, does not increase in proportion to the number of NO_2 groups added.

Reduction of the NO_2 groups to NH_2, as in changing nitrobenzene to aniline, reduces the toxicity slightly (for chronic effects). The introduction of an alkyl radical into the amido group likewise reduces the toxicity; thus the alkyl anilines are less toxic than aniline. The sulfonation of the amido compounds destroys their toxicity. The entrance of the carboxyl radical (COOH) brings about a similar change; nitrobenzoic acid is not toxic.

In addition to their action upon the blood the nitro-substitution products act, to some extent, upon the central nervous system, causing stimulation and then paralysis. With the amido compounds this action is much less. In chronic poisoning the liver may become involved from the excessive destruction of the red cells of the blood, and jaundice results.

Of the nitro and amino compounds, the most important in industry are nitrobenzene, aniline and toluidine.

Nitrobenzene, boiling point 210° to 211° C., is used in the manufacture of aniline and as a constituent of inks and shoe dyes. Poisoning is more common from absorption through the skin from clothing splashed with nitrobenzene, or from shoes dyed and worn before they are dry, than from inhalation of the vapors. The inhalation of high concentrations is followed by intoxication, extreme cyanosis, coma, and death from respiratory failure. Repeated prolonged inhalation of lower concentrations may lead to chronic poisoning with cyanosis, anemia, muscular weakness, loss of appetite and irritation of the bladder.

Table 40. Physiological Response to Various Concentrations of Nitrobenzene, Aniline and Toluidine.[7, 8, 14]

	Parts per million parts of air		
	Nitrobenzene	Aniline	Toluidine
Maximum concentration considered safe for daily exposure	1 to 5	5	
Slight symptoms after exposure of several hours	40 to 80	7 to 53	6 to 23
Maximum concentration that can be inhaled for 1 hour without serious disturbance	200	100 to 160	90 to 140

Aniline, boiling point 184.4° C., is used in the manufacture of dyes and drugs and as a constituent of inks, varnishes, and shoe polish.

Toluidine, boiling point 200° to 202° C., in the form of vapor may occur in the manufacture and use of dyes and in synthetic chemistry. The toxicology of these two compounds is essentially the same as for aniline.

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An excellent review of the literature on the physiological effects of the amino and nitro compounds is given by von Oettingen, Public Health Bulletin No. 271, 1941.

Chapter 16

Group IV. Inorganic and Organometallic Gases

The inorganic and organometallic volatile compounds have a wide diversity of composition and action. They are here classified together merely because they do not come under any of the other classes. The elements mercury and phosphorus and their organic compounds are essentially protoplasmic poisons, that is, inherently poisonous to all living matter. On the other hand, the hydric compounds, such as hydrogen sulfide, show a diversity of action which necessitates a separate description for each.

Protoplasmic Poisons

A protoplasmic poison is one which, even in very small amounts, destroys the vitality of any form of living matter with which it comes in contact. Such poisons are fundamental in their action and do not depend upon the disruption of some system of functions, such as respiration, circulation, or the nervous system, which the complexity of the body renders necessary for the maintenance of the whole organism. The distinction may be seen by comparing the action of mercury with that of carbon monoxide. Mercury is a protoplasmic poison, for in its ionized state it stops the metabolism of all living matter; carbon monoxide, on the other hand, only combines with the hemoglobin of the blood to the exclusion of oxygen. The lack of oxygen which develops interferes with the function of the nervous system even to the extent that respiration may fail and death result. But carbon monoxide itself does not appreciably affect the tissue of the nervous system.

Most of the substances classed as irritants are protoplasmic poisons in the strict sense, for they destroy any tissue with which they are brought in contact. Their action in most instances, however, prevents their absorption into the body and thus their effects are limited to surface tissues. Likewise the cyanides are

protoplasmic poisons, but their action is so specialized that they are better classified under the asphyxiants.

Although a substance is classed as a protoplasmic or general poison, it does not necessarily follow that its action is exerted equally upon all the tissues of the body. It may affect all tissues when it is present in high concentrations, but in low concentrations it may produce noticeable effects only in a single tissue or organ which is particularly sensitive to the action of the poison. Again, the poison may accumulate to a greater extent in one tissue than in another and exercise its main action at that point. Thus the protoplasmic poisons, when absorbed into the body, may select certain organs as the chief point of their action.

Mercury

Mercury evaporates even at ordinary temperatures and thus contaminates the air wherever it is exposed. The concentration reached by the vapor in the air depends upon the temperature, the extent of surface exposed and the rate of air exchange in ventilation. The vapor pressure of mercury and the weight of mercury per liter of air saturated at each temperature are given in Table 41.

Table 41. Vapor Pressures of Mercury.

Temperature (° C.)	Vapor pressure of mercury (mm.)	Concentration in air saturated with mercury (mg. per liter)	(parts per million)
20	0.0013	0.0152	1.84
30	0.0029	0.0339	4.10
40	0.0060	0.0700	8.50
60	0.0300	0.3500	42.50
100	0.2800	3.2600	396.00
200	18.3000	213.0000	25,800.00
300	246.0000	2,879.0000	348,000.00

There is a wide variation in the values given for the vapor pressure of mercury at temperatures below 100° C. Those given here seem to be accepted in most chemical tables. The practical utility of these figures is limited for the reason that they presuppose complete equilibrium between the mercury vapor in the air and the liquid metal. Only under quite unusual conditions is this state attained. In still air the heavy vapor tends to collect close to the surface of the exposed metallic mercury and thus opposes further volatilization. Where the air is moved by ventilation, a greater rate of volatilization is attained, but insufficient

time is allowed for the air to reach more than partial saturation with mercury. The values given in the table serve only to indicate the limit of attainable air contamination at the various temperatures. It is apparent that temperature is important, inasmuch as both the rapidity of volatilization and the equilibrium concentration increase greatly with rise of temperature.

The rate of volatilization of mercury at any temperature, and under otherwise similar conditions, varies proportionally with the surface exposed. This has a practical bearing because of the difference in the behavior of the mercury in various states of purity. Clean mercury is readily divided into globules, but these globules coalesce when brought together again. On the other hand, mercury soiled by grease and dust is prone to divide into minute globules which do not coalesce. For example, in the preparation of blue ointment, which is made by working the metal into a grease base, the separate particles cannot be seen with the naked eye and the mass assumes a dull greyish color. An analogous condition occurs when mercury is spilled on the floor of a workshop. Under the feet of the occupants of the room it becomes finely divided and is forced in minute particles into the rough surface of wooden flooring and into cracks. The greater the subdivision the larger is the surface which is presented for volatilization. In this manner a comparatively small amount of mercury in an almost or quite invisible state of subdivision may present an exposed surface equivalent to that of a large mass of mercury coalesced in a dish or pan. The vapor has neither taste nor odor to give warning of its presence.

Occupations Liable to Mercury Poisoning. Many occupations besides those of mining, smelting and refining involve the use of metallic mercury.[1, 2] Mercury is employed in the manufacture of thermometers, barometers, heat-regulating devices, gas analyzers and a large number of other forms of scientific and domestic apparatus. It is used in vacuum pumps employed for extracting air from incandescent bulbs, x-ray tubes, and other apparatus. It is also employed extensively as a conducting or displacement medium in electrical and chemical laboratories. Mercury vapors may escape from leaks in the boilers and piping of mercury turbines.

An extraordinary example of wholesale poisoning by the vapor from metallic mercury occurred in the year 1810 on the British

sloop *Triumph*. This vessel attempted to salvage the mercury from a wrecked Spanish ship which was loaded with this metal. After transfer to the British vessel, the mercury leaked into the hold and so into the bilges of the ship and the crew was poisoned by its vapor; 200 sailors were severely poisoned and 3 died.

Even more extensive poisoning occurred in 1804 during a fire in a quicksilver mine at Idria, Austria. Nine hundred inhabitants in the neighborhood developed mercurial tremor; cows and other domestic animals also showed symptoms.

Toxic Concentrations of Mercury Vapor. There appears to be uncertainty as to the concentration of mercury vapor which is entirely safe for prolonged exposure, and the approximations vary widely. This variation, in part at least, is probably due to individual differences in susceptibility. In view of these differences in susceptibility, and of the insidious nature of chronic mercury poisoning, it is advisable, in the present state of knowledge, to err in favor of low rather than high concentrations. The values approximated range from 0.1 [3, 4] to 0.2 [5, 6] and 0.25 [7] mg. of mercury per cubic meter of air, or 12, 24 and 30 parts per million parts of air.

When the rule of maximum absorption (see Chapter 5) is applied to these values, the total amount of mercury absorbed during a working day does not exceed 0.3, 0.6 and 0.75 mg. As compared to the dose of mercury salt which can be tolerated daily by stomach, these amounts of vapor appear small; but with mercury, contrary to the principles defined for most substances, the mode of entry modifies dose toxicity. This result is, in part, due to the state of ionization of the mercury. In part also it is because the mercury entering the body through the lungs passes directly into the general circulation of the blood, but mercury entering through the alimentary tract is, before entering the general blood stream, subjected to the action of the liver which may store the metal or alter the combination in which it exists.

Absorption of Mercury Vapor. Cole, Gericke and Sullivan [8] state that mercury vapor is not absorbed through the lungs, but only through the mucous membrane of the upper respiratory tract. They were working on the therapy of syphilis and were concerned with absorption of the fumes heated to a temperature higher than that of the body and inhaled directly. Under these

circumstances the mercury condensed from the heated air, on being cooled in the respiratory tract, and much was deposited in the mouth and pharynx. Mercury vapor in air inhaled at the temperature of the body or lower does not condense in this way. Because of its low solubility in water the vapor probably passes for the most part to the lungs to be absorbed there.

The mode of absorption from the lungs is unknown. It has been suggested that the mercury brought to the lungs as vapor is deposited as the metal and is then oxidized. It is more reasonable to suppose that the vapor dissolves in the fluid on the moist surfaces and thus passes into the blood. Although its solution is extremely dilute, it probably follows the laws governing the solution of gaseous substances in liquids. The rate at which it passes from the air into the blood is therefore dependent upon the concentration in the air in relation to that in the fluid. When mercury in solution is brought into contact with protein, it forms an albuminate which is soluble in a fluid containing an excess of unaffected protein. The mercury dissolved in the fluids in the lungs is thus constantly removed through combination with the proteins. In consequence of this removal a continuous passage of mercury from the air into the fluid is effected and a thorough and rapid absorption of the mercury from the air results. This conception is supported by the observation of Göthlin[9] that when the concentration of mercury vapor in the air does not exceed 0.25 mg. per cubic meter it is practically all absorbed.

Excretion of Mercury. The excretion of mercury takes place through both the urine and feces and in approximately equal amounts. A small amount of mercury appears also in the saliva and sweat, as well as in the bile and in the gastric and intestinal juices. The excretion begins within a few hours and, after a single dose, lasts from 1 to 2 weeks; after long-continued administration the excretion continues intermittently for many months. The tardiness of complete elimination appears to be due to the formation of deposits in various organs, especially the kidneys and liver. In these organs the mercury appears to be quite firmly bound, forming deposits from which traces of the metal may be mobilized long after the administration is discontinued.

Symptoms of Chronic Poisoning. The inhalation of mercury vapor in high concentrations results in a metallic taste in the mouth and some irritation of the throat. These symptoms do

not appear in exposures to low concentrations. In chronic poisoning the main symptoms are salivation, stomatitis, nervous disturbances and, in severe cases, damage to the kidneys and nutritional disorders. The patient complains of pain in chewing at a time when all other objective symptoms, except increased salivary secretion, are absent. The gums loosen from the teeth, become red and swollen, and bleed easily. A thin, pussy exudate may flow from under the reddened edges of the gums. The entire mucous membrane of the mouth becomes involved and turns a peculiar copper color. On the surfaces of the cheeks and lips, sharply defined yellow ulcers develop. The stomatitis is associated with swollen lymph and salivary glands. In severe cases the buccal inflammation may result in the teeth loosening and falling out, in necrosis of the jaw and in the consequent undermining of the general health. Mercurial stomatitis is usually associated with minor digestive disturbances, such as loss of appetite and diarrhea.

The most striking symptom of chronic mercury poisoning is the psychic disturbance *Erethismus mercuralis*. This consists of a peculiar form of excitement and timidity. In severe cases, the patient develops a high degree of self-consciousness and embarrassment, so that in the presence of strangers he is unable either to speak or to act normally. His disposition is changed so that he becomes excitable and nervous; there is sleeplessness or unpleasant dreams and headache. In mild cases the psychic changes are less marked and the patient merely complains of lassitude, fatigue and nervousness.

A further involvement of the nervous system is evident in the development of mercurial tremor. This begins with a slight twitching of the face and a more distinct trembling of the fingers. As the poisoning increases, the trembling increases in intensity and finally extends to all parts of the body. With the progress of the condition the patient loses more and more the control of his muscles and the tremor presents a distinct intentional character; thus it appears in greatly accentuated form when he tries to perform some act, such as that of lifting a glass of water to his mouth. When at complete rest the patient does not tremble. He can perform heavy rough work, but he is unable to perform delicate work requiring finer muscular movements. Since the tremor is initiated by movement, it becomes difficult, in very

severe cases, for the patient to walk unaided. Ataxia is, however, never due to this cause. Pain in the joints and extremities is common in chronic mercurial poisoning; paralysis and peripheral neuritis also occur in rare cases.

The stomatitis, erethism and tremor characteristic of chronic mercurial poisoning are not always, or usually, present simultaneously in all cases, nor to the same degree. Stomatitis is particularly evident in those cases in which the mercury has been absorbed over a comparatively short period; the same is true of the erethism. Tremor may occur without either of the other symptoms in cases in which the absorption has occurred very slowly over a long period of time. In these cases the other symptoms readily develop from increase in the severity of exposure. The first symptom of erethism is an increase in the tremor when the patient is under observation.

Treatment and Prevention. The treatment of chronic mercurial poisoning consists of terminating the exposure and, in general, hygienic and tonic measures. It is very doubtful whether medicinal treatment materially influences the course of the disease. Potassium iodide and baths are customarily tried with the intention of hastening the elimination, but they are of doubtful benefit.

Prophylaxis against poisoning with mercury vapor consists of limiting the area of mercury exposed to the air. Much can be accomplished along these lines by careful handling of the substance and particularly by avoiding spilling it upon the floors of workrooms. Raised edges around all sides of the tables or benches upon which mercury is handled prevent the mercury from being scattered about in a fine state of division. The floors should be made of smooth, impervious material free from cracks and should slope slightly to a collecting trough and basin. Wooden or cement floors should not be permitted. All vessels containing mercury should be kept covered as much as possible. The ventilation should also be very thorough in rooms where mercury is exposed and particular attention should be paid to maintaining a low general temperature to limit the volatilization of the metal.

Where exposure to mercury is unavoidable, the dental and oral hygiene of the workers should be closely supervised and enforced. The teeth should be brushed twice daily. They should

be examined at regular intervals and all carious teeth removed or repaired. There should also be a general medical examination at least every six months. Persons suffering from tuberculosis, or those who have had it, should be excluded from any employment involving the constant and extensive use of mercury. It is also advisable to exclude those with poor kidney function or pyorrhea alveolaris. Women of child-bearing age and young persons of both sexes should also be excluded as they are particularly susceptible to mercury poisoning.

Phosphorus

White phosphorus volatilizes slowly at room temperature. The vapor given off is partially oxidized in the air so that the fumes consist largely of phosphoric and phosphorous oxides together with some phosphorus. Of these three, the phosphorus alone appears to be toxic. There is a great difference in solubility between phosphorus and its oxides. The element itself is only slightly soluble and is probably absorbed largely through the lungs; the oxides which readily react with water are taken out of the air by the moisture in the mouth and upper respiratory passages and are there converted into phosphoric and phosphorous acids.

Toxicology. When elemental phosphorus is absorbed, it is believed to be carried in the blood unchanged. Phosphorus in small quantities, absorbed daily over a long period, exerts a destructive action on the bones. Different authors present widely different views of the fundamental nature of this action. It appears to be essentially a disturbance in the nutrition of the bones which renders them more than normally fragile; and even more important, it greatly diminishes the resistance of the bones to infection by organisms which induce necrosis.

So-called "spontaneous" fracture, the result of the fragility of the long bones, may occur in persons who have undergone prolonged poisoning by the fumes of white phosphorus. The lesion which especially characterizes phosphorus poisoning is necrosis of the jawbone, the so-called "phossy jaw." This necrosis and the accompanying conditions result from infection of the jawbone with organisms from the mouth. The entrance of bacteria is usually effected through a carious tooth or an injury in the gum. Phosphorus does not directly cause necrosis of the bone, but it

lowers its resistance to infection and prevents it from healing. The necrosis in some instances extends to the complete destruction of both jawbones. The particular election of the jawbones for necrosis is not due to a special selective affinity of phosphorus for these structures, but to the fact that these bones, more than any others, are exposed to microörganisms.

As phosphorus vapor has but one action in the body, that of lowering the vitality of the bones, both the necrotic and cachexial symptoms, which may accompany the weakening of the bones, are due to infection. The absorption of material from the necrotic and abscessed areas in the jaw is detrimental to the general health. Death from chronic phosphorus poisoning results from the spread of this infection. Among those seriously affected the mortality ranges between 15 and 20 per cent. The altered nutrition of the bones is apparently a change which persists for a long time. Cases have been reported in which the jawbone became infected and necrosis developed several years after the exposure to phosphorus had been discontinued. More often, after the patient is removed from phosphorus fumes, the necrosis ceases and in time heals, although often with great disfigurement.

The symptoms of phosphorus poisoning usually commence with a toothache arising from an abscess at the root of a tooth. The wound left by extraction heals incompletely. Suppuration develops, followed by abscess formation, offensive breath, discharge of pus from fistulas and gradual destruction of the bone.

Occurrence of Phosphorus Poisoning. Only a small proportion of individuals exposed to the fumes of white phosphorus develop "phossy jaw." The number of cases of poisoning and death which result is small in comparison with many other poisons common in industry, such as lead or carbon monoxide. Nevertheless the intense suffering, prolonged course and great disfiguration from phosphorus poisoning created a strong popular feeling against its use. In consequence, Finland abolished the use of white phosphorus in the manufacture of matches in 1872, and by 1906 practically all European countries had forbidden the manufacture or importation of white phosphorus matches. In 1909 the United States imposed a tax on these matches which resulted in their manufacture from the harmless sesquisulfide of phosphorus. As a result of this legislation, poisoning from the fumes of white phosphorus has been largely

eliminated. A few cases still occur in plants producing white phosphorus or in the conversion of the white to the comparatively harmless red phosphorus. The manufacture of phosphor-bronze is attended with some danger from phosphorus poisoning.

The treatment of phosphorus poisoning consists in terminating the patient's exposure to the fumes and in surgical treatment of the necrotic bone and abscesses.

Organometallic Compounds

The toxicology of the volatile organometallic compounds has been little studied. As a rule, their action depends upon that of the metal with which the organic group is combined; but their effects are usually far more acute than those of any other compounds of the metals. Their volatility results in their absorption from the lungs and thus renders the poisoning much more rapid than that ordinarily occurring when salts of the heavy metals are taken in through the alimentary tract. Chronic poisoning by the organometallic compounds is essentially similar to that induced by the corresponding heavy metals.

A number of organometallic compounds have been used in chemical warfare; their irritant action is primary and their systemic action secondary. As examples, there are methyl, ethyl, and phenyldichloroarsine. The halogen they contain contributes mainly to the irritant action. Acute poisoning from organometallic compounds, notably tetraethyl lead, may occur in industry. More commonly the poisoning is chronic in its nature.

Diethylarsine. Diethylarsine, boiling point 105° C., is said to arise from the action of the mold, *penicillium brevicaule,* growing upon wallpaper printed with arsenical colors. The effects of this compound usually appear as a mild chronic form of arsenical poisoning marked by vague disturbances of nutrition. One acute, but not fatal, case has been reported in which the symptoms appeared 9 hours after the exposure and were largely gastrointestinal.

Tetraethyl Lead. Tetraethyl lead, boiling point 200° C., is widely used as an anti-detonant for internal combustion engines. The danger of poisoning occurs particularly during the manufacture of the compounds, from which several deaths have already occurred, and in the process of blending it with gasoline. Poi-

soning may occur, to a less extent, among those handling the blended gasoline. Tetraethyl lead may be absorbed through the skin, and the vapors through the lungs.

In acute poisoning, lead encephalopathy may develop with symptoms of increased intracranial pressure, meningeal irritation and acute mania. Chronic poisoning by tetraethyl lead resembles the ordinary and far more common chronic form of lead poisoning from paint and lead dusts, and is characterized by nutritional disturbances, paralysis of motor nerves and increased susceptibility to such diseases as pyorrhea and tuberculosis.

Nickel and Iron Carbonyl. Nickel carbonyl is formed during the purification of nickel by the Mond Process. A current of carbon monoxide is passed over finely divided nickel; the nickel carbonyl thus formed is then decomposed by heat and nickel liberated. When inhaled, nickel carbonyl causes irritation of the lungs, in some cases leading to edema or pneumonia. Besides this local action there are sometimes disturbances of the central nervous system, such as convulsions and delirium. The amount of carbon monoxide liberated in the body by the decomposition of the carbonyl is too small to play more than an insignificant part in the poisoning. Slight symptoms, such as dyspnea and giddiness, develop when a high concentration of nickel carbonyl is inhaled; the symptoms pass off when the patient is removed to fresh air. After 12 to 36 hours the signs of lung irritation appear, as in the case of other slightly soluble irritants such as phosgene. In fatal cases death occurs from the fourth to the eleventh day after exposure.

Nickel carbonyl is said [10] to be at least 5 times as toxic as carbon monoxide; a concentration of 180 [11] parts per million is said to kill animals after 1 hour of exposure (approximately 10 times the toxicity of carbon monoxide).

Volatile compounds, such as iron tetracarbonyl and pentacarbonyl, are formed when carbon monoxide is passed over finely divided iron. To a small extent they may be formed during the passage of illuminating gas through iron pipes. The toxicity is similar to but somewhat less than that of nickel carbonyl.[10] Other metals than nickel and iron may form volatile carbonyls; most notable are chromium and molybdenum.[12]

Inorganic Hydric Compounds

The hydric compounds of arsenic, phosphorus, sulfur and selenium have a poisonous action different from their inorganic elements. All these compounds are highly toxic.

Hydrogen Arsenide-Arsine. Arsine is formed whenever nascent hydrogen is produced in the presence of a soluble compound of arsenic. The lead, zinc, copper and antimony used commercially often contain arsenic, as does iron obtained from pyrites. Commercial sulfuric acid made by the chamber process is likewise often contaminated with arsenic, and if this variety of acid is used to make hydrochloric acid the latter also becomes contaminated. Arsine is liberated when an acid acts upon a metal if either contains arsenic, as in the production of hydrogen by the action of hydrochloric acid on zinc. The poisoning which sometimes results is often mistakenly attributed to acid fumes. Poisoning by arsine may occur in those engaged in the manufacture and use of hydrogen for filling balloons when the gas is made from metallic zinc and hydrochloric acid. It may occur also in those who are engaged in charging electric storage batteries.

Toxicology. The specific action of arsine arises from its affinity for the hemoglobin of the blood corpuscles. On entering the blood stream, arsine is taken up by the hemoglobin forming a compound with this substance. The arsenic in the combination is gradually oxidized to arsenic oxide. Hemolysis occurs at the time of this formation of arsenic oxide within the corpuscles.

The symptoms of acute arsine poisoning result from the hemolysis of the red blood cells and arise mainly during excretion of the hemoglobin from the disintegrated corpuscles. The anemia resulting from the loss of red cells also contributes to the symptoms.

Hemoglobin, methemoglobin, hematin, and occasionally blood itself, are passed in the urine. Sometimes, however, the urine is suppressed owing to the tubules being plugged with the debris of the corpuscles. Jaundice develops from the formation of an excess of bile pigment and in severe cases is extreme; the red cells may fall below a million per cubic millimeter of blood. Many of the fatal cases show edema of the lungs, but it is uncertain whether this condition results from a primary irritation or is secondary to failure of the circulation. The symptoms of acute

poisoning usually develop a few hours after exposure to the gas. They begin as an indefinite feeling of illness and weakness, followed by nausea and vomiting with epigastric pains. In severe cases, the vomiting becomes continuous and the vomitus contains blood. Jaundice develops to a degree depending upon the severity of the poisoning. Cyanosis may also appear. Death from acute arsine poisoning occurs in from 2 to 6 days. The mortality of the recognized cases of arsine poisoning reported in the literature is approximately 30 per cent. Among those surviving these acute effects, symptoms more closely resembling those from ingestion of arsenous oxide may develop. The kidneys are particularly affected and death may follow.

Table 42. Physiological Response to Various Concentrations of Arsine.[5, 13, 18]

	Parts of arsine per million parts of air
Maximum concentration allowable for prolonged exposure	1
Slight symptoms after exposure of several hours	3 to 10
Maximum concentration that can be inhaled for 1 hour without serious consequences	6 to 30
Dangerous after exposure of 30 minutes to 1 hour	16 to 60
Fatal after exposures of 30 minutes	250

Chronic or subacute poisoning by arsine has been observed. In this condition both hemoglobin and albumen may appear in the urine and the skin may show some yellowness. The diagnosis is made from the presence of arsenic in the urine. The arsenous oxide found in the corpuscles, and liberated by their destruction, may possibly play a part in chronic poisoning by arsine in addition to the hemolytic activity of the gas.

Hydrogen Phosphide. Hydrogen phosphide, or phosphene, is evolved when water acts on calcium phosphide. The latter substance is sometimes used to charge marine buoys which, by the flare of the spontaneously inflammable phosphene, indicate their position on the water. Aside from this use, phosphene is not generated intentionally in industrial procedures. Calcium phosphide, however, is frequently a contaminant of calcium carbide and phosphene appears in the acetylene generated by contact with water. Ferro-silicon also contains phosphide as an impurity and phosphene is evolved when the alloy is moistened. In most cases of phosphene poisoning recorded in the literature the gas has been evolved from this source.

Toxicology. The toxicology of acute poisoning by phosphene has not been fully worked out. It does not alter the blood and its effects are apparently exerted largely through the central nervous system. Some inflammation of the lungs results from its inhalation; beyond this, no changes in the body are demonstrable.

The acute action of phosphene does not resemble that of phosphorus. Instead, there is marked dyspnea, purgation, weakness, tremor, and finally, violent convulsions and death. The symptoms in many ways resemble those resulting from food poisoning and have been mistaken for them. Mild cases recover without after-effects.

Prolonged exposure to small amounts of phosphene is said to give rise to chronic symptoms similar to those of phosphorus poisoning.

Table 43. Physiological Response to Various Concentrations of Phosphene.[5, 13–14, 18–20]

	Parts of phosphene per million parts of air
Maximum concentration allowable for prolonged exposure	2
Slight symptoms after exposure of several hours	7
Maximum concentration that can be inhaled for 1 hour without serious consequences	100 to 200
Dangerous after exposure of 30 minutes to 1 hour	400 to 600
Fatal after exposure of 30 minutes	1,000 to 2,000

Hydrogen Sulfide. Hydrogen sulfide is frequently evolved from the decomposition of organic material; if the material is held in containers which prevent the rapid escape of the gas, poisonous concentrations are built up. Poisonings from this cause occur in tanneries, fat rendering plants, glue factories and sewers.

Hydrogen sulfide is liberated in the course of chemical reactions occurring in the manufacture of chemicals such as dyes, sulfur monochloride, and barium carbonate made from the sulfide. The gas may also be present in the air of mines and is produced by the decomposition of pyrites. It is also present in the distillation of petroleum oil containing sulfur, in the handling of certain slags, and in the gas and coal industries. In the latter industries the hydrogen sulfide is encountered in cleaning out the iron oxide beds used for purification of the gas.

Toxicology. Hydrogen sulfide is primarily an irritant gas; the systemic action which, in acute poisoning, overshadows the

irritant action, results from the absorption of the products arising from the neutralization of the sulfide by the surface tissues of the respiratory tract. Hydrogen sulfide is discussed as an irritant gas in Chapters 8 and 9.

When hydrogen sulfide is brought into contact with moist tissue, it combines with the alkali present and sodium sulfide is formed. Irritation is produced both by the abstraction of alkali from the cells and by the sulfide, which is caustic. Part of the alkali sulfide is absorbed through the membranes of the respiratory tract and enters the blood stream. It is there hydrolyzed, with liberation of hydrogen sulfide. In the presence of oxygen the hydrogen sulfide is rapidly oxidized to the harmless sulfate. The systemic action of hydrogen sulfide is occasioned by the unoxidized hydrogen sulfide temporarily held in the blood.

Hydrogen sulfide is generally credited with forming a combination with the hemoglobin of the blood and inducing asphyxia from this cause. In fact, however, it does not combine with oxyhemoglobin, but only with methemoglobin.[21] Since this substance is normally present in the blood in only small amounts, no sulfur compound is formed with the hemoglobin as a result of inhalation of the gas. On the other hand, sulfmethemoglobin appears in the blood of cadavers and gives a bluish green color to the vessels about the intestines. The sulfmethemoglobin then formed results from post-mortem changes involving the formation of methemoglobin and its subsequent combination with the hydrogen sulfide liberated by the decomposition of the material in the intestines.

Sulfur compounds of hemoglobin are occasionally seen in the blood of persons who are not exposed to hydrogen sulfide; in fact, sulfmethemoglobinaemia is classed among the enterogenous cyanoses.

Free hydrogen sulfide in the blood acts upon nervous tissue throughout the body and causes systemic poisoning.[21] In small amounts the sulfide depresses the nervous system; in larger amounts it stimulates, and in very large amounts it paralyzes the nervous system. Bradycardia, convulsions, respiratory stimulation and paralysis all appear as results of this action of hydrogen sulfide upon the nervous system.

Death in acute hydrogen sulfide poisoning results from failure of respiration and the consequent asphyxia. This respiratory

failure is occasioned through two separate processes depending upon the concentration of the gas inhaled.[21] Moderately high concentrations may cause hyperpnea by stimulating the respiratory center. The excessive breathing lowers the carbon dioxide content of the blood and apnea vera results. Very high concentrations cause respiratory paralysis. Spontaneous breathing does not return after the paralytic form of failure, unless artificial respiration is applied. After the overstimulated form of failure, breathing may return spontaneously.

The action of hydrogen sulfide upon the nervous system is exerted only during the time the free hydrogen sulfide is in the blood and to a degree depending upon the concentration present. The symptoms of acute poisoning develop immediately on the inhalation of the gas; but because of its rapid oxidation in the blood they pass off when the inhalation ceases. Death in acute poisoning is as rapid as from poisoning by cyanides; a man inhaling a high concentration drops dead. Hydrogen sulfide is in a high degree a non-cumulative poison; thus if the victim is revived there are no systemic sequelae. In less severe poisoning, convulsions and dyspnea are marked symptoms. In subacute or chronic poisoning the main symptoms are those of irritation, particularly of the eyes and, to a less degree, of the respiratory tract. In some cases the depressing action of the gas is also evidenced in a mild degree of malaise.

Table 44. Physiological Response to Various Concentrations of Hydrogen Sulfide.[5, 13, 14, 18, 19, 21, 22, 23]

	Parts of hydrogen sulfide per million parts of air
Maximum allowable concentration for prolonged exposure	20
Slight symptoms after exposure of several hours	70 to 150
Maximum concentration that can be inhaled for 1 hour without serious consequences	170 to 300
Dangerous after exposure of 30 minutes to 1 hour	400 to 700
Fatal in exposure of 30 minutes	600

The treatment of acute hydrogen sulfide poisoning consists of restoring breathing by means of manual artificial respiration combined with inhalation of oxygen mixed with carbon dioxide.

Hydrogen Selenide. The exposure of animals to sufficiently high concentrations of hydrogen selenide results in damage to the liver and enlargement of the spleen. Death occurs several

days after exposure. Guinea pigs exposed to 175 parts of hydrogen selenide in a million parts of air for 10 minutes die within 5 days; more than 90 per cent of the animals exposed to 13 parts per million for 30 minutes die within 30 days; and all animals exposed to 6 parts per million for 60 minutes die within 25 days. Obviously this substance is highly toxic and is especially dangerous because of the delayed effects. No estimates have been reported of safe concentrations for prolonged and repeated exposures.

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Chapter 17

Methods of Resuscitation and Comparison of Various Treatments. First Aid

The various types of gases induce a number of forms of poisoning and inflict widely different injuries. The treatments differ correspondingly; a treatment that is best suited for one kind of poisoning and injury may be quite ill suited and even positively harmful for others. Even within a single class of gases there are sufficient degrees of difference in the character of the poisoning to justify specific and widely differing methods of resuscitation and after-care.

In the chapters describing the various classes of gases and their outstanding members, the appropriate treatments have, in most cases, been more or less fully described. The object in this chapter will be to bring out the differences and contrast the prime features in these treatments. In such comparisons and contrasts a certain amount of repetition of earlier discussions is necessary.

Treatment of Poisoning by Asphyxiants

As the sole action of the simple asphyxiants, discussed in Chapter 10, is to exclude oxygen from the lungs, their effect is sufficiently like that of drowning to make immediate manual artificial respiration in pure air the prime means of resuscitation. Simultaneous inhalation of a mixture of oxygen and 7 to 10 per cent carbon dioxide is, however, an accessory which is helpful after short periods of severe anoxia and even more valuable after prolonged periods of only moderately intense anoxemia: it prevents postasphyxial damage.

As the action of carbon monoxide, described in Chapter 11, is exerted through its combining with the hemoglobin of the blood, the object of treatment is not merely the prevention of immediate death by restoration of breathing, but also the rapid elimination of the carbon monoxide. For this purpose inhalation of a mixture of oxygen and 7 to 10 per cent carbon dioxide should be administered immediately, along with manual artificial respira-

tion if the patient has stopped breathing. The artificial respiration serves to introduce the resuscitant gas mixture into the lungs and thereby starts natural breathing. But artificial respiration should be discontinued as soon as natural breathing is developed, and treatment thereafter should be confined to inhalation.

As the action of hydrocyanic acid is exerted neither in the lungs nor, to any considerable extent, in the blood, resuscitation from severe poisoning can be effected neither by artificial respiration alone nor by inhalation of oxygen and carbon dioxide alone, nor even by the two together. Instead, an inhalation of amyl nitrite should be administered immediately by one man and, if the victim has stopped breathing, artificial respiration should be performed by another. The patient should be kept in absolute rest for at least an hour, with renewal of amyl nitrite and artificial respiration if needed, until the post-toxic nausea and other effects have passed off.

Treatment of Poisoning by Irritant Gases

The action of irritant gases, described in Chapters 8 and 9, is of a wholly different sort from that of the asphyxiants. It is true that both classes cause death by asphyxia; but the manner in which the asphyxia is brought about is fundamentally different. The asphyxiants, as stated above, do no damage to the lungs. Those organs remain fully capable as avenues for the intake of oxygen and the elimination of carbon dioxide. The lung irritants, on the contrary, cause such damage to the lungs, and the lining membranes of the airways become so swollen and thickened, and exude such quantities of fluid, that the diffusion of oxygen into the blood becomes impossible and the patient drowns in his own lymph.

Here, obviously, is a condition in which administration of oxygen, either under a tent or by nasal catheter, is called for, but the use of carbon dioxide is contraindicated. The patient, already gasping for breath, should not be stimulated to yet greater respiratory effort. On the contrary, the prime feature of treatment for the pulmonary edema induced by the irritant gases is absolute rest. Even the exertion of sitting up in bed to permit the physician to listen to the lungs may cause collapse and immediate death. The dispute among some authorities as to whether too high a concentration of oxygen may itself irritate the

lungs is unimportant. The concentration should be sufficient to prevent cyanosis.

Treatment of Poisoning by Anesthetics

The essential points in the treatment of acute poisoning by the anesthetic gases are first, to keep the patient alive until the anesthetic in the blood is eliminated, and second, to get it eliminated as quickly as possible. Death usually results from paralysis of the respiratory center; the heart generally continues to beat for a few minutes after breathing has stopped. The course of treatment is the same as for carbon monoxide poisoning.

Treatment of Poisoning by Nitrites

The action of nitrites upon the blood ceases as soon as the patient is removed from the poisonous atmosphere. The conversion of oxyhemoglobin to methemoglobin, that has already occurred, is treated by the inhalation of oxygen under a tent or by nasal catheter and, if severe, by blood transfusion also.

Treatment of Poisoning by Hydrogen Sulfide

Sudden acute poisoning by hydrogen sulfide induces a failure of respiration which should be treated by manual artificial respiration and inhalation of carbon dioxide and oxygen. Chronic poisoning requires termination of exposure by change of occupation.

Some Additional Remarks

The inhalational treatment first developed for resuscitation from carbon monoxide is a useful therapy also for a wide range of intoxications. But it should be emphasized that it is not applicable to poisoning by all noxious gases and vapors.

The transfusion of blood from an unpoisoned donor is effective in poisoning by the organic nitro compounds and arsine. Transfusion has also been used for carbon monoxide poisoning, but it can be of no benefit unless it is performed within a few minutes after the victim is removed from the gaseous atmosphere; and it is in fact never performed so soon. At later periods the elimination of carbon monoxide has already progressed to a point which renders transfusion unnecessary; the condition of the patient is then wholly the expression of the secondary effects of

asphyxia, for which transfusion is useless. At that time the intravenous injection of hypertonic saline may be of some benefit in relieving the headache and other symptoms.

Bleeding, alone or combined with infusion of saline, has been suggested as a measure of relief in edema of the lungs caused by irritants, but it is probable that such measures are of no benefit and may do harm.

Amyl nitrite has been employed in resuscitation; but, except in cases of poisoning by cyanides, it is harmful: the respiratory stimulation which it induces results from a fall in blood pressure.

Emetics have been given in gas poisoning, but are obviously useless when the toxic substance has been absorbed through the lungs.

No hypodermic injection of any known drug is of the slightest benefit in gas poisoning, or in general in first aid for accidents involving cessation of respiration. The once common practice of injecting camphor dissolved in ether is certainly not beneficial and may be distinctly harmful.

Manual Artificial Respiration

The principal methods of manual artificial respiration are those of Silvester, Howard, Nielsen, and the prone pressure method of Schafer. Their distinctive features are as follows:

Silvester Method. The subject is laid on his back. The operator, kneeling in front of the subject's head, grasps his arms at the elbows and first draws them forward beside his head and then thrusts them back beside and over his chest, which is firmly compressed to induce expiration. These maneuvers are repeated 10 or 15 times a minute. The exertion involved is considerable and the operator is soon exhausted. Yet, owing to the belief that drawing the arms forward expands the chest and induces inspiration, the Silvester method is still generally preferred in most non-English-speaking countries.

Howard Method. The subject is laid on his back. The operator at his side presses upon the sides of his chest 10 or 15 times a minute, with pauses of 2 to 4 seconds between compressions. This method is commonly used—indeed, it is generally the only one that can be used—in the surgical operating room.

Nielsen Method. The subject is laid on his stomach. The operator, kneeling beyond his head, first presses downward on

his shoulders to induce expiration and then lifts the shoulders—a maneuver which is claimed to induce inspiration.

Schafer or Prone Pressure Method. The subject is laid on his stomach. The operator kneels, straddling the subject's hips. With his hands on the subject's back, but with his elbows held straight, the operator leans forward so as to bring the weight of his body upon the subject's chest so as to compress it, press the diaphragm headward and induce expiration 10 or 15 times a minute. Nothing in this method is done to induce inspiration; but it is extremely important to allow sufficient time between compressions for the chest to reëxpand as fully as it will of its own elasticity. To facilitate this reëxpansion, it was suggested by Henderson that the subject's arms should be placed as far forward as possible, and one of them bent at the elbow with the head resting on the forearm. The prone pressure method, so modified from Schafer's original directions, is now used in all English-speaking countries to the virtual exclusion—except in the operating room—of all other manual methods.

In addition to these four methods there are numerous others, or modifications and variations of these four, in which the subject is rolled from side to side, his arms pulled this way and that, his shoulders or trunk lifted, his hands tied and elbows lifted (Hederer), and so on.

The advantages of the method of Schafer are that it is simple to learn, much less exhausting to apply, and therefore applicable by a single operator for a much longer time than any of the others. The advantage claimed for all the other methods by their inventors is that they actively induce inspiration, and over these claims an extensive literature has grown up. But these claims lose all validity when subjected to critical examination and experimental test.

This experimental test consists in applying artificial respiration to normal men and measuring the volume of air that can be moved in and out of the lungs and through a gas meter connected with a mask or mouthpiece. The subjects are directed to make no effort to breathe, but to submit themselves passively to whatever manipulation the operator applies. Some investigators using this test have measured only the first few breaths and have claimed that the volume of air moved by their technique is

greater than that by the prone pressure method. But this increase is really due only to the discomfort induced in a conscious subject under rough handling.

Investigations by the authors of this book, on the contrary, have shown decisively that when the volume of air which a normal man breathes in natural respiration is first measured, and then the volume of lung ventilation that can be induced and maintained for several minutes by any manual method whatsoever is also measured, the two measurements are always essentially the same in liters of air per minute. In other words, every manual method that involves rhythmic compressions of the chest—as all do—when applied for a time sufficient to afford a fair test, induces in a normal man a volume of lung ventilation closely approximating that of natural breathing. But no method, no matter how vigorously applied, ever produces, or can produce, any considerable degree of overventilation for more than a few seconds. And the truth of this statement is demonstrated by the finding that when the artificial respiration is stopped, the subject, after an apnea of only a few seconds at most, immediately begins to breathe again for himself. No method yet proposed is capable of promoting inspiration beyond the natural tonic expansion of the chest.

The Principle Determining the Volume of Both Natural and Artificial Respiration

From these facts it follows that in a normal man under experimental artificial respiration it is the man's own metabolism that determines how much pulmonary ventilation he needs, and this is the amount that can be, and is all that can be, induced by any method of manual artificial respiration. Evidently, also, it is under essentially the same control as natural breathing, the control exerted by the carbon dioxide and oxygen of the blood acting on the respiratory center. It is now recognized that the influence of the respiratory center on the diaphragm and thoracic muscles is largely that of controlling tonus, and it is the tonus of muscles that affords their elasticity, so called—not a mere mechanical elasticity but really an entirely vital property. It is largely for this reason that inhalation of carbon dioxide increases both the volume of natural breathing and the volume of pulmonary ventilation under manual artificial respiration

both of a normal man and of one who is unconscious and apneic. Conversely, if a man has overbreathed and has thereby decreased the carbon dioxide in his blood just before he receives manual artificial respiration, very little pulmonary ventilation can be induced. The tonus of the muscles is decreased, and after the chest is compressed it does not expand again with normal vigor. In deep asphyxia a similar decrease occurs. A few minutes after death the chest does not expand at all; tonicity and elasticity are gone. On the other hand, as has recently been shown by Lougheed, Janes and Hall in their important studies on resuscitation from drowning, the efficiency of manual artificial respiration is much increased and the patient is more rapidly resuscitated if the artificial respiration is supplemented by the simultaneous inhalation of carbon dioxide and oxygen. The influence of carbon dioxide on muscle tonus is potent also for the support of the venous return of the circulation and the efficiency of the heart.

The principle determining the efficiency of all methods of artificial respiration is thus found to be essentially the same as that controlling the volume of natural breathing. It is the influence of the blood gases on the respiratory center that largely determines the tonus of the respiratory muscles; and this tonus is a principal factor in the volume of lung ventilation both in natural breathing and in artificial respiration. Because of this principle, no manual method—neither prone pressure nor any other—can induce any larger volume of lung ventilation than the tonic elasticity of the body at the moment permits. The reason is that, if any degree of overventilation is induced for even a few seconds, the decrease of the carbon dioxide in the blood induces a decrease in the tonic elasticity of the body with a corresponding decrease in the amount of ventilation that can be produced.

Breathing Machines

In physiology laboratories animals under experiment, after being deprived of the capacity to breathe normally, either by some drug or by section of the vagus nerves, are kept alive by means of artificial respiration. It is generally administered with an air pump or bellows. Similarly, in cases of respiratory paralysis at the hospital the patient is kept alive for long periods

by means of the Drinker respirator. Neither in the laboratory nor in the hospital, however, are such appliances used for the purpose—strictly speaking—of resuscitation. They do not induce a rapid recovery of the capacity in the animal or man to breathe for himself; indeed, they are not so intended. They maintain life but do not restore the animal or man to normal condition—at least not quickly—as, for instance, does resuscitation from drowning or electric shock by manual artificial respiration.

It is a surprising fact, yet quite certainly true, that even a rather crude pump or bellows, provided it induces only inspirations under any moderate pressure, always administers almost exactly the amount of pulmonary ventilation that the respiratory metabolism—the exchange of oxygen and carbon dioxide—of the animal requires. With the Drinker respirator also no considerable degree of adjustment is needed; yet the lungs of the patient are neither overventilated nor underventilated. The same protective reaction comes into play as that described in relation to manual artificial respiration. Under the influence of the blood gases the respiratory center adjusts the tonic elasticity of the diaphragm and thoracic muscles and thus the amount of the recoil of the chest, so that just the required amount of pulmonary ventilation is obtained—no more, no less.

Nevertheless from time to time inventors with more knowledge of machine design than of the physiology of respiration have attempted to introduce such breathing machines as the pulmotor, lung motor and various so-called resuscitators. All such apparatus are designed on the so-called pulmotor principle of suck and blow mechanical ventilation. Instead of affording merely a rhythmic succession of inspirations alternating with pauses to allow the elasticity of the chest to produce expirations, they induce, or attempt to induce, both inflation of the lungs by positive air pressure and also deflation by negative pressure. And the forced deflations—unless the negative pressure is kept very low indeed—may induce overventilation, injure the lungs and do serious harm. For purposes of sales demonstration such apparatus make a rubber bag or doll "breathe" quite realistically; and if applied to a normal man, may coöperate with his natural breathing quite satisfactorily. But when they are applied to a victim of drowning or electric shock or gas asphyxia-

tion, instead of operating at a rate approximating that of normal breathing, they respond to any obstruction in the throat or to relapse of the tongue when the patient is on his back, by reversing their sucking and blowing phases so rapidly that no appreciable movement of the lungs is induced. The inhalator attachments of these so-called resuscitators are also usually quite inadequate.

The decisive objection to all apparatus of the pulmotor and resuscitator type is that the first essential for resuscitation from asphyxia is the immediate application of artificial respiration. And no apparatus can be applied as quickly as can a manual method. For this reason it is probable that mechanical breathing devices have been responsible for the loss of more lives than they have saved. Their use should be strongly opposed.

The Crucial Minutes

In several of the principal forms of acute asphyxia, artificial respiration is the prime means of saving life. This is true particularly in drowning, the apnea of electric shock and the anoxia induced by atmospheres devoid of oxygen in mines, sewers, silos, and holds of ships. It is important to know the length of time within which resuscitation is possible. Certainly resuscitation does not bring the dead back to life. It can be effective only before life is extinct and under complete anoxia it is extinct in a very few minutes.

Few, if any, human cases of asphyxial death or resuscitation have ever been accurately timed, or are ever likely to be timed. But experiments on dogs by many investigators and by many methods have afforded evidence for the following statements:

If artificial respiration is begun after only 2 minutes of complete anoxia—as by submersion in water—life can always be saved.

After 4 minutes, it can nearly always be saved.

After 5 minutes, it can rarely, if ever, be saved.

But after 6 minutes, probably never.

In applying these findings to men it is necessary to take into account the differences in the relation of oxygen consumption and the oxygen reserve in the lungs and blood of men as compared to dogs. But it is probably safe to conclude that in man:

If artificial respiration is begun after only 4 minutes of com-

plete anoxia, unless the man has died of shock or heart failure, life can nearly always be saved.

But after 7 minutes, probably never.

For practical purposes these statements amount to this: If, after a man has been under water or otherwise prevented from breathing for 4 minutes, there is then a delay of more than 2 minutes in starting artificial respiration, the last possibility of resuscitation may have been lost. But this should not deter prolonged efforts to resuscitate; for even if the victim has been in the water for 10 or 15 minutes, he may have got his head above water for one or two breaths.

In relation to electric shock it is noteworthy that, if time is lost in lowering a man from aloft before artificial respiration is begun, few cases are resuscitated, while by contrast, the so-called "pole top" method of artificial respiration, which can be applied in a few seconds, is now properly credited with a number of lives that would otherwise have been lost. The rule should be to apply artificial respiration at the earliest possible moment and to keep it up as long as there is any possibility of success.

Directions for the Prone Pressure Method

The standard procedure for the prone pressure or Schafer method of artificial respiration is as follows:

(1). Lay the patient on his belly, one arm extended directly overhead, the other bent at the elbow, with the face turned to one side and resting on the hand or forearm, so that the nose and mouth are free for breathing.

(2). Kneel, straddling the patient's hips with your knees just below the patient's hipbones or opening of pants pockets. Place the palms of your hands on the small of the patient's back with fingers over the ribs, the little finger just touching the lowest rib, the thumb alongside of the fingers, the tips of the fingers just out of sight.

(3). While counting 1, 2, and with the arms held straight, swing forward slowly, so that the weight of your body is gradually, but not violently, brought to bear upon the patient. This act should take from 2 to 3 seconds.

(4). While counting 3, swing backward so as to remove the pressure.

(5). While counting 4 and 5, rest.

(6). Repeat these operations deliberately, swinging forward and backward 12 to 15 times a minute, thus making a complete respiration in 4 to 5 seconds.

Fig. 7. Artificial Respiration by the Prone Pressure Method.

(7). As soon as artificial respiration has been started, and while it is being continued, an assistant should loosen all tight clothing about the patient's neck, chest, or waist, and wrap the patient warmly with a blanket.

(8). Continue artificial respiration without interruption until natural breathing is restored, if necessary for several hours, or until a physician declares *rigor mortis* (stiffening of the body) has set in. Do not stop merely because he says the patient is

dead; you may be able to revive him. If natural breathing stops, after being restored, use this method of resuscitation again.

Do not apply artificial respiration to a man who is breathing.

The Inhalational Method of Resuscitation

The prime need of an asphyxial patient is a renewed supply of oxygen to his brain; but until he breathes with some degree of vigor little oxygen will reach his lungs. Even pure oxygen administered by means of a mask covering his face does little to relieve asphyxia until it is deeply inhaled. Particularly in carbon monoxide asphyxia it is only by bringing the largest

Fig. 8. Inhalation Combined with Artificial Respiration.

possible mass of oxygen to bear on the blood in the lungs, and continually renewing it with fresh oxygen, that carbon monoxide can be removed with the rapidity that is essential if asphyxia is to be rapidly terminated and postasphyxial damage prevented. It is for the purpose of inducing such full deep breathing that carbon dioxide is administered with the oxygen.

If then the best results are to be attained, the inhalator with which the oxygen and carbon dioxide mixture is administered must meet certain specific requirements. (a) The mask must fit closely and be held tight against the face; and not merely held above the face as is sometimes done by inexperienced operators. (b) The flow of the gas must be regulated, preferably by means

of a stop cock adjusted by hand rather than by an automatic device, to supply the maximum amount that the breathing will take. And (c) there must be no rebreathing, for if any of the gases expired are reinspired the carbon monoxide in such expired and reinspired air opposes the elimination of more of that gas from the blood.

To meet these requirements the authors, at the same time that they introduced the inhalation of the mixture of oxygen and carbon dioxide, designed an apparatus for its administration. This apparatus consists of one or more steel cylinders or bottles

FIG. 9. Diagram of H-H Inhalator.

of the resuscitant gas mixture and a reducing valve. From this valve the gas passes under low pressure through a calibrated needle valve, and then into a collapsible reservoir bag. From this bag the gas is inhaled through a wide rubber tubing attached to a mask held tightly over the patient's face. A check valve opening outward on the facepiece allows the escape of expired air; another lightly weighted check valve placed near the collapsible bag permits the entrance of outside air in case the patient breathes a larger volume than that of the gas passed at the setting of the calibrated needle valve. The air inlet valve has the advantage also of preventing the volume of breathing from

becoming excessive; for when the volume of breathing exceeds the flow of gas, air enters, dilutes the carbon dioxide and diminishes the respiratory stimulation.

In using this inhalator the valve at the top of the steel bottle (or bottles, for there are usually 2) containing the mixed gas is opened, and the pointer of the calibrated needle valve is set at zero. The mask is then put over the patient's face; the lower part well down on the chin and the upper pressed firmly over the nose. As soon as the mask is properly applied the needle valve is turned to admit the mixture of oxygen and carbon dioxide into the bag and so to the mask, at a rate at first of 5 or 6 and then 10 liters per minute. If the man breathes less than the amount fed, the bag stays full; if he breathes more, the bag collapses. As the inhalation proceeds and the volume of breathing increases, the valve is adjusted so that the bag does not quite collapse at each breath. As the stimulating action of the carbon dioxide comes into play, the volume of breathing is increased to 20 or 30 liters. It does not appreciably exceed this volume for the reason that this is the maximum that the inhalator supplies; if the breathing rises above this volume, outside air is admitted through the check valve below the bag and the stimulus to respiration is thus automatically kept from increasing further.

Finally, in connection with the foregoing discussion of methods of resuscitation, mention should be made of intratracheal insufflation of oxygen or oxygen and a low percentage of carbon dioxide. This procedure, which is ideal for application to asphyxia pallida in the newborn and respiratory failure under spinal anesthesia, is, however, quite unsuitable for use outside the hospital.

Practical Rescue and First Aid

The life of a victim of gassing is often in the hands of the first arrival and the outcome depends upon his knowledge of the proper procedure. The doctor who treats the patient after he is taken to the hospital has far less influence on the final outcome.

The first step is to remove the man from the contaminated atmosphere and to bring him as rapidly as possible into uncontaminated and preferably warm air. But the rescuer must be careful not to breathe the gas himself, even for a short time.

No one is immune to the action of noxious gases. The well-intentioned rescuer who walks into an atmosphere of gas and succumbs gives no assistance to the original victim and merely adds to the work of subsequent rescuers. His action is similar to that of a man who cannot swim, but who jumps into deep water because he sees another man drowning. Such procedures are not heroic—they are silly. There are indeed occasional conditions in which it is possible to enter a short distance into air contaminated with gas and to drag out an unconscious man. But it is usually wiser to open the doors and windows from the outside and allow fresh air to sweep the gas from the room before the rescue is made. Otherwise the rescuer should not attempt to enter a gas-filled chamber without having a line tied around him and held by someone outside; if possible, he should wear a canister gas mask or a hose mask. When a rescue is to be made from a mine, the hold of a ship or other place at a distance from the outside air, the rescuer should wear a self-contained breathing apparatus, but he should do so only on condition that he is fully trained beforehand in the use of such apparatus.

If the case is one of carbon monoxide asphyxia, and the patient is not breathing, manual artificial respiration and inhalation of oxygen and carbon dioxide should be administered. In cold weather indoor air is preferable to outdoor. Chilling should be carefully avoided after any form of gassing, as it greatly increases the liability to subsequent pneumonia. The victim should be wrapped in blankets. Hot water bottles and heated bricks are often recommended, but they are more dangerous than beneficial in the hands of the overzealous; a man does not complain of being burned while he is unconscious, but the burns that result from hot water bottles or other heated objects placed next to the skin are, in many cases, the most serious sequel to the gassing.

It is not necessary nor beneficial to the patient, but rather the reverse, to apply artificial respiration to a man who is still breathing. But inhalation of oxygen and carbon dioxide for poisoning by any non-reactive gas, and oxygen alone after exposure to any irritant gas, should be administered at the earliest possible moment.

Artificial Respiration and the Physician

Only in exceptional cases is a physician on the spot or close at hand to take immediate charge of cases of poisoning by a noxious gas. First aid and resuscitation by artificial respiration and inhalation, to be effective, must therefore usually be carried out by the fellow workman who first reaches the victim in a factory or mine, and not a physician. If breathing has stopped and artificial respiration is delayed until a physician can arrive, death may result. Physicians, and particularly surgeons and anesthetists, have occasionally to perform artificial respiration when respiratory failure occurs during anesthesia. With the patient lying on his back on a narrow operating table it is not convenient to apply the prone pressure method, so either the Howard or Silvester method is generally used. These are frequently the only resuscitations that medical men see; and, as they are not called upon to perform artificial respiration by the prone pressure method, they are not, as a rule, familiar with its administration.

When the physician arrives on the scene of an accident, he properly assumes authority. But his lack of training in the treatment of acute asphyxia often leads to deplorable results. A physician who sees many deaths following illness comes to think that when respiration stops the patient is dead, for this is the case in most of the diseases. But it is not true under three important conditions: namely, gas poisoning, drowning, and electric shock. In these conditions the vital engine is merely stalled and needs to be started again by restoring the oxygen and carbon dioxide of the blood requisite for the activity of breathing. It has often happened that the victim of one of these accidents, who might have been restored, has instead been declared dead by a doctor, or sent to a hospital in an ambulance and died on the way. Fortunately nowadays in an increasing number of cases an electric lineman, a Boy Scout or a policeman persists in administering prone pressure artificial respiration and a life is saved.

Medication and After-Treatment

While most forms of medication are of no benefit in poisoning by noxious gases, some are positively harmful. All first-aid workers should be warned never, under any circumstances, to

give anything by mouth to an unconscious man. An unconscious man cannot swallow and the fluid often runs into his windpipe and chokes him. Alcohol in any form is likewise contraindicated; this is particularly true in asphyxia or in poisoning by the anesthetic hydrocarbons. Alcohol intensifies both of these conditions. Both the layman and the physician should remember that while treatment other than artificial respiration and inhalation, however well intended, can generally do little good, it may easily do great harm. Especially after exposure to an irritant gas absolute rest is essential; the slightest movement may cause death.

Harmful Practices

The zealous first-aid worker frequently feels that he must be continually doing something to aid the poisoned man. While his intentions are commendable, the results are often deplorable; such, for example, as tearing the victim's nose off by rubbing his face against a sharp stone or rough planking, or breaking his legs or ribs for the sake of the stimulus of "countershock." First and foremost the first-aider must be gentle; he must remember that he is dealing with a human being who may recover and will not wish to be maimed by his treatment. Next, he should follow the general directions and principles set forth above. If he feels that he must do something more, he may give the patient a cup of black coffee, but only after the patient is fully conscious.

Under no circumstances should a man who has been gassed be allowed to exercise. He must neither walk nor sit up, but must be kept recumbent and as quiet as possible until all symptoms have passed off.

In concluding this discussion of practices which are contraindicated in poisoning by noxious gases and vapors, especial mention must be made of the most reprehensible of all: countershock. Countershock consists in the application of external stimuli to the body as a means of restoring breathing and consciousness. Throwing cold water over a man who is gassed is a form of countershock. Cold water douches have only one place in first-aid treatment and that is for sunstroke. In gas poisoning they greatly increase the liability to pneumonia. The inhalation of dilute ammonia, or smelling salts, is a harmless but

unbeneficial form of countershock. The most brutal form of countershock practised is the beating of the unconscious victim on the soles of the feet with an axe or other heavy instrument, a procedure similar to that used by policemen to awaken tramps. Manual punishment is not resuscitation; it is sufficiently difficult to make the enthusiastic first-aid worker be gentle without suggesting to him that he beat his victim into consciousness. The picture here drawn of the methods of "resuscitation" as sometimes practiced is not overcolored, but is in accord with rather common actual occurrences.

For a fuller discussion of manual and mechanical artificial respiration see:
Henderson and Turner: *J. Am. Med. Assn.*, **116**, 1508 (1941).
For references to all recent literature see:
Karpovich: *Research Quart.*, **12**, 50 (1941).
See also:
Lougheed, Janes and Hall: *Can. Med. Assn. J.*, **40**, 423 (1939).
Henderson: *Science*, **95**, 539 (1942).

Chapter 18

Prevention of Poisoning by Noxious Gases

In order to prevent poisoning by noxious gases three requirements are essential: (1) The conditions under which each gas occurs must be known and also the physiological effects induced by various concentrations and by various durations of exposure. (2) Workrooms must be ventilated so as to prevent accumulation of concentrations of gas that are known to be harmful. And (3) if the contamination cannot be avoided, those who are exposed must be equipped with gas masks or other apparatus to protect them against inhalation of the gas.

Inadequacy of Legal Protection Against Noxious Gases

At the present time there is little Federal or state legislation applying specifically to the manufacture, handling and sale of substances which are poisonous, other than food and drugs. This lack of legal protection against harmful gases is the more striking when it is compared with the full and explicit regulations for inspection and analysis applying to the shipment and sale of food products. The public is effectively protected against food poisoning, and even against materials which are only mildly detrimental, if they are to be taken into the body through the alimentary tract. On the other hand, the injury to the public health induced by detrimental materials, even the most poisonous, which enter the body through the respiratory tract, is not generally recognized. For example, the addition of benzoate of soda or artificial coloring matter to a food product must be indicated by a label on the container; but the presence of benzene in a quick-drying paint, or of carbon disulfide or tetrachloroethane in a solvent, is often disguised under a trade name. Yet benzoate of soda in food can impair health only slightly, if at all, whereas benzene in paint has often caused the death of men who have used it in a confined space for only a few hours.

The importance of careful control is illustrated by a dangerous organometallic compound, tetraethyl lead, which is now

blended with gasoline and sold throughout the country. At first, it was handled carelessly and caused a number of deaths; but since strict regulations and warnings have been applied, casualties have ceased. It is noteworthy that some other countries are prohibiting the use of lead paints. The public does not know the dangers of benzene nor the insidious nature of lead poisoning. In respect to the volatile poisons, and indeed to all harmful substances in industry and in interstate trade, it is of the highest importance that the same sort of inspection and regulation should apply as in the matter of food products under the Pure Food Law. The Federal and state governments should also provide for more extensive scientific investigation and publication for the education of manufacturers, workmen and the public. Public funds expended for this purpose would bring an ample return, for industry would not then be hampered by the illness of workmen or loaded with the cost of their deaths.

With knowledge and care, even the most poisonous substance can be produced and used safely in industry. But, without regulation strictly enforced, the sale of such substances to the general public is fraught with great danger. New compounds of a volatile nature are now being introduced into manufacture and trade in increasing number and amount. Physiological investigation to define the risks attending the use of these substances prior to their introduction should be legally required under heavy penalties. On the contrary, at the present time the toxicity of these compounds generally remains unknown until deaths or serious injuries to health have resulted. Physiological information based largely upon experiments on animals would be more humane and less costly to industry, even in dollars, than is the information now gained from the statistics of illness, disablement and death of men.

At the present time these serious needs in this field of public health and sanitation are being met chiefly by the investigations promoted by the American Standards Association. The standards already set by it are contributions of high value.

Prevention of Atmospheric Contamination

Once the physical, chemical and physiological characteristics of new volatile substances are known, the prevention of poisonous or unhealthful conditions in workrooms resolves itself into

the engineering problem of controlling the degree of contamination of the air. The requisite standards of ventilation must first be determined experimentally and defined in practical terms; and then arrangements to maintain such standards must be developed and installed. An example of this type of problem on a large scale occurred in preparation for the construction of the first vehicular tunnels under the Hudson River. The first step was to determine the amount of carbon monoxide produced by motor vehicles of all types and sizes; the next, to define the allowable concentration of carbon monoxide in the air to be breathed during the time of passage through the tunnels; and the third, to develop the means of forced ventilation to maintain the standard thus defined.

When factories, petroleum refineries, garbage, fertilizer and similar plants produce harmful fumes or offensive odors, it is generally possible to prevent the escape of these gases and vapors by one of two methods. For both methods it is essential to collect, in a single large duct, the entire effluent air from the chambers where the fumes arise. One of the methods then consists in passing this air through activated carbon, which readily condenses a wide range of substances. Commercially valuable substances thus absorbed by carbon may be recovered by displacement with steam and the absorptive power of the carbon is regenerated.* The other process consists in mixing a relatively small amount of chlorine gas with the air in the duct. Minute amounts of chlorine in the presence of water vapor destroy many labile substances including most offensive odors, hydrogen sulfide, etc. It is essential that the volume of chlorine be accurately adjusted to the amount of odoriferous substance. For this purpose the same control apparatus is applied as that used for chlorinating city water supplies.

Other Precautionary Measures

No matter how much care is taken to prevent contamination of the air, accidental and temporary escape of the volatile substances used in industry must be anticipated, and provision should be made for such accidents. The general type of pre-

* For details, see Robinson, "Recovery of Vapors," New York, Reinhold Publishing Corp., 1942.

caution needed may be exemplified by the following rules applicable to an ammonia refrigerating plant:

(1). The refrigerating equipment, including valves and piping, should be inspected at short and regular intervals and needed repairs made immediately.

(2). Every employee should be instructed regarding the dangers from ammonia and trained to avoid them.

(3). No one should be allowed to sleep in rooms adjoining a refrigerating plant.

(4). The room or rooms in which the machinery is installed should have doors swinging outward and opening directly to the outside air. The relation of this room to other parts of the building should be such that escaping fumes cannot invade the other parts or cut off the escape of persons in them. Regulations should be prominently posted and strictly enforced requiring that the exits shall never, even for a few minutes, be obstructed by temporary scaffolding, wheelbarrows, or other impediments to egress.

(5). Gas masks with canisters affording protection against ammonia should be provided; they should be stored in some locality readily accessible to, but outside of, the room in which there is a possibility of the escape of ammonia.

(6). Every workman engaged in repair work on refrigerating apparatus should be required to carry at all times a gas mask strapped to his body or hung around his neck in anticipation of the possible escape of ammonia.

(7). A valve arranged to shut off the ammonia at the storage cylinders and to discharge it into the sewers with a large volume of water should be placed where it can be manipulated from the outside of the building.

Protective Apparatus

Three types of apparatus are used for protection against the inhalation of noxious gases: (1) canister gas masks; (2) hose masks; and (3) self-contained breathing apparatus. These three forms of apparatus differ from one another in principle and each has advantages and disadvantages in relation to the other types. Each is best for its own special use. The greatest care should be taken to avoid worn-out or otherwise defective protective apparatus, for it may add the death of a rescuer to that

of a first victim. As such apparatus, especially the rubber parts, deteriorate rapidly, it must be frequently inspected and regularly renewed.

Unfortunately there is a widely held belief that a handkerchief, or some other piece of fabric tied over the mouth and nose, constitutes a gas mask. Many lives have been sacrificed to this fallacy. Fabrics that will permit the passage of the respired air will also permit the passage of noxious gases. Moistening the cloth offers protection against a few substances only and for a short time. The more soluble irritant gases and vapors, when present only in low concentrations, may be partially and temporarily absorbed by the moisture; but such makeshift arrangements offer no protection against most of the asphyxiants and the volatile drug-like substances. Respirators designed to prevent the inhalation of dust afford no protection against noxious gases.

Gas Masks and Various Types of Canisters. A properly constructed gas mask consists of a facepiece of rubber or rubberized fabric which fits tightly across the forehead, along the cheeks and under the chin, and which is connected by a short piece of flexible and non-collapsible tube to a sheet-metal canister containing absorbent materials. The facepiece is fitted with windows of shatterproof glass placed in front of the eyes. The canister is worn suspended from the shoulders or strapped across the chest. At the bottom of the canister is a light disk check valve which opens only to admit air so that the breath is inspired, but not expired, through the canister. A second valve opens from the facepiece to the outside air; through this valve the breath is expired. The canister is filled with layers of various materials which remove, either by absorption or by chemical reaction, certain gases and vapors from the air. When the mask is fitted to the face, all the air inspired is filtered through these materials and thus purified.

The gas mask in its present form is the highly developed and extremely efficient product of very extensive and careful investigation. It is light, quickly applied, allows freedom of movement and can be purchased at a reasonable price. It affords effective protection against such gases and vapors as the materials in the canister are designed to absorb. Most canisters are charged with materials intended to absorb only a limited number of closely

related gases. The contaminant in the air must be known and the proper canister employed to absorb that type of gas. A canister charged to afford protection only against ammonia, for example, is useless for such gases as carbon monoxide or hydrochloric acid fumes; for each of these gases there is a special type

Fig. 10.
Diagram of a Gas Mask in Section.

of absorbent. There is one type of canister, however, the so-called "all-service canister," which gives protection against all gases and vapors found in industry excepting, of course, high concentrations of the simple asphyxiants. This type of canister is useful when the contaminant in the air is unknown, as is the case when firemen enter chemical storage depots. But it has the disadvantage of a relatively short life, because of the comparatively small amount of each absorbent in the canister when used against any one particular gas. In most industrial plants the

gases which may occur are known beforehand and the proper canisters should be provided. Canisters filled with only one type of absorbent material afford protection for a longer time than is possible with the all-service canister.

Types of Canisters for Protection under Various Conditions

Conditions	Contents of Canister	Color of Canister
(1) Protection against organic vapors, such as aniline, gasoline, benzene, ether, toluene, and the like (when not over 20% in air).	600 cubic milliliters or more of activated carbon.	Black
(2) Protection against acids, such as hydrochloric, sulfur dioxide, nitrogen peroxide, chlorine and the like (not over 1% in air).	600 cubic milliliters or more of soda lime or fused caustic soda.	White
(3) Protection against ammonia gas not over 3%. The 3% limit cannot be long endured by the wearer because of the skin irritation from the gas.	Copper sulfate and carbon.	Green
(4) Protection against carbon monoxide (not over 3%).	A mixture of metallic oxides known as "Hopcalite" which catalyzes the combustion of carbon monoxide with oxygen from the air to form carbon dioxide.	Blue
(5) Protection against all the above gases; the "all-service mask."	All the absorbents mentioned above, but only small amounts of each.	Red
(6) Protection against a combination of organic fumes and acid fumes.	Activated carbon and soda lime.	Yellow
(7) Protection against ammonia, acid, organic vapors, and smoke.	Copper sulfate and carbon with a filter pad for smoke.	Brown
(8) Dusts, smokes, mists in combination with any of the above gases.		One-half inch contrasting black or white stripe.

Canisters are supplied with eight main types of absorbing material. A stripe painted on the canister indicates that it is fitted with filter pads and will protect against smoke, dust and irritant mist. A gas mask cannot be safely used in an atmosphere seriously deficient in oxygen. The practical limit beyond which a mask should not be used is indicated by the extinction of the flame of a candle or safety lamp. This occurs at about

17 per cent of oxygen in the air; a man is not in serious danger until the oxygen falls below 14 per cent. When, owing to an excess of the simple asphyxiant gases, the oxygen falls below this limit, a gas mask ceases to afford protection even though the absorbent in the canister removes any actively toxic gas. Under such circumstances a hose mask or self-contained breathing apparatus must be used.

The facepieces of gas masks are constructed largely of rubberized fabric and the life of the mask while in storage is limited by the deterioration of the rubber. Each gas mask should be kept in a separate box. The box should be sealed with strips of gummed paper and upon this seal should be written the date on which the mask was last inspected and the amount that the canister has been used. As it is necessary to break the seal in order to remove the mask from the box, this practice affords assurance that the canister has not been exhausted by use on some occasion which has not been recorded. If properly stored, the fabric of a gas mask should last about two years; if carelessly stored, or exposed to sunlight, its life may not be more than one year.

After a mask has been used, it should be disinfected to render it safe for another user. The mask is separated from the canister, immersed in a 2 per cent solution of Lysol and then dried in the open air. When dry, the eyepieces are polished and the mask returned to its box. Special care should be taken that there are no sharp creases or folds in the fabric.

The life of the canister depends upon the concentration of the gases absorbed, the duration of exposure and the manner in which it is stored when not in use. As supplied by the manufacturer the canister is sealed by a cap over the inlet valve and by a cork in the hose nipple. Stored in this condition and without use the canister should last a year. If air is allowed to enter, the contents of the canister deteriorate rapidly, especially if it contains soda lime or caustic soda. If a canister has been used long enough to give reason to believe that it is nearly exhausted, a fresh canister should be substituted. Most of the absorbent materials are exhausted or saturated by use, while Hopcalite, the catalyst for carbon monoxide, is rendered inactive or "poisoned" by the absorption of water vapor. If the mask is to be used again, the valve opening should be capped, the cork

inserted in the upper opening of the canister and a record made of the exposure to which it has been subjected.

The worker who uses the mask should test the facepiece for leaks before entering a contaminated atmosphere. To do this the mask is put on and tried in fresh air. The resistance to breathing should be slight, not more than an inch (25 mm.) water gauge. The bottom opening is then closed with the palm of the hand and suction exerted by inhaling until the facepiece collapses. If the mask is thus shown to be tight, the wearer may proceed into the contaminated atmosphere. If fumes are noticed in the air inhaled, the wearer should immediately return to fresh air and obtain a fresh canister. Carbon monoxide has little odor and therefore gives no indication that the canister is exhausted, or that the concentration of the gas is above the 3 per cent limit which is the highest against which the blue or red canisters afford protection. It is therefore advisable to use an attachment to these masks, a breath-counting device, which indicates the approximate total time of exposure.

Hose Masks. The facepiece of a hose mask is essentially the same as that of a gas mask, but instead of the inspired air entering through a canister, it is drawn or blown in through a length of hose, the outer end of which is supplied with fresh air from

Fig. 11. Hose Mask and Air Pump.

outside the contaminated space. If the hose is not over 25 feet in length and the mask is tight, the force of inspiration will, without serious difficulty, draw air in against the resistance imposed by the hose. If the hose is over 25 feet in length, or if the worker must wear the mask for a considerable time, air should be blown in with a pump. In an emergency a bellows,

or even a jet of compressed air, may be used. The latter is not to be recommended, however, for the air may contain oil. If a jet of compressed air is used, the hose should be left open at the end and the jet should be shot in on the principle of an injector, for if the nozzle supplying the jet is inserted in the end of the hose the air pressure may blow the mask off the wearer's face. Whenever possible the air blower for a hose mask should be of the centrifugal type, so that in case it is run at too low a speed or stops entirely the air supply will not be cut off, for enough air may be drawn through a centrifugal pump, and even a long hose, to permit the wearer of the mask to escape from an irrespirable atmosphere.

If more than one length of hose is used, the couplings should be provided with locks to prevent them from unscrewing. Whenever a man wearing a hose mask enters an irrespirable atmosphere in a confined space such as a tank car or manhole, for example, he should also wear a safety belt to which is attached a life line, the other end of which is held by an assistant outside.

The hose mask is especially desirable for work in atmospheres contaminated with vapors of the lighter petroleum distillates. In such vapors the life of the canister of a gas mask is of uncertain duration, and poisoning may be rapid when the canister becomes exhausted. A self-contained breathing apparatus may also fail, for the vapors may penetrate the rubber fabric and accumulate in the circulated oxygen. A hose mask can be worn in any atmosphere regardless of oxygen content. Its only disadvantage lies in the fact that the wearer's activities are limited by the length of the hose.

Self-contained Breathing Apparatus

A self-contained breathing apparatus is a portable device for supplying an atmosphere of oxygen which the wearer continually rebreathes while the carbon dioxide which he exhales is absorbed by an alkali. It consists of a facepiece or mouthpiece fitted with two valves, one inspiratory, the other expiratory. To the inspiratory valve is attached a piece of corrugated tubing leading to a bellows or a bag of rubber fabric. A similar tube from the expiratory valve goes to a canister of soda lime and another tube from there to the bellows or bag. The bag is automatically filled with oxygen from a cylinder of the compressed gas which

is carried as part of the apparatus. The automatic feed must be capable of keeping the bag or bellows adequately filled at all times by admitting more oxygen whenever the bag collapses to a certain point. When the breath is inspired, oxygen is drawn from the bag; when it is expired, the breath passes through the soda lime which removes the carbon dioxide. The purified exhaled oxygen then goes into the bellows to be reinspired. By this circulation oxygen is drawn from the cylinder only in amounts sufficient to replace that consumed by the wearer. A

FIG. 12. Diagram of Self-contained Breathing Apparatus.

fixed rate of feed, as in some of the early types of apparatus, is highly undesirable and even dangerous. It tends to waste oxygen when the wearer is not working, and to afford an inadequate supply for vigorous exertion. In the latter case the wearer collapses from anoxia. A man doing heavy work may consume as much as 4 liters of oxygen a minute, or even more.

It is important also that the breathing bag should be so covered that it cannot be compressed and emptied if the wearer is forced to crawl through a narrow space. If the bag is so emptied and the wearer is unable to inspire, he may be induced to tear off the apparatus. It requires more than human coolness, endurance and courage to hold the breath with the lungs deflated.

Self-contained breathing apparatus is available in two gen-

eral types; one can be safely used for 30 minutes and the other for 2 hours. The first weighs from 15 to 17 pounds and the latter 30 to 45 pounds. After the apparatus has been worn for the specified time, the cylinder of oxygen must be replaced by a new one and the soda lime must be renewed in the canister.

Self-contained breathing apparatus has the same general application as the hose mask. It has a marked advantage over the latter in that the wearer's movements are not restricted by a long hose to the outer air and he may therefore penetrate as far as necessary into passages and chambers filled with an irrespirable atmosphere. But self-contained breathing apparatus has the disadvantage of being heavy and cumbersome; it is expensive and the rubber portions deteriorate rapidly. It is a complicated piece of apparatus and for its proper operation requires frequent inspection and adjustment. The apparatus is largely used in mine rescue work and to some extent by firemen. For purposes of exploration, work and rescue over considerable distances in atmospheres deficient in oxygen, where the flame of a safety lamp is extinguished, self-contained breathing apparatus is the only means available. On the other hand, for use even in very poisonous atmospheres, providing there is sufficient oxygen to support a flame, the gas mask and canister afford, not only a more practical working condition for the wearer but also a greater degree of safety. Unsuspected defects in self-contained apparatus have cost many lives; a small unnoticed crack in one of the rubber parts imposes the penalty of death. No one should ever attempt to use this form of apparatus unless he has been thoroughly trained in its use and knows that his particular apparatus is in perfect order.

The U. S. Bureau of Mines examines all types of mine rescue apparatus and publishes a list of those that meet the requirements of efficiency and safety. Until that Bureau conducted the investigations upon which this supervision is now based, self-contained breathing apparatus had cost more lives than it had saved. There is still, and always will be, danger that some apparatus may be devised and offered for sale without this supervision that may be mechanically ingenious, but that is not in accord with the principles of respiration. Such apparatus is likely to cost lives. Before it is used, even for amateur tests in the open air, it should be examined in the light of the evidence

presented in a paper entitled "Oxygen Mine Rescue Apparatus and Physiological Effects on Users" by Yandell Henderson and James W. Paul, U. S. Bureau of Mines Technical Paper No. 82, Government Printing Office, Washington, 1917.

Note on the Actions of Noxious Gases on Plants

Plants, and particularly trees, are well known to be injuriously affected, or even killed, by the low concentrations of industrial fumes in which large numbers of people in cities live. While they are comparatively insensitive to certain gases, to others, plants are more susceptible than animals. Around smelters and other factories producing acid vapors the trees may be killed for considerable distances, the effects depending upon the prevailing direction of the wind, heights of chimneys and topography of the neighborhood. Thus forests on hills around a factory town in a valley may be destroyed. In coal smoke, the actively injurious agent is sulfur dioxide, or rather the sulfuric acid into which sulfur dioxide changes in the presence of water vapor. In Germany, forests have sometimes suffered severely from the smoke from locomotives of a railroad with heavy traffic running through a valley. Conifers appear to be particularly sensitive. One part of sulfuric acid per million of air may produce noticeable effects. The ill effects are said to be produced only during the time that sunlight is also acting; that is, the fumes act only during photosynthesis.

The other principal gas hazard of vegetation is that due to illuminating gas leaking from the mains under the streets of cities. The poisonous constituent is not carbon monoxide but ethylene. The action upon growing plants appears to be largely through absorption by the roots. The effects are particularly noticeable in greenhouses into which there is even a slight leak of gas. The odor of the illuminating gas may be absorbed in the ground and the first effect noticed may be upon the flowers. Twelve parts of illuminating gas in a million of air cause the already open buds of carnations to close in the course of twelve hours, thus inducing the so-called sleep of these flowers. Twenty-five parts of illuminating gas in a million of air are sufficient to kill many hothouse plants in the course of a few days. The amount of ethylene, the active agent involved in these effects, is of the order of one part or less in a million of air.

Supplementary Statement on Breathing Machines

By Yandell Henderson

In the year 1912, three types of accidental death excited the authorities concerned to a search for means of prevention and resuscitation. The U. S. Bureau of Mines, then newly organized, found that among the major hazards of coal mining one of the most serious was asphyxiation by carbon monoxide. The National Electric Light Association—the predecessor of the Edison Electric Institue of today—was faced with the problem of what should be done for men who, after receiving a heavy electric shock, stop breathing and die on that account, although the heart in many cases continues to beat for a short time. The Red Cross was then, as ever since, interested particularly in resuscitation from drowning.

For a study and report on these matters, Director Joseph A. Holmes of the Bureau of Mines requested the American Medical Association to nominate the members of a Committee on Resuscitation from Mine Gases; and in June 1912, he appointed W. B. Cannon, G. W. Crile, J. Erlanger, S. J. Meltzer and Y. Henderson. At the request of the National Electric Light Association, the Committee was enlarged for the study of electric shock by the addition, among others, of Elihu Thompson and A. E. Kennelly. All methods of artificial respiration, known or proposed at that time, were studied.

The first method, or group of methods, studied by the Committee was that of manual artificial respiration as exemplified in the well-known method of Silvester and its variations, and particularly the then newly devised prone pressure method of Schafer. The main point developed by the Committee in regard to manual methods of artificial respiration was, not that any one of them induces a much larger ventilation of the lungs than any other—in fact, too large a ventilation is harmful—but that the prone pressure method has the great advantage that it can be

applied immediately: delay of even a few sceonds may lose a life. Prone pressure is also easier to teach and learn than any of the other methods; it can be continued longer without exhausting the operator; and it gives vitally important aid to the circulation of the blood.

These conclusions, which can be stated so briefly, were the results of prolonged investigation by the members of the Committee themselves. But that was not all: in later years, three other committees of investigation, two in this country—one in 1918, the other in 1921—and one in Britain in 1939, repeated and extended these investigations and confirmed their conclusions. Nor did investigation stop there. As late as 1939, one of the authors of this book crossed the ocean to attend an International Congress on First Aid and Resuscitation that met at Zurich. To that Congress came representatives from all the leading civilized countries of the world. And even that has not ended the scientific investigation of manual artificial respiration. Probably no subject applying to the saving of life has ever been more thoroughly studied or its value more certainly established.

The other method, or group of methods, studied by the Committee of 1912 was that of resuscitation by means of breathing machines, and particularly the first of such apparatus to gain public attention, the so-called "pulmotor." This device originated in Germany, where the engineers of the Draeger Company had already developed valuable rescue apparatus for use under water and in poisonous atmospheres in mines. In the pulmotor, compressed oxygen from a cylinder operated an injector and an automatic switch so as alternately to blow oxygen into the lungs and suck it out again: at least it was so intended. It was supposed that in this way carbon monoxide and other noxious gases would be washed out of the lungs and blood. For a time, the pulmotor was regarded as producinug a sort of modern miracle: the restoration of life by machinery. It appealed so strongly to the love of the marvelous in the public mind that the word "pulmotor" is still used metaphorically for any device or process that "pumps the breath of life" into a bankrupt concern.

The main argument offered for the pulmotor was a demonstration of its capacity alternately to blow a rubber bag full (simulating the lungs) and then to suck it flat. More recently a rubber doll has been used; and under the action of a pulmotor or other

suck and blow device the doll "breathes" quite realistically. The reversals from blowing to sucking and vice versa are automatically induced by the resistance of the bag or doll when full or empty. Of this feature of the device, the Committee reported: "Inflation and deflation of a bag is deceptive, because the bag, unlike the air passages of the body, offers no resistance till full. As soon as the inspiratory blast meets an obstacle in the air passages, however, it is automatically cut off and turned into expiration; and thus frequently no efficient inspirations are performed. . . . The second harmful factor brought out by these experiments is the performance of expiration by suction. In normal respiration, expiration is accomplished by a power that does not suck, but drives out the air by the elasticity of the distended or compressed tissues, aided sometimes by muscular contraction." The Committee recognized that in cases of deep asphyxiation the time lost when the apparatus merely clicks back and forth—as it frequently does—between inspiration and expiration must result in loss of life. In general, such apparatus scores successful resuscitations only on cases that would probably revive without any specific treatment.

The Committee also recognized that it is the popular belief in the capacity of the pulmotor to perform a miracle, produce breathing and restore life, that makes it so evil an opponent of manual artificial respiration. Always the proponents of such devices say, "We advocate using the prone pressure method until the apparatus comes." But in actuality, the miracle-believers at a drowning are more concerned to bring the apparatus than to apply manual resuscitation; and the boy lying limp on the river bank, who might be saved with prone pressure respiration, is often beyond even a miracle before the apparatus arrives. Even if the apparatus is immediately available, the treatment it administers is not so effective as that by hand. It does not aid, but rather impedes, the circulation of the blood.

Henderson had already (1911) seen the pulmotor in operation. It was on a case of carbon monoxide asphyxia. The man was unconscious; but was breathing naturally and needed no artificial respiration. The pulmotor was running, but its strokes were entirely out of step with the breathing, which it was impeding rather than aiding.

Careful consideration was given by the Committee to the

possibility that the application of a negative pressure—i.e., suction—might injure the lungs. The report noted that "In the *Journal of the American Medical Association*, March 8, 1912, page 738, Dr. Morris Fishbein of Chicago reports a case in which a patient who had been poisoned with CO was subjected to the action of the pulmotor for several hours. After nearly 5 days of unconsciousness, the patient died. At autopsy, hemorrhage into the lungs and visceral pleural emphysema (dilated areas) of the right lung were found, together with subpleural emphysema." Twenty-one other cases were studied and found "in no manner satisfactory for demonstrating the superiority of the pulmotor as a device for artificial respiration."

From various lines of investigation in laboratory and clinic, the Committee reached the conclusion that "the automatic mechanism of the pulmotor, although an ingenious technical contrivance, instead of assuring artificial respiration, may interfere greatly with its efficiency. . . ." The principle of suck and blow respiration was therefore unanimously disapproved; and the disapproval was confirmed by the Committees of 1918 and 1921, and by that of 1939 in Britain.

Such testimony might have been expected to put an end to all suck and blow apparatus. That it has not done so is due, first to the almost superstitious reverence of Americans generally toward all automatic apparatus, and second, to the general lack of acquaintance of many physicians with the modern physiology of respiration. The great scientific discoveries of the past 50 years in this field—as described in Chapter 2—are still widely neglected clinically, or even opposed. Particularly in drowning accidents, there is still need to warn boy scouts and policemen: "First: Don't let the doctor stop you. Even if he says the patient is dead, keep right on with manual artificial respiration and you may save a life. If the doctor sends the patient to the hospital, he will probably be dead when he gets there. And second: Don't let a doctor, or a rescue crew, or anyone else apply a pulmotor or one of the new devices called 'resuscitators' or any other kind of breathing machine. Stick to prone pressure respiration aided only by inhalation of carbon dioxide and oxygen when an inhalator is at hand." Most doctors see few cases of resuscitation from drowning or electric shock, or even from carbon monoxide asphyxia. They are not there. Many still believe that artificial

respiration is like the "cranking" of the motor in an automobile or boat; and that it is the artificially induced movements of breathing that induce the return and continuance of the natural movements. Too few realize that it is the chemical action of carbon dioxide and oxygen in the brain that sets the vital machine again in operation, and that this chemical action is entirely effective in restoring respiration when carbon dioxide and oxygen are introduced into the lungs merely by manual artificial respiration.

Accordingly, inventors with much mechanical skill and little or no knowledge of respiration have continued to produce and offer various forms of breathing machines. The best of these devices was the "lungmotor." It consisted of two automobile tire pumps, one of which blew out air or oxygen into a mask, and the other sucked it back. But that device, although it would be ideal if the pulmotor principle of cranking the lungs were sound, was too simple to fool people into buying it. On this account, it was not until other devices appeared, which are sufficiently automatic to impress the ignorant, that sound methods of resuscitation were again threatened. These devices are essentially pulmotors under other names: usually that of "resuscitator." They have generally been introduced without the support of any experimental study published in any scientific journal: but wholly on the basis of high powered salesmanship.

In spite of this lack of accurate laboratory tests or of any controlled clinical evidence, these neo-pulmotors have, in recent years, been rather widely introduced. All available evidence indicates that they have been responsible for the loss of many lives through failure to resuscitate both in cases of drowning and in those of carbon monoxide asphyxia. Particularly when applied to asphyxial babies, these devices are sometimes the cause of serious damage to the lungs.

On this account it seemed to us that a thorough re-investigation of the question of the value or harmfulness of suck and blow breathing machines was needed, and such an investigation was accordingly carried out in this laboratory by Henderson and Turner, and published in the *Journal of the American Medical Association.*

All makes of so-called "resuscitators" were carefully examined. They were found in every case to be ingeniously designed, well

constructed and capable of alternately inflating and deflating a rubber bag, and making a rubber doll "breathe" realistically. Each of these devices consists of two parts or actions which can be switched from one to the other. One of these actions sucks and blows and is therefore essentially that of a pulmotor. The other action is that of an inhalator, but a very inefficient inhalator: one that supplies only a small flow of oxygen, or of oxygen and carbon dioxide, during inspirations, and wastes as much during expirations. Consequently a patient deeply asphyxiated with carbon monoxide receives only an inadequate inhalation and undergoes serious asphyxial nervous injury. The prime object of the inhalation of oxygen and carbon dioxide, as introduced by Henderson and Haggard, is the prevention of such injuries to the brain; and for this purpose no "resuscitator" is adequate.

In the investigations of Henderson and Turner particular attention was devoted to 3 vitally important questions, namely: (1), whether a suck and blow apparatus can be applied as quickly as manual artificial respiration, so as to save life in drowning; (2), whether, after such an apparatus is applied, its action aids or opposes natural breathing; and (3), whether the sucking and blowing of the apparatus can remove carbon monoxide or other poisonous gases from the blood as rapidly as does the large volume of natural breathing induced by inhalation of carbon dioxide and oxygen.

The experiments were all made on healthy dogs weighing from 7 to 10 kg. Each animal was first kept for 20 to 25 minutes in a gassing chamber containing air to which 0.35 per cent of carbon monoxide had been added. At the end of that time every one of the animals had passed through the usual stages of the development of asphyxia and was in coma: completely unconscious and either convulsive or limp. In 6 of these experiments, the asphyxiation was continued until breathing had completely stopped. Three of these animals were then treated with one or another of the suck and blow apparatus, but unsuccessfully. It takes too long to adjust and start the apparatus. No return of breathing or pulse could be induced. The other 3 animals, on removal from the gassing chamber, were instantly treated with manual artificial respiration and inhalation of carbon dioxide and oxygen. All 3 were revived; and these animals, and

a number of others that had not ben quite so deeply asphyxiated, were then used for the following experiments:

As soon as the risk of immediate death was past and the animal was breathing, although feebly, mechanical artificial respiration with a suck and blow "resuscitator" was started. Under the influence of the mixture of carbon dioxide and oxygen thus supplied to the lungs, the animal's own respiratory efforts were increased; but in the large majority of cases—indeed, with only 1 exception—the rate of natural breathing and the rate at which the apparatus operated were entirely different. There was conflict, instead of coöperation: with the result merely of the waste of a large amount of the resuscitant gases. In a succession of experiments, we recorded the simultaneous rates of natural breathing (N. B.) and those of the mechanical respirator (M. R.) as follows: N. B. 60, M. R. 120; N. B. 30, M. R. 60; N. B. 22, M. R. 120; N. B. 30, M. R. 30; N. B. 8, M. R. 50; N. B. 16, M. R. 72; N. B. 16, M. R. 74.

All forms of suck and blow breathing machines—pulmotors, "resuscitators," and so on—are, it is claimed, adjustable to the patient's rate of breathing. On normal conscious men, such is the case, although more of the adjusting is effected by the subjects than by the apparatus. On comatose subjects, on the contrary, both dogs and men, synchronization is much more difficult. The directions which come with the apparatus are to the effect that, "after the patient is breathing, the inhalator attachment alone should be used." But actually the maximum flow of the resuscitant mixture of carbon dioxide and oxygen on the inhalator side is usually only 7 liters a minute, which is only the volume of normal resting respiration; and half the resuscitant gases are wasted during expirations. On the contrary, a man under inhalation of carbon dioxide and oxygen with a proper inhalator will breathe 20 or even 30 liters a minute; he rebreathes none of it; he wastes none of it; and he needs all of it for the rapid elimination of carbon monoxide from his blood.

The prime object of any sound treatment for carbon monoxide asphyxia, as shown by the investigations of Henderson and Haggard, is the elimination of the asphyxiant gas from the blood as rapidly as possible. The injury to the brain induced by carbon monoxide is determined, not merely by the length of time the patient remains in the gassing chamber, but even more

by the time before the gas is eliminated from his blood. That method is therefore best which will effect the elimination of the asphyxiant gas most rapidly. The crude inhalators attached to most "resuscitators" are, as stated above, quite inadequate, (See also pages 258 and 259).

The investigations of Henderson and Haggard have determined the time required for the elimination of carbon monoxide from the blood under 4 different conditions—namely: (1) breathing merely fresh air, (2) breathing oxygen, (3) breathing air and carbon dioxide, and (4) inhalation of carbon dioxide and oxygen; and these times were found to be respectively (1) 2 or 3 hours or more, (2) an hour and a half, (3) an hour and a half, and (4) 20 to 30 minutes. In comparison to these figures the best that can be attained with either the suck and blow action of a "resuscitator" or its inhalator action is at least an hour and a half. Wide experience has shown that in men the extent of the damage to the brain after such slow resuscitation is, as a minimum, a prolonged headache; and, as a maximum, the destruction of the intellect or even death. After a rapid resuscitation by means of a properly designed inhalator, on the contrary, the patient is often sufficiently restored to be able to go back to work within an hour or two, and suffers no subsequent ill effects.

To the authors of this book, these scientific facts seem to demonstrate that all of the neo-pulmotors, now being pushed by high-powered sales campaigns, are open to essentially the same objections as those that were applied to the original pulmotor 30 years ago. Although one of the standing committees of the American Medical Association—the Council on Physical Therapy—has approved for trial some of the neo-pulmotors now offered, this endorsement by the Council scarcely goes beyond certification that the particular apparatus is well constructed and will inflate and deflate a rubber bag.

Other than that partial endorsement, no scientific support of the pulmotor principle has been offered recently, except an investigation by Birnbaum and Thompson. But even in that study it was only by inserting a tube in the windpipe *before* the animals were asphyxiated, and then attaching a "resuscitator" to this tube immediately after asphyxiation that they were able to obtain results favorable to suck and blow respiration. These

observations are further deprived of practical significance by the fact that all of the animals had previously been deeply narcotized with a barbiturate: a drug which deprives the respiratory center of its responsiveness to carbon dioxide (as shown by Marshall and Rosenfeld). An undrugged—and therefore responsive—animal or man is, as Henderson and Turner have shown, more effectively resuscitated by stimulation with carbon dioxide than by "cranking" with a "resuscitator."

Finally, it is noteworthy that the American Red Cross, in its campaign for the teaching of first aid, has confined its support to manual artificial respiration; and it is as certain as scientific evidence can make it that to whatever extent manual artificial respiration and efficient inhalation are replaced by the use of breathing machines of the pulmotor type there will be a corresponding increase in the loss of life from drowning, carbon monoxide poisoning and other forms of asphyxia.

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