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MRS. HEPSA ELY SILLIMAN MEMORIAL
LECTURES

RESPIRATION

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RESPIRATION. *By* J. S. HALDANE, M.D., LL.D., F.R.S., *Fellow of New College, Oxford, Hon. Professor, Birmingham University.*

RESPIRATION

BY

J. S. HALDANE

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THE SILLIMAN FOUNDATION

In the year 1883 a legacy of eighty thousand dollars was left to the President and Fellows of Yale College in the city of New Haven, to be held in trust, as a gift from her children, in memory of their beloved and honored mother, Mrs. Hepsa Ely Silliman.

On this foundation Yale College was requested and directed to establish an annual course of lectures designed to illustrate the presence and providence, the wisdom and goodness of God, as manifested in the natural and moral world. These were to be designated as the Mrs. Hepsa Ely Silliman Memorial Lectures. It was the belief of the testator that any orderly presentation of the facts of nature or history contributed to the end of this foundation more effectively than any attempt to emphasize the elements of doctrine or of creed; and he therefore provided that lectures on dogmatic or polemical theology should be excluded from the scope of this foundation, and that the subjects should be selected rather from the domains of natural science and history, giving special prominence to astronomy, chemistry, geology, and anatomy.

It was further directed that each annual course should be made the basis of a volume to form part of a series constituting a memorial to Mrs. Silliman. The memorial fund came into the possession of the Corporation of Yale University in the year 1901; and the present volume constitutes the fourteenth of the series of memorial lectures.

PREFACE

WHEN Yale University invited me to deliver the Silliman Lectures for 1915 I was asked to deal with the physiology of breathing and include a general account of the long series of investigations with which I had been associated on this subject and its practical applications in clinical medicine and hygiene. Owing to the war I was unable to give the lectures in 1915, but in 1916 delivered four lectures which dealt only with some of the more general conclusions to which I had been led, and were published early in 1917 by the Yale University Press under the title "Organism and Environment as Illustrated by the Physiology of Breathing."

The war has greatly delayed the appearance of the present book, which treats the physiology of breathing fully in accordance with the original plan. I have, however, abandoned the lecture form, and what I had written four years ago has had to be largely recast owing to the rapid advance of knowledge. The book is not a mere compilation, but contains much that has never previously been published, and is an attempt to give a coherent statement and interpretation of what is known of the subject at present. I fear that I may sometimes have unwittingly overlooked observations by others which would have added completeness to my account. Yet I hope that what may have been lost in this way will be made up for by the fact that the book embodies the results of a continuous series of investigations leading to very definite and consistent conclusions.

About the middle of last century the younger physiologists broke away from the vitalistic traditions which had been handed down to them, and set about to investigate living organisms piece by piece, precisely as they would investigate the working of a complex mechanism. This method seemed to them to promise success, and was popularized by such masters of clear and forceful expression as Huxley. It is still the orthodox method of physiology, but the old confidence in it has steadily diminished in proportion as exact experimental investigation has shown that the various activities of a living organism cannot be interpreted in isolation from one another, since organic regulation dominates them. The keynote of this book is the organic regulation of breathing and its associated phenomena.

The mechanistic theory of life is now outworn and must soon take its place in history as a passing phase in the development of biology. But physiology will not go back to the vitalism which was threatening to strangle it, and from which it escaped last century. The real lesson of the movement of that time will never be lost.

The book belongs to a transition period, but the transition is forward and not backward. My treatment of the subject may possibly be looked on askance in some quarters as reactionary: for I have been largely influenced by the ideas and work of older physiologists. If, however, I have gone backward, it is only to pick up clues which had been temporarily lost; and all of these clues lead forward—forward to a new physiology which embodies what was really implicit in the old.

The leaders of the mechanistic movement of last century got rid of vitalism, but in doing so got rid of life itself. I have tried to paint a picture of the body as alive. Though the picture is imperfect, others will soon paint it more completely. The time has come for a far more clear realization of what life implies. The bondage of biology to the physical sciences has lasted more than half a century. It is now time for biology to take her rightful place as an exact independent science: to speak her own language, and not that of other sciences.

The endeavor to represent the facts of physiology as if they would fit into the general scheme of a mechanistic biology has led, it seems to me, to the present estrangement between physiology and medicine. Since the time of Hippocrates the growth of scientific medicine has in reality been based on the study of the manner in which what he called the "nature" (φύσις) of the living body expresses itself in response to changes in environment, and reasserts itself in face of disturbance and injury. The underlying assumption is that organic regulation and maintenance represent something very real, and that only through the study of it can we recognize and interpret disturbance of health, and effectively aid maintenance or restoration of health. I have endeavored to return to what seems to me the truly scientific Greek tradition, and to give it a form which is not only consistent with modern science and philosophy, but brings physiology and medicine into that close and special relation indicated by the common etymology of the words "physician" and "physiology."

Most of the investigations specially referred to in the book have been carried out on man. It was only by human experiments

that the almost incredible delicacy of the regulation of breathing was discovered; and human experiments have revealed to us in other ways how rough many of the experiments on animals, or on "preparations" from the bodies of animals, have been. Organic regulation, with its all-important relations to practical medicine and surgery, was often entirely overlooked. I hope that the book may contribute towards establishing human physiology in its rightful place, which has been usurped too long by experiments on fragments of frogs and other animals, or on the mere superficial physical and chemical aspects of bodily activity.

I wish to offer my sincere thanks to Yale University for the honor it has done me in inviting me to give the Silliman Lectures. Between Oxford and Yale Universities there is a traditional association, and to me in particular the association stands for friendship, hospitality, and community of ideas. My only regret is that in coming to Yale to lecture on the physiology of breathing I seemed to be doing what an Englishman calls bringing coals to Newcastle, since I had to refer so frequently to the results reached at Yale by Professor Yandell Henderson and his pupils.

The book sums up the results of more than twenty years of my own experimental work, thought, reading, and discussion. To the old pupils and other friends who have worked and thought with me, including friends in the mining and engineering professions and in the Navy and Army, I wish to express my debt. Their names are often quoted in the text, but I should like to say how much I have been aided more particularly by Professor Lorrain Smith, Professor Pembrey, Professor Boycott, Commander Damant, Mr. Mavrogardato, Dr. Priestley, Dr. Douglas, Professor Meakins, and my son. In connection with the Pike's Peak Scientific Expedition, the results of which occupy such a prominent place in the book, Dr. Douglas and I had the great advantage of being associated with Professor Yandell Henderson and another Yale graduate, Professor Schneider of Colorado Springs. The book owes much to the talks we had on the Peak in the summer evenings when our work was over and the lights were twinkling over the prairie far below from Denver to Pueblo.

Readers will easily see how many gaps remain to be filled up. To fill these gaps the observations and experiments required are not yet available. The words of Hippocrates are as true now as when he wrote them more than two thousand years ago: *ὁ βίος βραχύς, ἡ δὲ τέχνη μακρή*

OXFORD, MAY 1920.

Owing to the aftermath of the war there has been considerable delay in printing the book, and meanwhile a good deal of new work has appeared on the subjects of certain chapters. Where this could not be incorporated without serious recasting in the proofs it is referred to in addenda to the chapters in question.

MAY 1921.

CONTENTS

CHAPTER I

Historical Introduction.

In the history of physiological discovery the growth of knowledge as to the physiology of breathing was comparatively late. Before the middle of the seventeenth century hardly anything was known about breathing except its muscular mechanism and the facts that if the breathing of a man or higher animal is interrupted for more than a very short time death ensues, and that the breathing is increased by exertion and by some diseases. The discovery by Harvey of the circulation threw no positive light on the physiology of breathing, and it was still generally believed that the main function of respiration is to cool the blood. Progress was impossible without corresponding progress in chemistry.

The first beginnings of a better knowledge date from the work at Oxford of Robert Boyle[1] and Mayow[2] a young doctor. Boyle showed with the air pump that air is necessary to life, and Mayow investigated and compared together the influences of niter in the combustion of gunpowder, and of air in respiration and ordinary combustion in air. He drew the conclusion that in all of these processes a "nitro-aërial spirit" combines with "sulphur" (combustible matter). As regards respiration he concluded that the nitro-aërial spirit is present in limited proportion in air, and is absorbed from the air in the lungs by the blood, carried by the circulation to the brain, where it is separated off in the ventricles, and thence passes down the supposed nerve-tubules to the muscles, where it unites with "sulphur" and produces muscular contraction by the resulting explosions. He explained the increased breathing which accompanies muscular exertion as a necessary accompaniment of the increased consumption of the nitro-aërial spirit.

It will thus be seen that he had practically discovered oxygen, in so far as the rudimentary chemical ideas which he had formed permitted the discovery. He had also formed a sound physiological conception of the relation between muscular work and increased breathing. Mayow's conception of oxygen passing down the

[1] Boyle, *New experiments physico-mechanical, touching the Spring of the Air,* Oxford, 1666. Particularly Experiments XL and XLI, with the accompanying "Digression containing some Doubts touching Respiration."

[2] Mayow, *Tractatus Quinque Medico-physici,* Oxford, 1673. In particular Tractatus II, De Respiratione (2d Edition).

nerves was of course only a modification of the idea then current, and elaborated by Descartes among others, that muscular contraction depends upon the "animal spirits" passing down the supposed nerve tubules from the brain. This conception was apparently confirmed by the effects of cutting or ligaturing nerves; and Lower,[3] another Oxford physician, performed the striking experiment of completely disturbing the action of the heart by a ligature on the vagus nerve. He had stumbled upon inhibition and misinterpreted it in favor of Mayow's theory.

About the same time another significant observation was made by Hooke,[4] the Secretary of the Royal Society. He found that when the chest of an animal was opened so that the lungs collapsed, it could be revived and kept alive by artificial respiration, and, if holes were pricked in the lungs so that air could pass through them, the animal could still be kept alive if a stream of air was continuously blown through the lungs, although they did not move.

The foundations thus seemed to be laid of our present knowledge of the physiology of breathing; but unfortunately the significance of the discoveries made at Oxford was not appreciated, and indeed the study of physiology and other branches of natural science there was practically allowed to die out for the succeeding two hundred years.

The next important step in connection with respiration was the discovery, about the middle of the eighteenth century, by Joseph Black of Edinburgh, that "fixed air" (carbon dioxide) which he had found to be liberated by acids from mild alkalies (carbonates) is given off by the lungs in respiration. Priestley discovered soon afterward that what, in accordance with Stahl's phlogiston theory, he called "dephlogisticated air" (oxygen) disappears both in ordinary combustion and in animal respiration, while it is produced by green plants in sunlight. Lavoisier then followed up Black's and Priestley's work by showing that in combustion what he for the first time called oxygen combines with carbon and other substances, and that carbon dioxide is produced by the combination of carbon and oxygen, while water is produced by the combination of hydrogen and oxygen. He and Laplace[5] also showed that the carbon dioxide produced by an animal is nearly equivalent to the oxygen consumed, and that

[3] Lower, *Tractatus de Corde*, p. 86, 1669.

[4] Hooke, *Phil. Trans.*, II, p. 539, 1667. Hooke had been assistant to Willis and Boyle at Oxford.

[5] Lavoisier and Laplace, *Mémoires de l'Académie des Sciences*, p. 337, 1780.

the amount of heat formed by an animal is nearly equivalent to that formed in combustion of carbon when an equal quantity of oxygen is consumed in respiration and combustion. He thus made it clear that in the living body, just as in combustion, oxygen combines with carbon and other substances, producing carbon dioxide and other oxidation products: also that this combination is the source of animal heat.

He found in the course of experiments on man that during muscular work the consumption of oxygen and output of carbon dioxide is increased. Curiously enough, he expresses regret that this should be so, as the laboring classes, who have least money for buying food, consume more food than those who are better off.[6] The essential connection between physiological work and consumption of oxygen was still hidden from him, although, as already seen, Mayow had fairly correct ideas on this subject. It was not until 1845 that Mayer,[7] a German country doctor, pointed out in connection with the general formulation of the doctrine of conservation of energy, that in living animals, as in steam engines, ordinary kinetic energy as well as heat has its source in the potential energy liberated in the process of oxidation. Oxidation is thus the ultimate source of the energy of animal movements. Every exact experiment made since then on this subject has confirmed Mayer's conclusion, and the increased consumption of oxygen during muscular work became as intelligible as it was on Mayow's crude theory.

The discoveries with regard to the chemistry of respiration raised the further question as to what the exact nature of the combustible material is, and where the combination of oxygen with combustible matter occurs. As regards the first question it was evident that since on an average the composition of the adult living body remains constant, and the excreta, as compared with the food taken, contain very little combustible material, the material oxidized must correspond to the oxidizable matter of the food. This material was classified by Prout as belonging almost entirely to one or other of three groups of substances, known now under the names of proteins, carbohydrates, and fats. Of these the former alone contains nitrogen, which is excreted in the urine in the form, mainly, of urea when the protein is oxidized. Only water and carbon dioxide are formed in the oxidation of carbo-

[6] Lavoisier and Sequin, *Mém. de l'Acad.*, p. 185, 1789.

[7] Mayer, *Die organische Bewegung in ihrem Zusammenhange mit dem Stoffwechsel,* Heilbronn, 1845.

hydrates or fats, and by the ratios and amounts in which nitrogen compounds and carbon dioxide are excreted and oxygen consumed we can calculate how much protein, carbohydrate, and fat is being consumed in the body.

As regards the second question there was for long much doubt. It was, however, definitely shown by Magnus[8] in 1845 that much gas is liberated from blood on exposing it to a vacuum, and that less oxygen and more carbon dioxide are given off from venous than from arterial blood. The mercurial blood gas pump was then gradually perfected, mainly by Lothar Meyer, Ludwig, and Pflüger; and it was gradually established that the oxygen which disappears in the lungs is taken up by the blood almost entirely in the form of a loose chemical compound with haemoglobin, the colored albuminous substance in the red corpuscles. This compound yields up part of its oxygen as the blood passes round the systemic circulation, and returns to the lungs for a fresh charge, the charging being due to the higher partial pressure of oxygen in the lungs, while the partial discharging in the systemic circulation is due to the lower partial pressure there in consequence of consumption of oxygen. The discharging is accompanied by a change of color from scarlet to dark purple. Similarly carbon dioxide is taken up mainly in the form of a loose chemical combination with alkali, and discharged in the lungs as a consequence of the lower partial pressure of the gas in the lungs. For a considerable time there was much doubt as to how far the actual oxidation occurs in the blood or in the tissue elements; but the investigations of Pflüger[9] about 1872 showed clearly that practically all the oxidation occurs in the tissues.

So far I have discussed from an abstract physical and chemical standpoint the main outlines of discovery relating to respiration. It is now necessary to consider these discoveries more closely, and from a physiological standpoint. For a long time the brilliance of Lavoisier's discovery as to the relation between respiration and animal heat carried physiologists to some extent off their balance, as it came to be believed that heat production is a more or less blind mechanical process under no direct organic control, and presumably dependent simply upon the supply of oxygen and oxidizable material. Thus Liebig, who was not only a great chemist but also a great chemical physiologist, concluded that every increase in the food consumed or the amount of oxygen

[8] Magnus, *Annalen der Physik*, XL, 1838, and LXVI, 1845.
[9] Pflüger, *Pflüger's Archiv*, VI, p. 43, 1872.

introduced into the lungs must increase the rate of oxidation and heat production.[10] This conclusion seemed to be confirmed when he introduced his well-known method for the determination of urea in urine and it was found that every increase in the amount of nitrogenous food eaten was followed by a corresponding increase in the amount of urea excreted, although during complete starvation the excretion of urea was not diminished below a certain minimum. He inferred that it is only the "vital force" which protects the body against indefinite oxidation, and that when more food is introduced than is really required this protection is not extended, so that the food material falls a prey to oxygen. In assuming this influence of the "vital force" he was only applying to the phenomena of physiological oxidation the ideas held by the majority of contemporary physiologists.

When, however, the phenomena of physiological oxidation came to be studied more closely by Bidder and Schmidt, Voit, and other physiologists, it was found that although the excretion of urea might fall greatly during starvation there was very little fall in the consumption of oxygen. It thus became evident that any diminution in the consumption of protein was accompanied by increase in consumption of the fat and of any carbohydrate remaining in the body. Further investigation of the ratios in which protein, carbohydrate, and fat replaced one another in the oxidations occurring in the body resulted in the striking discovery by Rubner that within wide limits of variation in their supply to the body they replace one another in proportion to the energy which they liberate in their oxidation within the body.[11] Thus 1 gram of fat furnishes as much energy as 2¼ grams of protein or carbohydrate, and 1 gram of fat from the reserve in the body takes the place of 2¼ grams of protein or carbohydrate when the supply of the latter in the food is cut off. The idea that the rate of oxidation in the living body is determined by the rate of food supply is thus erroneous. On the contrary the oxidation is regulated with marvelous accuracy in accordance with its energy value in satisfaction of what are commonly called the "energy requirements" of the body. Rubner's discovery is one of the main physiological foundations of scientific dietetics.

Just as the rate of physiological combustion, other things being equal, is not determined in the higher organisms by the supply of food material, so it is not determined by the abundance of the

[10] Liebig, *Letters on Chemistry*, Third English Edition, p. 314, 1855.
[11] Rubner, *Zeitschr. f. Biologie*, XIX, p. 313, 1883.

oxygen supply. Lavoisier himself and afterwards Regnault and Reiset found that a warm-blooded animal breathing pure oxygen consumes no more oxygen than an animal breathing ordinary air; and subsequent investigations have shown that the oxygen percentage in air has to be reduced very low before the oxygen consumption is diminished. Pflüger also found that oxidation in the tissues is within wide limits independent of the rate of supply of oxygen through the blood circulation. We are thus again face to face with "physiological requirements."

When temperature and heat production in the living body came to be studied physiologically the first striking fact discovered was that however much the external temperature might vary within wide limits, the body temperature of warm-blooded animals remained practically the same during health. Similarly, although the heat production might be increased several times by muscular exertion there was no material increase of body temperature, and it became quite evident that the rise of temperature in fever is not due to increased heat production, but to disturbance in the nervous regulation of heat discharge from the body. Finally, when the influence of variations in external temperature on heat production in the body was measured, it was found by a succession of observers, including, besides Lavoisier,[12] Crawford in 1788, and Pflüger and others in more recent times, that, particularly in small animals, a lowering of external temperature evokes through the influence of the nervous system a rise in heat production, so that heat production becomes subservient to the maintenance of body temperature. This maintenance is therefore one of the factors determining physiological energy requirements.

When we inquire what determines the energy requirements of the body as a whole we find that the results of investigation point us towards a number of associated conditions which we can identify one by one by observation or experiment, but which ordinarily occur in conjunction with one another, and on an average remain very constant. Thus the activity of the nervous system in determining various forms of muscular and glandular activity constitutes one of the chief factors. But the activities of the nervous system are themselves subject to control in the form of what we call on the one hand "fatigue," or on the other "exuberance of spirits," finding its expression in man in games and what appear at first sight to be mere "luxus" activities of all kinds.

[12] Pflüger, *Pflüger's Archiv*, XII, p. 282, 1876.

Hence apart from seasonal variations the daily nervous activities are pretty constant in total amount.

Although the internal body temperature is actually very constant, yet a very moderate actual rise or actual fall in body temperature is sufficient to increase or diminish oxidation very materially. In fever, for instance, the oxidation in the body is greater than it would be without the rise of temperature but with other conditions the same. The oxidation in fever is, however, only a fraction of that during even very moderate exertion.

When we examine still more closely, and in the light of the facts which are continuously becoming revealed by pathology and pharmacology, we begin to realize that "energy requirements" depend on an infinite multitude of associated "normal conditions." An upset in the proportion of, say, calcium or potassium in the blood, or in that of substances produced in minute amounts in one or other of the "ductless glands" or supplied to the body along with the other main constituents in ordinary food, will dramatically end "energy requirements" by that mysterious phenomenon which we call death, and which we are so familiar with that we almost cease to speculate about its nature.

At first sight death may seem to become intelligible when we find that in the higher animals its immediate cause is want of oxygen in the tissues owing to interruption of the circulation or breathing. But further examination shows us that death is no mere stoppage of an engine owing to lack of air or fuel, but also total ruin of what we took to be machinery. It is a mysterious dissolution in the association together of the infinitely complex group of normals which constitute the life— the φύσις — of an organism; and an examination of the fragments left has thrown no light on why the association should have existed at all, or endured so long. The outward form and internal arrangement and composition of the dead body tell their story of life to him who can interpret their hieroglyphics; but there is no life visible. The gulf between the dead and the living is a gulf across which our present intellectual vision does not reach, and we only deceive ourselves when we sometimes imagine that it does. Thus when we ask what determines those "energy requirements" which determine consumption of oxygen and output of carbon dioxide in the living body, the only answer we can at present elicit from experimental investigation is that the energy requirements are one side of the φύσις of the organism. To those who object that the φύσις is a mere name, and that physiology *must* be simply physics and chemistry I can

only reply, following the example of Hippocrates who protested against the intrusion of abstract philosophical speculations into medicine, that there can be no doubt about the existence of the associated and persistent group of appearances which the word φύσις designates when applied to life. If we ignore this we reject the one thing which gives us that grasp of biological phenomena which enables us to predict them, and renders a scientific treatment of biology and medicine possible.

The immediate subject of this book is the side of physiology which concerns the means by which the supply of oxygen and removal of carbon dioxide are so carried out and regulated that physiological requirements are met. That this supply and removal are through the lungs and blood has already been pointed out; but the development of knowledge as to the means of regulation must now be traced. Much difficulty arises, however, from the fact that the problem itself was only recently realized with any clearness. Respiration and circulation have been to a large extent treated as if the requirements of the body were on the whole constant. Actually, however, the consumption of oxygen and production of carbon dioxide fluctuate greatly. A heavy exertion, for instance, will increase tenfold the consumption of oxygen and output of carbon dioxide for the whole body, and must certainly increase in a far higher ratio the consumption and output of the muscles actually at work.

It has of course been known from the earliest times that muscular activity causes great increase in the depth and frequency of the breathing, and that rebreathing the same air has a similar effect; but the very familiarity of these facts seems to have led to a relative neglect of the problem of how the respiratory activities are regulated. An undue specialism has led to the investigation of each form of bodily activity as if it were something separable from other bodily activities, and not a *physiological* activity. Further confusion has arisen through the roughness of many of the experiments made on animals, and corresponding failure to detect the delicacy of physiological regulation.

In 1811 it was discovered by Legallois that if a portion of tissue definitely localized in the medulla oblongata is destroyed respiration ceases and death ensues.[18] This part of the medulla has come to be known as the respiratory center; and round the responses of this "center" to various nervous and other stimuli the physiological investigation of breathing has been focused.

[18] Legallois, *Expériences sur la principe de la vie*, Paris, 1812.

It was found by Legallois and subsequent investigators that the nervous connections both above and below the respiratory center can be successively severed without preventing the rhythmic discharges of inspiratory and expiratory impulses except in so far as efferent nerves connected with the center are cut off from it. Thus the rhythmic discharges of the center are not dependent on afferent nervous impulses and continue regularly so long as normal arterial blood is supplied to it. In this sense the action of the center is automatic. On the other hand the mode of action of the center is much affected by nervous stimuli.

In the first place its action is to a large extent under voluntary control. Thus the breathing can easily be suspended for about a minute, and in the actions of speaking, singing, etc., is greatly interfered with. The rate and depth of breathing are also under voluntary control, and may be much affected by emotion. Consciously perceived stimuli of all kinds may also affect the breathing—particularly stimuli affecting the air passages. The irregularity and variability of the breathing owing to all these causes tended to direct the attention of physiologists away from the central problem of how the breathing responds to fundamental physiological requirements.

It was soon discovered that apart from consciously felt stimuli the breathing is specially affected by afferent stimuli conducted by the vagus nerve. Early last century it was noticed that when the vagus nerves are severed the breathing becomes less frequent and deeper; and on stimulating the vagi various marked effects, depending on the strength of stimulus, were found to be produced on the breathing.

In 1868 Hering and Breuer[14] made the striking discovery that on mechanically interrupting, at the end of inspiration, the expulsion of air from the lungs the rhythm of respiratory effort is interrupted for a time, until at last this interruption is broken by an inspiratory effort, followed by alternating expiratory and inspiratory efforts showing that the center has renewed its rhythmic activity. Similarly if at the end of expiration air is prevented from entering the lungs there is an interruption before the center returns to its normal rhythmic activity. These effects are completely absent if the vagi have been divided. The slow rhythmic discharges of the center go on quite independently of whether the inflation or deflation of the lungs is prevented or not.

[14] Hering and Breuer, *Sitzber. d. Wiener Akad., Math-naturw. Cl.* (2), LVII, p. 672 and LVIII, p. 909, 1868.

It was evident from these experiments, and from the marked slowing and deepening of breathing after the vagi are cut, that distention of the lungs stimulates the nerve endings of the vagi in the lungs in such a way as to terminate inspiration and initiate expiration, while deflation of the lungs produces a corresponding stimulus acting so as to terminate expiration and initiate inspiration. Thus inspiration seems to be the cause of expiration, and expiration of inspiration. Hering described this as the "self-regulation" of breathing.

Another series of observations relates to chemical stimulation of the respiratory center. It was found that if air containing very little oxygen is breathed, or a small volume of ordinary air is repeatedly rebreathed, great panting ensues, followed by general convulsions and final cessation of breathing. The same result was found by Küssmaul and Tenner to follow if the blood supply to the brain is completely cut off, so that the blood remaining in the vessels becomes venous. The respiratory center is thus first stimulated to excessive action by imperfectly oxygenated or venous blood, and later becomes exhausted and finally ceases to act. But another most significant fact was definitely discovered by Rosenthal in 1862.[15] If in an animal artificial respiration is pushed so that the ventilation of the lungs is abnormally great the activity of the respiratory center ceases entirely for a time, and this condition he designated as apnoea. In most persons apnoea can be produced easily by voluntarily forcing the breathing for a short time. After a few deep and rapid breaths it will be noticed that all natural tendency to breathe ceases for a time.

These observations suggested that ordinary breathing is determined by the degree of arterialization of the blood supplying the respiratory center. If the degree of arterialization is diminished the breathing is increased, and vice versa, so that the respiratory center automatically maintains a normal degree of arterialization. When the venous blood is arterialized in the lungs two changes occur, as we have already seen. The blood takes up oxygen, and also loses carbonic acid. It might be one or the other, or else both, of these changes that determines the activity of the respiratory center. The most immediately evident change in the blood during its passage through the lungs is its change in color from a bluish to a bright scarlet color, and this change, as already seen, is due solely to its oxygenation and not to loss of carbonic acid. We thus naturally tend to think of blue blood as venous and

[15] Rosenthal, *Die Athembewegungen*, 1862.

scarlet as arterial; and with the blood pump we can easily prove that the scarlet blood contains more dissociable oxygen than the blue.

Rosenthal came to the conclusion that it is solely or almost solely in virtue of its varying oxygen content that the blood stimulates the respiratory center or not.[16] Careful blood-gas determinations showed that when apnoea had been produced by forced ventilation of the lungs the arterial blood contained a little more oxygen. On the other hand, when oxygenation was rendered incomplete by letting an animal breathe air very poor in oxygen there was an immediate great increase in the breathing, although the discharge of carbonic acid was in no way interfered with. Moreover, when air containing a very large excess of CO_2 was breathed by an animal the rate of breathing remained normal. Rosenthal also brought forward other evidence which appeared to point in the same direction; but the weak point in his argument was the fact that there is no apnoea when pure oxygen is breathed, although the arterial blood contains a good deal more oxygen than usual. The truth is that he had been misled by the fact that a very high percentage of CO_2 in the air breathed has a narcotic effect, so that the breathing, which is in reality increased at first by raising the percentage of CO_2 in the air of the lungs, quiets down again when the percentage becomes very high. Pflüger and Dohmen[17] showed that both excess of CO_2 (provided that the CO_2 is not in too great excess) and want of oxygen excite the respiratory center.

A further fact, discovered originally by Traube,[18] but often overlooked by subsequent investigators, was that apnoea could be produced even by a gas such as nitrogen or hydrogen, in which no oxygen was present. Thus if apnoea is due to "over-arterialization" of the arterial blood it can be produced by the simple removal of CO_2, whether or not the oxygen is also diminished, although the artificial ventilation of the lungs must be much more vigorous if apnoea is produced in the absence of oxygen.

Meanwhile another theory of apnoea was put forward, and has led, as will be shown later, to the utmost confusion and complete misinterpretation of the facts. When the lungs are distended there is, as already mentioned, an interruption in the rhythm of discharge from the respiratory center. The inspiratory muscles,

[16] Rosenthal in Hermann's *Handbuch der Physiol.*, Vol. IV, 2, 1882.
[17] Pflüger, *Pflüger's Archiv*, I, p. 61, 1868.
[18] Traube, *Allgem. Med. Centralzeitung*, 1862, No. 38, and 1863, No. 97.

and specially the diaphragm, are, and remain till the interruption is broken by an inspiratory effort, relaxed. This interruption of *inspiratory* effort came to be interpreted as an apnoea, and appears so if only inspiratory muscular movements are recorded, as, for instance, with the method adopted in Hering's laboratory by Head,[19] in which only the contractions of the diaphragm are recorded, or with other methods which do not record tonic expiratory effort. Hence it came to be assumed that there exists what is called "vagus apnoea." The next step was to maintain that all apnoea is in reality vagus apnoea, and this inference was supported by the fact that "apnoea" can still be obtained when the arterial blood is blue owing to air containing a very low percentage of oxygen being breathed, and can also be produced (as Lorrain Smith and I found) by air very rich in CO_2. It was also affirmed by Brown-Sequard that after the vagi are cut apnoea cannot be produced, though this statement can easily be shown to be completely mistaken. With an efficient apparatus for increasing the ventilation of the lungs apnoea can quite readily be produced after section of the vagi.

On the other hand, increasingly clear evidence accumulated that apnoea due to over-ventilation of the blood passing through the lungs exists as a matter of fact. The most striking proof of this was afforded by experiments in which Fredericq[20] crossed the circulation of two animals by connecting the vessels in such a way that the respiratory center of each animal was supplied with arterial blood from the other animal. He then found that when excessive artificial respiration was produced in one of the animals apnoea was produced in the other, and when the artificial respiration ceased hyperpnoea continued in the animal which had had artificial respiration, since its respiratory center was now receiving blood which was venous owing to the cessation of breathing in the other animal. This hyperpnoea, on the other hand, maintained the apnoea in the other animal, so that one of the animals remained apnoeic while the other remained hyperpnoeic.

This experiment showed clearly the existence of a true "chemical" apnoea; but, as the existence of vagus apnoea was also considered to be firmly established, the existence of both forms of apnoea came to be generally assumed. As regards vagus apnoea the evidence was considered to show that when apnoea is produced by distending the lungs with air or hydrogen it is vagus apnoea that

[19] Head, *Journ. of Physiol.*, X, 1 and 279, 1889.
[20] Fredericq, *Arch. der Physiol.*, 17, p. 563, 1901.

lasts on after the distention ceases, and from this supposed fact the further inference was drawn that repeated distention of the lungs produces a summed vagus effect resulting in vagus apnoea after the distentions have ceased. Thus the same procedure that causes chemical apnoea seemed to produce also vagus apnoea, and the two kinds of apnoea could hardly be distinguished in practice. Moreover hyperpnoea due to any chemical cause such as want of oxygen or excess of CO_2 must apparently tend to be prevented by the production of vagus apnoea due to repeated distentions of the lungs. The two processes by which the breathing appeared to be regulated acted, therefore, in opposite directions.

As regards the chemical stimuli acting on the respiratory center, it remains to consider the further evidence as to the relative importance of want of oxygen and excess of CO_2; also whether other chemical stimuli act on the center. In 1885 Miescher[21] showed by experiments on man that a given small increase in the percentage of CO_2 in air affects the breathing considerably, while a corresponding diminution in the oxygen percentage has no such effect. He was thus led to the conclusion that it is the CO_2 percentage in the air of the lungs that ordinarily determines the chemical regulation of breathing, and not the oxygen percentage. Thus CO_2 protects the body from want of oxygen so long as ordinary air is breathed. It will be seen in the sequel how relatively correct this general view of Miescher's was, although he maintained the existence of vagus apnoea and thus shared in the mistakes of his time.

In 1888 Geppert and Zuntz[22] published the results of a very careful series of experiments on the effects of muscular work (produced by tetanizing the hind limbs of an animal after section of the spinal cord) on respiration. After bringing forward new evidence that it is the blood which carries the stimulus for increased breathing to the respiratory center they showed that during the work the proportion of CO_2 in the blood was greatly diminished, and that there was also a slight increase in the oxygen percentage of the blood. Hence, they argued, it is neither increase in CO_2 percentage nor diminution in oxygen percentage that causes the hyperpnoea accompanying muscular exertion. They believed that it is some acid substance produced in the muscles, and pointed out that Walter had found that the breathing is much increased in poisoning by acids.

[21] Miescher, *Arch. f.* (*Anat. u.*) *Physiol.*, p. 355, 1885.
[22] Geppert and Zuntz, *Pflüger's Archiv*, XLII, pp. 195, 209, 1888.

From the foregoing review of the knowledge existing up to the beginning of the present century on the physiological regulation of breathing it will be seen that the conclusions reached were unsatisfactory in many ways, and to some extent contradictory. On the one hand the nervous regulation through the vagi and other nerves seemed to have no relation to the requirements of the body for oxygen and for removal of CO_2, and in fact to act antagonistically to these requirements. On the other hand the excitation of the breathing during muscular work seemed also, from the results of Geppert and Zuntz, to have no definite relation to increased requirements for oxygen and CO_2. There was also no definite quantitative information as to why in normal breathing during rest the composition of the expired air is so constant as it is. Without more exact and consistent physiological knowledge it appeared to be very difficult to interpret the abnormal breathing so often met with in disease, or to know how to set about investigating it.

From still another standpoint the existing knowledge was very unsatisfactory to me personally. From a consideration of the general characteristics which distinguish a living organism from a machine I had become convinced that a living organism cannot be correctly studied piece by piece separately as the parts of a machine can be studied, the working of the whole machine being deduced synthetically from the separate study of each of the parts. A living organism is constantly showing itself to be a self-maintaining whole, and each part must therefore always be behaving as a part of such a self-maintaining whole. In the existing knowledge of the physiology of breathing this characteristic could not be clearly traced. The regulation of breathing did not, as represented in the existing theories, appear to be determined in accordance with the requirements of the body as a whole; and for this reason I doubted the correctness of these theories, and suspected that errors had arisen through the mistake of not studying the breathing as one of the coördinated activities of the whole body. In so far as the investigations detailed in succeeding chapters originated with me, they were mainly inspired by the considerations just mentioned; and, as will be seen in the sequel, the same considerations have led to a reinvestigation and reinterpretation of other physiological activities besides breathing.

CHAPTER II

Carbon Dioxide and Regulation of Breathing.

My attention was first directed to the regulation of breathing by a series of experiments carried out by Lorrain Smith and myself[1] as to the question whether, as had shortly before been asserted by Brown-Sequard and d'Arsonval as a result of a very definite and apparently convincing series of experiments, a poisonous organic substance is given off in expired air. The results of our experiments, which were made partly on man and partly on animals, were entirely negative, and left no doubt in our minds that the apparent positive results described were due partly to undetected air leaks which led to animals being asphyxiated, and partly to other experimental errors. In the human experiments we used an air-tight respiration chamber of about 70 cubic feet capacity, in which the air became more and more vitiated by respiration.

The effects of the vitiated air on our breathing attracted our attention specially. When the proportion of CO_2 in the air rose to about 3 per cent, and the oxygen fell to about 17 per cent (there being 20.94 per cent of oxygen and 0.03 per cent of CO_2 in pure atmospheric air) the breathing began to be noticeably increased. With further vitiation the increase in breathing became more and more marked, until with about 6 per cent of CO_2 and 13 per cent of oxygen the panting was very great, with much consequent exhaustion.

When the experiment was repeated, with the difference that the CO_2 was absorbed by means of soda lime, there was no noticeable increase in the breathing before the oxygen fell below about 14 per cent. When, finally, the CO_2 was left in the air, but oxygen was first added so that the oxygen remained abnormally high throughout, the panting was just the same as when ordinary air was used. In short experiments in which the same air was rebreathed from a large bag till we could no longer stand the experiment we found that we had to stop at about 10 per cent of CO_2, whether oxygen was added or not, and that the oxygen percentage made no difference to the distress produced. In these experiments there was only about 8 to 9 per cent of oxygen in the

[1] Haldane and Lorrain Smith, *Journal of Pathology and Bacteriology*, I, pp. 168 and 318, 1893.

rebreathed air at the end of the experiment; but even this made no difference to the breathing. When, on the other hand, a mixture containing a greatly reduced oxygen percentage, without any addition of CO_2, was breathed, the breathing was increased sensibly, as shown by graphic records, when the oxygen fell to about 12 per cent, and was greatly increased by lower percentages. With extremely low percentages, such as 2 per cent, consciousness was lost quite suddenly after about 50 seconds, before there was time to notice any increase in the breathing.

It was evident from these experiments that when the same air is rebreathed, or an insufficient proportion of fresh air is supplied, the increased breathing produced is due simply to excess of CO_2, until, at least, the oxygen percentage becomes extremely low. It appeared, therefore, that the variations in ordinary breathing in response to variations in the respiratory exchange must be due to the increased CO_2 produced, and not to the increased consumption of oxygen. This conclusion was the same as that of Miescher, and supported his views as to the regulation of respiration.

When more than about 10 per cent of CO_2 was breathed the effect of the mixture was to produce stupefaction, which was very marked with higher percentages. This effect was already well known in animals, and CO_2 was one of the gases tried as an anaesthetic by Sir James Simpson before he adopted chloroform. The effect of excess of CO_2 in producing ataxia, stupefaction, and loss of consciousness has become very familiar to me in connection with experiments with mine-rescue apparatus and diving apparatus. These effects are readily produced in the presence of a large excess of oxygen, and are therefore quite independent of the effects of want of oxygen. The narcotic effect of a large excess of CO_2 quiets down the respiration, and this effect in animals led many previous observers to overlook almost entirely the ordinary effects of CO_2 in stimulating the breathing.

During the next few years after our first experiments I was engaged in the investigation of other problems connected with general metabolism, respiration, and blood gases, but in 1903 returned to the regulation of breathing in a long series of experiments carried out in conjunction with Dr. J. G. Priestley, who was then a student at Oxford.

It seemed pretty evident that in order to reach clear ideas on the regulation of breathing it was necessary to study very carefully the composition of the alveolar air which is in contact, through the alveolar epithelium, with the blood passing through

the lungs; also that this could be best done on man. The composition of human alveolar air under different conditions had already been calculated by Loewy[2] and Zuntz from the volume occupied by a plaster cast of the respiratory passages in a dead body and the average composition and volume of a breath of expired air. The expired air is evidently a mixture of air from the alveoli with the air which remains in the respiratory tubes at the end of inspiration. This air is presumably but little altered by diffusion through the walls of the respiratory tubes, and so far as respiratory exchange is concerned the volume of the lumen of these tubes must constitute a "dead space" in breathing. The dead space is occupied by alveolar air at the end of expiration, and by more or less pure atmospheric air at the end of inspiration.

If we know the volume of the dead space, and the volume and composition of the air expired at each breath, we can calculate the average composition of the alveolar air. It is, however, impossible to estimate directly the volume of the dead space in a particular individual with any accuracy, or to be sure that it remains the same under different physiological conditions. The bronchi and bronchioles are provided with a muscular coat by means of which their lumen is capable of contracting or dilating. Apart from this the air in the alveoli which are nearest to the end of a bronchus will contain purer air during inspiration than during expiration, and this introduces a further complication.

To get a reliable knowledge of the composition of alveolar air it seemed desirable to make direct determinations. The method introduced by Priestley and myself[3] is simply to make a sharp and deep expiration through a piece of hose pipe about four feet long and one inch in diameter, and provided with a plain glass mouthpiece which is closed by the tongue at the end of the expiration (Figure 1). By means of a narrow bore glass tube filled with mercury and introduced air-tight into the hose pipe near the mouthpiece, a sample of the last part of the expired air is then at once taken directly into the gas analysis apparatus as indicated in Figure 1,[4] or else into a vacuous sampling tube.[5] If the sample is to be a normal one the breathing must be quite normal before

[2] Loewy, *Pflüger's Archiv*, LVIII, p. 416, 1894.

[3] Haldane and Priestley, *Journ. of Physiol.*, XXXII, p. 225, 1905.

[4] For physiological work methods of air analysis which are both accurate and rapid are required. A description of the methods which I introduced with this in view will be found in my book, *Methods of Air Analysis*, London, Charles Griffin & Co., Third Edition, 1920.

[5] If the sample is too large some pure air may be drawn in.

the deep expiration; and it requires some care to secure this. Under normal resting conditions the depth of expiration needed in order to give a reliable sample at the end of inspiration is at least 800 cc. With less than this the sample is likely to be mixed with air of

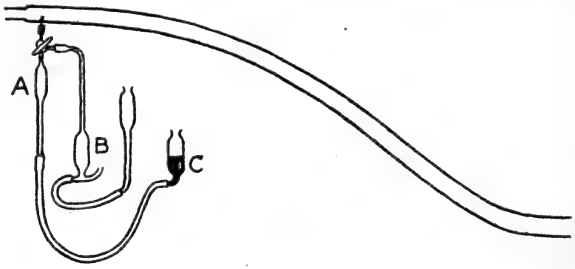

Figure 1.
Apparatus for obtaining and analysing alveolar air.

the apparent dead space; for though with normal breathing the volume of the apparent dead space is far less than 800 cc., at least three or four times its volume of alveolar air is needed in order to flush it and the breathing tube out thoroughly. If more than about 800 cc. are expired, the composition of the sample is the same whatever the depth of the expiration, and we designated air of this constant composition as "alveolar air" although, as will be shown later, the composition of the air in the alveoli is by no means such a simple matter as we thought. The following are the averages of results which I obtained on this point when the samples were taken just at the end of inspiration.[6]

Vol. of air expired through tube	*Per cent of CO_2 in sample taken from tube*
190 cc.	3.03
335	4.37
510	5.04
650	5.19
950	5.51
1350	5.48

As soon as this method of sampling the alveolar air was applied on ourselves and others it became evident that the alveolar CO_2 and O_2 percentage during rest under normal conditions are sur-

[6] Haldane, *Amer. Journ. of Physiol.*, XXXVIII, p. 20, 1915.

prisingly constant for each individual. As the depth of breathing cannot be kept absolutely steady and the composition of the alveolar air varies slightly with inspiration and expiration it is best to take at least two samples—one just at the end of inspiration, and another just at the end of expiration. The following tables give the CO_2 percentages in samples of our normal resting alveolar air, taken in the sitting position during rest at intervals over about 20 months in 1903 to 1905. Since then we have made many further determinations, but the percentages have remained nearly the same. They are slightly lower or higher on some days than on others, and other observers have noticed this in themselves.

J. S. H.

Barometric pressure in mm. of Hg.	*CO_2 per cent, end of inspiration*	*CO_2 per cent, end of expiration*	*CO_2 per cent, mean*
759	5.33	5.76	5.545
747	5.47	5.69	5.56
748	5.56	5.70	5.63
748	5.59	5.87	5.73
748	5.38	5.60	5.49
748	5.33	5.94	5.40
749	5.80	5.51	5.87
749	5.66	5.59	5.585
765	5.63	5.83	5.61
759	5.42	5.72	5.625
758	5.74	5.72	5.71
765	5.53	5.72	5.62
Mean 754	5.54	5.72	5.63

It will be seen that, as might be expected, the inspiratory samples give on an average a somewhat lower result than the expiratory ones. The average for one subject is 5.63 per cent and for the other 6.28. The slight variations of individual results from these averages are evidently not due merely to changes in barometric pressure.

When ordinary air was breathed the oxygen percentage in the alveolar air was nearly as steady as the CO_2 percentage. When, however, the oxygen and CO_2 percentages in the inspired air were varied it became quite evident that the breathing is regu-

J. G. P.

Barometric pressure in mm. of Hg.	*CO_2 per cent, end of inspiration*	*CO_2 per cent, end of expiration*	*CO_2 per cent, mean*
759	6.18	6.43	6.305
754	6.51	6.63	6.57
747	6.10	6.70	6.40
753	6.81	6.86	6.835
758	5.95	6.74	6.35
758	5.82	6.23	6.025
758	5.93	6.21	6.07
754	6.12	6.33	6.215
754	6.26	6.20	6.23
754	6.23	6.05	6.14
751	5.66	6.75	6.205
751	5.98	5.99	5.985
762	6.37	6.29	6.33
762	6.24	6.09	6.165
765	6.39	6.43	6.41
Mean 756	6.17	6.39	6.28

lated so as to give a constant percentage of CO_2 and not of oxygen. The following results were obtained with oxygen percentages varied at intervals in the same subject.

OXYGEN PERCENTAGE		CO_2 PERCENTAGE	
Inspired air	*Alveolar air*	*Inspired air*	*Alveolar air*
80.24	72.21	0.20	5.84
63.67	57.57	0.14	5.41
20.93	14.50	0.03	5.54
16.03	10.39	0.05	5.62
15.82	10.59	0.05	5.60
15.63	10.60	0.07	5.45
12.85	8.34	0.06	5.37
12.78	7.80	0.07	5.28
11.33	8.96	0.10	3.85
11.09	7.10	0.10	4.89
6.23	4.30	0.09	3.57

This table shows that increase in the oxygen percentage over short periods had no noticeable influence on the alveolar CO_2 percentage, and that not until the oxygen percentage in the in-

spired air was lowered to about 12 or 13 and the alveolar oxygen percentage to about 8 was there any marked decrease in the CO_2 percentage. With a greater lowering of the oxygen percentage than this, however, the breathing was so much increased as to lower the CO_2 percentage considerably.

When the CO_2 percentage in the inspired air was increased, on the other hand, the effect was strikingly different. Instead of the alveolar CO_2 rising in any direct correspondence to the rise in the inspired CO_2, the increase in alveolar CO_2 was so slight as to be hardly appreciable even with a rise of 2 or 3 per cent in the CO_2 of the inspired air. This is evident from the following experiments, made in the air-tight chamber.

SUBJECT	CO_2 PER CENT IN INSPIRED AIR	CO_2 PER CENT IN ALVEOLAR AIR		RELATIVE RATES OF ALVEOLAR VENTILATION	
		End of inspiration	*End of expiration*	*Mean*	
J. S. H.	0.03	5.42	5.83	5.62	100
"	**2.07**	**5.60**	—	—	**153**
"	3.80	6.03	5.92	5.97	258
"	0.03	5.74	5.72	5.71	100
"	1.74	5.59	5.71	5.65	143
"	3.98	5.99	6.16	6.03	277
"	5.28	6.44	6.66	6.55	447
J. G. P.	0.03	6.85	6.28	6.31	100
"	5.29	6.92	6.86	6.89	392
"	6.66	7.62	7.72	7.67	622
"	7.66	8.34	8.56	8.45	795

The evident effect of adding CO_2 to the inspired air was so to increase the breathing that, if the percentage added was not too high, the CO_2 percentage in the alveolar air was kept nearly constant. Of the delicacy of this reaction it is easy, from the figures, to form a fair estimate. With a moderate amount of hyperpnoea, and provided that, as was actually the case, sufficient time has elapsed to eliminate the influence of any temporary damming back of CO_2 within the body, the discharge of CO_2 by the lungs is about the same during hyperpnoea as during rest. Hence it is possible to calculate how great a relative increase in the alveolar ventilation is brought about by a given increase in the alveolar

CO_2 percentage. We found that about 0.23 per cent increase in the alveolar CO_2 gives 100 per cent increase in the resting alveolar ventilation. For instance with 4.16 per cent of CO_2 in the inspired air, the alveolar CO_2 percentage would rise to about 6.06 per cent, if it had been about 5.6 per cent when pure air was breathed. As the difference between 4.16 and 6.06 is only a third of the difference between 0.0 and 5.6, it follows that the alveolar ventilation is thrice as great with the slightly raised alveolar CO_2 percentage.

A more precise measure of the effects of raising the alveolar CO_2 percentage on the lung ventilation has more recently been obtained by Campbell, Douglas, and Hobson,[7] who found that for an increase of 10 liters per minute in the volume of air breathed there was an increase of 0.28 per cent (or 2 mm. of mercury pressure) in the alveolar CO_2. An increase of 0.17 per cent was sufficient to double the alveolar ventilation during complete rest in a deck chair.

If an increase of 0.2 per cent in the alveolar CO_2 is sufficient to double the alveolar ventilation it might be expected that a decrease of 0.2 per cent would cause the breathing to cease. As already mentioned, forced breathing or excessive artificial respiration causes temporary cessation of natural breathing, or apnoea. After forced breathing for about a minute the subsequent apnoea commonly lasts for about 1½ minutes in man. The alveolar CO_2 percentage is markedly diminished for a few seconds by even a single extra deep breath of pure air, and correspondingly increased by a breath of air containing more than 5 or 6 per cent of CO_2. It is easy to show, however, that the full effect of the diminished or increased percentage of CO_2 on the respiratory center is not immediate. This is just what might be expected. The arterial blood leaving the lungs at any moment is doubtless saturated with CO_2 to a point corresponding with the existing percentage of CO_2 in the alveolar air; but when this blood reaches the tissues it comes in contact with tissue and lymph saturated with CO_2 to the normal extent, but possessing a considerable capacity for absorbing more CO_2. In consequence of this the tissues, including the respiratory center, take some time to get into equilibrium with the new level of saturation with CO_2 in the arterial blood. Hence in order to measure the real effect of any increase or diminution in the alveolar CO_2 percentage, it is necessary to maintain this percentage constant for some time. When air containing an excess

[7] Campbell, Douglas, and Hobson, *Journ. of Physiol.*, XLVIII, p. 303, 1914.

of CO_2 is breathed, the alveolar CO_2 percentage naturally becomes constant after a few minutes; but with forced breathing of ordinary air it is not possible to maintain an alveolar CO_2 percentage which is below the normal by some required small amount.

To get over this difficulty we employed forced breathing with air to which CO_2 had been added, and found that on successive trials with increasing percentages of CO_2 in the inspired air the duration of apnoea following forced breathing diminished until, when there was more than about 4.7 per cent of CO_2 in the inspired air, no apnoea at all was produced. It was thus evident that a very small diminution in the alveolar CO_2 percentage produces apnoea. The actual composition of the alveolar air at the end of forced breathing in similar experiments was determined later by Douglas and myself.[8] It was found that with more than 4.7 per cent of CO_2 in the inspired air no apnoea could be produced by forced breathing, however hard, in a person whose normal alveolar CO_2 percentage was about 5.6, and that apnoea was only produced if the alveolar CO_2 was reduced by more than 0.2 per cent below the normal. When, however, the CO_2 in the inspired air was lower, so that the alveolar CO_2 percentage was reduced by more than 0.2 per cent, apnoea was produced.

It is thus clear that the cause of the apnoea following forced breathing is reduction in the CO_2 percentage in the alveolar air, and that a reduction of as little as 0.2 per cent is sufficient to cause apnoea. The astounding sensitiveness of the respiratory center to CO_2 is thus clearly established in both an upward and a downward direction. A mean increase or diminution of .01 per cent in the alveolar CO_2 will evidently produce an increase or diminution of 5 per cent in the alveolar ventilation, or of about 400 cc. per minute in the lung ventilation.

It may be useful to review briefly the sources of error in the views current until recently with regard to the causes of the apnoea produced by excessive ventilation of the lungs. One view was that the excess of oxygen in the arterial blood causes the apnoea. This theory had so little evidence to support it that it is very surprising that it should have remained current so long. It is true that during excessive artificial respiration the arterial blood contains slightly more oxygen than usual; but there is a still greater excess during the quiet normal breathing of pure oxygen, which causes not the smallest sign of apnoea. Rosenthal[9] laid great

[8] Campbell, Douglas, Haldane, and Hobson, *Journ. of Physiol.*, XLVI, p. 312, 1913.

[9] Rosenthal in Hermann's *Handbuch der Physiologie*, IV, 2, p. 266.

stress on an experiment in which on slightly raising the pressure in a spirometer from which an animal is breathing, the animal stops breathing; and he attributed this to increase in the partial pressure of the oxygen in the spirometer. The real cause was quite evidently the distention of the animal's lungs by the pressure, as in the experiments of Hering and Breuer. When a man or animal has been rendered hyperpnoeic from want of oxygen, and the hyperpnoea has reduced the normal percentage of CO_2 in the alveolar air and blood, apnoea is produced by supplying more oxygen; but this apnoea is of course dependent on deficiency of CO_2, and cannot, therefore, be cited in support of the oxygen theory of ordinary apnoea.

The other erroneous theory—that apnoea following forced breathing is due to a summation of inhibitory vagus stimuli arising from distention of the lungs in the forced breathing—was based on two fallacies. The first was that intact vagi are necessary for the production of apnoea by artificial respiration. This is certainly not the case; for apnoea can be produced quite promptly and easily after section of the vagi. It is necessary, however, to make sure that the excessive artificial ventilation is really effective in ventilating the lungs, since after section of the vagi the natural breathing does not follow the rhythm of the artificial respiration, and may thus partly annul the effects of the latter.

The other fallacy connected with the vagus theory of ordinary apnoea was that when air containing little or no oxygen is used for artificial respiration an apnoea due to excessive aëration of the blood is impossible. Advocates of the vagus theory wrongly thought only of oxygen want in connection with aëration of the blood. They thus attributed to vagus excitation any apnoea which was produced in presence of defective oxygenation of the blood, ignoring the fact that deficiency of CO_2 was present along with defective oxygenation, and that this fact explained the observed apnoea. Provided that the alveolar CO_2 percentage is sufficiently reduced, apnoea can be produced readily in spite of great deficiency of oxygen in the alveolar air.

The fact that apnoea is produced when forced breathing reduces the alveolar CO_2 percentage by as little as 0.2 per cent (with the alveolar oxygen percentage not abnormally low), and that if this reduction is prevented no amount of excessive lung ventilation will produce apnoea, affords, in conjunction with the other facts already referred to, conclusive evidence that the apnoea following

excessive lung ventilation is due to lowering of the alveolar CO_2 percentage, and not to either of the other causes to which the apnoea has also been attributed. The vagus theory of the apnoea caused by increased lung ventilation involved the very great improbability that a special arrangement exists in the body for bringing increased breathing to an end, regardless of whether a continuance of the increased breathing is physiologically required or not. It seemed almost incredible that such a theory could be correct.

The ease with which apnoea due to reduction of CO_2 in the alveolar air might be taken for an apnoea due to the after effect of mere distention of the lungs is clearly shown by the stethographic tracings of human breathings reproduced in Figures 2 to 7.[10] Figure 2 shows apnoea as an after effect of inflation of the lungs, while Figure 3 shows that when the inflation is made with air containing 4.6 per cent of CO_2, so as to prevent reduction of the alveolar CO_2 percentage, no apnoea succeeds the period of inflation. The apnoea appearing as an after effect in Figure 2 is therefore due to reduction of the alveolar CO_2 in consequence of the distention with pure air.

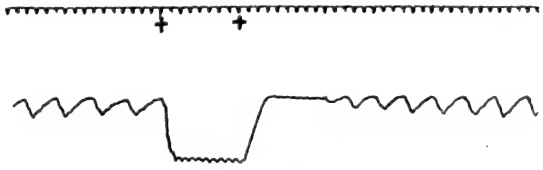

Figure 2.

Figure 3.

Effects of distention for 8 secs. Crosses show beginning and end of distention. To read from left to right. In Fig. 2 pure air is used for distention; in Fig. 3 air containing 4.62 per cent CO_2.

Figures 4, 5, and 6 illustrate the same point. In Figures 4 and 5 there is apnoea succeeding a short distention, but not immediately, since a few seconds were needed before the "apnoeic" blood

[10] Christiansen and Haldane, *Journ. of Physiol.*, XLVIII, p. 274, 1914.

could affect the respiratory center. In Figure 6 the distention was sufficiently prolonged for the "apnoeic" blood to affect the center before the end of distention. The effect is therefore similar to that in Figure 2.

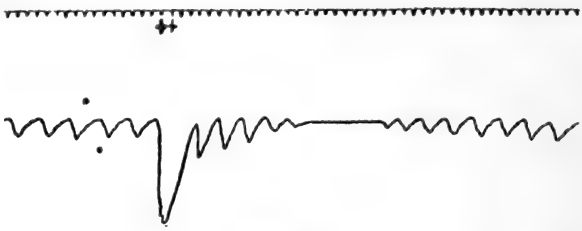

Figure 4.

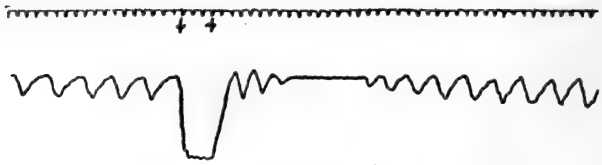

Figure 5.

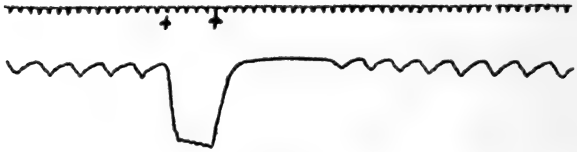

Figure 6.

Effects of distention with pure air for increasing short periods. Crosses show beginning and end of distention. To read from left to right. Fig. 4 distention for 1 sec.; Fig. 5 for 3 secs.; and Fig. 6 for 5 secs.

The regularity of ordinary breathing is constantly being interfered with in various ways, as for instance during talking or singing; and the breath can if necessary be held for about a minute by voluntary effort. The readiness with which these interruptions occur has given rise to the popular idea that the supply of air to the lungs is to a large extent under voluntary control, and can be increased or diminished by proper training. In reality the mean ventilation of the lungs is not affected by ordinary interruptions.

This is strikingly shown by experiments which we made on the effects of voluntarily varying the frequency of breathing.

The frequency of breathing varies considerably among normal individuals, or in the same individual at different times; and it is easy to vary the frequency while leaving the depth of breathing to regulate itself in a natural manner. On making experiments of this kind Priestley and I found the following percentages of CO_2 in the alveolar air:

	ALVEOLAR CO_2 PERCENTAGE			
	RESPIRATIONS PER MINUTE	*End of inspiration*	*End of expiration*	*Mean*
J. S. H.	9	5.59	5.87	5.73
	19	5.56	5.70	5.63
J. S. H.	9	5.33	5.47	5.40
	20	5.44	5.60	5.52
J. G. P.	10.5	5.95	6.74	6.35
	30	5.98	6.05	6.02

In a recent series, made on myself ten years later,[11] the frequency was varied within much wider limits, with the following results:

ALVEOLAR CO_2 PERCENTAGE			
RESPIRATIONS PER MINUTE	*End of inspiration*	*End of expiration*	*Mean*
30	5.66	5.70	5.62
4	5.24	6.09	5.66
24	5.48	5.49	5.48
6	5.40	5.73	5.56
36	5.63	5.73	5.68
4	5.11	6.34	5.72
3	5.10	6.24	5.71
60	6.17	6.16	6.16

It will be seen that in spite of variations from 3 to 36 per minute in the frequency of breathing the alveolar CO_2 percentage remained constant, since increased or diminished depth of breathing

[11] Haldane, *Amer. Journ. of Physiol.*, XXXVIII, p. 20, 1915.

compensated for diminished or increased frequency. The manner in which this correspondence between depth and frequency is brought about will be discussed in the next chapter.

During any considerable muscular exertion the discharge of CO_2 from the lungs is enormously increased; and in view of the facts already described we should expect to find the breathing similarly increased, with a rise in the alveolar CO_2 percentage corresponding to the rise observed when the breathing is correspondingly increased by breathing air containing an excess of CO_2. Priestley and I obtained the following mean results during work on a somewhat primitive bicycle ergometer.

			ALVEOLAR CO_2 PERCENTAGE		
	CALCULATED RESPIRATORY EXCHANGE		*End of inspiration*	*End of expiration*	*Mean*
J. S. H.	Rest	1	5.54	5.70	5.62
	Work	4.9	5.44	6.05	5.75
J. G. P.	Rest	1	6.17	6.39	6.28
	Work	3.8	6.45	6.98	6.72
Mean	Rest	1	5.85	6.045	5.95
	Work	4.3	5.945	6.545	6.235

In this series there was thus only a mean rise of 0.285 per cent in the alveolar CO_2, whereas we had expected to find a rise of about 0.6. The correspondence was, however, in the right direction, and we endeavored, mistakenly as afterwards appeared, to explain the lack of exact correspondence.

A more complete series was carried out later with much improved apparatus by Douglas and myself, with Douglas as subject.[12] The accompanying table shows the data for volume of air breathed, oxygen consumed, CO_2 given off, composition of expired air, and of alveolar air. In these experiments we used the now well-known bag method of Douglas for determining the respiratory exchange.[13]

It will be seen from this table that with a CO_2 production increased from 264 cc. per minute during rest standing to 1398 cc. per minute during walking at 4 miles on grass the alveolar CO_2 percentage rose from 5.70 to 6.36, i.e., by 0.66 per cent. The volume of air breathed per minute was increased from 10.4 to 37.3,

[12] Douglas and Haldane, *Journ. of Physiol.*, XLV, p. 235, 1912.
[13] Douglas, *Journ. of Physiol.*, XLII, Proc. Physiol. Soc., p. xvii, 1911.

	O_2 consumption in cc. per min. at 0°C. and 760 mm.	CO_2 production in cc. per min. at 0°C. and 760 mm.	Liters of air breathed per min. at 37°C. moist, and prevailing barometric pressure.	Breaths per min.	Vol. of each breath in cc. at 37°C. moist, and prevailing barometric pressure.	CO_2 per cent in expired air	CO_2 per cent in alveolar air
Rest—in bed	237	197	7.67	16.8	457	3.19	5.97
Rest—standing	328	264	10.4	17.1	612	3.14	5.70
Walking—							
2 miles an hour (laboratory)	668	561	16.3	12.7	1296	4.25	6.04
2 " " (grass)	780	662	18.6	14.7	1271	4.39	6.04
3 " " (laboratory)	907	737	20.9	14.9	1433	4.38	6.14
3 " " (grass)	1065	922	24.8	16.2	1535	4.62	6.10
4 " " (laboratory)	1182	1057	29.0	14.4	2010	4.55	6.23
4 " " (grass)	1595	1398	37.3	18.2	2064	4.67	6.36
4½ " " (laboratory)	1493	1251	34.2	17.2	2055	4.50	6.44
4½ " " (grass)	2005	1788	46.5	18.5	2524	4.72	6.20
5 " " (laboratory)	2125	2000	51.3	18.3	2810	4.80	6.28
5 " " (grass)	2543	2386	60.9	19.5	3145	4.79	6.10

or by 26.9 liters. This corresponds very closely to the estimate by Campbell, Douglas, and Hobson of an increase of 10 liters per minute in the breathing for every .26 per cent of increased alveolar CO_2 at normal barometric pressure.

When, however, the CO_2 production was increased still further, the alveolar CO_2 percentage, instead of continuing to increase, began to diminish, and was only 6.10 per cent with the maximum CO_2 production (2386 cc.) and volume of air breathed (60.9 liters). Quite clearly, an additional factor or factors besides mere increase in the alveolar CO_2 percentage was coming into play; for with the higher rates of CO_2 production the lung ventilation is not merely increasing in the same fixed proportion as before to the increased production of CO_2, but at a slightly higher rate. What this additional factor is will be discussed later; but meanwhile we may rest content with the broad fact that the increased ventilation is almost in proportion to the increased production of CO_2, just as we should expect from the other facts already discussed with regard to the regulation of breathing.

It was shown by Paul Bert[14] that the physiological actions of CO_2, oxygen, and other gases present in the air breathed depend on their partial pressure. It is only when the barometric pressure is constant that their action depends on the percentage proportions in which they are present in the air. The method of calculating the partial pressure of the CO_2 in the alveolar air may be illustrated by an example. Let us suppose that the barometric pressure is 760 mm., and that 5.6 per cent of CO_2 is found in the alveolar air. In the first place allowance must be made for the aqueous vapor present in the alveolar air, which in the living body must be saturated with aqueous vapor at the body temperature. The pressure exercised by this aqueous vapor is 47 mm. Hence the remaining gas pressure is 760—47=713 mm. Of this pressure 5.6 per cent is due to CO_2 (the results of the gas analysis being always in terms of *dry* air). Hence the pressure of CO_2 is

$$5.6 \times \frac{760—47}{100} = 39.9 \text{ mm., or } 5.25 \text{ per cent of an atmosphere,}$$

since 39.9 is 5.25 per cent of 760.

From Paul Bert's results it might be confidently predicted that it is not the mere percentage but the pressure of CO_2 in the alveolar air which regulates the breathing, and our experiments left no doubt on this point. On descending one of the deepest mines, and ascending the highest hill in Great Britain, we found that the

[14] Paul Bert, *La Pression barométrique*, Paris, 1878.

pressure of CO_2 in the alveolar air remained about constant, while the percentage varied. A more conclusive experiment was made in a large steel pressure chamber, employed at the Brompton Hospital, London, for the treatment of asthma. In this chamber—the only one then existing in England of the kind—we compared our alveolar air at normal atmospheric pressure, and at the highest pressure which the chamber would stand. The mean results were as follows:

	Barometric pressure in mm. Hg.	*CO_2 per cent in dry alveolar air*	*CO_2 pressure in per cent of one atmosphere*
J. G. P.	1261	3.64	5.83
	765	6.41	6.05
J. S. H.	1258	3.42	5.46
	765	5.62	5.31
Mean	1260	3.53	5.64
	765	6.01	5.68

It is quite clear from these results that it is the pressure of CO_2 in the alveolar air, and not its mere percentage, which regulates the breathing. It is also as evident from these experiments as from those already mentioned in which the oxygen percentage was varied, that the oxygen pressure in the alveolar air may be increased very greatly without at the time affecting the regulation of the CO_2 pressure. The actual alveolar oxygen pressure was 13.0 per cent of an atmosphere in the observations at ordinary pressure, and 26.8 per cent in those at the high pressure.

Still more striking results were obtained by Leonard Hill and Greenwood,[15] and by Boycott[16] in steel chambers erected later for the investigation of the effects of high atmospheric pressures. Hill and Greenwood obtained the following results.

They considered at the time that their results showed that the production of CO_2 remained unaltered during the experiments; and it is evident that had the *volume* of air breathed and the *mass* of CO_2 produced remained the same the results would have been as they found. But the constancy of the partial pressure of CO_2 was certainly due, not to the cause which they suggested, but to the fact that the breathing was regulated so as to keep the partial pressure of CO_2 steady.

[15] Hill and Greenwood, *Proc. Roy. Soc.*, 1906, B, LXXVII, p. 442, 1906.
[16] Boycott and Haldane, *Journ. of Physiol.*, XXXVII, p. 365, 1908.

ATMOSPHERIC PRESSURE IN IN MM. Hg.	ALVEOLAR CO_2 PERCENTAGE		ALVEOLAR CO_2 PRESSURE IN MM. Hg.	
	Hill	*Greenwood*	*Hill*	*Greenwood*
760	4.7	5.3	33.5	37.8
4640	0.75	0.9	34.4	41.3
3860	0.95	1.0	36.2	38.1
3090	1.2	1.3	36.5	39.5
2310	1.8	1.8	40.7	40.7
1540	2.5	2.7	37.5	40.5
760	5.0	5.4	35.6	38.5

The results of Boycott and Haldane with Boycott as subject are shown graphically in Figure 7. It will be seen that, provided that the alveolar oxygen pressure was prevented from falling so low as to cause want of oxygen, the alveolar CO_2 pressure remained steady with variations of the barometric pressure from 300 to 2800 mm. and corresponding variations in the alveolar CO_2 percentage from 15 to 1.5.

The daily variations of atmospheric pressure at any one place are not sufficiently great to cause any considerable variations in the alveolar CO_2 percentage, and there are other causes, discussed below, which cause distinct variations in the alveolar CO_2 present. Even, therefore, if we take into consideration the daily variations of atmospheric pressure, the resting alveolar CO_2 pressure is not quite constant at different times in the same individual, and varies considerably in different individuals.

The differences in the alveolar CO_2 pressure in different individuals, and in different sexes and at different ages, were investigated by Miss FitzGerald and myself. We obtained the following results from a number of different persons,[17] living at Oxford.

	ALVEOLAR CO_2 PRESSURES IN MM. OF MERCURY		
	Mean	*Maximum*	*Minimum*
Men	39.2	44.5	32.6
Women	36.3	41.0	30.4
Boys	37.2	42.1	30.6
Girls	35.2	40.1	31.2

[17] Haldane and FitzGerald, *Journ. of Physiol.*, XXXII, p. 491, 1905.

The investigations of Priestley and myself brought out the remarkable fact that the composition of the alveolar air is the same no matter how deep the breath may be from the last portion of which the sample is taken. According to descriptions commonly

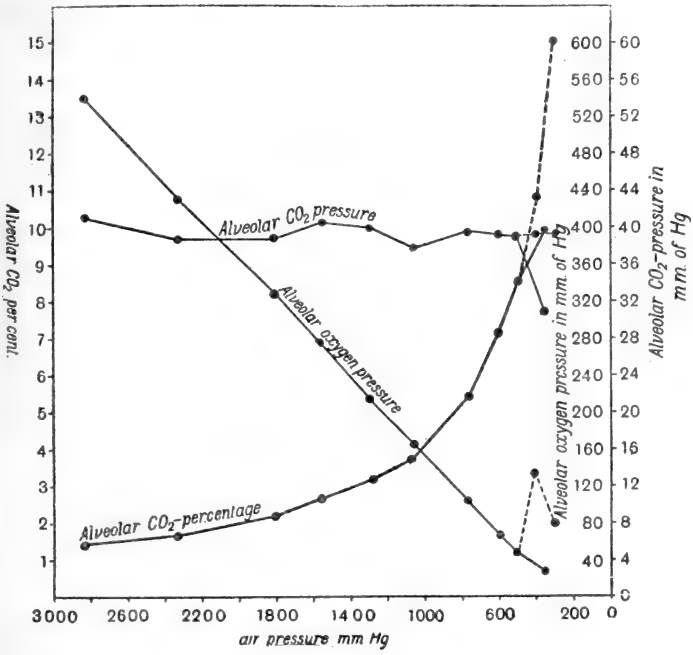

Figure 7.

Effects of variation in barometric pressure on alveolar gas pressures and percentage of CO_2 in A. E. B. The dotted lines show results when oxygen was added to the air.

current of the anatomical relations of bronchioles to alveoli one would have expected that the deeper parts of a breath, coming from alveoli far from the bronchioles, would contain more CO_2, since these alveoli must get less fresh air than the alveoli near a bronchiole. It was somewhat of a puzzle that this was not the case. I was unaware of the anatomical investigations which had been carried out ten years earlier by a distinguished American investigator, W. S. Miller, who by using the laborious "reconstruction" method had discovered the true anatomical arrangement.[18] Figure 8, modified from a colored plate in Miller's latest paper, shows

[18] Miller, *Journ. of Morphol.*, VIII, p. 165, 1893, and XXIV, p. 459, 1913.

diagrammatically this arrangement. The finest ordinary bronchioles divide up to form "respiratory bronchioles" with alveoli in

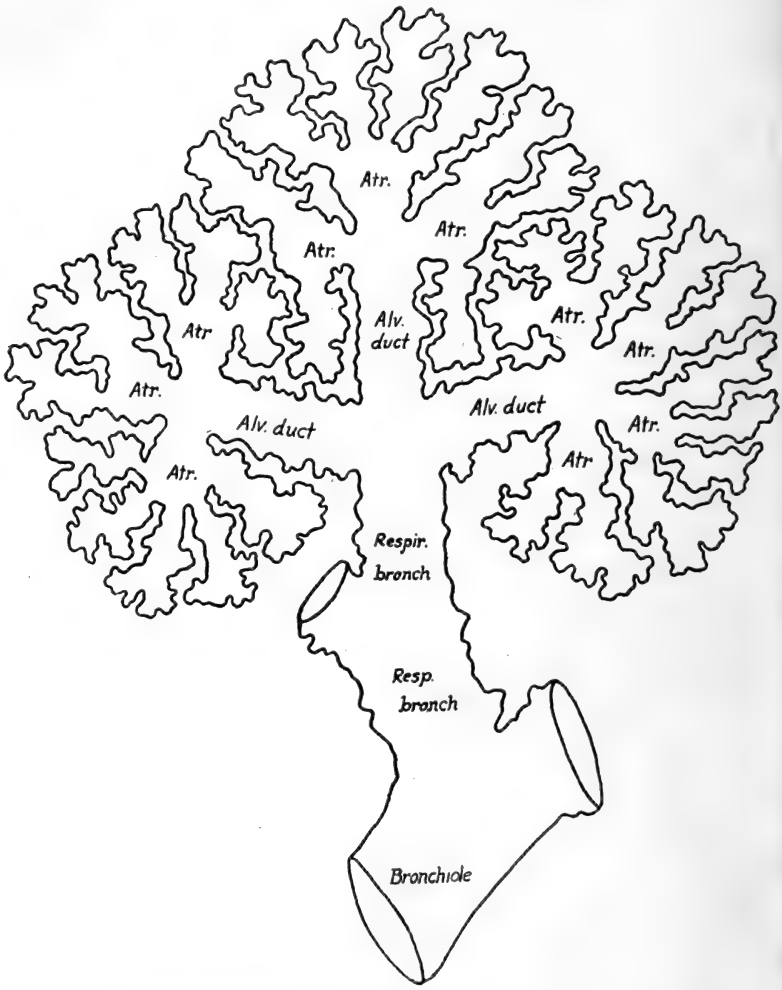

Figure 8.
Diagram showing arrangement of three lung lobules, with their bronchiole, respiratory bronchioles, alveolar ducts, atria, and air-sacs. (After colored plate by Miller, *Journ. of Morphol.* 24, p. 459, 1913.)

their walls, and the respiratory bronchioles branch into "alveolar ducts" lined with ordinary alveoli, and each opening into from

two to five distributing chambers which he named "atria," and which are also lined with alveoli. From each atrium a number of openings lead onwards into what he calls "air-sacs," which are main cavities of which the walls are also constituted of alveoli or air cells. By far the greater part of the alveoli belong to the air-sac system, but a certain number belong to the respiratory bronchioles, alveolar ducts and atria; and the latter act partly as air passages to the air sacs, and partly perform the same respiratory functions as the air sacs themselves.

With this anatomical arrangement the whole of an air-sac system is about equally well ventilated with fresh air, the only alveoli which receive an undue supply of fresh air being those of the respiratory bronchioles, alveolar ducts and atria. We can thus understand why it is that the deeper parts of a very deep breath have exactly the same composition as the middle parts. Evidently however what Priestley and I called "alveolar air" is air-sac air.

The fact that the atria, etc., have partly a respiratory function, and partly act as air passages to the air-sac system, enables us also to clear up some otherwise unintelligible facts with regard to the "dead space" in breathing. The dead space was first estimated roughly by Loewy from the volume of a cast of the respiratory passages, taken in a human lung after death. As this method seemed uncertain, Priestley and I made determinations by comparing the composition of a whole breath of expired air with the composition of what we took to be the whole alveolar air. We calculated the expired air as a mixture of this alveolar air with fresh air occupying the dead space. In this way we found that during rest the volume of the "effective dead space" is about 30 per cent of the volume of the average tidal air. For greater certainty Douglas and I collected the whole of the expired air over a certain period, and made the same calculation from the average volume and composition of each breath, compared with the composition of the alveolar air.[19] We then found that the "effective dead space" is far greater during the hyperpnoea of hard muscular work than during rest. As we were then still unaware of Miller's work we interpreted our observations as indicating that the bronchi or other respiratory passages become wider during hyperpnoea, so as to enable air to enter the lungs more easily. Any one who examines a section of lung must be struck at once by the fact that the mucous membrane of the bronchi is usually in folds, indicating that if the muscular coat relaxed the

[19] Douglas and Haldane, *Journ. of Physiol.*, XLV, p. 235, 1912.

folds would open out and the lumen of the bronchi would greatly increase. We thought it probable that such a relaxation occurs during hyperpnoea, and that this explains the increase of the dead space.

Using a method which Siebeck first introduced, Krogh and Lindhard[20] then redetermined the dead space, and concluded that it does not appreciably increase during hyperpnoea. Their method was to take in a small measured breath of a hydrogen mixture; they then made a deep expiration, which was measured, and from the deeper part of which a sample of the alveolar air was taken. From the percentage of hydrogen in the alveolar air, as compared with the higher percentage in the whole expired air, the volume of the dead space could be calculated on the assumption that it was filled with the original hydrogen mixture.

The question was then independently reinvestigated about the same time by Yandell Henderson, Chillingworth, and Whitney at Yale, and myself at Oxford. We reached the same conclusion—namely that the apparent effective dead space is enormously increased during hyperpnoea, as Douglas and I had found, but that the increase is due simply to mechanical causes, and occurs whether or not the respiratory center is excited by excess of CO_2 or other causes. Our papers appeared together in the *American Journal of Physiology*.[21] In their determinations Krogh and Lindhard had inspired the same volume of the hydrogen mixture whether there was air hunger at the time or not, and consequently they got the same dead space; whereas our experiments were made with the very deep breathing which is naturally associated with air hunger, and consequently the dead space was increased.

Miller's investigations enable us to explain the great increase of the "effective dead space" with deep inspirations. Considering the relative thickness and stoutness of the bronchial walls it seems very improbable that the bronchi, surrounded as they are by very yielding lung tissue, could passively dilate appreciably owing to a deeper inspiration, and this consideration led Douglas and and me to believe that they must dilate owing to a relaxation of their muscular walls—a theory negatived by the later experiments. What dilate during deep breathing are evidently not the bronchi but Miller's "alveolar ductules" and "atria," which serve as air passages to the "air sacs," and which must expand along

[20] Krogh and Lindhard. *Journ. of Physiol.*, XLVIII, p. 30, 1913.

[21] Yandell Henderson, Chillingworth, and Whitney; also Haldane, *Amer. Journ. of Physiol.*, XXXVIII, pp. 1 and 20, 1915.

with the general expansion of the lungs. In addition, they are more completely washed out by fresh air during inspiration. It also follows that the "effective or virtual dead space" is neither a definite anatomical space nor a fixed dead space in any sense, but a value dependent on several variable factors. These factors include the rates at which CO_2 passes outwards and oxygen passes inwards between the air and blood at different points in the alveolar system. For this reason the "effective dead space" is different for oxygen and CO_2. The over-ventilation of the atria, etc., removes from the blood circulating round them an extra proportion of carbon dioxide, but cannot, for a reason which will be discussed later, give to the blood any appreciable extra amount of oxygen. During inspiration this extra proportion of CO_2 passes on to the saccular alveoli, but not during expiration. The "respiratory quotient," or ratio between the volume of carbon dioxide given off and of oxygen absorbed, is thus abnormally high in the air expired from the atria, etc., and as a consequence abnormally low in the air sacs, so that the "effective dead space," as calculated from deficiency of oxygen in the expired air, compared with that in the "alveolar air," is greater than when the dead space is calculated from the relative CO_2 percentages. The respiratory quotient for the "alveolar air" is also below the correct value as calculated from the composition of the mixed expired air.

The following table, giving results on myself, shows the variations in the "effective dead space" with varying depth of breathing as calculated both from CO_2 and from oxygen, and also the differences between the respiratory quotient as calculated from the expired air and from the alveolar air. Using a slightly different method, Henderson, Chillingworth, and Whitney got similar results.

It will be seen from this table how enormously the apparent dead space varies with the depth of breathing and how much greater the dead space calculated from the oxygen is than that calculated from the CO_2. A further point which comes out is that with deep breathing the difference between the alveolar CO_2 percentages at the beginning and end of expiration is far less than the difference between the oxygen percentages. This is mainly because the extra CO_2 washed out of the alveolar ductules and atria passes on into the saccular alveoli during inspiration. A further point is that the true respiratory quotient is about a sixth higher than the alveolar respiratory quotient. The fact that the alveolar respiratory quotient is a good deal lower than the true

FREQUENCY OF RESPIRATIONS PER MINUTE	MEAN DEPTH OF EXPIRATIONS AT 37° SATURATED IN CC.	EXPIRED AIR			ALVEOLAR CO_2 PERCENTAGE			ALVEOLAR O_2 PERCENTAGE			ALVEOLAR RESPIRATORY QUOTIENT	EFFECTIVE DEAD SPACE MINUS THAT OF MOUTHPIECE, CC.	
		CO_2%	O_2%	Respiratory quotient	End of inspiration	End of expiration	Mean	End of inspiration	End or expiration	Mean		Calculated from CO_2	Calculated from O_2
3	2984	4.29	16.07	0.848	5.41	6.04	5.72	14.56	12.84	13.70	0.745	683	920
4	2438	4.56	16.91	0.875	5.24	6.09	5.66	14.98	13.07	14.02	0.814	467	619
6	1413	4.24	16.47	0.905	5.37	5.70	5.53	14.51	14.25	14.38	0.803	272	392
18.5	683	3.31	17.27	0.871	5.53	5.75	5.64					224	
17.0	650	3.59	17.01	0.887	5.63	5.79	5.71	13.95	13.74	13.84	0.762	171	223
17.7	643	3.58	16.98	0.888	5.50	5.59	5.55	13.44	13.99	13.72	0.721	161	231
24	410	3.22	17.15	0.780	5.45	5.46	5.45	13.88	13.42	13.65	0.692	111	136
60	357	1.89	18.75	0.820	5.87	6.06	5.96	13.15	12.85	13.00	0.703	185	199

Douglas + Haldane J. P. 45, 1912. 235
a. J. P. 38 1915. 1720

quotient had been noticed by us before this in the work of the Pike's Peak Expedition (to be referred to later), but had not been explained. It is quite evident from the table that the composition of the deep alveolar air cannot be exen approximately calculated from that of the expired air by assuming the existence of a constant dead space. The latter assumption has caused great confusion in recent years, particularly in the work of the Copenhagen School.

It was shown by Yandell Henderson and his coadjutors that when air passes along an air passage the axial stream is much faster than the peripheral stream, and that as a consequence of this the air in the dead space is not pushed out bodily in front of the alveolar air during expiration. Some of the tracheal and bronchial air is at first left behind, and before pure alveolar air issues at the nose or mouth the air passages have to be washed out by three or four times their volume of alveolar air. This is illus-

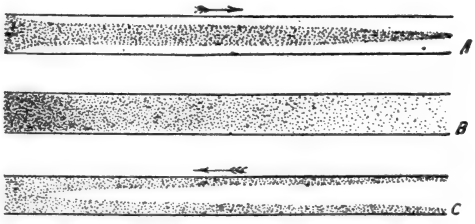

Figure 9.
(a) Shows a "spike" of smoke moving through a glass tube. (b) Shows the condition when the current is suddenly stopped and mixing instantaneously occurs. (c) Shows clear air drawn in.

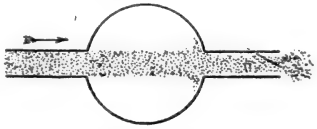

Figure 10.
Shows how a column of smoke crosses a bulb with little mixing or sweeping out of the air within it.

trated by Figures 9 and 10, taken from their paper, and drawn from experiments made with smoke. Both they and I found also that a pause before expiration diminishes the volume of the apparent dead space. This is easily understood, as the air in the atria, etc., will during the pause come nearer in composition to that of the saccular alveoli. With care in avoiding a pause I found

that during rest with normal breathing it was necessary to expire about 800 cc. of air before a reliable alveolar sample could be obtained at the end of inspiration. If the breathing was deep and slow much more air had to be expired. At the end of a normal expiration, however, the air issuing from the mouth is practically alveolar in composition.

The conclusion reached by Priestley, Douglas, and myself that increased production of CO_2, and consequent rise in the alveolar CO_2 percentage, determines increased breathing during muscular work was afterwards questioned by Krogh and Lindhard,[22] on the ground that our determinations of the alveolar CO_2 percentage were fallacious, and that the real alveolar CO_2 percentage during muscular work is not only lower than we found, but also considerably lower than during rest. Their argument is mainly based on the assumptions, which have already been shown to be wrong, that the "effective dead space" is not largely increased during deep breathing, and that reliable samples of alveolar air can be obtained at the end of a deep inspiration, without more than a very shallow expiration to clear the extra dead space. This part of their argument falls to the ground. They point out, however, what is a real source of slight error—namely that a delay of fully half a second occurs during the taking of an alveolar sample, and that during this interval the alveolar CO_2 percentage must rise appreciably. It was shown above that the difference in CO_2 percentage between samples of alveolar air taken at the beginning and end of expiration during work corresponding to an increase of 4.3 times in the CO_2 production was about 0.6 per cent. As an expiration took nearly 2 seconds, there would be a rise of 0.15 per cent in half a second, corresponding to the delay in taking the alveolar sample. During rest, according to a similar calculation, there would be a rise of 0.05 per cent. The net error in comparing rest with work would thus be only about 0.1 per cent, a difference too small to affect the conclusions materially. Owing to their defective methods of estimating and directly determining the alveolar CO_2 percentage at the beginning of expiration Krogh and Lindhard enormously overestimated the error due to a delay of half a second in obtaining a sample. The fact remains, however, that when the work was pushed in the case of Douglas, and even without pushing the work in my own case, the rise in alveolar CO_2 percentage was less than corresponded to the increase in breathing. This significant fact will be discussed later.

[22] Krogh and Lindhard, *Journ. of Physiol.*, XLVIII, p. 30, 1913.

It will be shown in Chapter IX that during rest under normal conditions the gas pressures in the alveolar air and blood passing through the alveoli come into exact equilibrium. Now it has just been shown that in a very appreciable part of the lung alveoli (those in the respiratory bronchioles, alveolar ducts, and atria) the CO_2 pressure is lower, and the oxygen pressure higher, than in the air-sac alveoli. We might therefore be led to infer that in the mixed arterial blood the CO_2 pressure will be lower, and the oxygen pressure higher, than in the blood from the air-sac alveoli, and that in consequence of this the mixed arterial blood will have a lower CO_2 pressure than that of the deep alveolar air. Further consideration shows, however, that this will not be the case. The walls of the alveoli of respiratory bronchioles, etc., are in contact on the one side with the air of air-passages, but on the other with air in the air-sac alveoli. Hence the extra proportion of CO_2 extracted from the blood in the air-passage alveoli is practically taken from the air-sac alveoli, and this is why the apparent respiratory quotient of the air-sac alveoli is lower than the true respiratory quotient. We should be counting the lowering twice if we assumed that in consequence of the extra discharge of CO_2 in the respiratory bronchioles, etc., the CO_2 pressure of the arterial blood is lower than corresponds to that of the air-sac alveoli. The same argument applies also as regards the oxygen pressure of the air-sac air, although under normal conditions hardly any extra oxygen can pass into a given volume of blood in its passage through the alveoli of respiratory bronchioles, etc. Hence the gas pressures of the air-sac alveoli represent truly the mean gas pressures to which the arterial blood is saturated in the various alveoli. This is why the gas pressures of the deep alveolar air as determined by the method which Priestley and I introduced are of so much importance.

Krogh and Lindhard[23] still maintain that the mean gas pressures to which the blood is equilibrated in passing through the lungs is given, not by the composition of the deep alveolar air, but by that of the alveolar air as calculated from a fixed, or almost fixed, dead space. This involves the conclusion that during deep breathing, including the deep breathing of muscular exertion, the arterial CO_2 pressure is far lower than is shown by the direct method of Priestley and myself. As, however, there is no corresponding apnoea, the whole theory of regulation of breathing in accordance with the CO_2 pressure of the arterial blood must be

[23] Krogh and Lindhard, *Journ. of Physiol.*, LI, p. 59, 1917.

abandoned if Krogh and Lindhard are correct. Their reasoning is quite logical, but their premises are unsound. They have failed to take into consideration the anatomical relations of the air-passage alveoli to the air-sac alveoli.

The fact that the mixed air from all the air sacs of the lungs is the same in composition however much of this air is expelled in taking a sample led us to assume almost unconsciously that the composition of the air in practically all the air sacs is the same. Nevertheless all that the experiments prove is that the average composition of the air expelled from the air sacs is the same, while in individual air sacs the composition may vary widely.

It is evident that in any particular air-sac system the mean composition of the contained air will depend on the ratio between the supply of fresh air and the flow of blood. If the supply of fresh air is unusually small in relation to the supply of venous blood there will be a lower percentage of oxygen and higher percentage of carbon dioxide in the air of the air sac, and vice versa. It seems probable that by some means at present unknown to us a fair adjustment is maintained normally between air supply and blood supply. For instance, the muscular walls of bronchioles may be concerned in adjusting the air supply, or the arterioles or capillaries may contract or dilate so as to adjust the blood supply. In any case what seems to matter is the degree of arterialization, not of the blood from individual air sacs, but of the mixed arterial blood; and if the composition of the mixed air-sac air served as a reliable index of the arterialization of the mixed arterial blood we might dismiss as a matter of only academic interest the question whether the air in individual air sacs varies in composition.

It will be shown below that there can be little doubt that under normal conditions the air in different air sacs varies appreciably in composition, and that under abnormal conditions the variation may be considerable. It will also be shown that the latter fact is one of great importance in pathology and therapeutics.

Meanwhile it is clear from the experiments described in the present chapter that under normal conditions, excluding heavy work, the breathing in man is on an average regulated by the alveolar CO_2 pressure; and a very slight increase or diminution in the alveolar CO_2 pressure suffices to cause a very great increase or diminution in the breathing. This conclusion has thrown a flood of clear light on the physiology of breathing.

CHAPTER III

The Nervous Control of Breathing.

It is now necessary to discuss more closely the influence of nervous control on breathing. The rhythmic activity of the respiratory center is for short periods of time very completely under voluntary control—a fact evidently connected with the very delicate use of the lungs in phonation, as well as in other voluntary acts not directly connected with "chemical" respiratory functions. Excitation of various afferent nerves may also excite or inhibit inspiration or expiration. Most of the effects thus produced appear to be protective in various ways, or preparatory to some particular effort, and they only disturb the main regulation of breathing occasionally, just as voluntary interference does. In view of the facts with regard to the control of breathing by chemical stimuli, we might thus be led to the conclusion that the respiratory center, when not interfered with by voluntary or other occasional nervous disturbances, acts simply by producing rhythmic inspiratory and expiratory discharges, determined in extent and frequency by nothing but chemical stimuli dependent on the blood supply.

This simple conception is entirely inadequate, in view, more particularly, of the facts discovered originally by Hering and Breuer, and already referred to. These facts, apart from the results of section of the vagi, can be observed very fully in man, without the complications introduced by anaesthetics, and were so studied in 1916 by Mavrogordato and myself.[1] We employed a very simple arrangement which enabled us to breathe through a wide-bored tap, and observe by a water manometer the pressure between the mouth and the tap when the latter was closed, the nostrils being closed by a clip. If the tap was closed at the end of natural or forced inspiration or expiration, or in any other phase of respiration, the phenomena could be studied. By connecting the far end of the tap with a reservoir containing pure air or air containing any required percentage of CO_2, we could observe the influence of hyperpnoea due to CO_2, and by suitable volume recorders connected with the far ends of the reservoir and gauge the breathing and pressure could be recorded.

If expiration is interrupted by turning the tap, and all voluntary

[1] *Journ. of Physiol.*, L; *Proc. Physiolog. Soc.*, p. xli, 1916.

effort is suspended, the previous rhythm of the respiratory center is interrupted by a prolonged expiratory phase, as indicated by the gauge. The expiratory pressure is at first slight and constant, but afterwards rises gradually and at an increasing rate, until, if expiration is still prevented, there is at length an inspiratory effort, as shown in Figure 11. Similarly, if the breathing is ob-

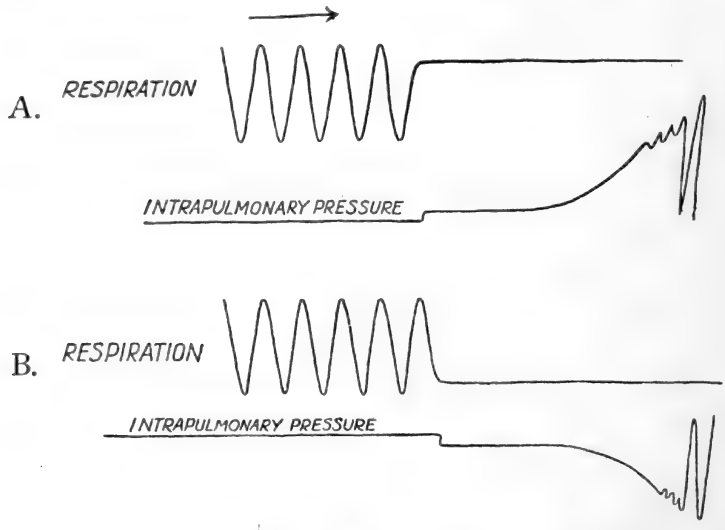

Figure 11.

Effects of interrupting natural breathing. A. Respiration interrupted during inspiration—near end. B. Respiration interrupted during expiration—near end. Respirations—inspiration up, expiration down. Intrapulmonary pressure—positive pressure down, negative pressure up.

structed during expiration there is a prolonged and increasing inspiratory effort (Figure 11). The initial inspiratory pressure is somewhat greater than the initial expiratory pressure, and this is in accordance with the opinion generally held that while ordinary quiet inspiration is always an active process the corresponding expiration is mainly passive.

With interruption at the end of an extra deep inflation or deflation of the lungs the phenomena are still more marked. If apnoea has previously been caused by forced breathing, the initial expiratory or inspiratory pressures are still produced as before, but a long interval elapses before they begin to increase, and the duration of the expiratory or inspiratory phase is much prolonged.

If, on the other hand, the inflation or deflation was made during the hyperpnoea caused by breathing air containing an excess of CO_2 the expiratory or inspiratory pressures mount up at once. The mounting up of the initial pressure is thus dependent on the accumulating chemical stimulus to the respiratory center. If the breathing is interrupted, not just after, but before the completion of inspiration or expiration, the inspiratory phase is continued if inspiration has been interrupted, and the expiratory if expiration has been interrupted, as shown in Figure 11.

If, instead of interrupting the breathing by means of a tap or other obstacle which cannot be overcome, the only interruption is by a limited adverse pressure capable of being overcome by the breathing, the apparent "apnoea" is terminated by an expiration if the pressure is positive, or an inspiration if the pressure is negative. This simply means that with a positive pressure the expiration occurs at the moment when the expiratory effort has increased sufficiently to overcome the adverse positive pressure, and similarly with a negative pressure. This is illustrated by Figures 12 and 13, which reproduce stethographic tracings obtained in man.[2] The subject at first breathed quietly through the limb of a wide-bore three-way tap open to the air. At the end of an inspiration the tap was suddenly turned so that the mouth of the subject was connected with the air of a bag under a pressure of about 3 inches of water. The consequence of this was that the

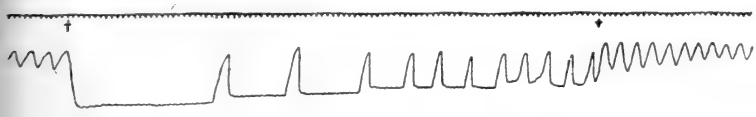

Figure 12.

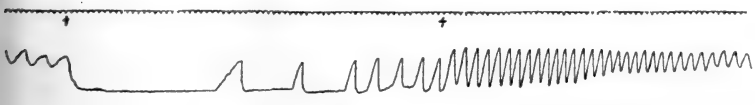

Figure 13.

Effects of prolonged distention of the lungs. To be read from left to right. Time marker = seconds. Distention continued between the two crosses. In Fig. 12 pure air was used for distention; in Fig. 13 air containing 7.3 per cent of CO_2 and 8.2 per cent of oxygen.

lungs were suddenly distended with a large volume of air. It will be seen that after about half a minute the apparent pause in

[2] Christiansen and Haldane, *Journ. of Physiol.*, XLVIII, p. 272, 1914.

the breathing was interrupted by an expiration, repeated afterwards at gradually diminishing intervals. The diminution in these intervals was evidently due to the fact that CO_2 was accumulating in the lungs; and this interpretation is confirmed by Figure 13.

Figure 14 shows a corresponding effect with a negative pressure applied, so as partially to deflate the lungs. In this case the apparent pause was much shorter, as CO_2 began to accumulate very rapidly, owing to the facts that not only had no fresh air been introduced, but the volume of air in the lungs was diminished.

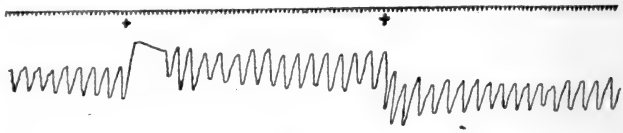

Figure 14.
Effects of partial deflation. Crosses show beginning and end of deflation. To read from left to right. Time-marker = 1 second.

The supposed apnoeic pause produced by distention or inflation of the lungs is simply a prolonged inspiratory or expiratory effort. This effect is produced regardless of the chemical stimulus to the center. Thus Lorrain Smith and I showed that it is even produced when the lungs are distended with air containing 20 per cent of CO_2, though the prolongation is much curtailed in such a case.[3]

It is thus clear that the continuance of an inspiratory or expiratory discharge of the respiratory center depends on the extent to which actual inspiration or expiration accompanies the discharge. If the movements of inspiration or expiration are not accomplished the ordinary respiratory rhythm is replaced by a prolonged and increasingly powerful inspiratory or expiratory discharge, tending to overcome the obstruction. The respiratory center does not act independently of the lung movements, but inspiratory or expiratory discharge of the center goes hand in hand with actual inspiration or expiration, as if the center were one piece with the lungs. The term "vagus apnoea" is evidently an entire misnomer, as prolonged inspiratory or expiratory effort cannot be called apnoea. The tracings which apparently demonstrate the existence of apnoea are only one-sided, and therefore misleading, records.

Hering and Breuer found, as already mentioned in Chapter I, that after section of both vagi the association of discharge of the

[3] Haldane and Lorrain Smith, *Journ. of Pathology*, I, p. 168, 1892.

center with the respiratory movements is annulled, so that inflation or deflation of the lungs has no immediate influence on the respiratory rhythm. Hence the afferent impulses through which the discharges of the center are coördinated with the movements of the lungs are conveyed by the vagi. After section, or better (so as to avoid excitatory effects produced by actual section), freezing of the vagi, the breathing, as has been known since early last century, becomes deeper and less frequent, the inspirations in particular taking on a dragging character which, until the work of Schäfer, referred to below, was entirely attributed to the absence of the normal inhibitory effect conveyed through the vagi on distention of the lungs to a certain point. Nevertheless the respirations continue to be rhythmic, and to respond in their depth to the stimulus dependent on varying percentages of CO_2 in the alveolar air. It was shown by Scott[4] however, that the control of the alveolar CO_2 percentage when excess of CO_2 is present in the air breathed becomes much less perfect, as the frequency of the breathing cannot increase.

The analogy between the Hering-Breuer stimuli transmitted through the vagi and what Sherrington has named the "proprioceptive" stimuli participating in reflex or voluntary movements of the limbs is evident; though the rhythmic discharges of the respiratory center are dependent on stimuli, not from the surface of the body, but from the blood acting on the center.

When, in addition to section of the vagi, the respiratory center is also severed from its connections above the medulla oblongata, the rhythmic discharges of the center become still less frequent, and may be inadequate to prevent death from asphyxia. The influence on the center of afferent stimuli from the respiratory muscles has not yet been demonstrated directly; but the fact, observed by Boothby and Shamoff,[5] that an animal in which the pulmonary branches of the vagi have been severed without injury to the recurrent laryngeal nerve recovers after a sufficient time a normal control over respiration seems to point to the existence of such stimuli. The same conclusion has been still more clearly reached in a quite recent paper by Schäfer,[6] who shows that the slowed breathing after section of the vagi is largely due to obstruction caused by laryngeal paralysis.

We must now endeavor to correlate the facts relating to the

[4] Scott, *Journ. of Physiol.*, XXXVII, p. 301, 1908.
[5] Boothby and Shamoff, *Amer. Journ. of Physiol.*, XXXVII, p. 418, 1915.
[6] Schäfer, *Quart. Journ. of Exper. Physiol.*, XII, p. 231, 1919.

Hering-Breuer phenomena with those relating to the governing of the lung ventilation by the charge of CO_2 in the alveolar air and arterial blood. It seems very clear that the immediate cause of the arrest of inspiration during ordinary breathing is the distention of the lungs to a certain point, and a consequent inhibitory stimulus transmitted up the vagi. The experiments of Head,[7] in which the movements of a slip of the diaphragm, the most prominent inspiratory muscle, were recorded, show that this inhibition produced an instant relaxation of the diaphragm. If the vagi have been frozen the relaxation is greatly delayed, and even after the delay is at first very imperfect. The inhibition of inspiration initiates an expiratory phase, which continues until, in its turn, it also is cut short by deflation to a certain point, at which the vagi transmit an influence which inhibits expiration and initiates the inspiratory phase. It appears from Head's experiments that if the vagi are frozen after the inspiratory or expiratory phase has been initiated, this phase still continues. If with vagi intact the breathing is partially obstructed, inspiration or expiration is continued till either act is complete. The influence transmitted through the vagi initiates inspiration or expiration, therefore; and the center persists in the inspiratory or expiratory phase till the vagus gives the signal which terminates the phase and initiates the complementary phase. The center behaves as if it always remembered the last signal; and the analogy between any act dependent on memory and the duration of the inspiratory or expiratory phases of breathing is evident. We are equally reminded of the "refractory period" in the phases of cardiac and other muscular activity.

Where the "chemical" regulation of the respiratory center exerts its preponderating influence is in determining the extent to which inflation or deflation of the lungs must extend in order that the Hering-Breuer stimuli should be effective, and also the vigor and consequently the rapidity of the inspiratory and expiratory movements. Thus an increased CO_2 stimulus causes increased depth of breathing, since a greater inflation or deflation of the lungs is required before the stimulus of inflation or deflation becomes effective. At the same time the movements of the chest wall become more rapid, so that the frequency of breathing is not diminished in consequence of the greater distances traveled by the chest walls. The net result is thus ordinarily increase in depth without diminution in frequency. But if the frequency

[7] Head, *Journ. of Physiol.*, X, pp. 1 and 279, 1889.

is diminished in consequence of voluntary or involuntary interference, the depth is correspondingly increased owing to a very slightly increased CO_2 stimulus. This is the explanation of why the mean alveolar CO_2 percentage remains so steady with varying frequency of breathing. It is only, as a rule, when there is very considerable increase in the breathing that there is any material increase in the frequency; and during health the frequency is hardly affected by moderate muscular exertions or moderate stimulation by CO_2 in other ways. The frequency of breathing is thus no measure of the amount of air breathed; but undue frequency of breathing, as will be shown later, is a very important abnormal sympton.

The response of the breathing to abnormal resistance has recently been investigated by Davies, Priestley, and myself.[8] For recording the depth and frequency of breathing we used the recording "concertina" described in Chapter VII (Figure 43). For a resistance to breathing we sometimes used partly closed taps, the effects of which could be thrown in suddenly by closing alternative inspiratory and expiratory air passages. In place of the taps we also sometimes employed cotton wool resistances, as with a cotton wool resistance the driving pressure varies directly as the air flow, while with a tap the pressure varies as the square of the air flow. The pressure was measured with a water manometer connected with the tubing between the mouth and the resistance.

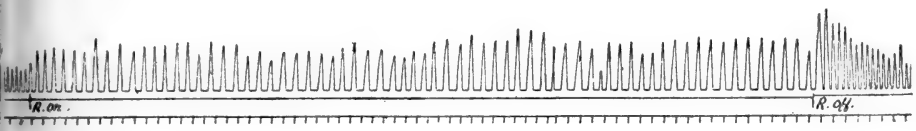

Figure 15.

Effects of resistance. In this and subsequent figures inspiration = upstroke. Time marker = 10 seconds. To read from left to right.

It was found that when a resistance is thrown in the immediate effect is a great slowing of the breathing. After the next breath the respirations become deeper and less slow, and after several breaths the breathing settles down to a rhythm in which the respirations are deeper and correspondingly less frequent. With a considerable resistance the frequency is often reduced to a fourth of the normal rate, while the depth is almost correspondingly in-

[8] Davies, Haldane, and Priestley, *Journ. of Physiol.*, LIII, p. 60, 1919.

creased (Figure 15). The explanation of this is obvious from the foregoing account of the physiology of the Hering-Breuer reflex. When a resistance is thrown in deflation or inflation of the lungs is slowed, but continues till the point is reached at which the phase of respiration is reversed by the reflex. Meanwhile, however, CO_2 has begun to accumulate, so that the next respiration is not only more vigorous but deeper; and the final result is deeper and less frequent respiration.

When there is no resistance to breathing the compensation of diminished frequency by increased depth is almost perfect, as shown by the experiments already quoted of Priestley and myself; but when the slowing is due to resistance the compensation is less perfect, since the extra work performed by the respiratory muscles implies a more powerful stimulus of CO_2 to the respiratory center. Accordingly the alveolar CO_2 percentage rises quite considerably with resistance to breathing. The following table shows the rises observed by Davies, Priestley, and myself with varying resistances.

Just as, in the absence of resistance a very slight increase in the alveolar CO_2 percentage, and consequent slight increase in the chemical stimulus to the respiratory center, increases the depth of breathing, so a slight diminution in alveolar CO_2 percentage diminishes the depth. It was recently discovered independently by Yandell Henderson in America and by Liljestrand, Wollin, and Nilsson in Sweden that if apnoea is first produced and artificial respiration then carried out by Schäfer's or one of the other usual methods the quantity of air which enters the chest at each artificial inspiration is only about a third or less of what enters during artificial respiration when the subject has simply suspended voluntarily his own breathing. With voluntary suspension of the natural breathing, moreover, the volume of air which enters at each artificial inspiration varies (roughly speaking) inversely as the frequency of the artificial breathing, so that it is impossible to produce a condition of true apnoea by increasing the frequency of the artificial breathing. If, finally, the air artificially inspired contains an excess of CO_2, the volume introduced by the artificial respiration increases just as it would with natural breathing. It is, in fact, just as if the subject were himself breathing naturally all the time, in spite of the undoubted fact that he has suspended his natural breathing.

These phenomena are completely intelligible on the theory that the limits within which inflation or deflation of the lungs inhibits

SUBJECT	ALVEOLAR CO_2 PERCENTAGE		RESISTANCE IN CM. OF H_2O		
	Normal.	*During resistance.*	*Inspiratory.*	*Expiratory.*	*Remarks.*
J. S. H.	5.40	5.34	4½	1½	Slight cotton-wool resistance. Breathing slowed
J. G. P.	5.60	5.80	4½	1½	Slight cotton-wool resistance. Breathing slowed
H. W. D.	5.97	6.24	13	5	Heavier cotton-wool resistance. Breathing slowed
”	5.99	5.93(?)	8	4	Lighter cotton-wool resistance. Breathing slowed
”	”	6.61	”	”	Lighter cotton-wool resistance. Breathing slowed
”	”	6.21	”	”	Lighter cotton-wool resistance. Breathing slowed
”	”	6.26	”	”	Lighter cotton-wool resistance. Breathing slowed
”	”	7.02	25	14	Heavy cotton-wool resistance. Breathing slowed
J. S. H.	5.4	6.40	”	”	Heavy cotton-wool resistance. Breathing quickened
”	”	6.60	”	”	Heavy cotton-wool resistance. Breathing about 66
”	”	6.76	?	?	Resistance lessened by partly opening taps. Respirations about 30
J. G. P.	5.37	5.76	?	?	Tap resistance lessened by partly opening taps. Respirations about 4
J. S. H.	5.33	6.50	?	?	Tap resistance lessened by partly opening taps. Respirations about 24
”	”	6.80	?	?	Tap resistance increased. Respirations about 40

inspiration or expiration depend on the alveolar CO_2 percentage. In apnoea a very slight amount of inflation or deflation is sufficient to cause inhibition of inspiration or expiration. In consequence of this the respiratory movements are nearly jammed in a mean position during apnoea unless considerable force is exerted, which is not the case with ordinary methods of artificial respiration. With a normal stimulation of the respiratory center by CO_2 and a normal respiratory frequency, the limits of inflation or deflation at which the Hering-Breuer inhibition occurs are a good deal wider, and with a diminished respiratory frequency, or an increased percentage of CO_2 in the air inspired, the limits are much wider still. Thus the respiratory center tends indirectly to govern artificial respiration unless the latter is of a specially vigorous kind.

That the center responds, even during apnoea, with tonic contraction of the diaphragm to deflation of the lungs, and with relaxation to inflation, was clearly shown by Head's experiments; and the inspiratory or expiratory pressures produced by the diaphragm and other respiratory muscles can easily be demonstrated in man. The continued control of respiratory movements during apnoea or voluntary suspension of the breathing, or during voluntary variations in the frequency of breathing, is thus readily intelligible. In voluntary forced breathing or in forcible artificial respiration, this control is broken down. It must not, however, be assumed that because the ordinary gentle methods of human artificial respiration have such a small effect during ordinary apnoea, the effect will be equally small where the suspension of breathing has been caused by asphyxiation or the action of an anaesthetic or other poison. In these cases the excitability of the respiratory center to the Hering-Breuer stimuli is possibly as much depressed as its excitability to CO_2, in which case the artificial respiration will not be insufficient.

The normal rate and depth of breathing in any individual is evidently an expression of the normal balance between chemical and nervous stimuli. The normal is fairly constant because the balance is a stable one. It may, however, be greatly altered under abnormal conditions, and it can easily be interfered with voluntarily.

It is evident from the foregoing discussion that we cannot separate the nervous from the "chemical" control of breathing, since each determines the other at every point. From too exclusive a consideration of the nervous side of the control it has been supposed, on the one hand, that the center is essentially automatic in

its action, or that its alternate inspiratory and expiratory discharges are, under normal resting conditions, determined simply by alternating stimuli transmitted through the vagus nerves. On the other hand a too exclusive consideration of the chemical side leads to the erroneous impression that the discharges of the center are, apart from occasional voluntary or other interferences, determined in strength and duration solely by chemical stimuli. If, finally, we attempt to determine, one by one, the "factors" in the regulation of breathing, the sum of the supposed factors turns out to be illusory, since no one of them is a constant quantity. The evaluation of each factor depends on its varying relation to the others.

The "respiratory center" is a small area situated in the medulla oblongata. It has been found that when this area is destroyed, all rhythmical respiratory movements cease, and that so long as this area is intact and in connection with any efferent nerves supplying respiratory muscles, discharges of the center through these nerves continue, as shown by the rhythmical contractions of the muscles, although all the other nervous connections upwards and downwards have been severed.

It is also now clear that the activity of the center depends upon the composition of the blood circulating through it, and not on chemical stimuli acting elsewhere. If the circulation to the medulla is interrupted by closure of all the four arteries supplying it, so that its blood has time to become venous, violent hyperpnoea results, as Küssmaul and Tenner showed about the middle of last century; and the crossed circulation experiments of Fredericq, already referred to, prove that either apnoea or hyperpnoea is produced, according as the blood supplied to the central nervous system is more aërated or less aërated in the lungs.

It has been suspected that although the stimuli dependent on the composition of the blood act directly within the brain, nervous end-organs situated elsewhere are also sensitive to these stimuli, so that the corresponding nerves convey impulses which play an important part in the regulation of breathing. It was, for instance, believed by Traube that chemical stimuli are conveyed directly from the lungs by the vagus nerve, and others have supposed that stimuli to increased breathing are conveyed by direct nervous paths from the muscles. This hypothesis was investigated with great care by Geppert and Zuntz,[9] who severed all the nervous connections between actively working muscles and the medulla,

[9] Geppert and Zuntz, *Pflüger's Archiv*, XLII, pp. 195, 209, 1888.

and found that the respiratory response to increased muscular work was the same as before, but was entirely absent if the circulation from the working muscles was interrupted. Similarly they found that severance of the nervous connection between the lungs and the center did not affect the response. Lorrain Smith and I found, similarly, that when air containing about 20 per cent of CO_2 was supplied to a rabbit there was no difference in the time required for the onset of hyperpnoea after the vagi were cut.

No definite anatomical group of nerve cells has been defined at the position occupied by the respiratory center; and the exact meaning which ought to be attached to the expression "respiratory center" is still doubtful. It seems pretty clear, however, that the center is at about the position which is sensitive to the chemical respiratory stimuli. To judge from analogy the sensitive elements are probably not the bodies of nerve cells, but end-organs or arborizations. The central paths for the innervation of inspiratory and expiratory movements must also be different, but in what sense the center itself is double is still obscure. Its excitation by chemical stimuli depends more upon the character of the blood supplied to it than on substances generated by its own local metabolism. Thus the temporary diminution of blood supply in fainting does not produce the same prompt effect on the center as changes in the arterial blood owing to imperfect aëration in the lungs. In this respect the center is very well suited to fulfill the function of taking a part in controlling the *quality* of the general arterial blood supply of the body. The *amount* of arterial blood supplied is controlled in other ways.

Like other parts of the central nervous system, the respiratory center can easily be fatigued; and, as will be explained later, fatigue of the respiratory center is of great importance in practical medicine. Fatigue of respiration was recently studied by Davies, Priestley, and myself, and its phenomena described in the paper already referred to. The fatigue was produced by breathing against a resistance, the breathing being also increased at the same time, if necessary, by muscular exertion. The resistance was produced by cotton wool in the manner already described.

So long as the center is functioning normally it responds to the resistance, in the manner indicated above, by producing a constant slow and deep type of breathing. When, however, the resistance is excessive and continued for some time, the breathing becomes progressively shallower and more frequent. At the same time the alveolar ventilation becomes less and less effective, until at last

asphyxial symptoms begin to develop. Figure 16 is a tracing which shows this change. Figure 17 shows a similar change produced, not by resistance alone, but by the combined effects of resistance and the increased breathing due to muscular work.

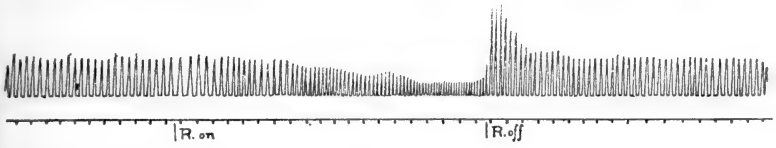

Figure 16.
Effects of heavy resistance. To read from left to right.

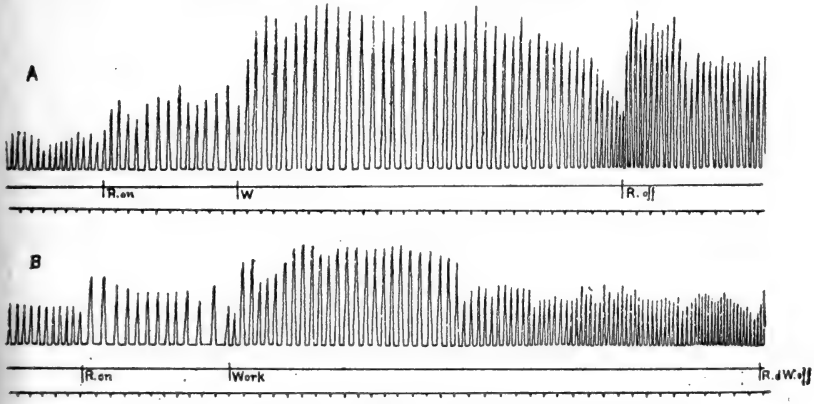

Figure 17.
Effects of resistance and gentle work. To read from left to right.

It will be shown later that even a slight deficiency in the oxygenation of the arterial blood favors greatly the development of fatigue symptoms in the respiratory center. But addition of oxygen to the air does not prevent the development of fatigue due simply to great extra work thrown on the respiratory center. When the breathing is quite free, and the oxygenation of the blood normal, fatigue does not at all readily show itself, and greatly increased breathing goes on in a normal manner over long periods. During muscular exertion, however, as will be shown later, the oxygenation of the blood may become impaired, in which case fatigue of the breathing may easily show itself, so that the subject becomes in a literal sense "short of breath," since each breath is short.

During the war cases were very common of what, according as one nervous symptom or another was most prominent, was designated as "chronic gas poisoning," "soldier's heart," "disordered action of the heart," "neurasthenia," etc. In these cases "shortness of breath" on exertion was a common and prominent symptom. Their breathing was investigated by Meakins, Priestley, and myself[10] and we found a marked deviation from normality in its regulation. In many of these persons the frequency of the breathing was very abnormally increased during rest, and in nearly all there was on exertion a quite abnormal increase of frequency, with a corresponding reduction of the normal increase of depth. The symptoms were thus the same as those of fatigue of the respiratory center, and on extra exertion these patients were liable to lose consciousness with asphyxial symptoms, just as in ordinary overfatigue of the center. Another prominent symptom was that the patients were unable to hold a deep breath for anything like a normal period, even if they were given oxygen to help. Many of them were also subject, particularly at night, to attacks of rapid shallow breathing with a sense of impending suffocation.

The condition of the breathing in these patients was evidently such as would be produced by an abnormal increase in the readiness with which the Hering-Breuer reflex is elicited, and we therefore described the respiratory condition as one of "reflex restriction" in the depth of breathing. At the time we were not aware of the symptoms of fatigue of the respiratory center. In the condition of fatigue the shallow and rapid breathing is just what would result from an increase in the strength of the Hering-Breuer reflex, and a similar apparent exaggeration of this reflex is present, as already seen in connection with the results of artificial respiration, in the condition of apnoea. In view, therefore, of all the facts relating to the respiratory movements in fatigue, apnoea, and neurasthenia, it seems probable that the apparent increased strength in the Hering-Breuer reflex is due to a diminution in the persistency of the individual inspiratory and expiratory discharges from the center, rather than to any real increase in the inhibitory Hering-Breuer discharges up the vagus nerves. It is thus only the weakness of the center that enables the Hering-Breuer reflex to gain the upper hand.

If we apply the same general conception to the other exag-

[10] Haldane, Meakins, and Priestley, *Reports of the Chemical Warfare Medical Committee*, No. 5, Reflex Restrictions of Breathing, 1918, and No. 11, Chronic Cases of Gas Poisoning, 1918; also *Journ. of Physiol.*, LII, p. 433, 1919.

gerated reflexes and general failure of nervous coördination in "neurasthenia," fatigue, and "shock," we seem to render these conditions more intelligible. Thus the great general nervous irritability, exaggeration of circulatory reflexes, tendency to sweating, and occasional instability of temperature, as observed in "neurasthenia," are probably analogous to the exaggerated reflex restriction in the depth of breathing and the inability to hold a breath. All these symptoms seem to be due to what Hughlings Jackson called "release of control."

In the causation of military neurasthenia the nervous overstrain of war, and the shocks to the nervous system in connection with various incidents of warfare and gross bodily injuries had evidently played a prominent part; but it was equally evident that infections of different sorts were also in part responsible for the condition, the nervous system being apparently weakened by toxic influences. In the same way ordinary fatigue of the respiratory center or other parts of the nervous system may be due not merely to extra work, but also partly to want of oxygen (as will be shown later), or to other chemical influences. Neurasthenia may thus be regarded as only a more lasting and persistent form of ordinary fatigue or exhaustion. It will be shown later that a very important secondary effect of the shallow breathing characteristic of neurasthenia or fatigue of the respiratory center is imperfect oxygenation of the blood.

The readiness with which a given resistance to breathing produces signs of fatigue of the breathing varies greatly in different individuals. In some persons a comparatively small resistance suffices to produce shallow breathing and rapid exhaustion of the respiratory center, though in other quite healthy persons a very considerable resistance is needed. Men with symptoms of neurasthenia are, as might be expected, particularly sensitive to resistance. This matter is, of course, important in connection with the design of respirators, etc. A respirator causing any considerable resistance may easily disable a man for muscular exertion.

The threshold alveolar CO_2 pressure at which the respiratory center begins to be excited may be altered by various abnormal conditions which will be discussed further in later chapters. The threshold may be lowered by want of oxygen or by the presence in the blood of an abnormally low proportion of available alkali, or by certain drugs, including, as Yandell Henderson[11] has pointed

[11] Yandell Henderson and Scarbrough, *Amer. Journ. of Physiol.*, XXVI, p. 279, 1910.

out, ether in low concentrations, or by massive afferent nervous stimuli. On the other hand the threshold is raised by such anaesthetics as chloroform, morphia, or chloral; and under their influence the alveolar CO_2 pressure is raised[12] and the breathing is commonly so much diminished that the arterial blood becomes markedly blue. These facts are of great importance in connection with the use of anaesthetics. Henderson showed also that morphia affects the chemical more than the afferent threshold of the respiratory center. Rise of body temperature has a marked effect in lowering the threshold.[13]

[12] Collingwood and Buswell, *Journ. of Physiol. (Proc. Physiol. Soc.)*, XXXV, p. xxxiv, and XXXVI, p. xxi, 1907.

[13] Haldane, *Journ. of Hygiene*, V, p. 503, 1905; see also Haggard, *Journ. of Biol. Chem.* XLIV, p. 131, 1920.

CHAPTER IV

The Blood as a Carrier of Oxygen.

THE evidence has already been referred to that nearly all the available oxygen in the blood is present in the form of a chemical compound with the haemoglobin of the red corpuscles, and that this compound has the remarkable property of dissociating with fall in the partial pressure of oxygen, at the same time changing its color from bright scarlet to a dark purple. It dissociates completely when the oxygen pressure is reduced to zero, and the readiness with which the dissociation occurs is dependent on temperature and other conditions which will be discussed below. It is contained in the corpuscles to the extent of about 30 per cent of their weight, and on liberation from them it can be crystallized out with comparative ease by the help of cold and of substances which diminish its solubility. There is considerable variation in the form of the crystals obtained from the blood of different animals.

To what extent, and in what directions, the elementary composition of haemoglobin varies is not yet definitely known; but the haemoglobin of birds has been found to contain phosphorus, while none is present in the haemoglobin of mammals. Iron is always present. A given amount of blood, whether or not the corpuscles have been dissolved and the haemoglobin liberated and diluted, takes up, on saturation with air at room temperature, a perfectly fixed and definite amount of oxygen in chemical combination. No further measurable quantity is taken up, except in simple physical solution, on saturation with oxygen. An exactly equal volume of carbon monoxide or nitric oxide is taken up in combination in presence of either of these gases. There is no shadow of doubt that the combination is a chemical one, though some extraordinary attempts, based on ignorance of well-ascertained facts, have recently been made to explain the combinations of oxygen and CO_2 in blood as due to adsorption.

Haemoglobin not only enters into dissociable chemical combinations with oxygen, carbon monoxide and nitric oxide, but also in presence of various oxidizing agents, such as ferricyanides or chlorates, or very weak acids, etc., when oxygen is also present, passes into a modification called by Hoppe Seyler methaemoglobin.

This substance, which crystallizes in a similar form to oxyhaemoglobin but has a dull brown color in acid solution and a brownish red color in alkaline solution, was found by Hüfner to take up in its formation from haemoglobin just as much oxygen as oxyhaemoglobin; but the oxygen is not given off in a vacuum. On the other hand it yields its oxygen much more rapidly to a reducing agent than oxyhaemoglobin or free oxygen does, and is thus an oxidizing agent of some activity. Thus if a drop of ammonium sulphide solution is mixed with a solution of methaemoglobin in the absence of free oxygen the methaemoglobin is instantly reduced to haemoglobin, as shown by the change of color and spectrum. But if free oxygen is present the color and spectrum of oxyhaemoglobin appear, since the ammonium sulphide combines far more slowly with free oxygen, or with the combined oxygen of oxyhaemoglobin, so that the haemoglobin formed instantly from the methaemoglobin is able to combine with the free oxygen and remain for a long time as oxyhaemoglobin.

While investigating the action of poisons which form methaemoglobin in the living body I noticed that when ferricyanide and certain other reagents act on oxyhaemoglobin to form methaemoglobin fine bubbles are liberated, and on further investigation the liberated gas was found to be oxygen.[1] I then measured accurately the liberated oxygen, and found that the volume of oxygen liberated by ferricyanide from blood agrees exactly with the volume liberated by the mercurial pump from combination in the blood. Ferricyanide also liberates carbon monoxide from its combination with haemoglobin, and the volume liberated corresponds with the volume of oxygen liberated by a corresponding quantity of oxyhaemoglobin. The following figures were obtained.

Combined gas in cc. liberated from the haemoglobin of 100 *cc. of blood and measured dry at* 0°*C and* 760 *mm.*	
By blood pump alone from blood saturated with air	18.18
By ferricyanide from blood saturated with air	18.20
By ferricyanide from blood saturated with CO	18.07

From their behavior, it appears that oxyhaemoglobin and CO-haemoglobin are molecular compounds in which the molecules of

[1] Haldane, *Journ. of Physiol.*, XXII, p. 298, 1898.

gas are directly combined as such with the molecules of haemoglobin, just as molecules of water are combined with molecules of a salt or other substance to form hydrate molecules. In methaemoglobin, on the other hand, the atoms in the molecules of oxygen which enter into combination are separately combined just as in ordinary chemical compounds containing oxygen. When the oxidation of haemoglobin to methaemoglobin occurs the new molecule formed loses its capacity for forming the molecular compounds oxyhaemoglobin and carboxyhaemoglobin. In consequence of this the molecular oxygen and carbon monoxide are liberated from oxyhaemoglobin or carboxyhaemoglobin by the action of ferricyanide, and can be measured with the greatest accuracy in the gaseous form by a simple method which I described in 1900 (see Appendix).[2]

The ferricyanide method afforded a ready means of measuring directly the gas combined in the molecular form with haemoglobin, and for this purpose replaced the complicated procedure and involved calculations required when the mercurial pump was used. One of the first discoveries made with the new method was that the coloring power of haemoglobin or any one of its molecular compounds with gases varies exactly as its capacity for combining with gas. Hence the "oxygen capacity" of the haemoglobin in blood—in other words its power of fulfilling its physiological function of carrying oxygen—can be measured easily by means of a reliable colorimetric method.[3] The following table (p. 62) shows the results we obtained on this point.

That oxygen capacity and depth of color run parallel also in various anaemias and other pathological conditions was shown by Morawitz;[4] and Douglas[5] showed that even during the rapid regeneration of haemoglobin after loss of blood this also holds.

At the time when the ferricyanide method was introduced there existed several well-known forms of "haemoglobinometer." Of these the apparatus of the late Sir William Gowers was by far the most convenient. In his method 20 cubic millimeters of blood, obtained from a prick of the skin, are introduced into a small graduated tube and diluted with water until the depth of color is the same as that of a standard solution of picrocarmine in another similar tube. The depth of color of the picrocarmine solution

[2] Haldane, *Journ. of Physiol.*, XXV, p. 295, 1900.
[3] Haldane and Lorrain Smith, *Journ. of Physiol.*, XXV, p. 331, 1900.
[4] Morawitz and Röhmer, *Deutsch. Arch. f. klin. Med.*, XCIII, p. 223, 1908.
[5] Douglas, *Journ. of Physiol.*, XXXIX, p. 453, 1910.

is that of normal human blood diluted to 1/100th; and the graduated tube gives the strength of color of the blood under examination in terms of this normal standard. One defect of the method was that the picrocarmine standard is not permanent, and another that the color of the picrocarmine solution is not the

	OXYGEN CAPACITY PER 100 CC.		PERCENTAGE DIFFERENCE IN RESULT BY COLORIMETRIC METHOD
	Ferricyanide method	*Colorimetric method*	
Ox blood	18.51	18.42	—0.5
"	15.05	15.33	+1.9
"	20.29	19.85	—2.2
"	15.04	15.17	+0.9
Horse blood	18.37	18.39	+0.1
Ox blood	19.75 19.90	20.00	+0.9
"	18.94	18.94	+0.0
Rabbit's blood	14.62 14.55	14.58	—0.1
Sheep's blood	17.44 17.44	17.30	—0.8
Ox blood	21.50 21.55	21.42	—0.4
"	16.16	16.06	—0.6
Human blood	21.08	21.27	+0.9
Mean	18.07	18.06	—0.055

same spectrally as that of the blood solution. As a consequence of this both the depth and the quality of the tints of the two solutions are differently affected by variations in the quality of the light at the time of using the instrument. Thus if the tints agree at one time of day they may be different at another; and in ordinary artificial light the results given are totally different from the results by daylight. Moreover, in consequence of individual differences in vision, a color match for one person is not the same as that for another person, even in the same light. To remedy these defects I substituted for the picrocarmine a one per cent solution of blood of the average oxygen capacity of the blood of adult men (18.5

cc. of oxygen per 100 cc. of blood), and introduced other improvements.[6]

In the presence of free oxygen haemoglobin is a very unstable substance, and soon decomposes, owing to the action of bacteria, etc.; but in the absence of oxygen the color of haemoglobin is perfectly stable, and this is also the case for carboxyhaemoglobin. The standard solution was therefore saturated with carbon monoxide in the absence of oxygen, and in this form is permanent. The blood under examination is also saturated with carbon monoxide by contact with coal gas or a little carbon monoxide. The two solutions are thus spectrally the same. With these improvements the Gowers haemoglobinometer became an extremely accurate instrument for ascertaining the oxygen capacity of blood, and the accuracy of any particular instrument could be controlled at once by the ferricyanide method. Certain ever-recurring criticisms of the instrument are almost entirely based on want of acquaintance with the physiological principles of colorimetric methods, or of the chemical facts on which the method is based. A detailed description of the method will be found in the Appendix.

The percentage oxygen capacity (or haemoglobin percentage) in the blood varies quite appreciably from hour to hour and day to day, according as the total volume of the blood varies from addition or withdrawal of liquid. There are also variations associated with age and sex; and pathological variations may be very marked and significant. As regards age and sex I found the following average relative figures for the percentage oxygen capacity of the blood.

Men	18.5
Women	16.5
Children	16.1

It has been known for long that when an oxyhaemoglobin solution is overheated or treated with various simple reagents the oxyhaemoglobin decomposes into a coagulated protein and a deeply-colored brown substance soluble in alcohol and certain other solvents, and known as haematin. The haematin contains 8.7 per cent of iron, and the coagulated protein is free from iron. To the haematin the formula $C_{34}H_{34}N_6O_5Fe$ has been assigned. By the action of reducing agents the haematin loses oxygen and changes to a purple color, with a corresponding change of spectrum, described by Stokes at the same time as he described the

[6] Haldane, *Journ. of Physiol.*, XXVI, p. 497.

spectra of oxyhaemoglobin and haemoglobin. To this reduced haematin Hoppe Seyler gave the very suitable name haemochromogen, as he believed it to be the parent substance of the color of haemoglobin and its varied derivatives. Thus we can regard haemoglobin as a compound of haemochromogen with a protein, also haematin as an oxygen compound of haemochromogen, while compounds of haemochromogen with carbon monoxide and nitric oxide are also known.

This conception is confirmed by the fact that the oxygen capacity of haemoglobin varies as its coloring power, and by another still more recently established fact. Till a few years ago it still seemed very doubtful whether there is a fixed and definite relationship between the iron in haemoglobin and its oxygen capacity; and Bohr[7] thought that he had obtained evidence of the existence of marked variations in the relation between iron and oxygen capacity; and that this relation differs in arterial and venous blood. The doubts on this subject turned round the reliability of the methods of determining iron. But in 1912 Peters, using a new and very reliable method of iron determination, found that there is a fixed and simple relationship between the oxygen capacity and iron, one molecule of combined oxygen corresponding to one atom of iron.[8]

Still other considerations point in the same direction. When we examine the colors and spectra of the various direct derivatives of haemoglobin and haemochromogen a striking general correspondence emerges. Methaemoglobin and haematin have very similar colors and spectra, which differ in a more or less similar manner in acid or alkaline solutions, and give a similar red color and corresponding spectrum on addition of hydrocyanic acid. With carbon monoxide haemochromogen gives the same color and spectrum and takes up the same volume of carbon monoxide as haemoglobin. With the nitric oxide compounds there appears also to be a correspondence. Thus I found that the red color of raw salted meat is due to the presence of NO-haemoglobin, formed by the action on haemoglobin of the reduction product of the niter which is mixed with the salt; and the color is still red after the meat is cooked and the NO-haemoglobin broken up to yield a haemochromogen compound on heating. NO-haemoglobin is also found post mortem in poisoning by nitrites. Between haemoglobin and haemochromogen there is also more or less of

[7] Bohr, Nagel's *Handbuch der Physiologie*, I, p. 95, 1905.
[8] Peters, *Journ. of Physiol.*, XLIV, p. 131, 1912.

correspondence; but oxyhaemochromogen, the molecular oxygen compound of haemochromogen, is missing, and it seems that haematin is so readily formed by haemochromogen in the presence of oxygen that oxyhaemochromogen cannot exist. Figure 18 shows the positions of the absorption bands in the spectra of NO-haemoglobin and NO-haemochromogen.

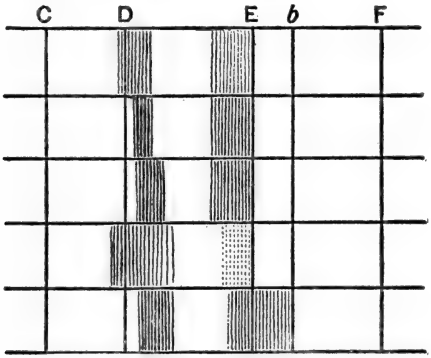

Figure 18.

1. Nitric oxide haemoglobin. 2. Oxyhaemoglobin. 3. Carbonic oxide haemoglobin. 4. Nitric oxide haemochromogen. 5. Obtained by action of nitrous acid on haematin.

If haemochromogen has been formed from haemoglobin by the action of acids or caustic alkali and heat, a substance possessing the spectrum and properties of natural haemoglobin is gradually re-formed on neutralization.[9] As proteins are greatly altered in properties by heating with alkali it would seem from this observation that there may be a number of different haemoglobins, in which, though the haemochromogen part of the molecule is the same in all, the protein part varies. As will be shown later, there is evidence that not only in different species, but also in different individuals of the same species, the protein part of the haemoglobin molecule varies, thus producing slight variations in the properties of the haemoglobin as a carrier of gases, although there is no variation in the oxygen capacity per unit weight of iron present. The haemochromogen part of the molecule seems, on the other hand, to be constant in all the different sorts of haemoglobin, and this brings about the identity of the relations between oxygen capacity, coloring power, and percentage of iron in all the different varieties of haemoglobin, although as regards other properties haemoglobins from different sources vary distinctly.

[9] See Menzies, *Journ. of Physiol.*, XVII, p. 415, 1895, and XLIX, p. 452, 1915.

The original ferricyanide method for determining the oxygen capacity of haemoglobin was very accurate, but required a good deal of blood, and was also slow on account of the time needed for exact equalization of temperature and gas pressures. Mr. Barcroft was then beginning his important series of investigations on the metabolism of the salivary glands and other organs. As he required a blood-gas method suitable for very small volumes of blood he asked me whether the ferricyanide method could be adapted for the purpose, and I designed an apparatus which we jointly tested and described, and which turned out so successfully that, in one form or another, it has now almost displaced the mercurial blood pump.[10] In this apparatus the oxygen combined in the haemoglobin of the very small quantity of blood required is liberated by ferricyanide, and the CO_2 by acid. The amount of gas liberated in either case is determined, not from the increase in volume which its liberation causes, but from the increase of pressure when the total volume of gas is kept rigorously constant. I adopted this principle as the result of much previous experience in the measurement of small differences in gas volumes. Certain causes of difficulty are eliminated by the pressure method, and by the adoption, as in the original ferricyanide method, of a control arrangement by which the effects of changes in temperature and barometric pressure during the experiment are eliminated. Various improvements in the technique of collecting and sampling blood drawn directly from blood vessels were also introduced by Mr. Barcroft.

This apparatus has been modified in various ways by different investigators, and some of the modifications are improvements. Others, however, seem to me to be the reverse. In the Appendix there is a description of a new and much more exact method in which the volumes of oxygen and CO_2 are measured directly.

Besides the oxygen chemically combined with haemoglobin, the blood contains a certain small amount of oxygen in simple solution. In accordance with Henry's law of solution of gases in liquids this amount varies with the partial pressure of oxygen in the atmosphere with which the blood is saturated, which in the case of arterial blood in the living body is (with certain reservations discussed in Chapters VII and VIII), the alveolar air. The amount of oxygen in free solution can be measured directly when the haemoglobin is by one means or another put out of action in respect to its power of entering into molecular combination with

[10] Barcroft and Haldane, *Journ. of Physiol.*, XXVIII, p. 232, 1902.

oxygen. Bohr found that at body temperature 2.2 cc. of oxygen (measured at 0° and 760 mm.) go into simple solution in 100 cc. of blood when the partial pressure of oxygen is one atmosphere,[11] and this is about 8 per cent less than dissolves in water. In the alveolar air the partial pressure of oxygen is only about 13 per cent of an atmosphere, and in the mixed arterial blood about 11 per cent, or 84 mm., of mercury. Hence the amount of free oxygen dissolved in the 100 cc. of the arterial blood of a man is only about 0.24 cc. (measured at 0°C. and 760 mm. pressure) whereas about 17.4 cc. are present in combination with haemoglobin, as will be shown below. It is evident, however, that the amount in free solution is of great importance; it depends upon the partial pressure of oxygen in the atmosphere with which the blood is in equilibrium; and, as already pointed out, Paul Bert found that the physiological action of oxygen and of any other gas depends upon its partial pressure in this atmosphere.

From the standpoint of physical chemistry the "partial pressure" of a gas in solution is simply the vapor pressure of the dissolved gas, i.e., its tendency to pass out of the solvent at any free surface, or the gas pressure which will just balance this tendency so that the amount of gas in solution neither increases nor decreases. But the vapor pressure of a substance in solution, or of the solvent itself, varies directly, as I showed in a recent paper,[12] with the diffusion pressure of the substance in solution. Hence vapor pressure is a direct index of diffusion pressure; and this is the reason why the partial pressure of a gas in solution is of so great importance. It is owing to differences in diffusion pressure that water or substances dissolved in it tend, independently of active "secretory" processes, to pass in one direction or another in the living body or outside it. For instance, when water passes through a semi-permeable membrane into a solution of sugar or salt, this is because the diffusion pressure of the pure water is greater than that of the diluted water in the sugar or salt solution. Van't Hoff's brilliant discovery that there is a connection between the fundamental "gas laws" and the phenomena of osmotic pressure was unfortunately marred by his failure to interpret either the connection or the experimental facts correctly. As a consequence, osmotic pressure and diffusion pressure were either completely misinterpreted or confused with one another. There seems now to be no doubt that it is the diffusion pressures, and not the

[11] Bohr, Nagel's *Handbuch der Physiol.*, I, p. 62, 1905.
[12] Haldane, *Bio-Chemical Journal*, XII, p. 464, 1918.

mere concentration of substances in the body, that are of physiological importance. To illustrate this distinction, the *concentration* of water in blood is much less than in a two per cent solution of sodium chloride; but the diffusion pressure of water in the blood is much greater than in the salt solution. Hence water will pass from the blood into salt solution. Similarly carbonic acid probably passes by diffusion from the muscular substance into the blood although the concentration of free carbonic acid in the muscle is less than in the blood.

Paul Bert's conclusion that it is the partial pressure of a gas which is of importance as regards its physiological action can thus be extended to every other substance present in the living body, not excepting water. The partial pressure of a dissolved gas is of decisive importance because the gaseous partial pressure, or vapor pressure, is an index of the diffusion pressure of a substance in solution; but where the gaseous partial pressure is so low that it cannot be measured, we must have recourse to other indices of the diffusion pressure.

It has been shown how important are the gas pressures in alveolar air. But the gas pressures of the blood in the systemic capillaries are of still more fundamental importance. It is clear that in order to understand how the oxygen pressure of the blood is regulated we must know the connection between dissociation of the oxyhaemoglobin of blood and fall in oxygen pressure. In other words we must know what is called the dissociation curve of oxyhaemoglobin in blood.

The history of the growth of knowledge on this subject is somewhat curious. Paul Bert[13] made some rough determinations with the pump of the amounts of oxygen in dogs' blood saturated with air in which the oxygen pressure was varied. His results indicated that in presence of oxygen reduced to a pressure of about 20 mm. the blood at body temperature had lost half its oxygen. In a living animal breathing air with an oxygen pressure of about 55 mm. (the alveolar oxygen pressure being unknown) the blood had also lost half its oxygen. When the blood was at a temperature below that of the body the oxygen was dissociated much less readily.

The subject was taken up again by Hüfner, who used a solution of oxyhaemoglobin crystals in dilute sodium carbonate solution. As the result, partly of experiments, and partly of calculation, he published in 1890 a very symmetrical curve, according to which oxyhaemoglobin does not lose half its oxygen till the oxygen pres-

[13] Paul Bert, *La Pression Barométrique*, p. 694, 1878.

sure is reduced to 2.6 mm.[14] This curve was totally at variance with Paul Bert's results, and made it very difficult to understand the effects on animals breathing air with a low oxygen pressure. In 1904 Loewy and Zuntz[15] published further experiments with defibrinated blood giving results much nearer to those of Paul Bert. Meanwhile the subject was taken up by Bohr,[16] who not only confirmed Paul Bert in the main, but for the first time showed that the dissociation curve for blood or haemoglobin solutions has a very peculiar shape, with a double bend (Figure 19), and that the

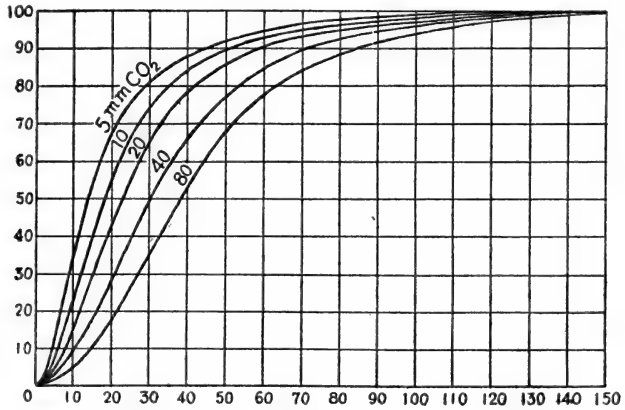

Figure 19.

Curves representing the percentage saturation of haemoglobin with oxygen at different partial pressures of oxygen and CO_2. Dog's blood at 38°C. Ordinates = percentage saturation with oxygen; abscissae = partial pressures of oxygen in millimeters of mercury. (Bohr, Hasselbalch, and Krogh.)

curve for a haemoglobin solution differs considerably from that for blood. For this reason he inferred that the haemoglobin in blood ("haemochrome") differs chemically from crystallized haemoglobin. Bohr, Hasselbalch and Krogh[17] then made the important discovery that the dissociation curve of haemoglobin or "haemochrome" is greatly influenced by the partial pressure of the CO_2 present (Figure 19), the CO_2 helping to expel oxygen from its combination, so that, as the blood takes up CO_2 in its passage through the capillaries, oxygen is liberated from the oxy-haemoglobin more readily than would otherwise be the case.

[14] Hüfner, *Arch. f. (Anat. u.) Physiol.*, p. 1, 1890.
[15] Loewy and Zuntz, *Arch. f. (Anat. u.) Physiol.*, p. 166, 1904.
[16] Bohr, *Centralbl. f. Physiol.*, 17, p. 688, 1904.
[17] *Skand. Arch. f. Physiol.*, 16, p. 602, 1904.

The investigation was now taken up by Barcroft and his pupils, who have made a number of important advances during the last few years with the help of one form or another of the ferricyanide apparatus.[18]

They found that the form taken by the dissociation curve of oxyhaemoglobin is greatly influenced by the salts present in the red blood corpuscles, or in a solution of their oxyhaemoglobin.[19] When all the salts were removed by dialysis the curve became a rectangular hyperbola,[20] as in the curve published by Hüfner. If the reversible reaction between oxygen and haemoglobin is represented by the uncomplicated equation $Hb + O_2 \rightleftarrows HbO_2$, the curve would, in accordance with the well-known law of Guldberg and Waage, be a rectangular hyperbola. This is the case when salts are absent and the solution is neutral, as in the dialysed solution. When, however, salts are present, the form of the curve is altered towards the characteristic form given by blood, and the nature and extent of the alteration was found to depend on the nature and concentration of the salts. Thus when dialysed dogs' haemoglobin was dissolved in a salt solution of the same composition and concentration as in human blood corpuscles the dissociation curve obtained was similar to that of human blood.

These discoveries rendered it unnecessary to assume with Bohr and others that there is any essential chemical difference between the haemoglobin present in blood corpuscles and in a solution of crystallized haemoglobin. At the same time they furnished a key to the explanation of the apparently divergent observations as to the dissociation curve of oxyhaemoglobin. Barcroft and Orbeli[21] found that not only does CO_2 shift the curve in the direction discovered by Bohr and his pupils, but that other acids added in such small quantities as not to decompose the haemoglobin have a similar effect, while alkalies have the opposite effect. As will be explained later Barcroft and his associates concluded that this alteration affords a very sensitive measure of any alteration in the reaction, or hydrogen ion concentration of the blood; and they have used it for this purpose.

The form of the dissociation curve of the oxyhaemoglobin in human blood at body temperature and with a constant pressure of

[18] A summary of these investigations is given in Barcroft's book, *The Respiratory Function of the Blood*, 1914.

[19] Barcroft and Camis, *Journ. of Physiol.*, XXXIX, p. 118, 1909.

[20] Barcroft and Roberts, *Ibid.*, XXXIX, p. 143, 1909.

[21] Barcroft and Orbeli, *Journ. of Physiol.*, XLI, p. 353, 1910. Barcroft, *Ibid.*, XLII, p. 44, 1911.

40 mm. of CO_2, as in average human alveolar air, was worked out by Barcroft, and his results for one individual (Douglas) were

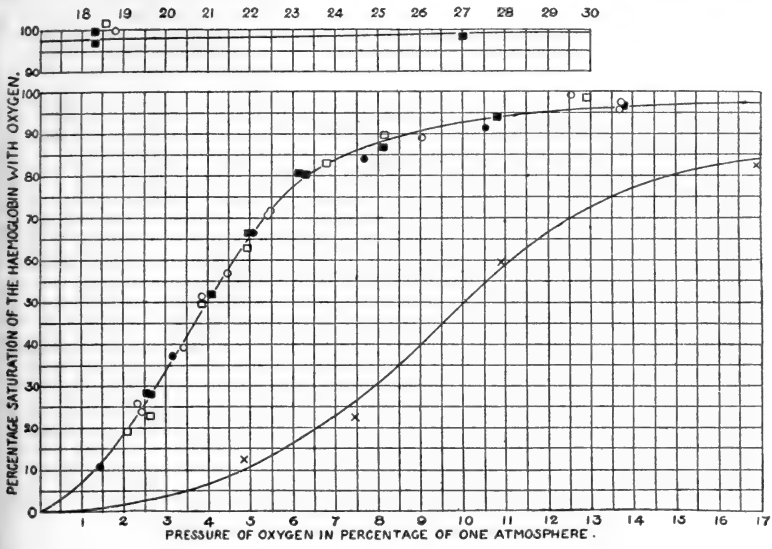

Figure 20.

Dissociation curves of oxyhaemoglobin in presence of 40 mm. pressure of CO_2 at 38° (1 per cent of an atmosphere = 7.60 mm. pressure).

○ Blood of C. G. D., using ammonia in blood-gas apparatus.
● Blood of C. G. D., using Na_2CO_3 in blood-gas apparatus.
□ Blood of J. S. H., using ammonia in blood-gas apparatus.
■ Blood of J. S. H., using Na_2CO_3 in blood-gas apparatus.
× Mixed blood of six mice, using ammonia in blood-gas apparatus.

approximately confirmed by Douglas and myself, working with a different apparatus. Figure 20 shows the curves given by the blood of Douglas and myself in a very exact series of observations, with the individual observations marked. Our curves as will be seen are sensibly the same; but Barcroft has found that the curves of different individuals may vary very distinctly. With the blood of Douglas and myself, for instance, half-saturation of the haemoglobin with oxygen occurs at an oxygen pressure of 4.0 per cent of an atmosphere or 30.4 mm. With that of other individuals, and the same pressure (40 mm.) of CO_2, half-saturation may, according to Barcroft, occur at as low an oxygen pressure as 24 mm.[22]

[22] Barcroft, *The Respiratory Function of the Blood*, p. 218, 1913.

On examining the dissociation curve it will be seen that the steepest part of the curve is in the middle. In the case of oxyhaemoglobin dissociating in the living body as the blood passes through the capillaries, and in doing so taking up CO_2, this part of the curve is still steeper, for the reason given by Bohr and his pupils. It is clear that with this form of curve the oxygen pressure in the capillaries must tend, after the first fifth of the oxygen has been given off, to remain comparatively steady during the giving off of the next three-fifths: for at this stage a large amount of oxygen is given off from the oxyhaemoglobin with a comparatively small fall in the oxygen pressure. In this way the oxygen supply to the tissues is maintained at a far higher and also much steadier pressure than if the curve were a rectangular hyperbola. As will be seen later, a man would die on the spot of asphyxia if the oxygen dissociation curve of his blood were suddenly altered so as to assume the form which Hüfner supposed it to have in the living body. The salts of the red corpuscles and the particular hydrogen ion concentration of the blood are of essential importance in connection with the oxygen supply of the tissues.

Haemoglobin, as already mentioned, forms specially colored dissociable compounds, not only with oxygen, but also with carbon monoxide and nitric oxide, and the compound with CO is of special physiological interest, apart from its practical importance in connection with the frequency of CO poisoning. As compared with the oxygen compound the CO compound, which was discovered by Claude Bernard,[23] is characterized by its relative stability, which is so great that at one time it was supposed that CO-haemoglobin is not dissociable.

Blood of which the haemoglobin is saturated with CO has a scarlet color similar to that of blood saturated with oxygen; but if the CO-haemoglobin is highly diluted, or examined in a very thin layer, its color is pink, as compared with the yellow color of diluted oxyhaemoglobin. By taking advantage of this fact one can easily recognize the presence of CO-haemoglobin in blood. This test, as I have often pointed out, is far more delicate than the older spectroscopic test, but requires daylight or some similar light. By adding carmine solution to diluted normal blood one can exactly match the color of the diluted blood containing CO,[24] and by using a suitable carmine solution I found it possible to estimate

[23] Claude Bernard, *Compt. Rend.*, XLVIII, p. 393, 1858.

[24] A detailed description of this method in its latest form will be found in the Appendix.

with great accuracy the percentage saturation of haemoglobin with CO.

With the help of this method Douglas and I worked out dissociation curves for the CO-haemoglobin of human blood at 38°C—in the absence, of course, of oxygen, but in the presence of varying partial pressure of CO_2.[25] The results are shown in Figure 21.

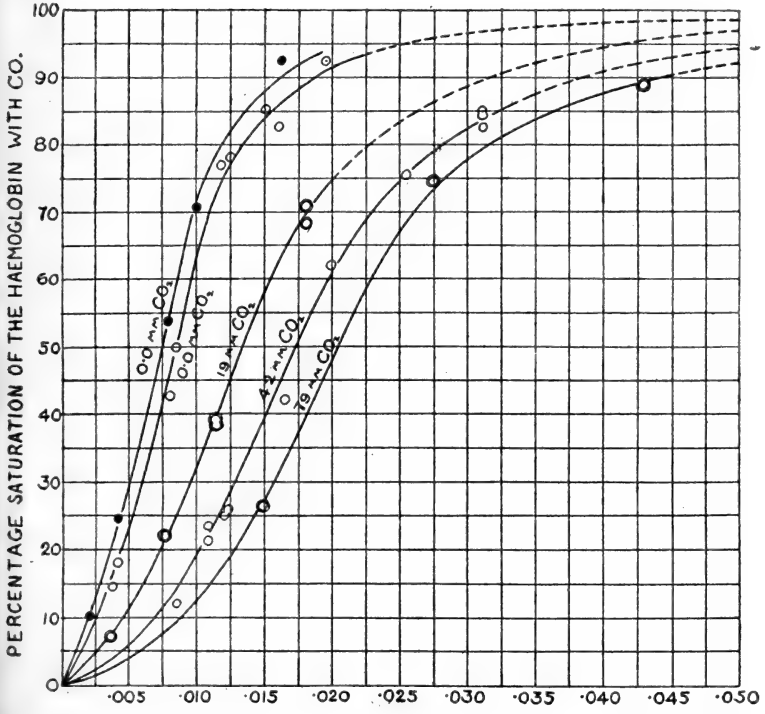

Figure 21.

Dissociation curves of CO haemoglobin in absence of oxygen, at 38° and with various pressures of CO_2. ○ Blood of C. G. D. ● Blood of J. S. H.

These curves, like the curve for the oxyhaemoglobin of human blood in Figure 20 are drawn free-hand. On comparing them we found that, allowing for possible small errors due to insufficient determinations, they are all the same curve when the scale on which the abscissae of each are plotted is altered by a suitable

[25] Douglas, J. S. Haldane, and J. B. S. Haldane, *Journ. of Physiol.*, XLIV, p. 275, 1912.

constant. It thus appears that the effect of substituting CO for O_2, or of varying the partial pressure of CO_2, is only to alter a simple constant in the equation to the curve. In other words it is only the affinity of haemoglobin for the gas saturating it which alters. With respect to the oxyhaemoglobin curve the same conclusion was reached by Barcroft and Poulton,[26] who found that variations in the partial pressure of CO_2 had, within wide limits, the same effects on the dissociation curve of oxyhaemoglobin, as on that of CO-haemoglobin. In the case of Barcroft's blood it requires a little over twice as high a partial pressure of oxygen to produce half-saturation of the haemoglobin in presence of 40 mm. pressure of CO_2 as when CO_2 is absent; just as in the blood of Douglas it takes a little over twice as high a partial pressure of CO. Barcroft and Means[27] have, however, also shown that in the case of a salt-free or nearly salt-free solution of haemoglobin the effect of CO_2 is not merely to alter the affinity of oxygen for haemoglobin, but also to alter the mathematical form of the curve, just as salts do. Hence it is only in the case of whole blood that the affinity alone is altered; and probably we should find that it is only within definite limits of variations in the hydrogen ion concentration of whole blood that the mathematical form of the dissociation curve is sensibly unaltered.

When blood or haemoglobin solution is exposed to a mixture of CO and air the haemoglobin becomes partly saturated with CO and for the rest with O_2. I found many years ago that with a dilute solution of blood the curve representing the percentage saturation of the haemoglobin with CO when increasing percentages of CO are added to the air in the saturating vessel is a rectangular hyperbola.[28] Figure 22 shows curves obtained by Douglas and myself with undiluted blood at body temperature from two persons and two mice.[29]

It will be seen that in each case the curve is a rectangular hyperbola, corresponding to the simple reversible reaction $HbO_2 + CO \rightleftarrows HbCO + O_2$. Thus for my own blood the proportions of HbCO to HbO_2 are 1 : 1 with .07 per cent of CO, 2 : 1 with 2 x .07 per cent of CO, 3 : 1 with 3 x .07 per cent of CO, etc. For each kind

[26] Barcroft and Poulton, *Journ. of Physiol.*, XLVI, *Proc. Physiol. Soc.*, p. iv, 1913.

[27] Barcroft and Means, *Journ. of Physiol.*, XLVII, *Proc. Physiol. Soc.*, p. xxvii, 1914.

[28] Haldane, *Journ. of Physiol.*, Vol. XVIII, p. 449, 1895.

[29] *Journ. of Physiol.*, Vol. XLIV, p. 278, 1912.

of blood the curve remains exactly the same when the blood is diluted, or rendered less or more alkaline, or when neutral salts are added. This is of course quite different from what happens with the simple dissociation curves of oxyhaemoglobin and CO-haemoglobin.

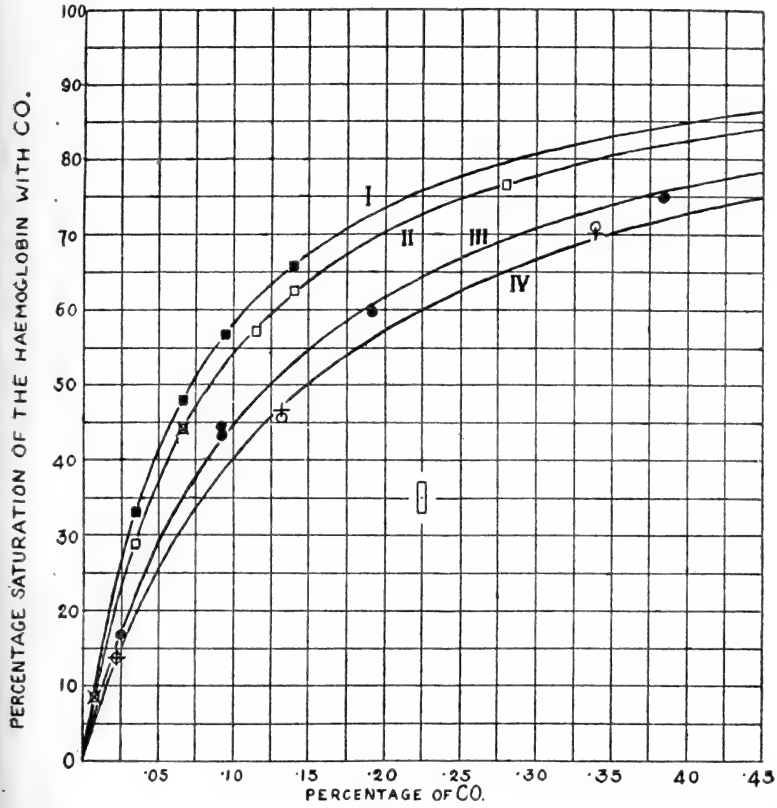

Figure 22.

Dissociation curves of CO haemoglobin in presence of air (20.9 per cent O_2) at temperature of 38°. I. Blood of J. S. H. II. Blood of C. G. D. III. Blood of mouse A. IV. Blood of mouse B. The crosses indicate points determined in the presence of 40 mm. pressure of added CO_2.

When the percentage of CO in the air is kept constant and the percentage of oxygen is varied the curve is again a complete rectangular hyperbola, as shown in Figure 23, provided that the percentage of CO is sufficient to saturate the haemoglobin completely in the absence of O_2, as in the upper curve.

It is thus evident that when we have determined the percentage saturations of a sample of haemoglobin with CO and O_2 in a solution saturated with a gas mixture containing CO and O_2 at known concentrations or partial pressures, what we have really determined is the relative affinities of the haemoglobin for CO and

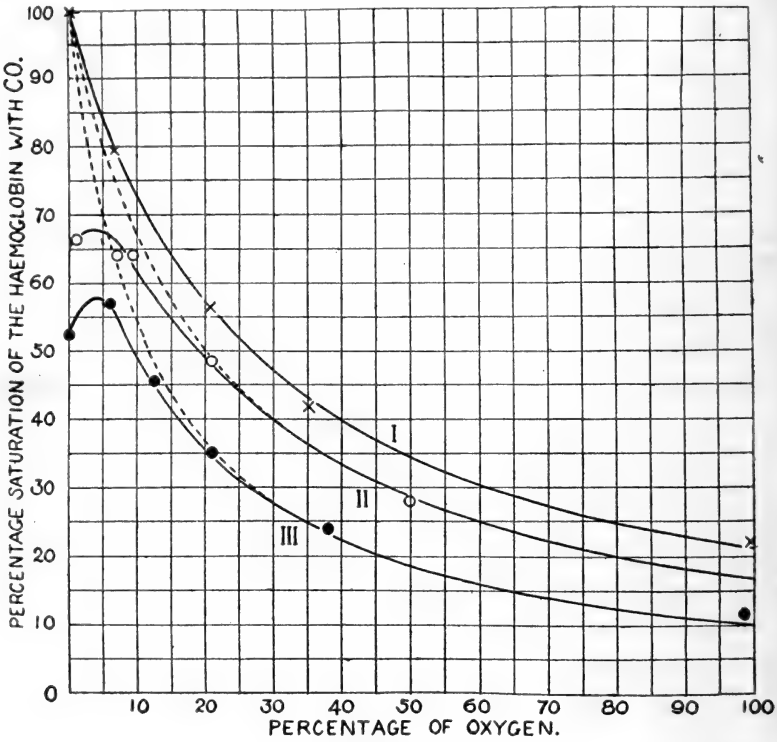

Figure 23.

Dissociation curves of CO-haemoglobin in presence of constant percentage of CO and varying percentage of oxygen, at atmospheric pressure. I. Blood of J. S. H.: CO = 0.0945 per cent. Blood of mouse C: CO = 0.090 per cent. III. Blood of mouse D: CO = 0.0635 per cent.

O_2 (without allowing, however, for the slight difference in solubility between the two gases). In my own blood the haemoglobin is equally divided between CO and O_2 when the partial pressures of CO and O_2 are as .07 to 20.9—i.e., as 1 to 299. Hence the affinity of the haemoglobin for CO is 299 times its affinity for O_2. For the haemoglobin of Douglas the corresponding figure is 246. For his haemoglobin we can also compare the affinities for CO and

O_2 in another way. In presence of 40 mm. of CO_2 his blood becomes half-saturated with CO (in the absence of oxygen) at a pressure of .017 per cent of an atmosphere of CO, as shown in Figure 21, and half-saturated with O_2 (in the absence of CO) at a pressure of 4.0 per cent of an atmosphere, as shown in Figure 20. These pressures are in the ratio of 1 : 235, which is nearly the same ratio as when the relative affinities are estimated by the previous method.

As already seen, we may be able to account for varying dissociation curves of the oxyhaemoglobin in whole blood by the varying composition and concentration of the salts contained in the red corpuscles, and by varying alkalinity; but we cannot so account for the varying relative affinities of different specimens of haemoglobin for CO and O_2, since the curves in Figure 22 are not affected by varying concentration of salts or degrees of alkalinity. There seems to be no escape from the conclusion that in different individuals of the same species, as well as in different species, the haemoglobin molecules are different. Whether the haemoglobin in each individual is made up of homogeneous molecules, or is a mixture in some definite proportion of two or more different kinds of haemoglobin, we do not as yet know. What seems pretty certain, however, is that each individual has a specific kind of haemoglobin just as he has a specific shape of nose. At whatever time we have investigated my own and Dr. Douglas's haemoglobin their specific differential characters have appeared to be sensibly the same. It seems pretty certain that, since the ratio of oxygen capacity to both the coloring power and amount of iron in haemoglobin is constant, the difference in the haemoglobin molecule in different kinds of blood is due to the protein and not the haemochromogen fraction of the molecule; but as yet there are no data to indicate more specifically the nature of the difference. It is of considerable biological significance to have found, however, that, looking at living organisms from a purely chemical standpoint, individual differences express themselves, not merely in the relative amounts of the different molecules which can be separated from different parts of the body, but also in their chemical constitution.

Since the dissociation curve of CO-haemoglobin in presence of a constant pressure of oxygen and varying pressure of CO, or in presence of a constant pressure of CO and varying pressure of oxygen, is a rectangular hyperbola, provided that the gases are present at sufficient pressure to saturate the haemoglobin, it is

clear that provided we know the relative affinities of the two gases for the haemoglobin, and the pressure at which one is present, we can tell from an observation of the percentage saturation of the haemoglobin the pressure of the other. Hence we can use haemoglobin solutions for determining small percentages of CO in air. All that is necessary is to introduce a little blood solution into a small bottle of the air, shake till the solution takes up no more CO, and then determine colorimetrically the percentage saturation of the haemoglobin with CO, and calculate the percentage of CO present.[30] Still more important in physiological work is the converse determination of the oxygen pressure by observation of the percentage saturation of haemoglobin exposed to a constant pressure of CO. By this means, as we shall see later, it is possible to measure the partial pressure of oxygen in the arterial blood within the living body and so decide the question whether active secretion of oxygen inwards occurs in the lungs.

Douglas and I found that when the combined pressure of O_2 and CO are insufficient to saturate the haemoglobin the dissociation curve of CO-haemoglobin in presence of a constant pressure of CO and diminishing pressure of O_2 begins to diverge from the rectangular hyperbola which it would otherwise have followed, and then proceeds to trace out the peculiar hump shown on the lower two curves in Figure 23, and in greater detail in Figure 24. We thus have what seems at first sight a most anomalous fact, namely that although all other facts show that increase in the pressure of oxygen tends to keep out CO more and more from combination with haemoglobin, yet at very low pressure of oxygen and CO the reverse is the case, and increase of oxygen pressure helps the CO to combine with haemoglobin. There can be no doubt that the converse is also the case—namely that at low pressures of CO the presence of the CO helps the oxygen to combine with the haemoglobin. This explains a very anomalous fact noticed by Lorrain Smith and myself many years ago[31]—namely that the presence of a small percentage of CO helps animals to resist the effect of a very low oxygen pressure, or at any rate does not make them worse. We had expected that a given percentage of CO would become more and more poisonous the more the oxygen pressure was diminished, and this was the case within certain limits; but we were then quite at a loss to understand why with very low oxygen pressures the CO seemed to do no harm.

[30] Haldane, *Methods of Air Analysis*, p. 119, 1919.
[31] Haldane and Lorrain Smith, *Journ. of Physiol.*, XXII, p. 246, 1897.

The explanation of the anomalous hump in the curves on Figures 23 and 24 is in reality easy enough in view of the peculiar double-bended form of the simple dissociation curves of oxy-haemoglobin and CO-haemoglobin in whole blood. When CO is present at a pressure insufficient to saturate the blood, and the

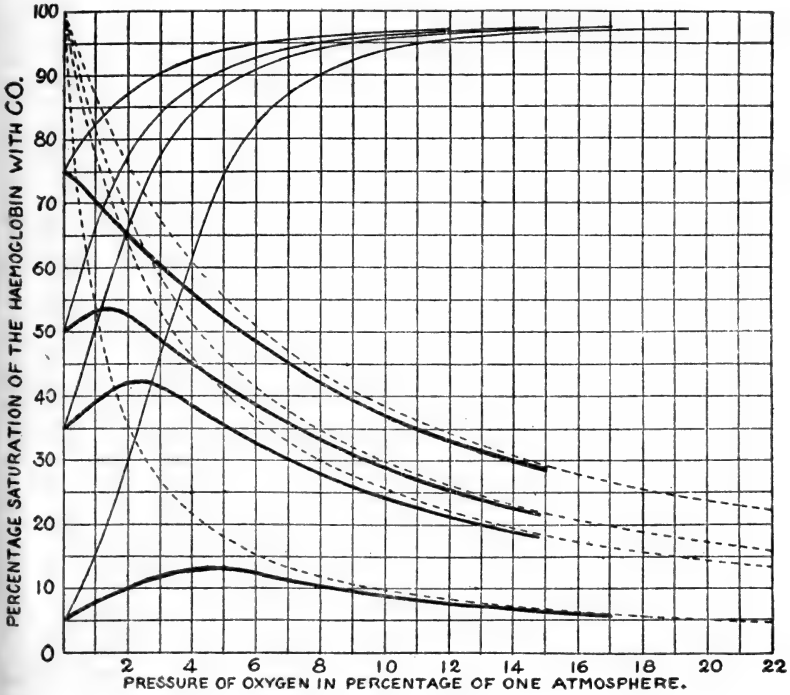

Figure 24.

Dissociation curves of CO haemoglobin in blood at 38° and in presence of 40 mm. CO_2, with constant pressure of CO and varying pressures of oxygen.

oxygen pressure is gradually raised from zero, the two gases together will trace out curves representing the total saturation of the haemoglobin, as shown in the thin lines on Figure 24. These curves are calculated on the theory that the proportion of oxy-haemoglobin to CO-haemoglobin is exactly what is required in view of the known relative affinities of oxygen and CO for the haemoglobin of the blood used. As, however, the thin curves start at the steep part of the joint curve a very small addition of oxygen

will produce such a large effect that not only will a large amount of oxygen go into combination, but also an increased proportion of CO. The thick lines show the curve for CO-haemoglobin as calculated on this hypothesis, and the dots show the actual observations. There is in reality perfect agreement with the theory that oxygen and CO combine with haemoglobin in exact proportion to their relative affinities for haemoglobin and their partial pressures, just as in the upper curve of Figure 23. The great significance of this in connection with the explanation of CO poisoning will be referred to later.

It remains to discuss the explanation of the various dissociation curves to which reference has been made. We have seen above that Barcroft and his pupils found that when a solution of oxyhaemoglobin is freed, or approximately freed, from salts it gives a dissociation curve which is a simple rectangular hyperbola, in accordance with the simple reaction

$$Hb + O_2 \rightleftarrows HbO_2.$$

A. V. Hill pointed out in 1910 that the varying values obtained for the osmotic pressure of haemoglobin solutions in presence of salts indicates that the molecules are more or less aggregated together owing to the influence of the salts; and he showed that this fact was capable of explaining the deviation from a rectangular hyperbola of the dissociation curve. Thus if, in consequence of the aggregation, the reaction were

$$Hb_2 + 2O_2 \rightleftarrows Hb_2O_4,$$

the curve would no longer be a rectangular hyperbola but would approximate to that given for oxyhaemoglobin in presence of a certain proportion of salts. By assuming a suitable proportion of aggregation of the haemoglobin molecules as Hb_2, Hb_3, etc., we can therefore construct equations which will give the actual dissociation curves. He also gave a general form of equation to meet the varying cases. In this equation there are two constants, which must be suitably chosen.

The subject was also taken up by Douglas, J. B. S. Haldane, and myself. We adopted Hill's aggregation theory, but in a different form. It seemed to us that the aggregation in protein solutions is a phenomenon of the same general nature as precipitation, the precipitate being, however, only formed in very small particles consisting of only two, three, or at any rate a few molecules.

On this view the aggregated haemoglobin molecules have their molecular affinities saturated, and therefore go out of the reaction between oxygen or CO and haemoglobin, thus following the general principle that *corpora non agunt nisi soluta.* The only reaction taking place between the haemoglobin and oxygen is thus the first one mentioned above. To explain the actual form of the dissociation curve for blood or salt solutions we assumed that the degree of aggregation depends on the concentration of the haemoglobin or oxyhaemoglobin in the solution, in accordance with the reactions

$$\begin{aligned} &Hb + Hb \rightleftarrows Hb_2 \\ &Hb + Hb_2 \rightleftarrows Hb_3 \text{ etc.} \\ &HbO_2 + HbO_2 \rightleftarrows Hb_2O_4 \\ &HbO_2 + Hb_2O_4 \rightleftarrows Hb_3O_6 \text{ etc.} \end{aligned}$$

Thus reduced haemoglobin and oxyhaemoglobin molecules aggregate separately; and if we assume that reduced haemoglobin aggregates more readily than oxyhaemoglobin we can explain at once the distortion of the curve from the primary rectangular hyperbola obtained by Barcroft. For as the oxyhaemoglobin becomes reduced the aggregation of the reduced haemoglobin molecules must increase more rapidly than the aggregation of the oxyhaemoglobin diminishes. Hence at what would, but for the aggregation, be half-saturation, there are fewer free reduced haemoglobin molecules and more free oxyhaemoglobin molecules than would be the case if the oxyhaemoglobin molecules aggregated as readily as the reduced haemoglobin molecules. Hence the actual saturation will be much less than half, and not just half, as would be the case if the tendency to aggregation were the same for the two kinds of molecules. The actual dissociation curve will also have the double bend which is characteristic of it. We also assumed that the saturated molecules of HbCO have just as much tendency to aggregate with one another and with the saturated molecules of HbO_2 as have the molecules of HbO_2. For this reason the dissociation curve of HbCO in blood in presence of oxygen must be a rectangular hyperbola, as is actually the case, though its dissociation curve in the absence of oxygen has the same form as the dissociation curve of HbO_2.

By making certain assumptions (for a statement of which I must refer to our original paper) J. B. S. Haldane found that the following equation to the curve for human blood in Figure 20

resulted, and fitted the experimentally determined curve very closely.[32]

$$p = \frac{1.6S \quad (9—8S)}{(1—S) \quad (1+2S)}$$

where p = pressure in percentages of one atmosphere, and
S = fractional saturation of the haemoglobin with oxygen.

Thus if S be 50 per cent $= \frac{50}{100} = \frac{1}{2}$, p will be 4.0, as we actually found to be the case. To express the result in millimeters of mercury pressure, p must of course be multiplied by 7.6, and would thus become, in the above example, 30.4.

As explained above, the simple dissociation curves for oxyhaemoglobin or CO-haemoglobin in *normal* human blood[33] are, so far as our present knowledge goes, the same, when allowance is made for the differing affinities of the two gases for haemoglobin. The above equation may therefore be generalized in the form

$$pa = \frac{1.6S \quad (9—8S)}{(1—S) \quad (1+2S)}$$

taking a as representing the affinity of the gas for haemoglobin as compared with the affinity represented in the curve on Figure 20, giving half-saturation with a gas pressure of 4.0 per cent of an atmosphere. Thus for the fourth curve on Figure 21 (dissociation curve of CO-haemoglobin in the blood of Douglas, in presence of 42 mm. CO_2 pressure), at half-saturation $pa = 4.0$. Hence as p was .017, a was 235, or the affinity of the haemoglobin for the CO (determined without taking into account the solubilities of CO and O_2) was 235 times its affinity for oxygen in the standard curve of Figure 20. This is a convenient and easily intelligible method of putting the results.

[32] In working out this equation it was assumed that (as found by Barcroft and Roberts for dogs' haemoglobin) a dialysed solution of the haemoglobin of Douglas and myself becomes half-saturated with oxygen at 38°C and a pressure of 1.6 per cent of an atmosphere of oxygen, and that in human blood saturated with oxygen 2/3 of the oxyhaemoglobin is aggregated, and in completely reduced blood 8/9 of the reduced haemoglobin. The curve of the dialysed solution would give the equation $p = \frac{1-S}{1.6S}$

[33] For abnormal human blood the curves are probably different, as will be pointed out in Chapter VIII.

The corresponding equation worked out by Hill is

$$\frac{y}{100} = \frac{Kx^{2.5}}{1 + Kx^{2.5}}$$

where x = oxygen pressure in mm. of mercury,
y = percentage saturation of the haemoglobin,
K = a constant varying for different curves.

For the blood of Douglas (which was the first to be investigated completely by Barcroft, and which was also investigated by ourselves) the value of K was .000196.[34]

Hill's equation gives curves almost identical with ours, and as he had kindly communicated it to us by letter we should certainly have adopted it had we seen how the theory on which it is based could be brought into definite relation with the particular rectangular hyperbola given by dialysed haemoglobin, or reconciled with the fact that the dissociation curve of CO-haemoglobin in presence of a constant oxygen pressure is a rectangular hyperbola. Hill soon afterwards offered a possible explanation as regards the latter point.[35] It seems to me that this explanation is improbable, but so also, it must be confessed, are certain assumptions connected with the deduction of our own equation. At present the data are lacking for a decision as to whether either theory is correct, although both equations are for all practical purposes satisfactory. I cannot see, however, how to escape the conclusion that there is more aggregation among the unsaturated than among the saturated molecules of haemoglobin. It is evident that far more data are needed to enable us to understand the dissociation of oxyhaemoglobin in blood.

With the help of the chemical facts described in the present chapter we might proceed at once to the discussion of a number of physiological and pathological problems; but such a discussion would be incomplete and misleading in the absence of the facts relating to the carriage of CO_2 by the blood, and this subject will therefore be considered in the next chapter.

[34] The value of K as calculated from our own results (Fig. 20) is, for the blood of both Douglas and myself, outside the normal limits given by Barcroft and represented graphically in Figure 109, page 226, of his book *The Respiratory Function of the Blood*. The cause of this discrepancy is not yet clear.

[35] A. V. Hill, *Bio-Chemical Journal*, VII, p. 471, 1913.

CHAPTER V

The Blood as a Carrier of Carbon Dioxide.

We must now turn to the consideration of the blood as a carrier of CO_2. Mammalian arterial blood has usually been found to contain about 40 or 50 volumes of CO_2 per 100 volumes of blood, while venous blood from the right side of the heart contains several volumes more. The following average results obtained with the mercurial pump by Schoeffer[1] illustrate the difference between venous and arterial dogs' blood, although much doubt must exist as to whether the circulation and respiration were at normal resting values when the samples were taken. Much more reliable data will be given for man in Chapter X.

	OXYGEN	CO_2
Arterial blood	19.2	39.5
Venous blood from right heart	11.9	45.3
Difference	7.3	5.8

In man, as will be shown below, normal arterial blood contains during rest about 53 volumes per cent of CO_2 if the blood is saturated with CO_2 at the pressure (about 40 mm.) existing in average alveolar air of adult men. As 100 volumes of blood, according to Bohr's[2] calculation, take up in simple solution about 51 volumes of CO_2 in presence of a pressure of one atmosphere of CO_2 at body temperature, they can only take up $\frac{40}{760} \times 51 = 2.7$ volumes at the normal alveolar pressure of 40 millimeters or 5.3 per cent of an atmosphere. Hence only 2.7 volumes per cent of the CO_2 are in simple solution, the other 50.3 volumes being in chemical combination. As will be shown below, the difference between the partial pressures of CO_2 in human arterial and venous blood during rest is only about 6 mm. or 0.8 per cent of an atmosphere. Hence the physically dissolved CO_2 given off in the lungs is only 0.4 volumes

[1] Schoeffer, *Sitz. ber. d. Wiener Acad, math. nat. cl.*, XLI, p. 589, 1860.
[2] Bohr, Nagel's *Handbuch der Physiol.*, II, p. 63, 1905.

per cent, while actually about 4 volumes per cent are given off. It is evident, therefore, that the giving off of CO_2 in the lungs is almost entirely dependent on the dissociation of its chemical combinations in the blood.

In what form is CO_2 chemically combined in the blood? We cannot answer this question in the same comparatively simple and definite manner as in the case of the combination of oxygen with blood. CO_2 dissolved in water has acid properties, and by the addition of other stronger acids to blood the dissociable chemical combinations with CO_2 are entirely broken up and CO_2 liberated. It is thus quite evidently as an acid (i.e., as H_2CO_3) that CO_2 enters into combination with blood. On analysis blood is found to contain an excess of alkali (for the greater part soda) not combined with mineral acids. In other words hydrochloric, phosphoric, and small amounts of sulphuric, acids are present in blood, but not in sufficient amounts to saturate the alkali. Hence CO_2 is apparently free to combine with the excess of alkali, forming, since an excess of free CO_2 is present, bicarbonates. As Zuntz[3] pointed out, if blood were nothing but a solution of the well-recognized acids and bases present in it, we could account for the quantity of CO_2 which it is capable of combining with chemically. Zuntz calculated that the excess of alkali present in the blood is equivalent to at least a 0.2 per cent solution of soda. This could take up as bicarbonate as much CO_2 as blood can take up in combination. Nevertheless the properties of such a solution in respect to the carriage of CO_2 would not approach to those of blood: for the soda would remain completely saturated as bicarbonate when exposed to the CO_2 in the alveolar air, and there would not be any appreciable dissociation, so that the solution would be no better than distilled water as a physiological carrier of CO_2. This point has been rendered specially clear by Bohr, who investigated the dissociation curve for CO_2 of a dilute sodium bicarbonate solution.

To reach an insight into the actual behavior of blood as a carrier of CO_2 we have to take into consideration another factor. Proteins have the very peculiar property of being able to act either as weak alkalies towards acids or as weak acids towards alkalies. This is shown, for instance, by the familiar fact that an ordinary indicator such as litmus ceases to give a sharp end-point when a protein is present, and that not only neutral but even slightly acid

[3] Zuntz, Hermann's *Handbuch der Physiol.*, IV, 2, p. 65, 1882. To Zuntz's admirably clear and thorough discussion of the subject I am greatly indebted. This discussion is far ahead of most of what has appeared in later textbooks and papers.

protein solutions will combine with CO_2. A considerable excess of acid or alkali must be added to a neutral protein solution before a marked acid or alkaline reaction is reached. The protein acts as a "weak," or very slightly ionized, acid, such as carbonic acid, and likewise acts as a correspondingly weak alkali, since the protein molecule possesses both acid and alkaline affinities. It is thus, like carbonic acid, or any other weak acid, or weak alkali, a buffer substance, which prevents any abrupt change from acid to alkaline reaction or vice versa. Not until all the CO_2 combined in a solution of carbonate has been liberated by acid is there a sudden development of acid reaction, or so long as any free CO_2 is present of strong alkaline reaction. The CO_2 acts as a buffer substance on the alkaline side only, whereas protein is capable of acting on either side of the neutral point. In the living body, however, blood is always a little alkaline, so that the combination of CO_2 with proteins does not come into account.

We can now see a reason why blood should act towards CO_2 as it does in the living body and in the vacuum pump. The total alkali in the blood is combined, partly with strong acids, such as HCl, partly with carbonic acid, and partly with protein compounds; partly also, perhaps, with other substances capable of acting, like the proteins, as very weak acids. In the living body, however, free carbonic acid is always present, and the mass influence of the free carbonic acid prevents part of the protein from combining with alkali, while the protein in a similar manner keeps out the carbonic acid. We have thus a chemical system which is disturbed at once by any variation in the concentration of free carbonic acid present, i.e., by any variation in the partial pressure at which the blood is saturated with CO_2. When the pressure of CO_2 falls, more of the proteins are at once enabled to take the place previously occupied by the carbonic acid in the chemical combinations which constitute the system; and vice versa with a rise of CO_2 pressure. In the vacuum pump the CO_2 pressure is reduced to zero, since, although the total pressure in the vacuum chamber of the pump is, owing to aqueous vapor, always above zero, the CO_2 is carried off in the stream of aqueous vapor passing away. To recover the whole of this CO_2 in the same gaseous form, however, a perfect and dry vacuum in the receiving chambers of the pump is needed. Since the CO_2 pressure is zero the whole of the CO_2 in combination is expelled by the mass influence of protein acting as an acid. Pflüger showed that even when a moderate amount of sodium carbonate is added to blood, the additional CO_2 in the

carbonate is expelled in the vacuum pump, and can be recovered in the gaseous form with the help of the perfect vacuum of the Pflüger blood pump.[4] This can now be easily understood in terms of the theory just stated. The blood must be either boiled or shaken: otherwise the disengagement of CO_2 is excessively slow.

When serum alone, and not whole blood, is exposed to the vacuum of the pump, most of the CO_2 can be pumped out, but not quite all. It is necessary to add some acid in order to obtain the whole of the CO_2—at any rate within any reasonable time. The proteins of the serum are not present in sufficient amount to effect the dissociation of the whole of the sodium carbonate, but the expulsion is easy when the haemoglobin of the corpuscles is added. Both haemoglobin and serum proteins act towards sodium carbonate as acids, and it was shown by Sertoli[5] that much of the CO_2 can be expelled in the pump from sodium carbonate solution if serum proteins are first added.

Bohr found that haemoglobin solutions, even if they are first rendered slightly acid, will combine with considerable amounts of CO_2, and he was thus led to what seems to me to be the erroneous conclusion that haemoglobin has a specific power, apart from its alternative acid or basic properties, of combining with CO_2. Equally erroneous, as Priestley[6] has recently shown, is a similar conclusion which was put forward on spectroscopic grounds.

We have already seen what predominant physiological importance is attached to the pressure of CO_2 in the arterial blood, and with what exactitude this pressure is regulated. We should therefore expect to find that the pressure of CO_2 in the tissues of the body generally is of the same importance and subject to similar regulation. To understand this regulation it is of primary importance that we should know the laws of dissociation of CO_2 from its combination in blood. Until quite recently our knowledge on this subject was very limited, although Bohr[7] had constructed a tentative dissociation curve from observations partly by Jacquet and partly by himself, on samples of blood from the ox and dog.

The matter was taken up a short time ago by Christiansen, Douglas and myself[8] with the help of the new method of blood-

[4] Pflüger, *Ueber die Kohlensäure des Blutes*, p. 6, 1864.
[5] Sertoli, Hoppe-Seyler's *Med.-Chem. Unters.*, III, p. 356, 1868.
[6] Priestley, *Journ. of Physiol.*, LIII, *Proc. Physiol. Sic.*, p. LVIII, 1920.
[7] Bohr, Nagel's *Handbuch der Physiol.*, II, p. 106, 1905.
[8] Christiansen, Douglas, and Haldane, *Journ. of Physiol.*, XLVIII, p. 244, 1914.

gas determination mentioned in Chapter IV. Warned by previous failures of physiologists to recognize the exactitude of normal physiological regulations, we used defibrinated human blood, of which fresh samples could be obtained at any time from the same individual under normal conditions. At the outset we wasted much time, however, through failing to realize that it was necessary to have the blood fresh for each experiment, as blood outside the body undergoes slow changes which diminish its capacity for carrying CO_2.

Figure 25 shows the results obtained with my own blood.

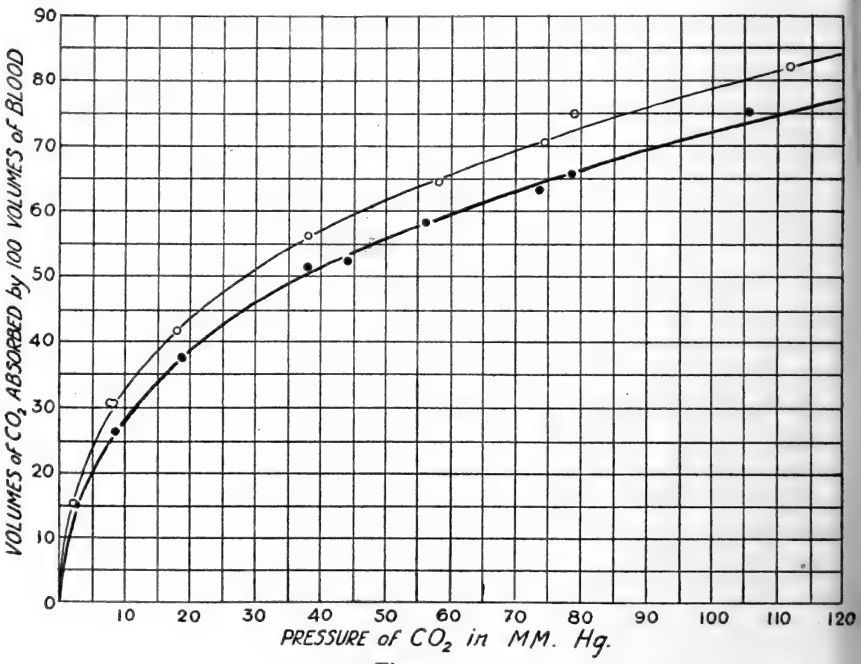

Figure 25.

Lower curve—absorption of CO_2 by blood of J. S. H. in presence of air and CO_2. Upper curve—absorption of CO_2 by blood of J. S. H. in presence of hydrogen and CO_2.

Attention may first be directed to the lower curve, showing the amounts of CO_2 taken up in the presence of air and varying pressures of CO_2. The first, and by far the most striking, point to be noted is that, although the different determinations were made on different days covering a period of about six months, they all lie on one curve. The samples were taken at different times of the day

during ordinary laboratory work. In regulating the temperature of the bath containing the saturator, analyzing the samples of air from the saturator, observing the barometric pressure, measuring the sample of blood (of which about 1 cc. was used for each analysis), and determining the CO_2 by means of the blood-gas apparatus (we used Brodie's modification of the original apparatus), it was impossible to avoid combined errors of 1 or 2 per cent of the quantities to be measured, so that we could not say how exact Nature's regulation of the curve is. At any rate it was so exact for my blood that the most exact existing chemical methods did not show any deviations from the curve, any more than they could show deviations from the oxyhaemoglobin or CO-haemoglobin dissociation curves. Marked temporary deviations could, however, be produced by severe muscular exertion; and probably very distinct deviations may occur after meals.

With the blood of other persons the results were only slightly different. Thus the curves, so far as ascertained, for the blood of Miss Christiansen and Dr. Douglas were slightly below, and otherwise parallel to mine under normal conditions. The blood of most persons seemed to take up about 50 volumes of CO_2 per 100 volumes of blood at 40 millimeters pressure of CO_2; but under abnormal conditions, as will be shown below, there are great temporary variations from this standard, corresponding to the great variations observed under the unfavorable conditions in experiments on animals.

More than 50 years ago it was suspected by Ludwig that oxygen may have some influence in turning out CO_2 from the venous blood which comes to the lungs. The experiments made to ascertain whether oxygen helps to turn out CO_2 from blood gave, however, only a negative result, and more recent work by Bohr, Hasselbalch, and Krogh[9] led to similar negative conclusions. We had been making experiments to investigate the rise of alveolar CO_2 pressure when the breath was held, or when a small quantity of air was rebreathed. One result of these experiments was to show that if the alveolar oxygen pressure fell much below normal the percentage of CO_2 in the alveolar or rebreathed air was always, without exception, lower after any definite interval of time, than was the case under the same conditions but with the alveolar oxygen percentage high. This brought us back to Ludwig's old question, which with the new blood-gas method we could investigate

[9] Bohr, Hasselbalch, and Krogh, *Skand. Arch. f. Physiol.*, XVI, p. 411, 1904.

far more easily and exactly than when nothing but the blood pump and the old methods of gas analysis were available.

The first pair of experiments showed us that Ludwig's old suspicion was correct, and that at the same pressure of CO_2 blood takes up considerably more CO_2 in the absence than in the presence of oxygen. The upper curve in Figure 25 is the absorption curve for my own blood in the absence of oxygen, and shows that at the physiologically important part of the curve the blood takes up from 5 to 6 volumes per cent more of CO_2 if oxygen is absent. We found that the excess of CO_2 taken up runs parallel, not to the partial pressure of oxygen, but to the extent to which the oxyhaemoglobin of the blood is dissociated. Saturation of the haemoglobin with CO had just the same effect on the curve as saturation with oxygen. The effect may be due to saturated haemoglobin being a less alkaline substance than reduced haemoglobin, but is more probably dependent on the molecules of reduced haemoglobin having a much greater tendency to aggregate than those of saturated haemoglobin. The reasons for this assumption with regard to aggregation were given at the end of last chapter. The aggregated haemoglobin molecules would presumably have less mass influence in keeping out the CO_2 from combination with alkali than the unaggregated molecules.

Let us now see what physiological deductions can be drawn from the absorption curves in Figure 25. Human blood contains about 18 volumes per cent of oxygen, and if all this oxygen were used up in the tissues about 15 volumes of CO_2 would be formed. But during the using up of the oxygen the absorption curve for CO_2 starting from 40 mm. would pass from the lower to the upper curve of Figure 25, following upwards the thick line shown in Figure 26.

Hence the CO_2 pressure, instead of rising to 80 mm., as would be the case if the lower curve were followed, would only rise to 62 mm. Actually, as will be shown later, not more than about a fifth of the oxygen is used up during rest, so the pressure of CO_2 in the mixed venous blood rises only about 5 or 6 mm. This makes it far more easy to understand why the pressure of CO_2 in the arterial blood should be so exactly regulated as it is. If it had been the case that the resting CO_2 pressure in the systemic capillaries were far above the arterial CO_2 pressure, the necessity for such exact regulation of the arterial CO_2 pressure would have been hard to understand.

While the venous blood is being aërated in the lungs, the ab-

sorption curve for CO_2 will follow the thick line downwards. It will be seen that, if we assume the resting excess pressure of CO_2 in the venous blood, the quantity of CO_2 given off when the CO_2 pressure in the lung capillaries falls to that of the alveolar air will be about 55 per cent greater than if no oxygenation had occurred. If, on the other hand, we assume a certain excess charge

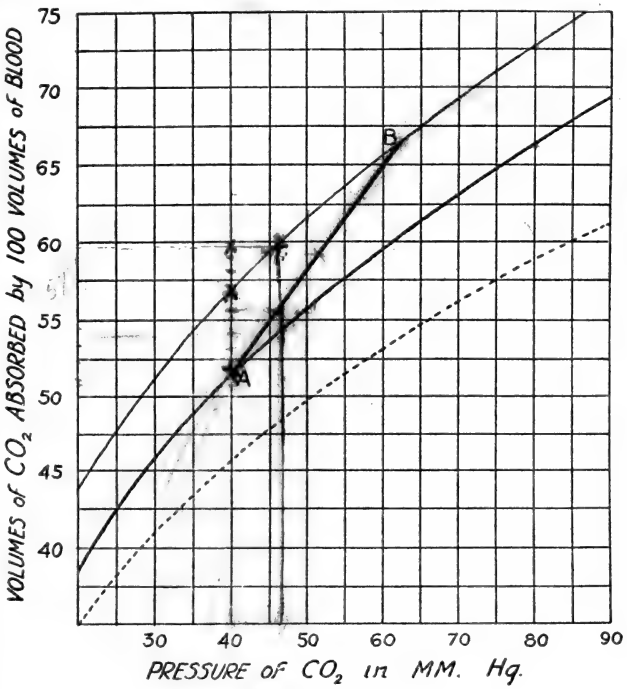

Figure 26.

Upper curve—absorption of CO_2 by blood of J. S. H. in presence of hydrogen and CO_2.

Middle curve—absorption of CO_2 by blood of J. S. H. in presence of hydrogen and CO_2.

Lower curve—absorption of CO_2 in blood of ox and dog in presence of air and CO_2 (Bohr's data).

Thick line A—B represents the absorption of CO_2 by the blood of J. S. H. within the body.

of CO_2 in volumes per cent in the venous blood, the discharge of CO_2 will ordinarily be about 55 per cent greater than if no oxygenation had occurred.

We can also see that under abnormal conditions, such as may easily occur when the breathing is suspended or reduced in

amount, as after forced breathing, or during excessive artificial respiration, or other respiratory disturbances, CO_2 may easily be given off by the lungs when there is no excess of venous over alveolar CO_2 pressure, or even when the venous CO_2 pressure is considerably lower than that of the alveolar air. For when the blood reaches the lungs the process of oxygenation so reduces the capacity of the blood for CO_2 that its CO_2 pressure is raised above that of the air, and diffusion results. If the respiratory quotient has fallen temporarily to a third or less of its normal value, the thick line of Figure 26 will become vertical in the living body, or incline to the left instead of to the right. It is merely necessary to suspend the breathing for a very short time in order to realize this condition. Only if air containing a large excess of CO_2 is breathed, will CO_2 be absorbed backwards, and the thick line pass downwards as well as to the left.

The discovery that oxygenation of the haemoglobin helps to turn out CO_2 from blood gives us the key to the proper interpretation of the fact that, as was found by ourselves in human experiments, and earlier by Werigo,[10] and by Bohr and Halberstadt,[11] more CO_2 is given off into the air of the lungs when oxygen is present. Thus in Halberstadt's experiments it was found that if one lung was ventilated with air, and the other with hydrogen, the lung ventilated with air gave off nearly 50 per cent more CO_2 than the lung ventilated with hydrogen. This result is precisely what would be expected in view of the facts just described; but as Bohr was misled by the apparent results of his experiments with blood outside the body, he wrongly attributed Halberstadt's and Werigo's results to the supposed fact that in presence of air there is a large formation of CO_2 in the lungs, owing to a process of oxidation occurring there. As will be shown later, hardly any formation of CO_2 occurs in the lungs.

In a quite recent paper Parsons[12] has investigated mathematically the form of the absorption curve of blood for CO_2 on the theory that the blood is a chemical system consisting of carbonic acid and what may be regarded as one other free acid (consisting of the proteins present) with a fixed concentration of available alkali distributed between them. This fixed concentration he estimated from blood-ash analyses and in other ways, to be about 4.5×10^{-2}N. He found that the form of the curve given by calcula-

[10] Werigo, *Pflüger's Archiv.*, LI, p. 321, 1892.
[11] Bohr, Nagel's *Handb. der Physiol.*, I, p. 208.
[12] Parsons, *Journ. of Physiol.*, LIII, p. 42, 1919.

tion corresponded satisfactorily with the curves which both we and he had obtained experimentally for human blood. This is illustrated in Figure 27, reproduced from his paper. We had not attempted to calculate the form of the curve, as several proteins are involved in the chemical system; but by the simplifying assumption which he made Parsons overcame this difficulty.

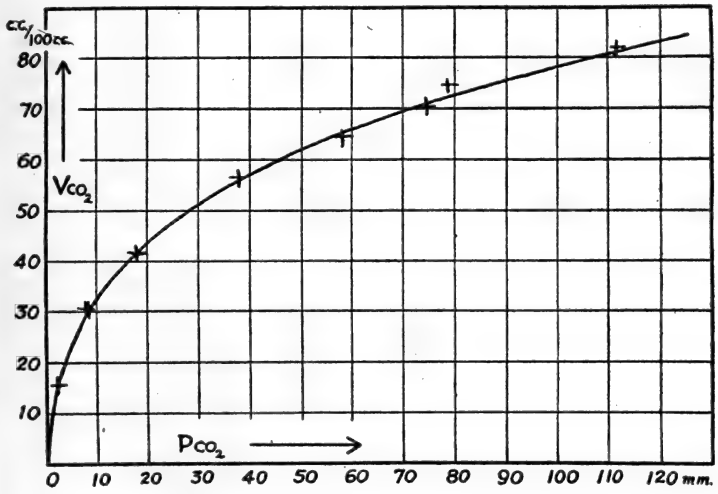

Figure 27.

Comparison between the theoretical curve and experimental results for completely reduced blood of Haldane.

In the previous chapter we have seen that, other things being equal, a rise of CO_2 pressure shifts the dissociation curve of oxyhaemoglobin to the right if the curve is represented as in Figures 19 or 28. In the living body the pressure of CO_2 is constantly rising as the blood becomes more and more venous in its passage through the systemic capillaries. The data embodied in Figure 25 gave us the means of calculating this rise, and it will be seen that it is much less than previously existing knowledge would have led us to believe. Figure 27 shows the oxygen dissociation curve of my own blood in the living body, calculated from Figure 26, on the assumption that the shifting of the curve to the right is proportional to the increase of CO_2 pressure in the blood as it passes along the systemic capillaries.

Bohr believed that the shifting of the dissociation curve to the right by the influence of increasing CO_2 pressure in the systemic

capillaries is an important factor in facilitating the unloading of oxygen from the blood; and this line of argument has been further elaborated by Barcroft. The actual shifting is, however, very small under normal conditions, and of much less physiological importance than the effect of the shifting of the CO_2 absorption curve in consequence of reduction of oxyhaemoglobin.

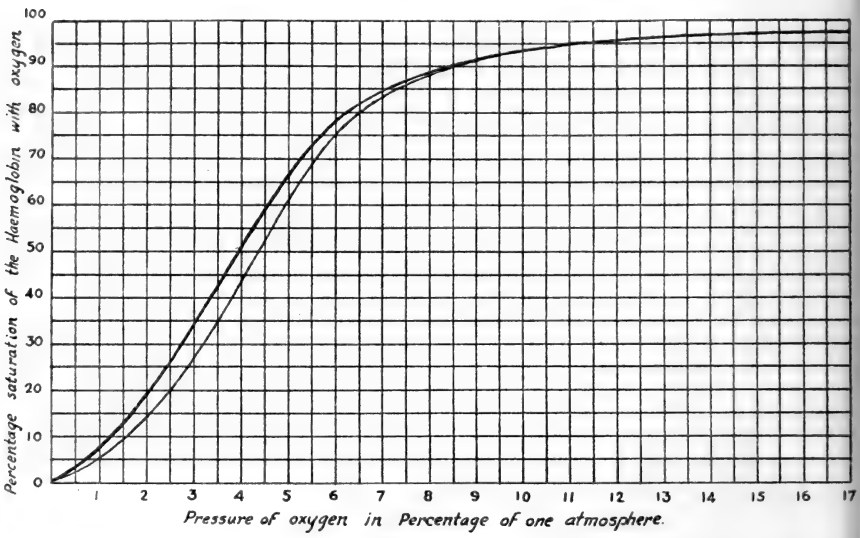

Figure 28.

The thick line shows the dissociation curve of oxyhaemoglobin in the blood of J. S. H. and C. G. D. in the presence of 40 mm. pressure of CO_2. The thin line represents the dissociation curve of oxyhaemoglobin in the blood of J. S. H. and C. G. D. within the body.

We are now in a position to interpret much more completely the facts concerning the regulation of breathing by small variations in the alveolar CO_2 pressure. How very small the mean variations are, we have already seen. On the other hand the breathing is constantly being interrupted or interfered with in one way or another during ordinary occupations, such as speaking or singing, and the breath can be held for a few seconds without any noticeable air hunger being produced. During these interferences the alveolar CO_2 pressure must be constantly rising and falling on either side of the normal limit, but the physiological effect seems almost nil, and to popular imagination it seems as if the breathing, instead of being regulated so rigorously as was shown to be the case in the second chapter, is hardly regulated at

all. We are also familiar with instructions to increase the breathing so as to "improve the oxygenation of the blood" and with quack advertisements based on the same idea. How does it come about that although the regulation is so exact on the average, yet temporary deviations from this average exactitude do not cause any discomfort? How is it, also, that when the production of CO_2 is suddenly increased to perhaps ten times the normal, as on a sudden muscular exertion, yet the breathing responds gradually and easily to the new conditions?

The answer to this question is that there are physiological buffers between the stimulus of increased production of CO_2, or increase in the alveolar CO_2 pressure, and stimulation of the respiratory center, and that if it were not so the respiratory center would work in a jerky, irregular, and extremely inconvenient manner. The first of these buffers is the large volume of air always present in the lungs. Thus in my own case the mean volume of air in the lungs at the end of inspiration during rest is 3650 cc., measured dry at 0°C., including about 3000 cc. of saccular alveolar air containing about 5.6 per cent of CO_2. Let us assume that the breath is held at the end of inspiration during rest, and consider what happens. About 250 cc. of CO_2 would be normally given off per minute, or 20 cc. in 5 seconds; and if the latter quantity were given off with the breath held the mean CO_2 pressure in the lung air would rise by 0.6 per cent in 5 seconds. But, as will be shown later, about 700 cc. of blood will pass through the lungs in 5 seconds, and as the arterial blood will be more highly saturated with CO_2 if the alveolar CO_2 percentage rises, some of the CO_2 which would ordinarily have been given off will be dammed back in the blood. Figure 25 shows that for every rise of 2.5 mm. or .36 per cent in the alveolar CO_2 pressure the blood will take up, or hold back, 1 volume per cent of CO_2. Hence the actual rise in the mean CO_2 pressure within the lungs cannot be more than about 0.4 per cent in the 5 seconds during which the breath is held. The net result is that about two-thirds of the CO_2 which the suspension of the breathing prevents from escaping from the body is temporarily accommodated in the lung air, which thus acts as a first buffer for preventing too sudden a change in the arterial CO_2 pressure.

A second buffer is provided by the tissues and lymph in and around the respiratory center itself. So far as we know the reaction in all parts of the body is slightly alkaline, just as in the blood; and the tissues and lymph have, like the blood, a con-

siderable capacity for absorbing CO_2. Hence it will take some time for the blood to saturate the tissues and lymph up, or desaturate them down, to a new CO_2 pressure. Here we have a second, and very powerful, buffer action, tending to smooth out the influence on the respiratory center and other tissues of all variations of short duration in the CO_2 pressure of the arterial blood, and also to prolong the influence of variations of longer duration.

This subject was investigated by Douglas and myself.[18] The following table shows the results we obtained on determining the alveolar CO_2 pressure at various times after holding the breath. In order to throw out disturbing effects due to the action of oxygen want on the respiratory center, some of the experiments were made after a few normal breaths of oxygen had been taken, so that there should be plenty of oxygen in the lungs up to the end of the stoppage of respiration.

	PRESSURE IN MM. OF HG. IN ALVEOLAR AIR	
	CO_2	O_2
At end of period of holding breath for 30″	49.2	62.6
At fifth expiration following	29.1	—
At ninth expiration following	31.5	—
At twelfth expiration following	32.0	—
At twentieth expiration following	33.8	—
At thirtieth expiration following	37.0	—
At fortieth expiration following	38.8	—
At fifth expiration after holding 40″	28.4	117.
At eighth expiration following	29.4	—
At end of holding breath for 130″ after oxygen	61.9	274.
At sixth expiration afterwards	24.8	—
At twentieth expiration afterwards	33.3	—
At fortieth expiration afterwards	31.2	—
Normal average	39.75	105.

Figure 29 is a stethographic tracing of the respirations during an experiment, and shows that the breathing returns gradually to normal after the hyperpnoea following the stoppage.

The table is extremely instructive, and shows very clearly what a long period of increased breathing, with the alveolar CO_2 pressure distinctly below normal, is required in order to compensate

[18] Douglas and Haldane, *Journ of Physiol.*, XXXVIII, p. 420, 1919.

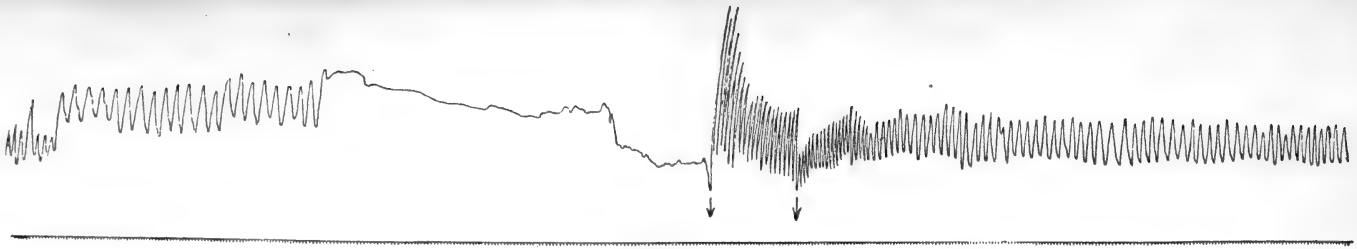

Figure 29.
Stethograph tracing. Breath held 130 seconds after six normal breaths of oxygen. At first arrow alveolar $CO_2 = 8.66$ per cent, $O_2 = 38.22$ per cent; at second arrow $CO_2 = 4.65$ per cent.

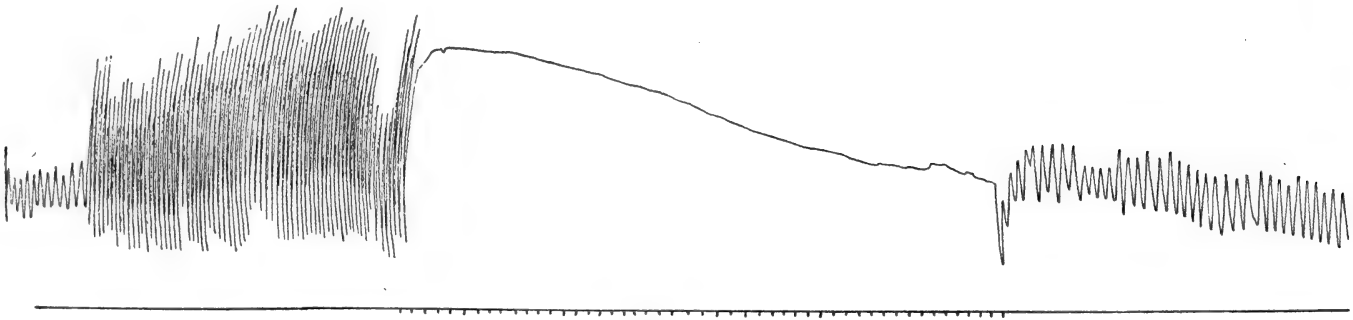

Figure 30.
Forced breathing for two minutes with six breaths of oxygen at the end. Apnoea 4′ 21″. At end of apnoea sample of alveolar air, $O_2 = 56.22$ per cent, $CO_2 = 7.12$ per cent.

for the cumulative action of the stoppage of breathing. After the long stoppage of 130 seconds the breathing and alveolar CO_2 pressure had not nearly returned to normal, even after the fortieth breath following the stoppage.

Figure 30 shows the converse experiment. Forced breathing was continued two minutes so as to wash out CO_2 from the lungs, arterial blood, and respiratory center; and oxygen had been taken into the lungs, so as to cut out the effects of want of oxygen. The apnoea lasted 4⅛ minutes, and an alveolar sample (the taking of which is recorded on the tracing and somewhat disturbs it) was obtained as soon as the slightest inclination to breathe was noticed. It will be seen that the CO_2 percentage in this sample was 7.12 per cent (51.5 mm. of CO_2 pressure) a value far above the normal 40 mm. required to excite the center under normal conditions. Separate experiments showed that by the end of two minutes of forced breathing the alveolar CO_2 pressure had fallen to about 13 mm. and during the apnoea rose to normal again at the end of 2⅓ minutes. During the last 2 minutes the alveolar CO_2 pressure was above normal; but sufficient CO_2 had not accumulated in the tissues of the respiratory center to stimulate it, till the alveolar CO_2 pressure had gradually risen to 51.5 mm. At this point the center, which had now just reached its normal CO_2 pressure, began to work quietly and smoothly, reducing the alveolar CO_2 pressure to normal, and picking up the normal regulating activity. The breathing cannot indicate a gradual return of the CO_2 pressure in the center to normal, corresponding to the gradual return in Figure 29, since, as is shown by the experiments described in Chapter II, complete apnoea results from a fall of 0.2 per cent or 1.5 mm. of the CO_2 pressure in the respiratory center.

The apnoea following forced breathing can be temporarily interrupted by sending a block of blood highly charged with CO_2 to the respiratory center. The effect of this is shown in Figure 31. As soon as the breathing and the "apnoeic" venous blood returning to the lungs have removed the extra CO_2 introduced into the lungs the apnoea returns again.

The washing out of CO_2 from the body during forced breathing, and its gradual reaccumulation during the next ten or twenty minutes, were strikingly illustrated in some experiments carried out by Boothby.[14] Thus in an experiment on myself he found that during 1½ minutes of forced breathing I had removed about 1,400 cc. extra of CO_2 from the body. During the subsequent ap-

[14] Boothby, *Journ. of Physiol.*, XLV, p. 328, 1912.

noea of 2 minutes about 600 cc. of CO_2 were regained, and about 200 cc. more during two minutes of periodic breathing which followed. The remainder was regained during the following six or eight minutes. In this latter period the alveolar CO_2 pressure

Figure 31.

Effect of a breath of air containing 9.0 per cent of CO_2 during apnoea following forced breathing. Crosses show inspiration and expiration of breath. After an interval there are three deep, and two shallow, breaths, followed by a long apnoeic interval, after which the usual periodic breathing begins. To read from left to right. Time-marker = 1 second.

was practically normal, but the respiratory quotient very low, in correspondence with the very high respiratory quotient during the forced breathing.

What approximately happens to the CO_2 pressure in the alveolar air and respiratory center is represented in Figures 32 and

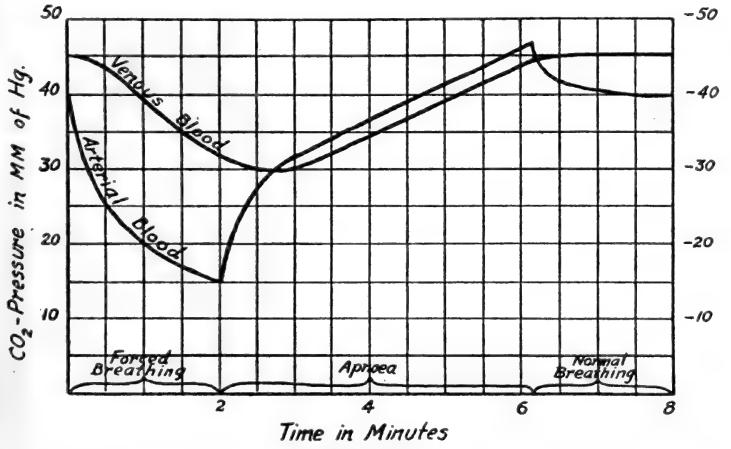

Figure 32.

Approximate variations in CO_2 pressure of arterial and venous blood during and after forced breathing of oxygen for two minutes.

33. The pressure of CO_2 in the respiratory center is assumed to be about equal to that of the mixed venous blood, though it is probably lower.

The very powerful steadying influence on the CO_2 pressure of the capacity of the tissues for taking up CO_2 is evident from these figures. In consequence of this influence, and in a much less degree that of the reserve of air in the lungs, variations of short duration in the alveolar CO_2 pressure hardly count, although even the slightest variations of a more prolonged character count a great deal.

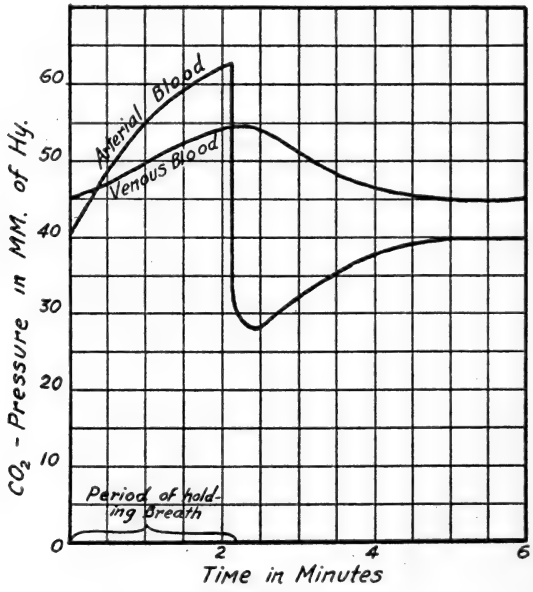

Figure 33.

Approximate variations in CO_2 pressure of arterial and venous blood during and after holding the breath for 130 seconds with oxygen.

On examining Figure 32 it will be seen that, although the venous CO_2 pressure is below that of the alveolar air during most of the apnoea, CO_2 is being given off all the time into the alveolar air. This is due to the effect of oxygenation in decreasing the capacity for CO_2 and thus raising its pressure in the blood. This effect is explained by the fact that the thick line of Figure 26 will be inclined to the left, as very little CO_2 is being given off by the tissues, impoverished as they are of CO_2 by the forced breathing.

In order to realize how important the steadying influence just mentioned is, we have only to turn to what happens when want of oxygen, instead of CO_2, is exciting the center. Oxygen is no

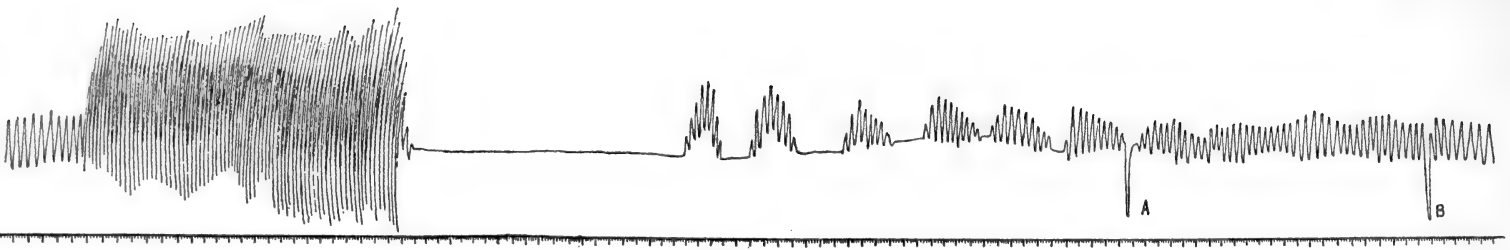

Figure 34

Forced breathing of air for two minutes, followed by apnoea for two minutes and periodic breathing for about five minutes. At A sample of alveolar air, $O_2 = 11.44$ per cent, $CO_2 = 5.58$ per cent. Second sample at B, $O_2 = 13.55$ per cent, $CO_2 = 5.57$ per cent.

more soluble in the tissues and lymph than in water. They have thus practically no power of storing free oxygen. In the course of our investigations on the effects of want of oxygen it became evident that the center works very jerkily when excited by want of oxygen, and the subject was studied in further detail by Douglas and myself.[15] We found that the effects of regulation of the center by oxygen want could be observed very conveniently at the end of the apnoea caused by forced breathing of ordinary air. When apnoea is produced by forced breathing of air for about two minutes, the oxygen percentage in the lungs runs down very low before the pressure of CO_2 in the respiratory center has nearly risen to its normal value. In some subjects there is an alarming

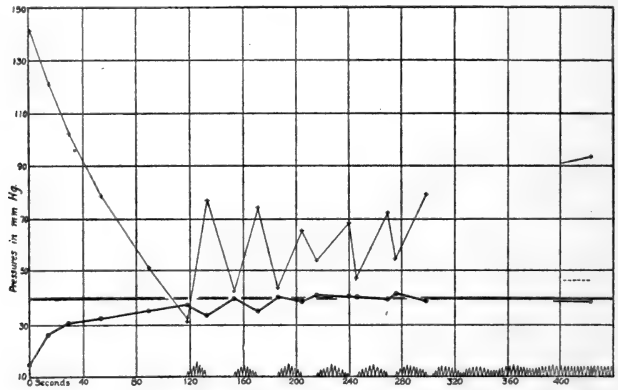

Figure 35.

Variations in alveolar gas pressures after forced breathing for two minutes. Thin line = oxygen pressure, thick line = CO_2 pressure. Double line = normal alveolar CO_2 pressure. The actual breathing is indicated at the lower part of the figure.

appearance of blueness in the face before any desire to breathe is felt. Ultimately, however, the stimulus of oxygen want (together with the subliminal CO_2 stimulus) suffices to start the breathing. But the first four or five breaths greatly raise the alveolar oxygen percentage and thus quiet the center down again, so that apnoea again follows, which is again followed by breathing and subsequent apnoea, this periodic rising and dying away of the breathing going on for about five minutes, as shown in Figure 34, though not all subjects react alike.

Figure 35 shows the variations of the alveolar oxygen and CO_2

[15] Douglas and Haldane, *Journ. of Physiol.*, XXXVIII, p. 401, 1909.

pressure, as determined in samples of alveolar air. Reference to Figure 31 shows that at no time during the periodic breathing is the CO_2 pressure in the respiratory center more than just sufficient to excite the center by itself.

It is very easy to see what has been happening. The oxygen want caused by the partially reduced blood coming from the lungs at the end of the apnoea has, along with the CO_2 present, sufficed to excite the center; but this oxygen want is at once relieved by the breaths which follow, since the oxygen pressure in the lungs is raised beyond the exciting point. The result is a prompt return of the apnoea, till the oxygen in the alveolar air again returns to the stimulating point. The respiratory governor is "hunting" just as the governor of a steam engine or turbine hunts if there is no heavy flywheel or other steadying influence. The chief flywheel of the respiratory center is the great storage

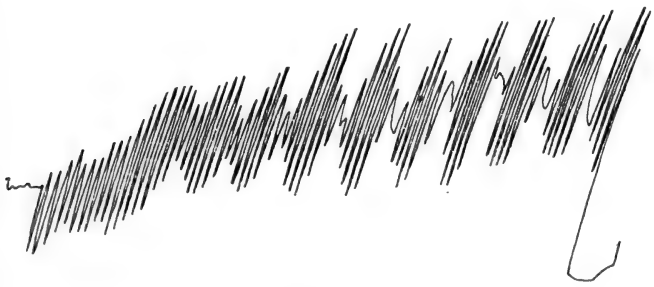

Figure 36.

Breathing through soda lime and long tube. Sample of alveolar air at the end of a dyspnoeis period, $O_2 = 8.70$ per cent, $CO_2 = 5.48$ per cent.

capacity in the tissues for CO_2. There is no such storage capacity in connection with oxygen, so the flywheel has disappeared.

When slight oxygen want, and not merely excess of CO_2, is exciting the center, the breathing very readily becomes periodic. To realize this condition in a permanent manner we only had to breathe in and out through a tin of soda lime with a piece of hose pipe of variable length attached on the far side, so as to give a suitable dead space. By this means the alveolar oxygen pressure can be reduced to any required extent. Figure 36 shows the effect of such an arrangement. This effect is at once knocked out if oxygen is breathed.

Some years ago it was discovered by Pembrey and Allen[16] that the well-known pathological form of periodic breathing named after Drs. Cheyne and Stokes, who described it (though it was previously described by John Hunter), is abolished by giving the patient pure oxygen to breathe. This observation indicates with great certainty that ordinary pathological Cheyne-Stokes breathing is caused also by want of oxygen participating in the excitation of the center. Pathological periodic breathing and that of hibernating animals will be discussed later.

The normal pressure of oxygen in the alveolar air is about 100 mm. or 13.1 per cent of an atmosphere. On looking at the dissociation curve of oxyhaemoglobin in human blood (Figure 20) it will be seen that a fall of 4 per cent of an atmosphere, or 30 mm., makes very little difference to the saturation of the haemoglobin. Nor has such a fall any appreciable influence on the resting breathing at the time. It is thus evident that, although there is no appreciable store of readily available oxygen in the liquids of the body outside the red corpuscles and certain muscles which contain a little haemoglobin, there is a store of oxygen, available without any inconvenience, in the air of the lungs. If the breathing is temporarily stopped during some occupation this store is drawn on. Thus if the breath is held for half a minute the oxygen runs down by about 4 per cent in the alveolar air during rest; but under normal conditions it is quite impossible to hold the breath long enough to imperil seriously the oxygen supply to the tissues. In spite of the gradual manner in which, as we have just seen, CO_2 acts on the respiratory center, there is never, except under very artificial conditions, any considerable oxygen want. The comparatively large volume of air which is always in the lungs gives sufficient oxygen storage to guard against the temporary want of oxygen. Were this amount of air much less the danger would be always present, and, as we shall see later, this danger or inconvenience is present at high altitudes, when the mass of oxygen in the lungs is greatly diminished. At a high altitude one cannot hold the breath for more than a few seconds without feeling an imperative desire to breathe, and such operations as shaving, or reading a barometer, are thus rendered troublesome. Nature sees to it that ordinary mortals who live under a pressure of about one atmosphere carry about sufficient oxygen in their lungs to prevent oxygen want; and there seems to be some evidence that

[16] Pembrey and Allen, *Journ. of Physiol.*, XXXII, *Proc. Physiol. Soc.*, p. xviii, 1905; also *Medico- Chirurg. Trans.*, XI, p. 49, 1907.

persons who inhabit very high parts of the earth develop a greatly increased chest capacity.

Addendum. The account given in this chapter of the manner in which CO_2 is carried by the blood represents what I have taught for many years, and is largely based, as mentioned above, on the teaching of Pflüger and Zuntz. A very different view of the subject has recently been presented by Buckmaster, Bayliss, and others. According to this view the extra CO_2 taken up in the venous blood is combined, not with alkali, but with haemoglobin, and may also be in part adsorbed by haemoglobin and other proteins. As evidence that haemoglobin and other proteins do not play the part of weak acids in expelling CO_2 from its combination with alkali, Buckmaster cites experiments in which he found that, contrary to Pflüger's statement, blood or haemoglobin is not capable of expelling CO_2 from a weak carbonate solution in the vacuum of a blood pump at body temperature.[1] It seems to me that these experiments were fallacious because the blood was neither boiled nor shaken. Boiling, shaking, or bubbling is necessary to remove the CO_2. When Pflüger's experiment was repeated in a simple form by Adolph in my laboratory the expulsion of CO_2 from sodium carbonate by blood was found to occur quite readily.[2] As already mentioned, Buckmaster's contention that haemoglobin gives a characteristic spectrum with CO_2 was also found to be incorrect.

The supposition that an extra amount of gas is adsorbed by the proteins of blood has no basis. The careful experiments of Bohr and other previous observers show clearly that apart from chemical combination blood takes up, not more, but considerably less, gas than an equal volume of water. The only apparent exception to this rule was the fact that oxygenated blood (but not reduced blood) yields slightly more nitrogen than the quantity calculated from its estimated solubility. The existence of this small surplus was confirmed by Buckmaster and Gardner.[3] The apparent surplus is almost certainly due to what is a rather common source of slight error in gas analysis. When the gas pumped off from oxygenated blood is analyzed, the first step is to bring the gas into contact with potash solution to absorb the CO_2. When this is absorbed a gas mixture consisting almost wholly of oxygen is left in contact with the potash solution. But the latter is saturated

[1] Buckmaster, *Journ. of Physiol.*, LI, p. 105, 1917.
[2] Adolph, *Journ. of Physiol.*, LIV, *Proc. Physiol. Soc.* p. XXXIV, 1920.
[3] Buckmaster and Gardner, *Journ. of Physiol.*, XLIII, p. 401, 1912.

with air, and as a consequence nitrogen diffuses from the potash solution into the gas mixture, while oxygen diffuses into the potash solution. The consequence is that the residue of nitrogen found in the gas after the oxygen has been absorbed is greater than was originally present in the gas. This source of error is absent if little or no oxygen is present in the gas pumped off from the blood. We can thus explain why no extra nitrogen has been found in reduced blood.

Bayliss[4] contends that the bicarbonate and the plasma proteins present in blood play no part in the physiological carriage of CO_2 between the tissues and the lungs, and that haemoglobin is alone concerned in the carriage, since it does not, under actual physiological conditions, compete as an acid with CO_2 for the alkali available in the blood. The experiments cited in support of this conclusion seem to me quite unconvincing; and if it were correct we should expect to find that blood saturated at the alveolar partial pressure with CO_2 would contain more combined CO_2 than a solution of bicarbonate of the same strength in titratable alkali as the blood. Actually, the blood, especially at body temperature, contains far less combined CO_2. It seems quite impossible to reconcile Bayliss' theory with this fact; and I cannot see how any other theory than that given in the first part of this chapter is capable of interpreting the facts as a whole. It may be that a small amount of CO_2 is combined with free haemoglobin; but it seems evident that under physiological conditions haemoglobin and other proteins act, for all practical purposes, simply as weak acids. It is in virtue of this action, and the more powerful action of oxyhaemoglobin than reduced haemoglobin as an acid, that blood functions so efficiently as a pysiological carrier of CO_2. Campbell and Poulton, who entirely disagree, and on substantially the same grounds as I do, with the conclusions of Buckmaster and Bayliss, have recently shown that an artificial mixture of dialysed corpuscles and dilute sodium bicarbonate solution takes up, within physiological limits of CO_2 pressure, much less CO_2 than the bicarbonate alone holds.[5]

For the sake of simplicity I did not discuss separately the action of plasma and corpuscles in combining with CO_2; but much attention has been given recently to this subject. Zuntz[6] pointed out that when plasma or serum is separated from blood collected

[4] Bayliss, *Journ. of Physiol.*, LIII, p. 162, 1919.
[5] Campbell and Poulton, *Journ. of Physiol.*, LIV, p. 157, 1920.
[6] Zuntz, Hermann's *Handbuch der Physiol.*, IV, 2, p. 77, 1882.

as it flows from a vessel, the corpuscles are capable of taking up from pure CO_2, more combined CO_2 than an equal volume of the plasma. If, on the other hand, the blood is artificially saturated with pure CO_2, or air containing a high percentage of CO_2, and then separated into plasma and corpuscles, the plasma contains more combined CO_2 than the corpuscles. He concluded that alkali previously combined with haemoglobin in the corpuscles combines with CO_2 when a high concentration of the latter is present, and passes out as bicarbonate into the plasma. Further investigation of this phenomenon by Gürber[7] showed that alkali does not pass out of the corpuscles, but acid passes in, leaving the corresponding alkali behind in the plasma. The walls of the corpuscles seem, therefore, as Hamburger[8] in particular has pointed out, to be practically impermeable to sodium and potassium ions, but permeable to chlorine and other anions. Hence the proportions of alkali to chlorine, etc., in the plasma depend upon the corpuscles, and are regulated by them according as the pressure of CO_2 in the blood rises or falls. Yandell Henderson and Haggard, who have quite recently investigated this phenomenon closely from the physiological standpoint, point out what striking effects this regulating action may produce.[9] During forced breathing, for instance, the weakly combined alkali of the plasma may be considerably diminished, although the total weakly combined alkali in the blood need not necessarily be altered.

The relation of the corpuscles to the available alkali in the plasma suggests at once the question whether there is not a similar relation as regards other tissue elements. Henderson and Haggard showed that with vigorous and continued artificial respiration the available alkali in the whole blood, and not merely in the plasma, diminishes greatly, and that this diminution is accompanied by signs of irretrievable damage to the body. This suggests excessive draining of acid from the tissue elements with the result that the whole body suffers, although the alkalinity of the blood itself is partly prevented from falling. The matter will, however, be discussed further in Chapter VIII.

[7] Gürber, *Sitz-ber. d. physik-med. Gesellsch. zu Wurzburg*, p. 28, 1895.

[8] *Anionenwanderungen in serum und Blut unter den einfluss von CO_2, saure und alkali. Biochem. Zeit.* Vol. 86, p. 309-324, 1918.

[9] Haggard and Henderson, *Journ. of Biol. Chem.*, XLV, p. 199, 1920.

CHAPTER VI

The Effects of Want of Oxygen.

In the higher organisms, as Paul Bert first pointed out, the immediate cause of death of the body as a whole is practically always want of oxygen, owing to failure of the circulation or breathing. This fact arises from the circumstance that the body has hardly any internal storage capacity for oxygen, but depends from moment to moment for its supply from the air. We can deprive the body for long periods of its external supplies of food or water, or we can prevent for some time the excretion of urinary products or even of carbon dioxide, but we cannot interfere with the supply of oxygen to the blood without producing at once the most threatening symptoms. Almost the only appreciable storage capacity for surplus oxygen is in the lungs. In virtue of this small store breathing can be prevented for about 1¼ minutes in a man at rest and previously breathing normally before urgent symptoms of oxygen want appear; but if the oxygen in the lungs and blood is rapidly washed out by breathing pure nitrogen, nitrous oxide, or other gas free from oxygen, loss of consciousness occurs almost at once. Lorrain Smith and I found that even with quiet breathing of pure hydrogen, so that some time was needed to wash out the lungs, sudden and complete loss of consciousness was produced within 50 seconds.

Even when the oxygen supply, though not cut off, is insufficiently free, the ill effects develop rapidly, and may very soon become serious. Hence few things are of more importance in practical medicine than the causes and effects of want of oxygen.

Want of oxygen in the systemic circulation may be produced either by deficiency in the available oxygen in the arterial blood, or by abnormal slowing of the circulation, so that too much of the available oxygen is used up in the systemic capillaries. It will be convenient to consider first the effects of want of oxygen or "anoxaemia," and afterwards discuss the various ways in which it may be produced.

The effects of anoxaemia can be observed most conveniently in persons breathing air from which part of the oxygen has been removed without the addition of any other gas producing by itself a physiological effect; or in persons breathing pure air at

reduced atmospheric pressure. In either case the partial pressure of the oxygen breathed is reduced, and the haemoglobin tends to become imperfectly saturated with oxygen in the lungs in correspondence with the dissociation curve for the oxygen in human blood (Figure 20).

The effects on the breathing have already been touched upon in Chapter II, but must now be discussed fully. In most persons the percentage of oxygen in the air breathed, or the barometric pressure, must be reduced by about a third before any evident effect on the breathing is produced at the time; and this effect differs according as the reduction is produced rapidly or slowly. With a greater reduction the contrast in this latter respect is still more marked. With rapid reduction there is at first a quite noticeable increase in the depth, and also in the frequency, of breathing. In the course of several minutes, however, the increase diminishes markedly. This phenomenon and the causes of it were described and investigated by Poulton and myself.[1] We found that the increased breathing causes, as could be anticipated, a distinct fall in the alveolar CO_2 pressure. As a consequence, more CO_2 than usual is washed out of the blood, and the respiratory quotient, or ratio of the volume of CO_2 given off to that of oxygen absorbed, is increased. Thus it increased from the normal of about 0.8 to as much as 2.8 when there was sudden and considerable oxygen deficiency. Soon, however, the extra discharge of CO_2 from the blood began to cease and there was only a slight further fall in the alveolar CO_2 pressure. *Pari passu* the breathing quieted down so as, in spite of the diminished discharge of CO_2, to maintain a certain level of alveolar CO_2 pressure, this level being of course below the normal level. At the same time the alveolar oxygen pressure dropped, since the lung ventilation had diminished while the rate of absorption of oxygen remained undiminished. The drop in alveolar oxygen pressure tended, of course, to increase the symptoms of want of oxygen and thus prolong the period of increased breathing; but finally a balance was struck, for the time at any rate. When the deficiency of oxygen was produced quite gradually the initial marked increase of breathing was not noticeable, as the extra CO_2 was washed out gradually.

By further experiments, we found that the new and lower level of alveolar CO_2 pressure had become the regulating level for the atmosphere breathed. That is to say, a small increase above this level caused a great increase in the breathing, while a small

[1] Haldane and Poulton, *Journ. of Physiol.*, XXXVII, p. 390, 1908.

diminution caused apnoea, just as when pure air is breathed. It was evident, therefore, that the CO_2 pressure, though at a lower level, was controlling the breathing still. The primary marked increase in the breathing was due to the alveolar CO_2 pressure and the CO_2 pressure in the whole of the body being above the new level, and the quieting down of the breathing was due to the gradual washing out of CO_2 from the whole body till the attainment of the new normal level, which was itself determined by the alveolar oxygen pressure.

A fuller discussion of these facts, and of the ultimate physiological response to long-continued slight anoxaemia, must be postponed to Chapter VII, but meanwhile it is evident that they throw a new light on the physiology of breathing. Hitherto we have considered the amount of lung ventilation as if it were determined solely by a certain excess of partial pressure of CO_2 in the arterial blood; but now we see that the excess is something variable and dependent, for one thing, on the pressure of oxygen in the arterial blood, just as the action of the Hering-Breuer reflex depends, not merely on the amount of distention or collapse of the lungs, but also on the pressure of CO_2 in the arterial blood. Similarly the action of want of oxygen on the breathing depends on the CO_2 pressure. On how many other factors which together make up "normal conditions" the action of CO_2 or want of oxygen on the respiratory center depends we do not know. We always find normal conditions in a healthy organism, and we are therefore apt to overlook their unknown complexity. If we represented the relation between arterial CO_2 pressure, oxygen pressure, and lung ventilation in the form of an equation, this equation would only be valid under conditions otherwise normal. In other words an unknown constant C would have to be set down in the equation.

That this constant exists during life—in other words that living organisms maintain fundamental normals of structure and activity representing the φύσις of Hippocrates—is one basis of biological science. Apart from this basis physiology would be a mere chaos of unconnected "bio-physical" and "bio-chemical" fragments.

The effect produced on the breathing by a given reduction in the oxygen pressure of the inspired air or alveolar air varies considerably in different individuals. Some respond much more readily by increased breathing than others, and for this reason seem to be better protected against the other and more serious effects of want of oxygen, since the increased breathing raises the al-

veolar oxygen percentage. In some persons a lowering by as little as 5 per cent in the oxygen percentage of the inspired air will sensibly increase the breathing, but in most persons a lowering of at least 7 per cent (i.e., from 20.94 to 14) is needed to produce a measurable effect, while in others very little effect is produced before consciousness is lost from want of oxygen. It is thus for many persons peculiarly dangerous to pass into an atmosphere in which the oxygen percentage is very low, or to ascend to a very great height in a balloon, since increased breathing may give very little warning, particularly if the change is gradual, so that the extra CO_2 is blown off gradually.

It was discovered in 1908 by Yandell Henderson[2] that when effective artificial respiration in an animal has been pushed to excess for some time, so that the pressure of CO_2 in the blood and tissues is very greatly reduced, there is not only a prolonged succeeding apnoea, but the animal dies of want of oxygen without attempting to draw a single breath. The artificial respiration must be performed somewhat forcibly, by means of a suction and exhaust pump; and the reason for this will be evident from what has already been said in Chapter III as to the control of the chest-movements by the Hering-Breuer reflex during artificial respiration produced by ordinary means.

This important experiment shows that when the CO_2 pressure is reduced below a certain point in the respiratory center the latter ceases to respond to even the extremest stimulus of want of oxygen. The apnoea produced in the ordinary way by voluntary forced breathing is terminated, as shown in Chapter V, by the combined stimulus of CO_2 and want of oxygen, and in some persons the oxyhaemoglobin in the arterial blood runs down so low that the lips and face become alarmingly blue before breathing begins. In the case of Poulton, for instance, his face presented such an alarming appearance when he demonstrated our experiments at a meeting of the Physiological Society that one or two members of the Society could hardly be restrained from applying artificial respiration on the spot. In my own case, and that of many others, the blueness is much less marked, although, as already shown, the termination of the apnoea is quite clearly due to want of oxygen, and not merely to accumulation of CO_2.

It is evident from the foregoing account that the respiratory response to the stimulus of uncomplicated oxygen want is a complex one. The anoxaemia tends to increase the breathing, but the

[2] Yandell Henderson, *Amer. Journ. of Physiol.*, XXI, p. 142, 1908.

increased breathing, by washing out CO_2, checks this increase very quickly, so that the net result for the time is only a small increase. Where the anoxaemia is only slight this net increase will be practically inappreciable, and this, as will be shown in Chapter VIII, is due, not to the fact that there is no appreciable anoxaemia, but to the masking of the natural response to anoxaemia by the opposite response to the washing out of CO_2. After a sufficient interval of time the former response, as we shall see, becomes unmasked by the compensation of the latter response, so that in the long run there is a very definite response of the breathing to even a very small fall in the oxygen pressure of the inspired air.

When diminution in the oxygen pressure of the inspired air is accompanied by a corresponding increase in the pressure of carbon dioxide, it is evident that within wide limits the pressure of oxygen in the alveolar air will remain almost normal, since the increased breathing due to the extra carbon dioxide will so raise the alveolar oxygen pressure as to compensate approximately for the oxygen deficiency in the inspired air. There will thus be no appreciable anoxaemia, and consequently the oxygen deficiency in the inspired air will produce no effect at all, although a similar deficiency in the absence of the excess of CO_2 would produce a marked effect. For instance, by adding CO_2 to the inspired air we can easily compensate within wide limits for the deficient oxygen pressure which affects airmen at high altitudes. This is not because, as Mosso[3] imagined, the effects of high altitude are due primarily to excessive loss of CO_2 ("acapnia"), but because the oxygen pressure, as well as that of CO_2, is kept approximately constant by the increased breathing due to the CO_2. When, however, the conditions are such that the extra breathing due to excess of CO_2 does not prevent the alveolar oxygen pressure from falling very low, the stimulus of anoxaemia is added to that of CO_2, and an enormously greater effect is produced on the breathing than by the CO_2 stimulus alone. This extra effect, as was recently shown by Meakins, Priestley, and myself[4] is due to increase in the *frequency* of the breathing; and increased frequency, provided the depth of breathing is sufficient, is, for a reason which will appear in the next chapter, particularly effective in preventing anoxaemia.

A further complication in the effects of anoxaemia and forced breathing on the respiratory center and the body as a whole is

[3] Mosso, *Life of Man on the High Alps*, Chapter XXII, London, 1898.
[4] Haldane, Meakins, and Priestley, *Journ. of Physiol.*, LII, p. 420, 1919.

introduced by the fact that, as Bohr discovered (see Chapter V and Figure 19), deficiency of carbon dioxide causes haemoglobin to hold on more tightly to oxygen. The consequence of this is, that when increased breathing lowers the pressure of CO_2 in the alveolar air and in the body as a whole, on the one hand the haemoglobin of the blood passing through the lungs is more highly saturated with oxygen than it otherwise would be; on the other hand the blood holds this oxygen so firmly that the oxygen pressure in the tissues falls lower than it otherwise would. There may thus be considerable anoxaemia though the blood is almost as red as usual, and the existence of this anoxaemia is only revealed by the immediate physiological effects of raising the alveolar oxygen pressure.[5]

On reducing, in a steel chamber, the atmospheric pressure to half an atmosphere there is a quite appreciable permanent increase in the breathing, and consequent drop in alveolar CO_2 pressure caused by anoxaemia, but, in my own case at any rate, no very striking blueness of the lips, although at the time the alveolar oxygen pressure is only about 34 mm. This pressure would only be sufficient to saturate the oxyhaemoglobin of the blood to the extent of 57 per cent if the pressure of CO_2 were that of normal alveolar air (see Figure 20). Blood with this percentage saturation would be very strikingly blue. Owing, however, to the diminished pressure of CO_2, the saturation is much higher, and this accounts for the color of the lips being nearly normal. The existence of considerable anoxaemia was, however, revealed at once by the effects of adding oxygen to the inspired air: for vision and hearing were at once strikingly improved and the breathing diminished. The degree of blueness of the lips is thus only a rough index of anoxaemia when anoxaemia is taken in its physiological meaning, as diminution in the oxygen pressure, rather than merely of the oxygen content, of the blood. It is the diminution in the amount of free oxygen, whether or not the amount of reserve oxygen combined with the haemoglobin is also diminished, which is functionally important.

Thus the benefit produced by diminished pressure of CO_2 (as, for example, during forced breathing) in increasing the percentage saturation of the haemoglobin in the arterial blood is neutralized by the disadvantage in the tissues owing to the same cause. The venous blood may, in fact, be as red as usual, although the venous oxygen pressure is abnormally low: for the saturation of

[5] Haldane, *British Medical Journal*, July 19, 1919.

the arterial blood with oxygen can be only very slightly increased by the lowering of alveolar CO_2 pressure. The oxygen pressure of the venous blood must in consequence be lowered, so that anoxaemia might be produced without any diminution, and even with a slight increase, in the saturation of the haemoglobin of the venous blood. On the other hand if the haemoglobin of the arterial blood, with normal alveolar CO_2 pressure, were only half-saturated, a lowering of the alveolar CO_2 pressure would considerably increase the saturation of the haemoglobin in both arterial and venous blood, but without sensible alteration of the venous oxygen pressure. Only in the practically impossible case of the saturation of the arterial haemoglobin being much below half would there be any rise in the venous oxygen pressure. Practically speaking, therefore, the Bohr effect, the increased oxygen content in blood, due to lowering of alveolar CO_2 pressure, is never of service in increasing the real oxygen supply to the tissues, and is sometimes of great disservice, although it always tends to make the venous blood less blue, and so diminishes cyanosis. On the other hand the corresponding effect due to raising of alveolar CO_2 pressure will practically never diminish the oxygen supply to the tissues, and will usually increase it, though the venous blood will always be more blue.

With forced breathing of normal air there is, as mentioned in Chapter I, a slight increase in the oxygen present in the arterial blood. This is due, partly to the Bohr effect and partly to the effect of the increased alveolar oxygen pressure. Hence the saturation of the haemoglobin is increased from about 95 to 100 per cent. There is also a small increase in the free oxygen dissolved in the arterial blood. On the other hand the amount of CO_2 and its partial pressure are enormously reduced in the arterial blood, and to a less extent the venous blood, since the circulation rate, as will be shown in Chapter X, is much diminished. The net result must be a considerable fall in the oxygen pressure in the tissues. Now it is well known that forced breathing produces a train of symptoms which, if the forced breathing is pushed, tend towards unconsciousness, so that forced breathing has even been used by dentists as a means of producing partial anaesthesia. In many respects these symptoms are similar to those of anoxaemia, except for the absence of spontaneous increased breathing. It was discovered by Hill and Flack[6] that when the forced breathing is with oxygen instead of with air the symptoms

[6] Hill and Flack, *Journ. of Physiol.*, XL, p. 347, 1910.

are greatly diminished. The most natural explanation of this is that the oxygen, by increasing largely the amount of free oxygen in the blood, diminishes the anoxaemia, since an oxygen supply which is not dependent on the Bohr effect is added to the ordinary oxygen supply from oxyhaemoglobin. Probably, therefore, the symptoms referred to are mainly produced by anoxaemia caused by the Bohr effect. The subject will be discussed further in Chapter X.

It is a very interesting fact that in many persons forced breathing does not produce apnoea at all, although in such persons the breathing is regulated in accordance with the alveolar CO_2 pressure, just as in other persons. This fact was investigated by Dr. Boothby some years ago while he was working with me.[7] He found that at the end of continuous forced breathing for one or two minutes there was in himself not only no sign of apnoea, but, on the contrary, increased natural breathing for a short time. This soon passed away, but at no time was there any apnoea, though the excretion of CO_2 in the expired air was much diminished for a considerable period. The cause of this absence of apnoea is not yet clear. It seemed possible that the stimulus of anoxaemia from the Bohr effect might, in persons who do not become apnoeic, account for the absence of apnoea; but even after forced breathing of oxygen the apnoea was absent in one of these persons whom I tested. His power of voluntarily holding a deep breath was markedly increased by forced breathing of air, but natural apnoea did not occur.

Owing, apparently, to the existence of the Bohr effect, the influence of CO_2 in relieving the general symptoms of anoxaemia is not due merely to increased breathing and consequent rise in the alveolar oxygen pressure. Lorrain Smith and I observed that animals in a semi-comatose state from the anoxaemia of carbon monoxide poisoning were revived by substituting expired air for pure air without alteration of the percentage of carbon monoxide. With the expired air mixture there could be no rise in the alveolar oxygen pressure, and there was no alteration in the percentage saturation of the blood with carbon monoxide. A still more striking effect is produced by simply adding CO_2 to the air inspired during CO poisoning. At the time we could not understand this effect, as Bohr's discovery had not yet been made. But this discovery furnishes an explanation of why a rise in the alveolar CO_2 pressure, without alteration of the alveolar oxygen pressure,

[7] Boothby, *Journ. of Physiol.*, XLV, p. 328, 1912.

should relieve the symptoms in CO poisoning: for the increased CO_2 pressure will enable the oxygen to come off more easily from the oxyhaemoglobin present in the blood, and will thus tend to relieve the anoxaemia. The circulation rate will also be increased, as will appear in Chapter X. There would seem to be a considerable future scope for the therapeutic use of CO_2 in anoxaemic condi-

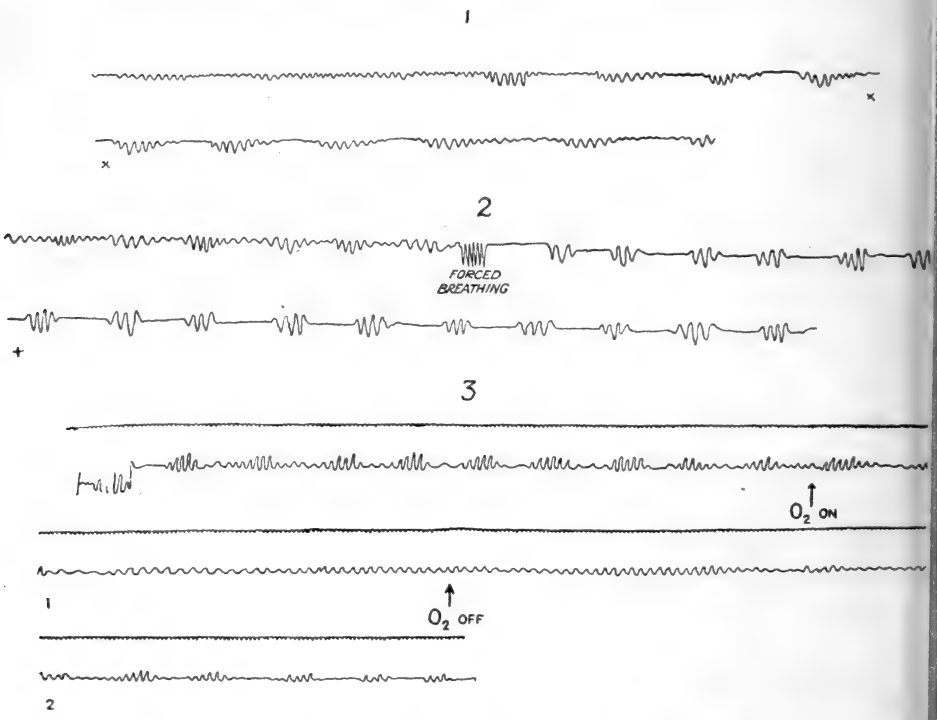

Figure 37.

Tracing 1. (Stethograph) Douglas, July 12. Evening of arrival on Pike's Peak. Natu periodic breathing.

Tracing 2. Haldane, July 12. Evening of arrival. Natural periodic breathing with m sharply defined periods after making six forced breaths.

Tracing 3. July 16, Haldane. Natural periodic breathing abolished by administration oxygen. Reappearance of periodic breathing after withdrawing the oxygen.

tions of all kinds, whether or not these conditions are due to imperfect oxygenation of the arterial blood.

Even when simple anoxaemia is so extreme that consciousness is on the point of being lost, the breathing in man, except at first, is hardly more than doubled, as shown by the fact that the alveolar

CO_2 pressure is only reduced to about half. During heavy muscular exertion, on the other hand, the breathing may easily be increased to ten or fifteen times its normal amount. The relatively slight increase in the amount of air breathed during very serious anoxaemia is frequently lost sight of in the interpretation of clinical symptoms. There is nearly always a considerable increase in the frequency of breathing, but the depth of breathing is usually only slightly increased, and may be diminished, as will be explained more fully below. In the very dangerous pure anoxaemia of high altitudes or CO poisoning, increase in the breathing is not a prominent symptom.

It has been known for long that at high altitudes the breathing is very apt to be periodic. This phenomenon was fully observed on Monte Rosa by Mosso,[8] who, however, had completely failed to realize the significance of Paul Bert's researches on the effects of gases, and thus failed to interpret correctly the cause of the periodic breathing. The periodic breathing is usually not continuous, but can easily be started by disturbing the ordinary rhythm of breathing, as by taking a few long breaths, or holding the breath. It is also very apt to occur at night. It is distinguished from ordinary clinical Cheyne-Stokes breathing by the shortness

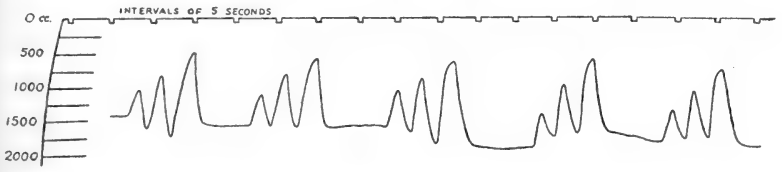

Figure 38.

Henderson, August 13. Quantitative record of the respiration during periodic breathing. Inspiration upwards.

of the periods. There are usually groups of only about three to six breaths, followed by a pause, and this periodic sequence continues almost indefinitely (Figure 37). Sometimes the middle breath of the group is deepest, sometimes the last breath (Figure 38) or sometimes the breaths are about equal in depth. Sometimes the periodicity only shows itself by periodically recurring single deep breaths.

The general explanation of this periodic breathing has already been given in Chapter V. That this explanation is the correct one is shown by the fact that, as is seen in Figure 37, on adding oxy-

[8] Mosso, *Life of Man on the High Alps*, Chapter III, London, 1898.

gen to the inspired air the periodicity disappears. This experiment was carried out repeatedly by Douglas, Yandell Henderson, Schneider, and myself, on Pike's Peak, and never failed.[9] Mosso had attempted to carry it out, but got a negative result owing to a defective mode of administering the oxygen.

As already seen periodic breathing can easily be produced at ordinary barometric pressure by suitable means. As the barometric pressure is reduced the periodic breathing is produced more and more readily, and is more and more persistent, just as might be expected; and the same is true if, instead of a reduction of barometric pressure, there is a reduction in the oxygen percentage of the inspired air. This form of periodic breathing has no pathological significance, and occurs during perfect health.

The special characters of the increased breathing caused by

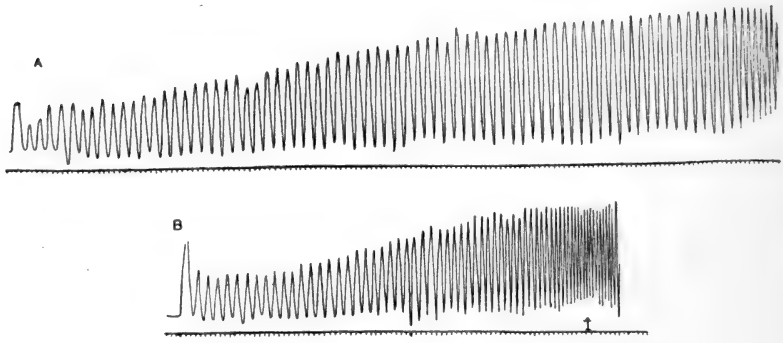

Figure 39.

(a) Rebreathing—Concertina filled with oxygen—CO_2 accumulating,
(b) Rebreathing—Concertina filled with air—CO_2 accumulating.
Time-marker = 2 seconds. Arrow shows point where lips were distinctly blue.

anoxaemia were recently studied by Meakins, Priestley, and myself.[10] The differences between increased breathing caused by excess of CO_2 and that caused by anoxaemia, or by anoxaemia accompanied by excess of CO_2, are very striking. Speaking generally, the effect of excess of CO_2 is mainly to increase the depth of breathing, and only a moderate increase of frequency is produced. On the other hand anoxaemia produces a marked increase in frequency and only a moderate increase in depth. But when the

[9] Douglas, Haldane, Yandell Henderson, and Schneider, *Philos. Trans. Royal Society*, B. 203, p. 231.
[10] Meakins, Haldane, and Priestley, *Journ. of Physiol.*, LII, p. 420, 1919.

effects of excess of CO_2 and anoxaemia are combined there is great increase of both depth and frequency, so that far more air is breathed than when either excess of CO_2 alone, or anoxaemia alone, is the stimulus. In my own case, for instance, when the breathing was pushed, in short experiments, to as much as seemed bearable, 131 liters per minute, with a depth of 1.98 liters and a frequency of 66 per minute, were breathed when the effects of excess of CO_2 and anoxaemia were combined; and only 81 liters, with a depth of 2.69 and a frequency of 30, when the only stimulus was excess of CO_2.

Figure 39 shows quantitatively the effects of rebreathing a small volume (about 2 liters) of air or oxygen from the recording concertina already described. It will be seen that the increase in frequency was much less when the effects of anoxaemia were cut out by the oxygen.

Figure 40 A shows the effect on the same subject of similar rebreathing when the accumulation of CO_2 was prevented by inter-

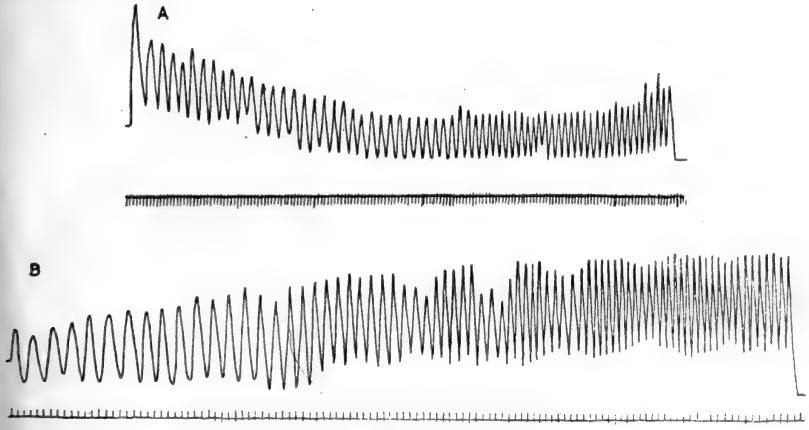

Figure 40.

Rebreathing through soda-lime from concertina. Time-marker = 2 seconds. (a) Subject Cpl. M. (b) Subject J. S. H.

posing a layer of soda lime. It will be seen that the frequency increases, but not the depth. Figure 40 B shows the effects on another subject, whose respiratory center responds much more readily to the effects of anoxaemia. In this case depth as well as frequency are considerably increased. It must, however, be borne in mind that, in short experiments such as these, the increased breathing, as already explained, is mainly due to the necessity of

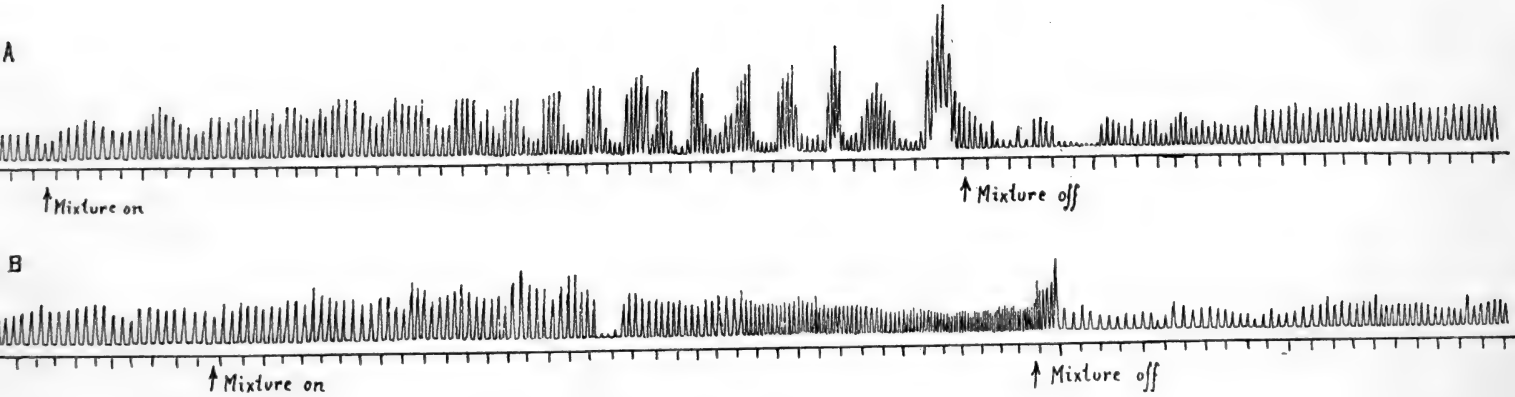

Figure 41.

Subject J. G. P. Time marker = 10 seconds. (a) Breathing 10.33 per cent oxygen, (b) Breathing 9.59 per cent oxygen.

removing from the body the large amount of preformed CO_2 which has become superfluous owing to the effect of anoxaemia in lowering the threshold of CO_2 pressure.

Figures 41 and 42 show the effects of anoxaemia combined with those of the slight resistance associated with the recording apparatus. The effects are complicated owing to the fact that with a certain degree of anoxaemia, varying greatly for different individuals, periodic breathing is produced readily, as shown in some of the tracings. Periodic breathing, or else very shallow breathing, is also produced invariably after the anoxaemia, as shown in all the tracings. This is of course due to the fact that so much CO_2 has been removed from the body by the hyperpnoea of anoxaemia, just as it is removed by forced breathing.

In Figure 41 B and Figure 42, A, C, and D, it will be seen that after an initial increase in depth the breathing became progressively shallower and more frequent just as in fatigue due to excessive resistance; and after a time asphyxial symptoms were usually impending owing to the ineffectiveness of the shallow breaths. When the experiments were made we had not investigated the effects of fatigue caused by resistance, and there is now no doubt that the slight resistance due to the apparatus, combined with the effects of anoxaemia on the respiratory center, accounted for the specially rapid failure of breathing shown in the figures. When the breathing is quite free, as in a steel chamber at low pressures, failure of the respiratory center does not occur nearly so readily, but the difference is only one of degree; and failure of the respiratory center, as shown by shallow and frequent respirations, is the inevitable result of serious arterial anoxaemia. With the increasing shallowness of the breaths the arterial anoxaemia increases, owing to causes discussed in Chapter VII. This increases the failure of the respiratory center; and unless relief comes the inevitable result of the vicious circle thus produced is death.

We must now turn to the other symptoms and signs of want of oxygen, beginning with the circulatory symptoms. Unfortunately we cannot as yet measure the volume of blood circulated per minute in the same easy way in which we can measure the volume of air breathed. Our knowledge of the effects of want of oxygen on the circulation is thus imperfect as yet. It will be discussed more fully in Chaper X. When moderate symptoms of anoxaemia are produced experimentally, as in a steel chamber at reduced atmospheric pressure, or when air deficient in oxygen is breathed,

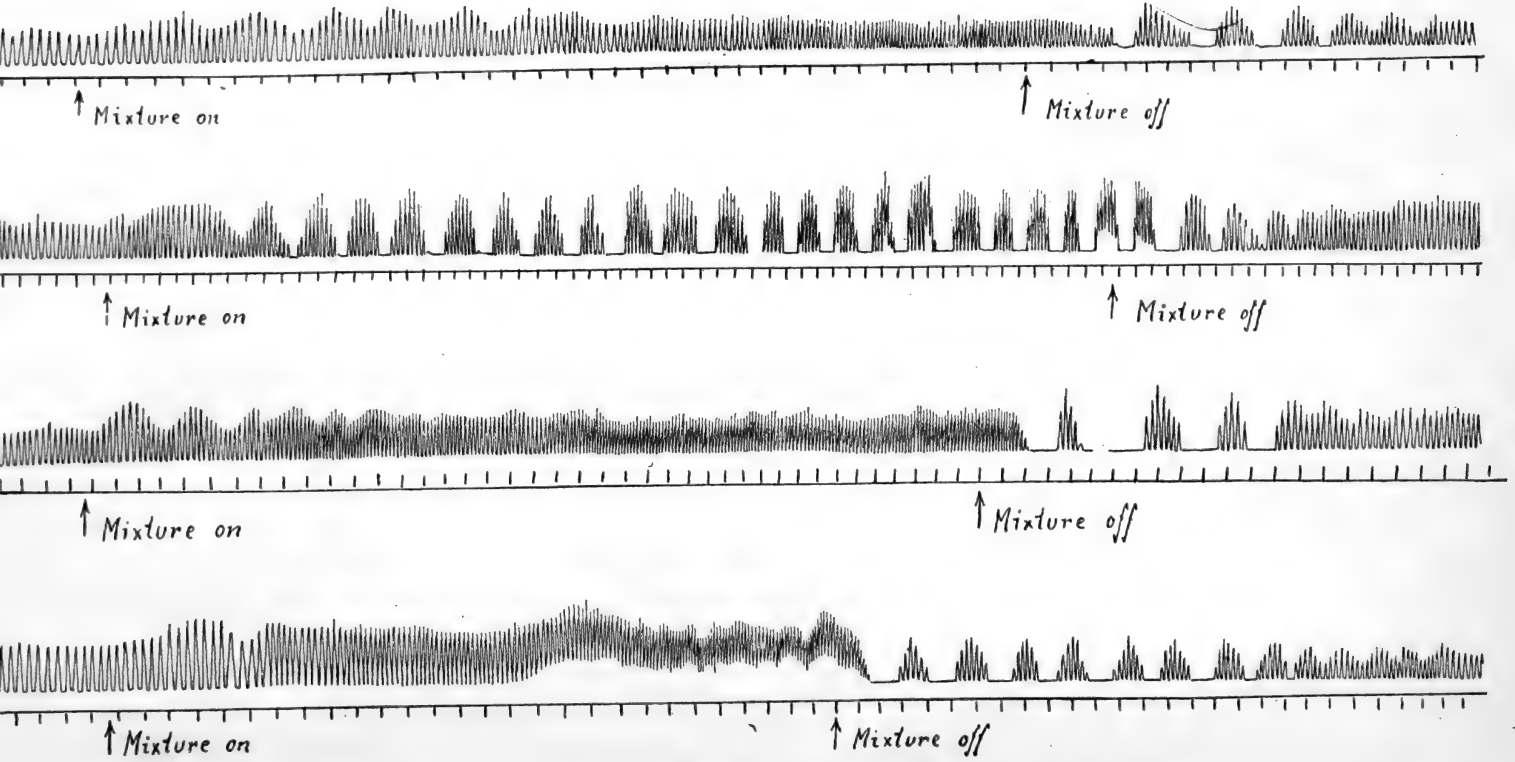

Figure 42.

Subject J. S. H. Time marker= 10 seconds. (a) Breathing 11.19 per cent oxygen, (b) Breathing 11.05 per cent oxygen + 0.7 per cent CO_2, (c) Breathing 10.64 per cent oxygen, (d) Breathing
[illegible] per cent oxygen

there is at first an increase of the frequency, and apparently also in the strength, of the heartbeats. This indicates an increase in the circulation rate. But just as in the case of the respirations, the frequency and vigor of the pulse soon fall again, though the frequency remains above normal, just as does the frequency of respiration. Thus the pulse may rise to about 120 at first, and then fall after a few minutes to about 90, and remain steady. With greater anoxaemia the increase in rate is more marked. The great temporary increase in blood pressure with acute anoxaemia in animals is also a well-known phenomenon.

At first sight it might seem that a great increase in both respirations and circulation would be the natural physiological response to anoxaemia, since the increased respiration will raise the alveolar oxygen pressure and the increased circulation rate will increase the amount of oxygen left in the red corpuscles of the blood passing through the capillaries. But, as already seen, the increased respiration lowers the pressure of CO_2 in the respiratory center and tissues, and this lowering rapidly reduces the increased breathing to within relatively narrow limits. A similar lowering of CO_2 pressure in the tissues must also be produced by increased circulation rate; and the falling-off in the initial increase of pulse rate is probably at bottom due to the same cause as the falling-off in the initial depth and frequency of breathing. With further increase in the anoxaemia the heartbeats, like the respirations, become more and more feeble. A fuller discussion of the relatively little that is at present known definitely as to the physiological regulation of the circulation will be found in Chapter X. It is of course evident that the physiology (not the mere physics) of the circulation is intimately related to that of the breathing.

As a sign of anoxaemia, the appearance of the lips, tongue, and face is of much importance, but requires careful interpretation. The bluish color or cyanosis seen in the lips and skin during ordinary anoxaemia is, of course, due to the fact that in the blood passing through the capillaries the proportion of oxyhaemoglobin to haemoglobin is abnormally low. A somewhat similar color may be produced by the action of poisons which produce methaemoglobin and other colored decomposition products in the blood; and this condition, which is of course quite exceptional, and can quite easily be distinguished, will be referred to in Chapter VII. Cyanosis may either be due to general or local slowing of the circulation, or to the fact that the arterial blood is imperfectly oxygenated, and the latter cause, as will be shown in Chapter VII,

is far more common than was, till recently, supposed. Portions of the skin may be blue from local slowing of the circulation due to cold and other causes; but abnormal blueness of the lips and tongue points to either imperfect oxygenation of the arterial blood or general slowing of circulation. According as there is much or little blood in the capillaries the color is full or unsaturated. Thus in extreme cyanosis the lips may be either almost black, or only leaden gray; and in slight cyanosis the color may be either a full or a pale purplish red.

Ordinary cyanosis of one kind or another is commonly seen in patients who, though suffering from some chronic ailment, are not particularly ill. Hence the significance of cyanosis under other conditions is apt to be overlooked unless all the symptoms and other circumstances are taken into account. It must, in the first place, be pointed out that the degree of cyanosis is no direct measure of the degree of physiological anoxaemia. The latter is due to a lowering in the partial pressure of oxygen in the blood of the capillaries, while the former is due to a diminution in the ratio of oxyhaemoglobin to haemoglobin. Under ordinary conditions the latter effect is an index, though, owing to the form of the dissociation curve of oxyhaemoglobin (Figure 20), not a direct measure, of the former effect. When, however, the matter is complicated by an alteration in the Bohr effect of CO_2 pressure on the dissociation of oxyhaemoglobin, the relationship between oxygen pressure and dissociation of oxyhaemoglobin is at once altered. If, for instance, the pressure of CO_2 in the arterial blood is reduced by increased breathing, there may be much less cyanosis for a given degree of physiological anoxaemia than when the CO_2 pressure in the blood is normal. Thus there is no fixed relationship between cyanosis and physiological anoxaemia; and this fact is of great importance in the clinical interpretation of cyanosis. Moreover, as Barcroft showed, the Bohr effect is due to the action of CO_2 as an acid. Hence, owing to the adjustments which, as will be shown in Chapter IX, occur in the living body when time is given, the CO_2 pressure in the alveolar air may be no guide as to how far the Bohr effect is disturbing the ordinary relations between cyanosis and true anoxaemia. The word "anoxaemia" should evidently be taken as signifying a condition in which the *free* oxygen in the systemic capillary blood is abnormally diminished; and this of course, in accordance with Henry's law, comes to the same thing as diminution in the oxygen pressure.

The symptoms produced in the nervous system generally by

anoxaemia must now be described. A knowledge of them is of great importance in practical medicine. If a pure anoxaemia is produced very suddenly, as by breathing pure nitrogen, hydrogen, methane, or nitrous oxide, loss of consciousness occurs quite suddenly and with no previous warning symptoms. Thus a miner who puts his head into a cavity in the roof full of pure, or nearly pure, methane drops suddenly as if he had been felled; and when he recovers after breathing pure air for a few seconds he sometimes even imagines that he has been knocked down by another man, and acts accordingly. If the anoxaemia is produced with only moderate rapidity the marked temporary disturbances, already referred to, in the breathing and circulation give, as a rule, some warning of what is coming. But when the onset is gradual there is little or no preliminary discomfort, and for this reason the onset of pure anoxaemia is very insidious, and the condition is, therefore, in practice a dangerous one, as is well seen in CO poisoning, or in ascents to very high altitudes in balloons or aëroplanes, or in many clinical cases. Thus although CO is not very poisonous as compared with other gaseous poisons, it is responsible for a far larger number of deaths than any other gaseous poison not used in warfare.

As the slow onset of anoxaemia advances, the senses and intellect become dulled without the person being aware of it; and if the anoxaemia is suddenly relieved by means of oxygen or ordinary air, the corresponding sudden increase in powers of vision, hearing, etc., is an intense surprise. The power of memory is affected early, and is finally almost annulled, so that persons who have apparently never lost consciousness can nevertheless remember nothing of what has occurred. Powers of sane judgment are much impaired, and anoxaemic persons become subject more or less to irrational fixed ideas, and to uncontrolled emotional outbursts. Muscular coördination is also affected, so that a man cannot walk straight or write steadily. With further increase in the anoxaemia, power over the limbs is lost; the legs first being paralyzed, then the arms, and finally the head. The senses are lost one by one, hearing being apparently the last to go. The sense of painful impressions on the skin seems to be lost early. Thus miners suffering from CO poisoning, but not to the point of losing consciousness, are often burnt by their lamps or candles without their being aware of the burn at the time.

In many respects the symptoms of anoxaemia resemble those of drunkenness, and a man suffering from anoxaemia cannot be

held responsible for his actions. Without reason he may begin to laugh, shout, sing, burst into tears, or become dangerously violent. He is, however, always quite confident that he himself is perfectly sane and reasonable, though he may notice, for instance, that he cannot walk or write properly, cannot remember what has just happened, and cannot properly interpret his visual impressions. When unable even to stand, owing to experimental CO poisoning or to anoxaemia produced by low pressures in a steel chamber, I have always been quite confident in my own sanity, and it was only afterwards that I realized that I could not have been in a sane state of mind.

A recent experience of this kind was in a steel chamber in which Dr. Kellas, who is an experienced climber in the Himalayas and has exceptional powers of resisting anoxaemia, was with me.[11] We had reduced the pressure to 320 mm., and as I could no longer write or make any observations I handed him the notebook. He afterwards told me that I remained sitting, but always answered his questions quite deliberately and confidently, and insisted on his keeping the pressure at 320 mm. This went on for an hour and a quarter, of which time I could afterwards remember absolutely nothing. At last Dr. Kellas obtained my assent to raising the pressure to 350 mm., after which I took up a mirror to look at my lips, though Dr. Kellas observed that for some time I looked at the back instead of the front of the mirror. I had, however, begun to realize that we had been far longer at the low pressure than we had intended, and agreed to a rise to 450 mm. On reaching this pressure my mind had cleared and I noticed a return of feeling and power in my legs. After coming out I could vaguely remember taking up the mirror, but nothing before that, after handing over the notebook. We had no intention of staying at so low a pressure that it was impossible for me to take notes, and my persistence was quite irrational. Dr. Kellas was much bluer than I was during the stay at 320 mm., but could still write quite well, watch the barometer, and manage the regulating tap; but whether he was quite normal mentally seemed rather doubtful. Perhaps he shared to some extent my irrational desire to continue the experiment: otherwise I think he would have noticed how abnormal my condition was. We were both at the time unacclimatized to low pressures.

This personal experience illustrates some of the peculiar dangers associated with atmospheres which produce anoxaemia,

[11] Haldane, Kellas, and Kennaway, *Journ. of Physiol.*, LIII, p. 181, 1919.

whether in virtue of defective oxygen pressure or of the presence of poisonous proportions of CO. In the first place it is evident that a man may advance for some distance into such an atmosphere before he begins to be seriously affected; for the temporary marked increase in the breathing may, when the oxygen pressure is defective, at first prevent an appreciable fall in the alveolar oxygen pressure. This must, for instance, happen while a balloon or aëroplane is rising rapidly, or while a miner is advancing with an electric lamp into an atmosphere very highly charged with fire-damp. When the breathing begins to quiet down again the effects of the atmosphere will develop fully and it may then be too late to turn. At 320 mm., for instance, I was at first quite capable of making observations and taking notes, including a note of the increased breathing and its subsequent quieting down.

Another, and often still more serious, danger arises from the gradual and insensible failure of judgment. A man suffering from anoxaemia will usually go on, and insist in going on, with what he set out to do. An airman will very probably continue to ascend, oblivious to danger; and a miner engaged in rescue or exploration work, or in dealing with an underground fire, will insist in going on when he is suffering from the anoxaemia of CO poisoning, and will often fight any one who tries to make him desist.

All these considerations apply equally to clinical cases of anoxaemia; and for this reason the condition is quite commonly never recognized till too late. The early recognition of clinical anoxaemia is a matter of great importance.

Besides the immediate symptoms of anoxaemia there are a number of delayed symptoms or after effects. They depend partly on the length, and partly on the severity, of the exposure. A short exposure, even with loss of consciousness, produces no serious after symptoms; but occasionally a man's behavior is very abnormal for a few minutes after recovery. One of my acquaintances has twice knocked persons down on waking up from a short loss of consciousness caused by anoxaemia; and my own behavior was distinctly abnormal just after coming out from the steel chamber in the experiment alluded to above. Similar abnormalities after slight CO poisoning have often come under my observation. Thus a well-known inspector of mines, on returning to the surface after he had been affected by CO from an underground fire, first shook hands very cordially with all the bystanders. A doctor who was present then offered him an arm; but this the inspector regarded as an insult, with the result that he took off his coat and challenged the doctor to a fight.

The best-known delayed effect of slight anoxaemia is the train of symptoms originally called "mountain sickness." This is a condition in the typical form of which there is nausea, vomiting, headache, sometimes diarrhœa, and always great depression. The symptoms appear, as a rule, some hours after the beginning of the exposure, and may not appear at all till after the exposure is over. In CO poisoning it is usually after the exposure, and often after the CO has practically disappeared from the blood, that these symptoms begin. The duration of exposure required for their production depends upon the degree of anoxaemia. Thus the higher a mountain is, or the greater the altitude at which an airman has been flying, the shorter is the exposure required. On Pike's Peak, at 14,100 feet (barometer about 458 mm.) the usual stay (an hour or two) of visitors by train is too short to produce mountain sickness, though the ordinary immediate symptoms of anoxaemia are usually very evident, and even very great cyanosis and fainting are observed occasionally. A stay of several hours is usually required to induce mountain sickness, which usually begins about 8 to 12 hours after the beginning of the exposure. Thus the symptoms may only develop after the return downwards.

With a sufficient period of exposure mountain sickness may develop at much lower altitudes than that of Pike's Peak. It is often observed at even 7,000 or 8,000 feet, where the degree of anoxaemia is not sufficient to produce any noticeable immediate effect on the breathing. Similarly a percentage of CO which produces no noticeable immediate effect will, with sufficiently long exposure, cause headache, nausea, etc. These facts are of the greatest significance in clinical medicine, for it is now evident that even a very slight degree of continued anoxaemia is of much importance to the patient. Mountain sickness and the effects of CO poisoning are not isolated phenomena unrelated to the rest of physiology and pathology, but symptoms of anoxaemia, which is in reality one of the commonest conditions during illness. At present we can only conjecture as to the nature of the slight temporary pathological changes of which the mountain sickness symptoms are the manifestations.

With severe and prolonged exposure to want of oxygen the nervous after symptoms are of an extremely formidable nature, and often end in death.[12] For a reason which will be explained

[12] An interesting description of these symptoms by Dr. Shaw Little will be found in Appendix B to my Report on the Causes of Death in Colliery Explosions *Parliamentary Paper C. 8112*, 1896.

in a later chapter they are most commonly met with after CO poisoning, and whatever their origin they are often grossly misinterpreted. The patient does not recover at once on removal of the oxygen want, as in short exposures. In cases of CO poisoning consciousness may not be recovered, although within an hour or two after removal to fresh air most of the CO has already disappeared from the blood. It is exactly the same with men who have remained unconscious for, perhaps, several hours in air very poor in oxygen. Or if consciousness has been partially recovered the patient may lapse again into unconsciousness. During gradual recovery there is usually a very marked spastic condition of the muscles, and occasional epileptiform seizures, and there may be various partial paralyses and other nervous symptoms. Sometimes the patient lingers on for weeks in a comatose condition with spastic muscles and occasional opisthotonos. The body temperature is unstable, and every function of the central nervous system seems to be more or less affected. Gross hemorrhages in the brain have been described, and Mott has found small multiple hemorrhages. The symptoms are, however, evidently due in the main to widespread injury to the nerve cells themselves during the exposure. Loss of memory, mental incapacity, and even definite mania may follow the exposure; but whatever the nature of the symptoms may be, they nearly always pass off gradually if the patient survives the first few days. One interesting nervous after effect occasionally observed is what appears from the symptoms to be peripheral neuritis.

The heart may also suffer severely in prolonged exposure to want of oxygen; and if the exposure has been accompanied by much muscular exertion, as in efforts to escape or to rescue other men, the after symptoms may be mainly cardiac. In these cases the pulse is feeble and irregular, the heart dilated, with a blowing systolic murmur; and any muscular exertion produces collapse. It may be a considerable time before the heart fully recovers.

Probably every other organ and tissue in the body feels the after effects of severe exposure to want of oxygen. The patient often enough dies of pneumonia. Acute nephritis and gangrene of extremities have been noticed as sequelae to the acute bronchopneumonia and oedema of the lungs in chlorine poisoning. As the patients have been exposed to very grave oxygen want in consequence of the lung condition, it seems probable that the affections just mentioned are after effects of the oxygen want, aggravated by the after effects on the heart, and often complicated by secondary infections.

With anoxaemia, as already explained, the respiratory center becomes very easily susceptible of fatigue, as manifested by diminishing depth of the breathing. It is now well known that in the resuscitation of persons who have been nearly asphyxiated by drowning, asphyxiating atmospheres, etc., the most effective remedy is artificial respiration. This is because the respiratory center has completely or almost completely failed or become "fatigued," and the patient would die if this condition were not compensated for by artificial respiration. Respiration seems almost always to fail before the heart fails. The respiratory center may also take a long time to recover sufficiently to be able, without artificial aid, to keep the patient alive. For this reason it may be necessary to prolong the artificial respiration for hours.

Diminishing depth with increasing rate of respiration is always a sign of the onset of fatigue of the breathing; and when the depth continues to diminish without compensation from increased rate the condition rapidly becomes dangerous, as will be shown in Chapter VII, since secondary anoxaemia develops. In a person dying quietly the diminishing depth can be observed until the resulting anoxaemia ends in death. The immediate cause of death seems to be failure of the respiratory center. When death from anoxaemia occurs at very high altitudes (as, for instance, in the case referred to in Chapter XII, of the balloonists, Tissandier and Crocé Spinelli) it is evidently failure of the respiratory center which precipitates the anoxaemia, thus making the conditions so very dangerous; and the same remark applies to asphyxiation in atmospheres containing a low percentage of oxygen in mines, wells, etc. In CO poisoning, as will be explained in Chapter VII, there is not so much danger from this cause, so that extreme anoxaemia may exist for a long time without death occurring.

After the respiratory center has been over-fatigued in consequence of anoxaemia, the effects may not pass off for a very long period. The breathing on exertion, or even during rest, is abnormally shallow; and the peculiar group of symptoms observed in the neurasthenic condition so familiar during the war, and already referred to in Chapter III, is observed. This condition may remain for months after severe anoxaemia, and is often mistaken for organic heart injury.

In considering the effects of anoxaemia a factor comes in which must always be borne in mind—namely that of adaptation or acclimatization. This may act in two different ways. In the first place adaptation may bring it about that the anoxaemia which

would, without adaptation, exist is greatly diminished. This form of adaptation is very clearly seen in persons living at great altitudes, and will be discussed in detail in later chapters. In the second place the tissues may adapt themselves to a lower partial pressure of oxygen. About this second form of adaptation our knowledge is at present very imperfect; but it seems to me that clinical evidence points strongly to its existence. Perhaps the clearest evidence is afforded by cases of congenital heart defect, in which part of the venous blood passes direct to the left side of the heart without first passing through the lungs. In these cases of "Morbus coeruleus" the arterial blood is always more or less blue, and becomes extremely blue on muscular exertion, so that one can always recognize this condition in persons walking in the street. The remarkable point, however, is that in spite of the anoxaemic condition of the arterial blood these persons may get on quite well, and be able to walk at a good pace. On account of the large increase in their haemoglobin percentage, they have plenty of oxygen in their blood, but at a low partial pressure. It seems hardly possible to doubt, therefore, that their tissues have become adapted to the low partial pressure of oxygen; and the same adaptation probably exists to a considerable extent in many chronic cases of valvular heart disease, emphysema, etc.

The fact that cyanosis may exist without harm in chronic cases of disease has certainly contributed greatly to the general failure to recognize the gravity of anoxaemia in persons not adapted. Adaptation is a process which always requires time, and the time factor must, therefore, be taken into account in judging of the physiological effects of anoxaemia.

CHAPTER VII

The Causes of Anoxaemia.

In the previous chapter anoxaemia has been defined as the condition in which the partial pressure of oxygen, or, what comes to practically the same thing, the amount of *free* oxygen, in the systemic capillaries generally, is abnormally low. The causes of this condition must now be examined.

The first and most important cause of anoxaemia is defective saturation of the arterial haemoglobin with oxygen. This may, as we shall see, arise from several causes; but the most obvious of these is defective partial pressure of oxygen in the alveolar air. It will be shown in Chapter IX that during rest under normal conditions oxygen passes into the blood through the alveolar epithelium by a process of simple diffusion, and that the oxygen pressure in the arterialized blood leaving each alveolus is exactly that of the air in the alveolus. For the purposes of the present discussion we may provisionally assume that this is always the case during rest, so long as the lungs and the inspired air are normal, although modifications in this assumption must be introduced later.

In the light of this assumption and of our knowledge of the dissociation curve of oxyhaemoglobin, it might seem at first that we are justified in assuming that the oxygen pressure of mixed arterial blood is simply that of mixed alveolar air as ordinarily obtained for analysis by the methods already described. In favor of this assumption is the now well-ascertained fact that the breathing is regulated under ordinary conditions in close accordance with the pressure of CO_2 in the mixed alveolar air, as explained in Chapter II. Variations in average alveolar CO_2 pressure are thus a direct measure of variations in the CO_2 pressure of the arterial blood; and it was natural to assume, as was done by myself and others till lately, that variations in alveolar oxygen pressure must also be a measure of variations in the oxygen pressure of the arterial blood. One known difficulty in this assumption lay in the fact that the arterial oxygen pressure, as measured in animals by the aërotonometer (Chapter IX) is nearly always lower, and sometimes considerably lower, than the alveolar oxygen pressure; but various explanations of this difficulty had been adopted by myself and others.

A new and important light was thrown on the whole subject in the course of a study by Meakins, Priestley, and myself of the "neurasthenia" produced by gassing and other causes during the war.[1] As mentioned in Chapter III, the breathing in these patients is abnormally frequent and shallow, particularly on exertion. It was also found that addition of oxygen to their inspired air was of considerable service during any ordinary exertion, and that in some of them the lips became blue on exertion unless oxygen was given. As there was no sign of anything seriously abnormal in their lungs, we were led to suspect that the shallow breathing was somehow causing anoxaemia. This led us to make experiments

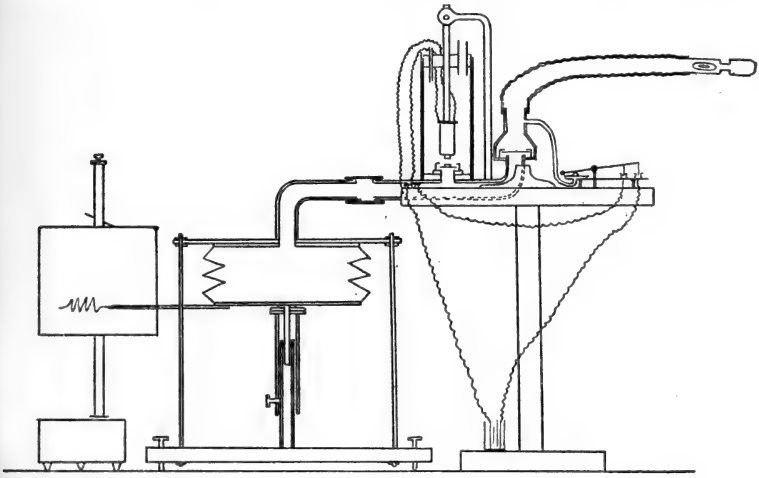

Figure 43.
"Concertina" apparatus for continuous record of respiration.

on the effects of shallow breathing in normal persons, and for this purpose we devised the apparatus[2] shown in Figure 43. The subject inspires through the mouthpiece and inspiratory valve from the recording "concertina." The bottom of this moves upwards with inspiration, and records the movement by means of an inked pen on the drum. The bottom comes down on a movable stop, and by moving this upwards the maximum capacity of the concertina can be reduced to whatever is desired. During expiration the expired air passes out by the rubber expiratory valve. At the same time the expiratory pressure is communicated to a

[1] Haldane, Meakins, and Priestley, *Journ. of Physiol.*, LII, p. 433, 1919.
[2] Made by Messrs. Siebe Gorman & Co., 187 Westminster Bridge Road, London.

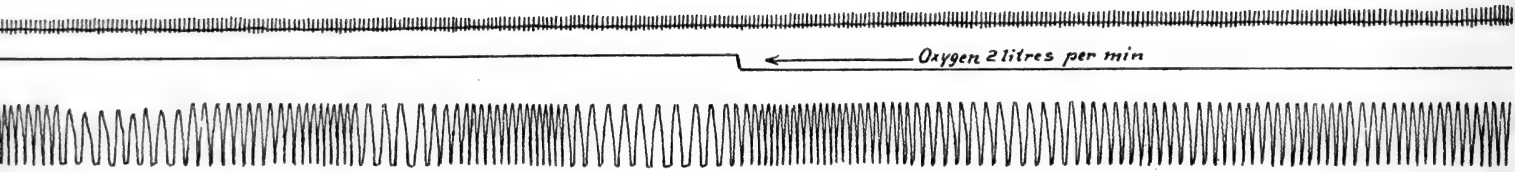

Figure 44.
Subject J. G. P. Time marker = seconds.

tambour the movement of which, as shown, closes a circuit from an accumulator or from the lighting circuit through a rheostat. This circuit passes through an electromagnet which instantly lifts a valve and admits air freely into the concertina, which at once refills itself. At the end of expiration the circuit is instantly broken and the valve closes, so that only the volume of air contained in the concertina can be inspired at the next inspiration. In this way the amount of air taken in per breath can be limited, and a continuous record is at the same time obtained of the depth and frequency of respiration. With the concertina fully open ordinary records of the breathing are obtained, and any gaseous mixture can be supplied through a glass cylinder which incloses the electromagnet and valve. The advantage of this method is that it is capable, not merely of permitting a study of shallow breathing, but also of giving a continuous quantitative record of any sort of breathing. The old stethographic method of recording the breathing is apt to be misleading, since it does not give a quantitative record.

When the depth of inspiration is limited by means of this apparatus the natural impulse, at first, is to continue the inspiratory effort at the end of each inspiration, as the Hering-Breuer reflex has not given the signal for expiration. With a little practice, however, the breathing goes quite easily, and the frequency increases in proportion as the depth is diminished. When the depth is greatly limited the breathing becomes very frequent—100 or more a minute.

On observing the breathing when the depth was gradually more and more limited, we found that the breathing became periodic very readily. As already explained, periodic breathing is a symptom of anoxaemia, and this fact led us to try the effect of adding a little oxygen to the inspired air. This promptly abolished the periodic breathing, as shown in Figure 44. There could thus be no doubt that the periodic breathing was due to imperfect oxygenation of the arterial blood. In some persons, such as myself, the periodic breathing was produced much more readily, and in a more striking degree, than in other persons. This, as already mentioned in Chapter VI, is due to individual differences in the response of the respiratory center to anoxaemia.

We at first thought that the anoxaemia must be due to the fresh air not penetrating properly to the deep (air-sac) alveoli when the breathing was shallow; but on examining samples of the deep alveolar air during a prolonged experiment, we were disappointed

to find that in the deepest alveolar air the oxygen percentage, so far from being lower, was actually higher than usual. There was thus hyperpnoea from want of oxygen, and yet the deep alveolar air contained more oxygen than usual. The breathing was, however, very inefficient and therefore greatly increased in amount, as the dead space told much more than with normal breathing, so that the percentage of CO_2 in the expired air was very low.

On turning the matter over, we bethought ourselves of some anatomical observations collected by Professor Arthur Keith in "Further Advances in Physiology," edited by Professor Leonard Hill, 1909. He showed in this essay that during inspiration the lungs do not expand equally and simultaneously at all parts, but open out part by part, somewhat like the opening of a lady's fan. The parts nearest the moving chest walls (for instance the diaphragm) expand first, and other parts follow. It follows from this, that in shallow breathing the lungs will be very unevenly ventilated. Only certain parts will expand properly, and on ac-

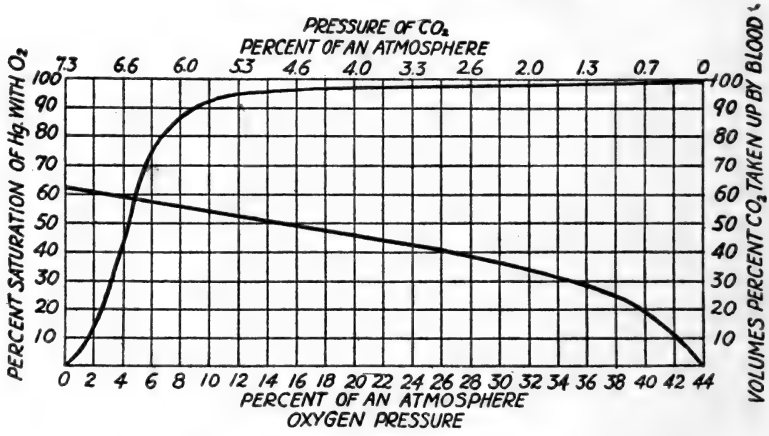

Figure 45.
Dissociation curves of blood for CO_2 and oxygen.

count of the increased frequency of breathing they will receive much more than their proper share of fresh air, while the other parts which do not expand will receive much less.

The consequence of this will be that the venous blood passing through the unexpanded parts of the lungs will be very imperfectly arterialized, whereas in the expanded parts the blood will be more arterialized than usual. The mixed arterial blood will thus be a mixture of over-arterialized and under-arterialized

blood. To see what the results of this mixture will be, we must refer to the respective dissociation curves for the oxygen and the CO_2 present in blood, taking also into account the action of oxygen in expelling CO_2 from venous blood, as shown on the curve in Figure 26. For convenience' sake the two relevant curves are plotted together in Figure 45, taken from our paper. It will at once be seen that the over-ventilation in some parts of the lungs will wash out CO_2 from the blood in the same proportion as the under-ventilation fails to wash it out. The mixed arterial blood will thus be normal as regards its content of CO_2 if the *total* alveolar ventilation is normal. On the other hand, the over-ventilation will hardly increase at all the charge of oxygen in the blood from the over-ventilated alveoli, since this blood is on the flat part of the curve with the alveolar oxygen pressure at perhaps 16 or 18 per cent of an atmosphere. The under-ventilation, on the other hand, will leave the venous blood nearly venous and on the steep part of the oxyhaemoglobin curve, with a large deficiency of oxygen. The mixed arterial blood will, therefore, be seriously deficient in oxygen, and symptoms of anoxaemia will consequently be produced. As one of these symptoms is increase in the breathing, there will be some compensation, and the CO_2 percentage of the mixed alveolar air will fall somewhat, there being a corresponding rise also in the oxygen percentage, as was actually found in our experiments.

There is thus a very complete explanation of our experimental results, and also of the symptoms of anoxaemia in the neurasthenic cases; but clearly it is necessary to modify radically the idea that the alveolar oxygen pressure gives the oxygen pressure of the mixed arterial blood. We have no guarantee that even during quite normal breathing the distribution of air in the individual lung alveoli corresponds exactly with the distribution of blood to them. Unless this correspondence is exact some alveoli will receive more air in proportion to their blood supply than others, and as a consequence the mixed arterial blood will be a mixture of more and less fully arterialized blood, with some of the consequences first discussed. It is probable indeed that in some way or other the air supply is proportioned to the blood supply, whether by regulation through the muscular coats of the bronchioles or regulation of the blood distribution; but it is also certain that this proportioning is only an approximation. The fact that in animals the aërotonometer gives a lower arterial oxygen pressure than the alveolar oxygen pressure (Chapter IX) is most

naturally explained on the theory that the proportioning is only approximate, and there are various other facts which point in the same direction.

One of these facts is as follows. When the breathing is suddenly interrupted voluntarily the breath can be held for a certain time—usually about 40 seconds if only an ordinary breath is inspired before the interruption. Leonard Hill and Flack[3] discovered, however, that if the lungs are filled with oxygen first the breath can be held for two or three times longer; also that the alveolar CO_2 percentage is considerably higher at the breaking point. On the other hand, when the same air was rebreathed continuously from a small bag filled at the start with a breath of alveolar air, the alveolar CO_2 percentage went as high as when the breath was held with oxygen, though not so high as when oxygen was rebreathed from the bag. The following table, illustrating these results, is taken from Hill and Flack's paper.

It was difficult, at the time, to interpret these results satisfactorily, since the alveolar oxygen percentages, when the breath was held after breathing ordinary air, did not seem to be low enough to stimulate the breathing appreciably. In order to obtain still more definite information Douglas and I repeated the observations, but in such a way as to have great variations in the alveolar oxygen percentage.[4] We then found that the beneficial effects of increasing the alveolar oxygen percentage were still evident, though to a diminishing extent, till 17 per cent of oxygen was present in the alveolar air. Oxygen in excess of this made no difference. But 17 per cent is 3 per cent more than what is present in normal alveolar air; and, as we have already seen, there are no effects on the breathing from want of oxygen when ordinary air is breathed by normal persons, or even when the oxygen percentage of the alveolar runs down to 10 or even 8 per cent. The results were therefore very mysterious at the time, and we were compelled to adopt the improbable hypothesis that holding the breath has some considerable effect on the circulation in the brain, leading to anoxaemia of the respiratory center. There is, however, no reason whatever to expect such an effect.

The experiments on shallow breathing have furnished the solution to this mystery. It is evident that the relation between blood supply and ventilation in individual groups of alveoli is not an even one. In some alveoli the oxygen runs down and CO_2

[3] Leonard Hill and Flack, *Journ. of Physiol.*, XXXVII, p. 77, 1908.
[4] Douglas and Haldane, *Journ. of Physiol.*, XXXVIII, p. 425, 1909.

Subject	*After holding breath*		*Time held in seconds*	*After three breaths of oxygen*		*Time held in seconds*	*Breathing expired air from bag*		*Time in seconds*	*Breathing oxygen from bag*		*Time in seconds*
	CO_2	O_2		CO_2	O_2		CO_2	O_2		CO_2	O_2	
F. H. R.	6.32	9.65	32	7.06	excess	72	8.22	8.39	80	8.77	43.86	165
L. H.	6.87	9.02	25	7.58	35.93	65	7.80	5.11	—	10.70	41.82	330
M. G.	6.82	9.08	40	8.25	44.33	130	7.96	—	—	10.16	excess	250
M. F.	7.31	9.23	35	8.01	31.60	55	—	8.36	100	10.01	34.56	240
H. N.	7.70	9.28	40	8.07	excess	90	7.82	4.40	125	10.29	32.89	255

accumulates faster than in others. Hence in some the blood is less perfectly oxygenated; and if the breath is held for a time this imperfect oxygenation becomes more and more marked till at last the mixed arterial blood is very considerably short of oxygen, just as when the breathing is very shallow. Hence the oxygen percentage of the mixed alveolar air becomes altogether deceptive as an index of the degree of oxygenation of the mixed arterial blood, although the CO_2 percentage remains, for the reasons already given, a reliable index of the degree of saturation of arterial blood with CO_2. The results of these experiments on holding the breath are thus very valuable as furnishing evidence that, even with normal or increased inspirations, the relation between blood supply and air supply varies considerably in different alveoli.

That the arterial blood does actually become imperfectly oxygenated when the breath is held has been quite recently demonstrated by Meakins and Davies.[5] They found that on holding a deep breath of air for 40 seconds, the haemoglobin of the arterial

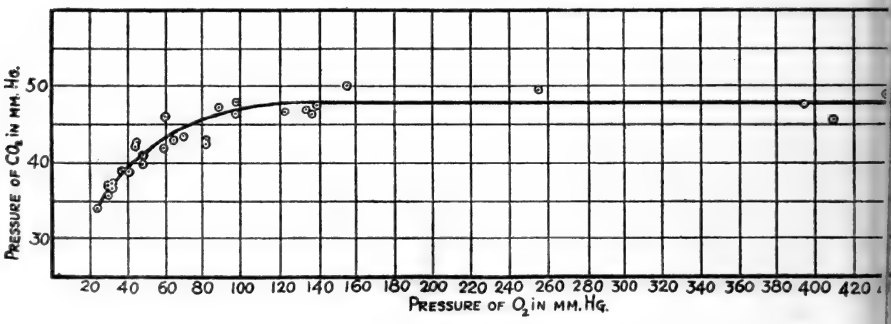

Figure 46.

Alveolar CO_2 during breath holding after inhalation of oxygen.

blood drawn from the radial artery was only 83.8 per cent saturated with oxygen, although the mixed alveolar air contained 13.4 per cent of oxygen. Had air of this composition been distributed evenly throughout the alveoli the haemoglobin would have been 97 per cent saturated with oxygen.

A further series of experiments which Douglas and I performed is very instructive in this connection. As already mentioned in Chapter V, the alveolar CO_2 percentage rises high above its normal value before the end of an apnoea after forced breathing with extra oxygen. We observed how high the alveolar CO_2 pressure went when there were varying pressures of oxygen in the

[5] Meakins and Davies, *Journ. of Pathol. and Bacter.*, XXIII, p. 451, 1920.

mixed alveolar air at the end of the apnoea produced by two minutes of forced breathing, and the results are plotted in Figure 46.[6] It will be seen that the CO_2 pressure (and of course also the length of the apnoea) rises with the alveolar oxygen pressure until the latter reaches about 120 mm. (corresponding to about 17 per cent of oxygen in the dry alveolar air), beyond which a further rise in alveolar oxygen pressure has no effect. In this case the oxygen pressure in all the lung alveoli would be at a more or less equal high level at the beginning of an apnoea, but would fall at unequal rates in the different alveoli. Accordingly at the end of apnoea the mixed arterial blood would be getting venous unless the average alveolar air contained more than 17 per cent of oxygen. And yet as little as 8 per cent would be enough to prevent this effect if the air was evenly distributed in relation to the blood supply of the alveoli, or if respiratory movements prevented anything more than comparatively slight variations in the oxygen percentages in different alveoli.

Judging from aërotonometer experiments on normal animals, and from direct determinations on human arterial blood, the haemoglobin of average human arterial blood is only about 94 to 96 per cent saturated with oxygen—about 2 per cent less than if the whole arterial blood was saturated to the oxygen pressure of the mixed alveolar air. A very accurate series of determinations described by Meakins and Davies in the paper just quoted showed that in different healthy persons the saturation varies from 94 to 96 per cent. The slight variations seem to be due to the variations which Barcroft described in the oxyhaemoglobin dissociation curves of different individuals.

The periodic breathing produced by shallow breathing differs strikingly from the periodic breathing produced by anoxaemia in normal persons. As will be seen from Figure 44, the periods are much longer, and in this respect bear a striking resemblance to ordinary clinical Cheyne-Stokes breathing. The reason why the periods are longer is evident enough: for the shallow breathing is very ineffective in raising the oxygen percentage in the badly ventilated parts of the lungs and so relieving the anoxaemia. The relief thus comes slowly. The breathing, therefore, "waxes and wanes" gradually, as in clinical Cheyne-Stokes breathing. In hibernating animals similar breathing is often observed and can be explained in the same way, as, owing to the small production of CO_2, the breathing is very shallow.

[6] Douglas and Haldane, *Journ. of Physiol.*, XXXVIII, p. 401, 1909.

Ordinary clinical Cheyne-Stokes breathing is evidently a symptom of anoxaemia due often to the shallow breathing which characterizes a failing respiratory center. This failure may be that of approaching death, since the anoxaemia itself tends to hasten the failure of the center, as already explained in Chapter VI. There is thus a vicious circle which, unless broken in some way, must end in death from anoxaemia, just as in the case of an airman at a dangerously high altitude. The color of the lips, in conjunction with the diminishing depth of the breathing, points clearly to what is happening.

It is now evident that the anoxaemia so often present in disease, but so seldom recognized as such, is due in a large number of cases to the shallow breathing characteristic of a damaged or "fatigued" respiratory center, whatever the original cause of the damage or fatigue may be. It is also evident that frequency of breathing has assumed a significance which it did not previously possess, since frequency is very often an index of shallowness of breathing, damage to the respiratory center, and consequently impending danger from anoxaemia. The frequent and shallow breathing in surgical shock, or in various forms of influenza and pneumonic conditions, or as it may occur in many other forms of disease, is a symptom of which the possible deadly import will be evident enough to those who have read the preceding chapter in connection with what has just been said. In this connection I should like also to emphasize the fact that, as fully explained in the last chapter, it is unsafe to judge of the degree of anoxaemia by the degree of cyanosis. The anoxaemia is, and must be, accompanied by alkalosis, so that the oxyhaemoglobin holds on more tightly to its oxygen, and this alkalosis may become extreme with very shallow and rapid breathing.

Chronic fatigue or failure of the respiratory center is seen in neurasthenia and various other forms of disease; but failure of the respiratory center may also occur in acute and sudden attacks, which are often associated, either primarily or secondarily, with anginal pain. The patient may feel that he cannot expand his chest to breathe, just as if it were mechanically constricted; and he rapidly develops asphyxial symptoms, with very frequent and shallow breathing. In reality, apparently, he is in the grip of the Hering-Breuer reflex, which, as explained in Chapter III, assumes exaggerated influence, owing to the failure of the respiratory center. These attacks, though they usually pass off, are sometimes very dangerous; and many sudden deaths appear to be due to

them. They are specially liable to occur at night. The rapid breathing is apt to produce the impression in a physician that it is the heart and not the breathing, that has failed; and this impression may be apparently confirmed by the presence of secondary anginal pain. In all doubtful cases, the effects of properly administering oxygen will decide the diagnosis. If the immediate cause of the symptoms is failure of the respiratory center, the effects of the oxygen are rapid and prompt, and have been so in cases which have chanced to come under my own observation.

It is evident that anoxaemia caused by irregular distribution of oxygen among the lung alveoli may be due to a variety of causes. One of these is emphysema; for the emphysematous parts of a lung will naturally be supplied with far more than the proper proportion of air to suit their greatly diminished respiratory surface, while the other parts will receive correspondingly less air. The arterial blood will thus be a mixture of over-arterialized

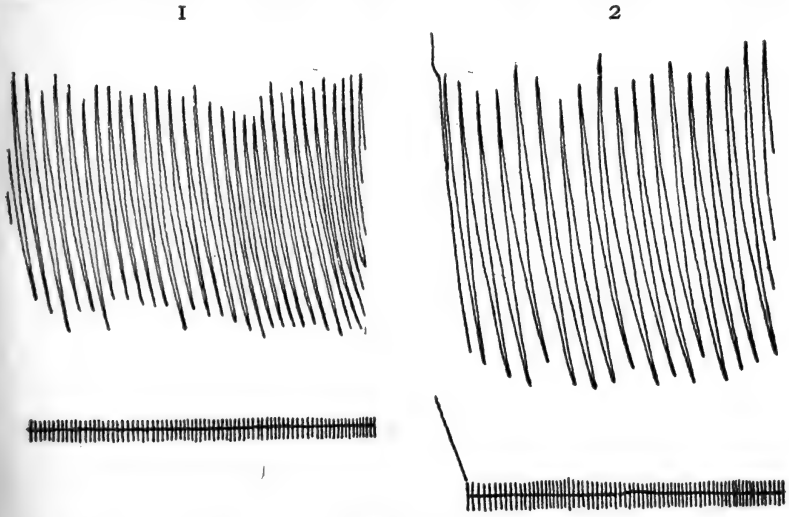

Figure 47.
Subject J. S. H. Rebreathing in and out of 50 liter cylinder. Time marker = 2 seconds. 1. Sitting. 2. Lying.

and under-arterialized blood, with resulting anoxaemia, which may or may not be compensated by one or other of the processes to be described in succeeding chapters.

Another cause of the same general character is bronchitis or asthma. The irregular partial blocking or muscular constriction of the bronchi and bronchioles in these conditions must lead to

irregular distribution of fresh air to the alveoli, even though the average distribution, as shown by the volume of air breathed, is greatly increased. Hence the mixed arterial blood will be deficient in oxygen, and grave anoxaemia may develop. Here, also, the effects of oxygen administration will decide the diagnosis of the condition.

We found that the recumbent position greatly favors the development of periodic breathing, and therefore of anoxaemia. We also found that when a normal person assumes the recumbent position, the usual result is that the breathing becomes slower and deeper. In my own case, for instance, the frequency diminishes from about 15 in the sitting or upright position to 7 or 8, while the depth correspondingly increases, so as to keep the alveolar CO_2 pressure nearly the same (see Figure 47). The cause of this phenomenon is not altogether clear, but is probably the increased resistance thrown on the diaphragm in the recumbent position, as the weight of the liver and other abdominal organs assists the descent of the diaphragm in the upright position. Röntgen ray

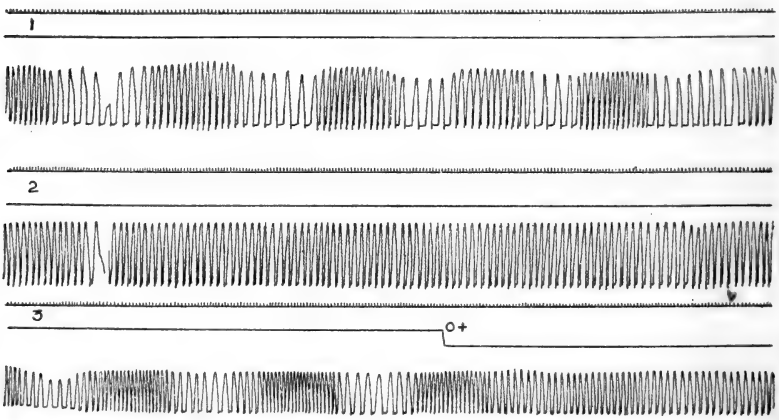

Figure 48.

Subject J. G. P. 1. Breathing restricted by concertina—lying. 2. Breathing restricted to same extent—sitting. 3. Breathing further restricted—sitting. Oxygen given. Curves read left to right. Inspiration upstroke. Time marker = seconds.

photographs which we took to show the position of the diaphragm favored this explanation; and, assuming it to be correct, the effect of the recumbent position may well be similar to the slowing effect produced by resistance as shown in Chapter III. Whatever

the cause of the natural increased depth may be, it is evident that in the recumbent position the tendency to irregular distribution of fresh air in the lung alveoli with any given depth of breathing is much increased, so that anoxaemia from this cause, as shown in normal persons by periodic breathing, is much more readily produced. In my own case periodic breathing is rapidly produced in the recumbent position when the breathing is kept at over 20 per minute by artificially limiting the depth by means of our apparatus, whereas in the upright position there is no such effect. The effect of the recumbent position is shown in Figure 48.

We have thus a simple explanation of a phenomenon which has been familiar to physicians since early times, but which has hitherto never been satisfactorily explained. When patients are

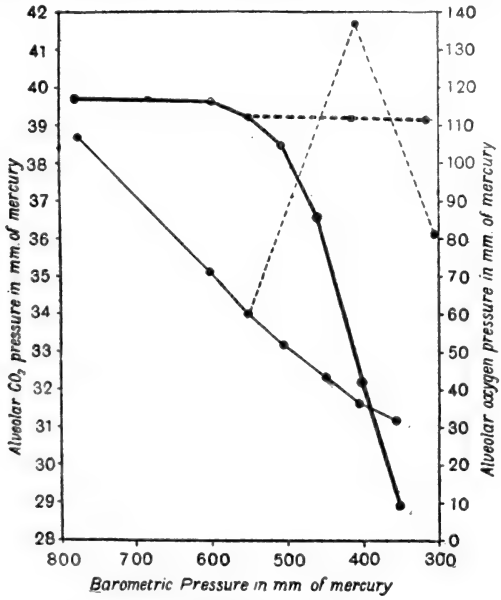

Figure 49.

Effects of diminished barometric pressure on the alveolar gas-pressures. The thick lines show the alveolar CO_2 pressure, and the thin lines the alveolar O_2 pressure. The dotted lines refer to the experiment in which oxygen was added to the air.

short of breath during illness they are often very uncomfortable in the recumbent position, and may become dangerously worse if not propped up in bed or in a chair. This condition is known as

orthopnoea, and its causation now seems evident. With a failing respiratory center, and consequent abnormal shallowness of respiration, anoxaemia is the natural result of the recumbent position; and the prevention of this anoxaemia by keeping the patient in a sitting position becomes an important part of treatment unless the same object is attained by oxygen administration.

Defective distribution of air in the lung alveoli is, of course, only one of the causes of defective oxygenation of the arterial blood; but I have dealt with this cause first, not only because it is of very great importance in medicine, but because an understanding of it is essential to the understanding of other causes of defective oxygenation.

A second and hitherto much better known cause of defective oxygenation of the arterial blood is a deficiency in the partial pressure of oxygen in the inspired air, and consequent fall in the alveolar oxygen pressure. As shown in Chapter II, it usually requires a fall in oxygen percentage from the normal of 20.9 to about 14 per cent, or a third, before any evident effect on the breathing is produced at the time by the oxygen deficiency. Similarly a fall of about a third in barometric pressure (corresponding to about 11,500 feet above sea level) is required. Figure 49, from a paper by Boycott and myself,[7] shows that until the barometric pressure in a steel chamber falls by about a third, the normal alveolar CO_2 pressure is very little disturbed. The alveolar CO_2 percentage simply goes up as the barometric pressure goes down, but the pressure of CO_2 remains almost the same in the alveolar air. In the same investigation we found that even when the barometric pressure was reduced to 300 mm. the alveolar CO_2 pressure remained the same, provided that any excessive fall in the oxygen pressure of the inspired air was prevented by adding oxygen to the air of the chamber. There is thus no trace of foundation for Mosso's contention[8] that the diminished mechanical pressure of the air produces by itself a diminished saturation of the blood with CO_2.

Since the alveolar air, with the breathing normal, contains about a third less oxygen than the inspired air, it follows that when the oxygen percentage or partial pressure in the inspired air is reduced by a third the alveolar oxygen percentage will be reduced to about half—i.e., from about 13 per cent of an atmosphere to about 6.5 per cent. On comparing this with the dissociation curve of oxyhaemoglobin it will be seen that such a diminution corresponds

[7] Boycott and Haldane, *Journ. of Physiol.*, XXXVII, p. 355, 1908.
[8] Mosso, *Life of Man on the High Alps*, London, p. 287, 1898.

to a saturation of about 80 per cent of the haemoglobin with oxygen, and that any further diminution will cause a rapid fall in the saturation. The air produces at the time no noticeable discomfort, and the breathing is not sensibly affected, although the lips are slightly bluish. The natural conclusion is that a diminution of about 15 per cent in the saturation of the haemoglobin, or a diminution to half in the arterial oxygen pressure, is of no physiological importance, even though the lips are rather dull in color. This wholly mistaken idea is, however, rudely shaken by the effects of remaining for a sufficient time in the atmosphere: for the observer will be almost certainly prostrated by an attack of mountain sickness which he is never likely to forget afterwards.

If, now, in order to escape mountain sickness, the pressure of oxygen in the inspired air is only diminished by one-seventh (corresponding to a height of 4,500 feet; or an oxygen percentage of 17 at ordinary atmospheric pressure), there will be no appreciable blueness, and the corresponding saturation on the oxyhaemoglobin dissociation curve will be only 3.5 per cent below that for normal alveolar air. Nevertheless there will, if sufficient time is given, be quite appreciable physiological responses, which will be discussed in succeeding chapters. The truth is that in the long run the body responds in a fairly delicate manner to quite small diminutions in the oxygen pressure of the inspired air.

Let us now look at the matter in the light of the new knowledge as to the somewhat imperfect manner in which air is distributed in the alveoli. In the course of our investigation on military neurasthenia, we placed several of the patients in a steel chamber and observed the effects of diminished pressure. A very slight diminution, corresponding to only about 5,000 feet, was sufficient to produce in them urgent respiratory and other symptoms, although they were doing no work. Even in normal persons the dissociation curve of oxyhaemoglobin and composition of the mixed alveolar air are, as was shown above, no certain guides to the percentage saturation of the haemoglobin, or oxygen pressure in the mixed arterial blood. As a matter of fact the blueness of the lips seen in persons freshly exposed to very low atmospheric pressure seems to be often much greater than would correspond to the oxygen pressure in their alveolar air when due allowance is made for the Bohr effect of lowered alveolar CO_2 pressure. We may thus be quite sure that at diminished atmospheric pressure the saturation of the mixed arterial blood with oxygen is or may be distinctly lower than corresponds to the oxygen pressure of the alveolar air.

Poulton and I found that when a small quantity of air—about 6 liters—was rebreathed continuously up to the verge of loss of consciousness, the CO_2 being completely absorbed by soda lime, the inspired air contained only 4.8 per cent of oxygen, and the alveolar air 3.7 per cent. There was very great hyperpnoea; for the preformed CO_2 had not had time to escape in the manner already referred to in Chapter VI. The respiratory quotient of the alveolar air was as high as 2.8. The experiment was then repeated with a large volume of air, and under such conditions that the oxygen percentage only fell very slowly. The lowest percentage of oxygen that could now be reached in the inspired air without great confusion of mind was about 9.4, with about 4.6 per cent (or 33 mm.) in the alveolar air. There was no noticeable hyperpnoea, and the respiratory quotient was normal. The alveolar CO_2 percentage was only reduced from the normal of 5.7 per cent to 4.6, indicating that the alveolar ventilation was only increased by about a fourth.

From these experiments we may conclude that air containing less than 9.5 per cent of oxygen would ordinarily cause disablement within half an hour. At a barometric pressure of 368 mm., or a little less than half an atmosphere, corresponding to about 20,500 feet above sea level, there would be a corresponding drop in the alveolar oxygen pressure; but judging from my own observations the physiological effects are very distinctly less severe. This is probably due to the fact that in rarefied air the diffusion of oxygen within the lung alveoli is much more free than at atmospheric pressure.[9] As a rule no very serious symptoms are experienced at the time till the barometric pressure has fallen to about 350 mm. (corresponding to 21,500 feet) ; but in this respect different individuals vary considerably. It must also be borne in mind that nervous symptoms of anoxaemia begin to appear at altitudes not nearly so great. At 320 mm. (about 24,000 feet) most persons, including myself, are soon very seriously affected in the manner described in Chapter VI, unless they are acclimatized.

Another cause of imperfect oxygenation of the arterial blood is that there may not be sufficient time for the required quantity of oxygen to pass into the blood through the alveolar epithelium. This cause of anoxaemia came into prominence in connection with the effects of lung-irritant poison gas during the war. It was evident from the first cases which I saw in April, 1915, that there was

[9] Haldane, Kellas, and Kennaway, *Journ. of Physiol.*, LIII, p. 195, 1915.

acute anoxaemia due to imperfect oxygenation of the arterial blood. There were the ordinary chlorine symptoms of acute bronchitis, alveolar inflammation, and oedema of the lungs. The faces of the patients were deeply cyanosed, in spite of considerably increased breathing of adequate depth. At first it was suspected that the cyanosis was due to "toxaemia," causing the formation in the blood of methaemoglobin or some similar dark-colored decomposition product; but on diluting a drop of the blood, saturating with CO, and comparing the solution with the tint of similarly treated normal blood, I found that there was no abnormal pigment present, so that the blue color was due simply to anoxaemia. That this anoxaemia was, in the main at least, due to delay in the passage of oxygen into the arterial blood was then confirmed by the fact that on administering oxygen the blue color changed to red, and the patients improved in other respects. It was evident that with the greatly increased partial pressure of oxygen in the alveolar air, the oxygen was able to pass into the blood at a sufficient rate to saturate or nearly saturate the blood, and thus maintain life. The delayed passage was probably due mainly to the fact that the alveolar walls were swollen and oedematous, so that they did not allow oxygen to pass inwards at a normal rate. As will be pointed out in Chapter IX, this condition was produced experimentally in animals by Lorrain Smith. The distribution of air in the lung alveoli was doubtless also gravely interfered with by the bronchitis and emphysema caused by the actions of chlorine, though at the time I was ignorant of the importance of this cause. To judge by the increased breathing there was also much disturbance in the excretion of CO_2 by the lungs; and the great distention of the veins and other signs in the chlorine cases pointed in this direction also.

In the cases of poisoning by phosgene and other lung irritants used later, the symptoms of irritation of the air passages were much less prominent. The general symptoms corresponded more closely with those of pure anoxaemia. This was particularly true in the earlier seen, or less severe, cases, when there was no evident oedema of the lungs. Thus, at first, the symptoms of acute anoxaemia were shown only on muscular exertion sufficient to cause a greatly increased need for oxygen; and some of the men who were apparently at the time only slightly affected lost consciousness or died as a result of muscular exertion. Others suffered only from general malaise or symptoms similar to those of mountain sickness, and apparently due to slight anoxaemia. In

the graver cases the anoxaemia was usually unaccompanied by distention of the lips and veins with blood, and the cyanosis was thus of the leaden or gray type, just as in cases of slowly advancing anoxaemia from other causes. In death from gradual CO poisoning, for instance, there is no extra distention of the lips or veins with blood, although, of course, the lips are not gray but light pink. Death, in the phosgene cases and probably in others, seems to have been finally due to failure of the respiratory center, the breathing becoming more and more shallow till the resulting increase in the anoxaemia ended in death. Orthopnoea was a very common symptom so long as the men were conscious.

In favorable cases of ordinary croupous pneumonia the lips remain of a good color, and there are no evident signs of anoxaemia; but the breathing is rapid, and correspondingly shallow. The danger of anoxaemia is therefore not far off. At Cripple Creek (at an altitude of about 10,000 feet) I was told that cases of commencing pneumonia were at once put on the train and sent down to the prairie level, as it had been found that they had a very poor chance if treated locally. This indicates the danger from anoxaemia, and led us, in the Report of the Pike's Peak Expedition, to advocate the use of chambers containing air enriched with oxygen for treating pneumonia. The fact that there is often no cyanosis in spite of very extensive lung consolidation seems to show that the pulmonary circulation has practically ceased in the consolidated areas. The blood supply of these areas may be solely through the bronchial arteries, the high-pressure supply from which joins the pulmonary circulation. This inference has recently been confirmed by Gross,[10] who found by means of X-ray photographs of lungs injected with an injection mass opaque to X-rays, that the pulmonary vessels are nearly blocked off in the consolidated parts in pneumonia. In the unaffected parts of the lungs, the oxygen seems to penetrate the alveolar walls readily enough in pneumonia. Where anoxaemia becomes dangerous in croupous or disseminated pneumonia it seems usually to be failure of the respiratory center and consequent shallow breathing that is mainly responsible for the anoxaemia.

The fact that in pneumonias of all kinds the arterial blood is commonly more or less imperfectly saturated with oxygen has quite recently been shown directly by Stadie,[11] who examined

[10] Gross, *Canadian Med. Assoc. Journ.*, p. 632, 1919.
[11] Stadie, *Journ. of Exper. Med.*, XXX, p. 215, 1919.

samples of arterial blood drawn usually from the radial artery by means of a syringe. In normal persons he found an average of 95 per cent saturation of the haemoglobin with oxygen; and this is about what might be expected in view of what has been said above. In cases of pneumonia the saturation varied from 95 to 42 per cent; and as a rule the cases where the saturation was below 76 per cent ended fatally. Cardiac cases were soon afterwards investigated by Harrop,[12] who found that in many of them there was imperfect saturation of the arterial blood. This was almost certainly due, frequently, to partial failure of the respiratory center and consequent shallow breathing.

The significance of these analyses will be evident from what has been said in the previous and present chapters; and the danger to a patient of permitting any serious arterial anoxaemia to continue when it can be prevented is, I hope, already evident.

As anoxaemia is such a common and often dangerous condition, and can frequently be combated by the addition of oxygen to the inspired air, it will be in place to refer here to clinical methods of administering oxygen. In the first place it is necessary to have clear ideas as to the objects aimed at, in administering oxygen. If the oxygen is only given to enable a patient to surmount some quite temporary crisis due to anoxaemia—produced, it may be, by one of the sudden angina-like attacks of reflex restriction of breathing referred above—a very simple method of administration will suffice. A small cylinder of oxygen furnished with an india-rubber tube by means of which a stream of oxygen may be directed into the patient's open mouth will suffice; and such an arrangement would probably often be useful in certain cases, as the oxygen could be given promptly by a competent nurse at any time.

In the great majority of cases, however, the cause of the anoxaemia is one which may last for a considerable time, so that the administration of oxygen, in order to be useful, must be continued. In this connection it should be clearly realized that the object of the oxygen administration is not simply palliative, but curative. By preventing the anoxaemia we not only avert temporarily a cause of danger or damage to the patient; but give the body an interval for recovery from the original cause, whatever it may be, of the anoxaemia, or for adaptation. We also break a vicious circle: for if the anoxaemia is allowed to continue, it will itself make the patient worse, or tend to prevent the recovery which would otherwise naturally occur. We are not dealing with

[12] Harrop, *Journ. of Exper. Med.*, XXX, p. 241, 1919.

a machine, but with a living organism; and a living organism always tends to return to the normal if the opportunity is given.

Oxygen is still often given by methods which are either quite ineffective or extremely wasteful. One method is to place a funnel over the patient's face, and allow some quite indefinite amount of oxygen to pass into the funnel. By this method the patient rebreathes a good deal of expired air, but may hardly get any of the oxygen, as the latter, being heavier, runs out below. A far better method is to insert a rubber catheter or other soft tube into the patient's mouth or nose, and pass a stream of oxygen through the tube. Another good method, when pure oxygen has to be given, is to allow the oxygen to pass at a sufficient rate into a rubber bag connected with the inspiratory valve of an anaesthetic mask placed over the patient's mouth and nose. The patient inhales from the bag, and exhales to the outside through the expiratory valve in the mask.

In ordinary cases the patient does not require pure oxygen, but only a sufficient addition to the air of oxygen to prevent the anoxaemia. In any case it would be very undesirable to continue the administration of pure oxygen for more than a limited time, as pure, or nearly pure, oxygen has a slow irritant action on the lungs, as will be shown in Chapter XII. If the mask is left open to the air, so that the patient can breathe as much air as he likes, and a stream of oxygen is allowed to pass into the mask directly, the oxygen which passes in during expiration is of course wasted.

It became evident during the war that an efficient apparatus for the continuous administration of oxygen with maximum economy in oxygen was greatly needed, particularly in the treatment of acute cases of poisoning by lung-irritant gas. I therefore devised an apparatus so arranged that by a simple device the patient inspired through a face piece the whole of the added oxygen, without waste during expiration, while the proportion of oxygen could easily be cut down or increased, according as was needful. The original form of this apparatus was described in the *British Medical Journal,* February 10, 1917, page 181, after it had already been supplied extensively to the army in France. Its use there for gas cases was initiated, and the managment of it carefully investigated, by Lieutenant Colonel C. G. Douglas of Oxford. Other well-known medical officers also made very valuable observations on the effects of oxygen inhalation. The results, particularly in gas cases, were strikingly successful; and practically continuous administration could easily be carried out over the two or three

days during which there was danger from anoxaemia. Patients can sleep comfortably during the administration.

The apparatus was afterwards simplified, with the special object of making it both easy for a nurse to handle, and available for front line and stretcher work, including treatment of "shock" cases. Figure 50 shows the arrangement of the apparatus. It consists of: (1) an oxygen cylinder provided with an easily worked

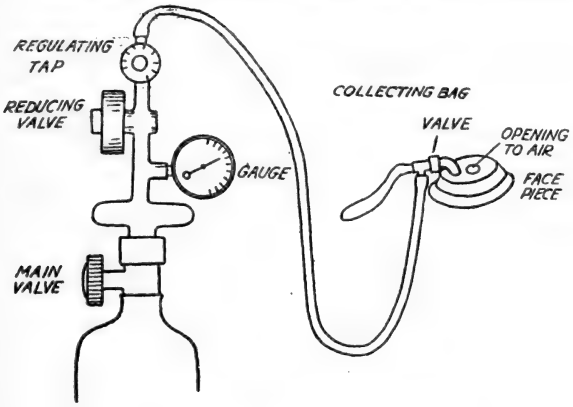

Figure 50.
Apparatus for administering oxygen.

and efficient main valve; (2) a pressure gauge showing how much oxygen is in the cylinder; (3) a reducing valve which reduces the pressure to a small amount which remains constant till the cylinder is exhausted; (4) a graduated tap indicating the flow of oxygen in liters per minute; (5) thick-walled rubber tubing conveying the oxygen to the patient and a light rubber bag; (6) a face piece with a minimum of dead space, and provided with elastic straps and a pneumatic cushion which can be taken off for disinfection.

The patient can inspire and expire freely through an opening in which there is a rubber flap to cause a very slight resistance. During expiration the oxygen collects in the bag, and is sucked into the face piece at the beginning of inspiration. From the movements of the bag it can be seen at any time whether the patient is receiving the oxygen. To put the apparatus in action the main valve is opened freely, and the tap is adjusted to give 2 liters a minute or whatever greater or less amount suffices. With a delivery of 2 liters a minute a 40-foot cylinder would last nearly ten hours.

The effects of continuous oxygen inhalation with this apparatus on the arterial blood in pneumonia and bronchitis have quite recently been investigated by Meakins.[13] He found that with 2 liters a minute the percentage saturation of the haemoglobin in a pneumonia case with almost complete consolidation of one lung rose from 82 per cent to 91 per cent, but went back on stopping the oxygen to 84 per cent, slight cyanosis returning also. On then giving 3 liters a minute, the saturation rose to 97 per cent, which is 2 per cent above the normal value for healthy persons. In a bronchitis case with slight cyanosis and orthopnoea, the saturation rose from 88.6 to 97.0 per cent on giving 2 liters a minute, and the cyanosis and orthopnoea disappeared. In a normal man the saturation rose from 95.6 to 98.1 on giving 2 liters a minute.

The plan of treating patients in an air-tight chamber containing a high percentage of oxygen was introduced towards the end of the war at Cambridge under Barcroft's direction;[14] and a similar chamber was erected at Stoke-on-Trent. Favorable results were obtained in chronic cases of gas poisoning, as might be anticipated in view of the disturbed nervous control of breathing, already described in Chapters III and VII. It now seems evident that the administration of air enriched with oxygen is likely to be successfully introduced in the treatment of various illnesses in which arterial anoxaemia is present.

During considerable muscular exertion the rate at which oxygen has to penetrate from the alveoli into the blood is enormously increased. Hence it is during muscular work that we should expect to find any signs of anoxaemia in healthy persons breathing normal air at normal atmospheric pressure. That a certain amount of anoxaemia is commonly produced can be shown indirectly in various ways. In the first place the alveolar CO_2 pressure, particularly in some persons, does not rise during muscular exertion in the proportion that would be expected if the increased breathing were simply due to the increased production of CO_2 and consequent rise in the alveolar CO_2 pressure. Thus in the experiments of Priestley and myself, my own alveolar CO_2 pressure rose only by .13 per cent, in place of an expected rise of about .8 per cent, if the increased breathing had been due to CO_2 alone; while in the case of Priestley (who was in much better

[13] Meakins, *Brit. Med. Journ.*, March 5, 1920. A number of further cases have still more recently been recorded by Meakins, *Journ. of Pathol. and Bacter.*, XXIV, p. 79, 1921.

[14] Barcroft, Dufton, and Hunt, *Quarterly Journ. of Medicine*, XIII, p. 179, 1920.

physical training than I was) the rise was .44 per cent in place of an expected rise of about .56. I have since then frequently found that my alveolar CO_2 pressure does not rise appreciably with muscular exertion, and falls if the exertion is very great; though in younger men there is almost always a marked rise, as in the experiments on Douglas, mentioned in Chapter II. The absence of a rise in me when ordinary air is breathed is not due to the formation of lactic acid referred to in Chaper VIII. I found in 1917, however, that there is a well-marked rise when a little oxygen is added to the inspired air. The failure of my alveolar CO_2 to rise was therefore due apparently to slight anoxaemia during muscular exertion.

It has for long been well known to engineers that men perform hard physical work more easily when they are working in compressed air. This was very evident, for instance, during the work on the Blackwall tunnel under the Thames, which I visited about 25 years ago. At the existing air pressure the alveolar oxygen pressure would have 3½ times its normal value. In breathing nearly pure oxygen while wearing a mine rescue apparatus, I share the very common experience, that in spite of the weight of the apparatus, heavy exertion, such as walking very fast, is much easier. On the other hand, even a very moderate increase in altitude increases considerably the panting on exertion.

Some years ago Hill and Flack[15] published a number of observations on the apparent effects of oxygen before and after muscular exertion. Many of their observations were concerned with very striking effects, already referred to, of oxygen in prolonging the time during which the breath can be held. They showed that this effect is just as marked when exertion is performed with the breath held as during rest. They also found that oxygen given during the distress immediately following severe exertion has a distinct effect in raising the blood pressure, improving the pulse, and alleviating the distress. This indicates that a raised partial pressure of oxygen in the alveolar air increases the oxygenation of the blood, and that part of the distress caused by severe muscular work is caused by deficient oxygenation of the arterial blood. I am unable to agree, however, with their further conclusion that when oxygen is breathed a large amount of free oxygen is stored in the blood and tissues, and that for this reason a man who has breathed oxygen for a time has a distinct physio-

[15] Hill and Flack, *Journ. of Physiol.*, XXXVIII, *Pro. Physiol. Soc.*, p. xxviii, 1909; and XL, p. 347, 1910.

logical advantage as regards performance of work over a man who has simply breathed air. Douglas and I found[16] that if oxygen is breathed quietly before an exertion there is no physiological advantage if the breath is not held. The extra oxygen in the lungs is quickly washed out by the breathing, and there is nothing to indicate the existence of any other extra store of oxygen in the body. If, however, the breathing is forced before the exertion, there is considerable advantage whether air or oxygen is breathed during the forced breathing; and this advantage is due simply to washing out of CO_2. As will be shown in Chapter XII, the tissues and venous blood cannot become highly saturated with oxygen when this gas is simply breathed at ordinary atmospheric pressure; and if oxygen had any appreciable effect apart from that due to the actual presence of an increased percentage of oxygen in the lungs the result would be very unintelligible.

A clear and striking light has been thrown on this subject by some recent experiments by Dr. Henry Briggs.[17] He found that when equal work is done on a Martin's ergometer the percentage of CO_2 in the expired air is, in persons not in good physical training, considerably higher when air rich in oxygen is breathed than when ordinary air is breathed. In persons in the best physical training, on the other hand, there is practically no difference until the work done is very excessive. The following table is from his paper. Subject A was out of training, and Subject B in good training.

Work in foot pounds per minute Pedaling with brake off	PERCENTAGE CO_2 IN EXPIRED AIR			
	Subject A		*Subject B*	
	Breathing air	*Breathing oxygen*	*Breathing air*	*Breathing oxygen*
	3.9	4.1	4.4	4.5
3,000	4.65	5.25	5.3	5.45
6,000	4.7	5.8	6.2	6.2
9,000	4.3	5.8	6.1	6.3
10,000	4.1	5.7	6.0	6.2
12,000	—	—	5.6	6.0

[16] Douglas and Haldane, *Journ. of Physiol.*, XXXIX, *Proc. Physiol. Soc.*, p. i, 1909.

[17] Briggs, Henry—Fitness and breathing during exertion, *J. Physiology*, Vol. 53, 1919-1920, *Proc. Physiological Soc.*, p. 38-40.

The reason why anoxaemia is absent in persons who are in good training will be discussed in Chapter IX.

There can be little doubt, in view of all the evidence adduced above, that muscular work produces some degree of anoxaemia in untrained persons, and that the anoxaemia increases with the work. The anoxaemia can hardly be due to any other cause than

LITERS GAS INSPIRED PER MINUTE

Subject A		*Subject B*	
Breathing air	*Breathing oxygen*	*Breathing air*	*Breathing oxygen*
12	13	14	11
25	22.5	20	18
40	33	27	27
54	43	37	37
57	46	40.5	40.5
—	—	50	48

that the blood is passing through the lungs so quickly that sufficient oxygen to saturate the haemoglobin has not time to pass in through the alveolar epithelium, just as occurs to a far greater extent even during rest in a case of phosgene poisoning.

Another possible explanation might perhaps suggest itself, and seems, indeed, to be suggested in Chapter XI of Mr. Barcroft's book, "The Respiratory Functions of the Blood." This is that the velocity of the chemical reaction, which occurs when haemoglobin comes into contact with oxygen at a certain partial pressure of oxygen, is so low that there is not time for the change to complete itself in the lungs during muscular exertion. The rate at which haemoglobin takes up oxygen, or oxyhaemoglobin gives it off, in presence of a certain partial pressure of oxygen is so extremely rapid that at present we have no means of measuring it. We can form some conception of what must be the velocity if we consider what is happening in the circulation of a small warm-blooded animal, such as a mouse or bird. As was shown by Dr. Florence Buchanan[18] the pulse rate of such an animal is, even during rest, about 700 to 800 a minute. A volume of blood equal to the whole

[18] Buchanan, *Journ. of Physiol.*, XXXVII, *Proc. Physiol. Soc.*, p. lxxix, 1908; and XXXVIII, *Proc. Physiol. Soc.*, p. lxii, 1909.

of that in the animal will pass round the circulation in one or two seconds during exertion, so that any portion of blood will only be present for an instant in the pulmonary capillaries in each round of the circulation. Yet the time is sufficient for the chemical change to occur in the blood, and doubtless far more than sufficient, since we have to allow also for the time needed for the passage of oxygen through the layer of living tissue separating the air from the blood. In man the time available is much greater, so that the absolute velocity of the chemical change does not come into consideration at all, though of course the *relative* rates at which oxygen is chemically associated with or dissociated from haemoglobin at varying partial pressures of oxygen and varying temperatures, determine the corresponding dissociation curves as experimentally determined.

A further group of causes of anoxaemia depends not on defective saturation in the lungs, but on defect in the charge of available oxygen carried by the arterial blood, so that, with the existing rate of circulation, the oxygen pressure in the systemic capillaries falls too low. Of this group, carbon monoxide anoxaemia will be considered first.

The laws of combination of carbon monoxide with haemoglobin have already been discussed in Chapter IV. My own interest in carbon monoxide arose out of my connection with coal mining, as it had become evident to me that carbon monoxide poisoning was a common occurrence, and I wished to understand it as thoroughly as possible. When Claude Bernard discovered the combination of CO with haemoglobin he attributed death from CO poisoning to the anoxaemia resulting from the fact that CO displaces the oxygen of oxyhaemoglobin. CO was, however, very generally believed to have other physiological actions than those of anoxaemia, and my first experiments were made with a view to clearing this matter up.

To put the matter to the test, I devised the following experiment[19] (Figure 51). A mouse was dropped into a thick glass measuring vessel filled with pure oxygen, and the pressure of oxygen in this cylinder was then raised to two atmospheres by connecting it with an oxygen cylinder in the manner shown. The oxygen was then clamped off and another clamp opened, through which the oxygen was directed into the top of another measuring vessel full of water, and the water driven over into a third measuring vessel filled with pure carbon monoxide, so arranged that the

[19] Haldane, *Journ. of Physiol.*, XVII, p. 201, 1905.

gas was driven into the vessel containing the mouse. The animal was now in a mixture consisting of two parts of oxygen and one of carbon monoxide, at a total pressure of two atmospheres of oxygen and one of carbon monoxide. It could also be killed by drowning in this atmosphere if water was forced over.

My calculation was that in the presence of two atmospheres of oxygen the animal would have in simple solution sufficient oxygen in its arterial blood to supply the oxygen requirements of its tissues, at any rate during rest; and that it would thus be independent of the oxygen supply shut off through the action of the

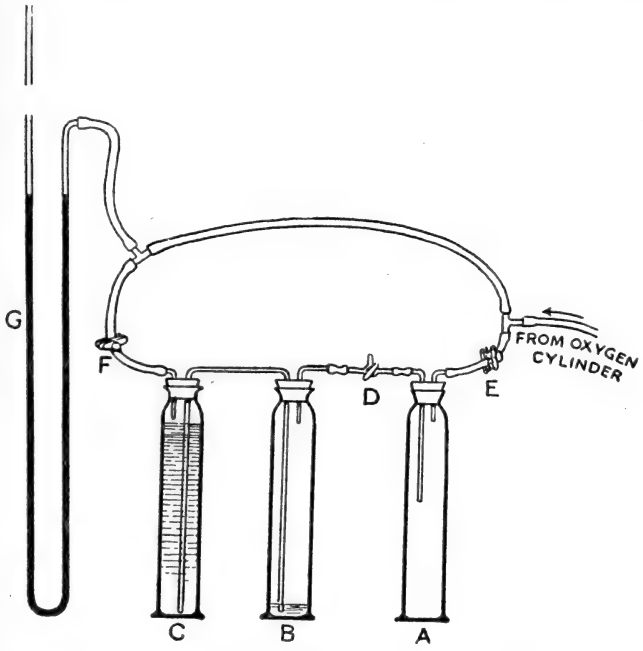

Figure 51.
Apparatus for exposing mouse to atmosphere of oxygen and CO.

CO, with which the haemoglobin would be almost completely saturated. If, however, the CO had any toxic action apart from its action in producing anoxaemia this action would certainly manifest itself at once, since the partial pressure of the CO was 100 per cent of an atmosphere, whereas in CO poisoning as ordinarily met with in non-fatal cases, the partial pressure of CO is not more than about 0.2 per cent of an atmosphere. The amount

of free oxygen which would go into solution in blood at the body temperature with an atmospheric pressure of two atmospheres is 4.2 volumes per 100 cc. of blood, which is just about as much as is ordinarily taken from the blood as it passes through the tissues (see Chapter X).

The mouse remained quite normal and seemingly unconcerned, except that when it exerted itself in climbing up the jar it seemed to become more easily tired than usual. Thus CO has no appreciable physiological action except that of producing anoxaemia. It is, physiologically speaking, an indifferent gas, like nitrogen, hydrogen, or methane, and, like these gases, only acts physiologically by cutting off the supply of oxygen. Its only specific physiological action, so far as I am aware, is that it has a slight garlic-like odor. It is not an "odorless gas" except to those who are afraid even to smell it on account of the mythical properties commonly attributed to it. Animals which have no haemoglobin pay no more attention to CO than to nitrogen. I kept a cockroach for a fortnight in an atmosphere consisting of 80 per cent of CO and 20 per cent of oxygen, and it remained perfectly well. CO is not oxidized or otherwise decomposed in the living body of any animal.[20] It passes in by the lungs and passes out—far more rapidly than is generally supposed—by the lungs, without there being the smallest loss. For this and other reasons it is a most valuable physiological reagent.

The popular idea that CO remains for long in the blood is based simply on failure to realize the nature of the symptoms which follow severe or long-continued anoxaemia. In the light of present knowledge it is childish to suppose that as soon as anoxaemia is relieved a patient will recover, or that anoxaemia is in itself a trifling matter if life is not immediately imperiled. If there were only one clinical lesson derived from a perusal of this book, I hope it would be that anoxaemia is a very serious condition, the continuance of which ought to be prevented if at all possible.

The properties of CO as a poison can now in the main be understood in the light of preceding chapters. As the molecular affinity of haemoglobin for CO is enormously more powerful than its affinity for oxygen, it is evident that a very small proportion of CO in the air is capable of saturating the blood to a noticeable extent. The proportion of oxygen in dry alveolar air is about 14 per cent, and the affinity of haemoglobin for CO (in my own case

[20] For experiments and references on this subject see Haldane, *Journ. of Physiol.*, XXV, p. 225, 1899, and M. Krogh, *Pflüger's Archiv*, 162, p. 94, 1915.

at least) is about 300 times its affinity for oxygen. It follows that, if we assume for the moment that the oxygen pressure of the blood is that of the normal alveolar air, the blood will gradually become half-saturated with CO if air containing $\frac{14}{300} = .047$ per cent of CO is breathed continuously for a sufficient time. If the percentage is .0235 per cent, the final saturation will only be one third; and if the percentage is .012 the saturation will be a fourth; and so on. If pure air were again breathed the CO would be expelled from the body through the unbalanced action of the alveolar oxygen pressure in expelling CO from its combination. The rates of absorption and of elimination of the CO can also be calculated on the same principles from the mean percentage of CO in the alveolar air, allowing for the fact that as the haemoglobin approaches the balancing saturation the rate of absorption will gradually fall off; and similarly the rate of elimination will gradually fall off as the blood loses CO. As will be shown in Chapter IX, however, this theoretical course of events is profoundly modified by active secretion of oxygen inwards by the lung epithelium.

It is evident also that in air abnormally poor in oxygen a given percentage of CO will become more poisonous, and in air abnormally rich in oxygen less poisonous. This I verified experimentally on animals. It remained to ascertain in man what effects corresponded to a given saturation of the haemoglobin; and this I ascertained by experiments on myself,[21] using for the purpose the carmine titration method referred to in Chapter IV, and fully described in its latest form in the Appendix.

I found in these experiments that no particular effect was observed until the haemoglobin was about 20 per cent saturated. At about this saturation an extra exertion, such as running upstairs, produced a very slight feeling of dizziness and some extra palpitation and hyperpnoea. At about 30 per cent saturation very slight symptoms, such as slight increase of pulse rate, deeper breathing, and slight palpitations, become observable during rest, and running upstairs was followed in about half a minute by dizziness, dimness of vision, and abnormally increased breathing and pulse rate. At 40 per cent saturation these symptoms were more marked, and exertions had to be made with caution for fear of fainting. At 50 per cent saturation there was no real discomfort during rest, but the breathing and pulse rate were distinctly increased,

[21] Haldane, *Journ. of Physiol.*, XVIII, p. 430, 1895.

vision and hearing impaired, and intelligence probably greatly impaired. It was also hardly possible to rise from the chair without assistance. Writing was very bad, and spelling uncertain. Movements were very uncertain, and it was difficult to recognize objects distinctly or estimate their distance correctly, so that things a long way off were grasped at in vain. Attempts to go any distance caused failure of the legs and collapse on the floor. In one experiment the saturation reached 56 per cent. It was then hardly possible to stand, and impossible to walk. After each of these experiments the saturation of the blood fell rapidly when fresh air was breathed; and within three hours the saturation had fallen below 20 per cent.

Shortly after these experiments, I examined the bodies of a large number of men who had been killed in colliery explosions, and found that nearly all had died of CO poisoning. The saturation of the haemoglobin with CO was usually about 80 per cent, but in some cases not more than 60 per cent. In fatal cases of poisoning by lighting gas Lorrain Smith found similar saturations.

The general similarity between the symptoms of CO poisoning and those of anoxaemia produced in other ways is evident; and the after-symptoms appear to be identical with those of mountain sickness and related disorders. There is, however, a difference between the symptoms of CO poisoning and those of anoxaemia produced by imperfect oxygenation of the arterial haemoglobin. This difference lies in the fact that in CO poisoning fainting, or a tendency to fainting, is much more prominent than respiratory distress. A man at a high altitude pants excessively on exertion, but does not easily faint. A man suffering from CO poisoning faints very readily on exertion, and the tendency to dizziness and collapse is far more prominent than the hyperpnoea. The fainting on exertion is evidently due to the fact that from lack of the mass of oxygen needed the heart cannot compensate by sufficiently increased output of blood for the greatly increased flow of blood through the working muscles. The blood pressure therefore falls, with the result that the circulation to the brain is diminished and anoxaemia then causes loss of consciousness. But why does this occur so much more readily in CO poisoning? The fact that it does so indicates that relatively speaking the respiratory center is less affected in the anoxaemia of CO poisoning, in which the mass of oxygen in the blood is reduced but the pressure of oxygen in the arterial blood remains normal. That is to say, with a degree of

anoxaemia which would not seriously affect the heart in anoxaemia from imperfect oxygenation of the available haemoglobin there will be marked response to anoxaemia in the respiratory center, but not in CO poisoning. This points clearly to the very important conclusion that it is practically speaking to the oxygen pressure of the *arterial* blood that the respiratory center responds. The blood which bathes the receptive end-organs (or whatever else is sensitive to the respiratory chemical stimuli) of the respiratory center must therefore be blood which has lost very little of its arterial charge of oxygen.

There are other facts pointing in the same direction. Thus in fainting or dizziness from fall of blood pressure there is no immediate panting, although the anoxaemia which immediately results in the cerebrum is sufficient to cause loss or impairment of consciousness. The arterial blood, however, remains normal as regards its pressures of oxygen and CO_2 during fainting; and in accordance with the conclusion just reached, the breathing is not stimulated till the stagnation of blood in the respiratory center is very marked.

It is to be kept in mind that at a moderate altitude the pressure of oxygen in the arterial blood is diminished far more than the mass of the oxygen, as expressed by the percentage saturation of the haemoglobin. With CO it is the mass of oxygen which is diminished in the blood, while the pressure may be normal.

It also seems a priori probable that the respiratory center should be continuously sampling and controlling the gas pressures of the *arterial* blood. For it has to act for the whole body. Its function is evidently, not to keep normal the gas pressures in the capillaries of one particular part of the body, such as the medulla oblongata, but to keep normal the arterial blood upon which every part of the body draws in accordance with varying local requirements. It keeps the gas pressures normal just as the heart keeps the blood pressure normal, so that every part of the body can always indent for arterial blood of standard quality and sufficient quantity.

A further peculiarity of CO poisoning is that quite commonly consciousness is lost for long periods in the poisonous atmosphere without death occurring. Thus cases of CO poisoning afford striking opportunities of studying the effects of prolonged general anoxaemia of the brain and every other organ in the body. The reason why death does not occur more readily seems to be that, although the amount of oxygen transported by the blood is diminished, the oxygen pressure in the *arterial* blood remains normal,

and as a consequence the respiratory center does not rapidly fail in the same manner as it does when the arterial oxygen pressure is very low, as explained in Chapter VI. This characteristic seems to be common to all forms of anoxaemia in which the arterial oxygen pressure remains about normal, including anoxaemia due simply to a failing heart.

If the action of CO were simply to diminish the oxygen-carrying power of the haemoglobin, without modification of the properties of the remaining haemoglobin, the symptoms of CO poisoning would be very difficult to understand in the light of other knowledge. Thus a person whose blood is half-saturated

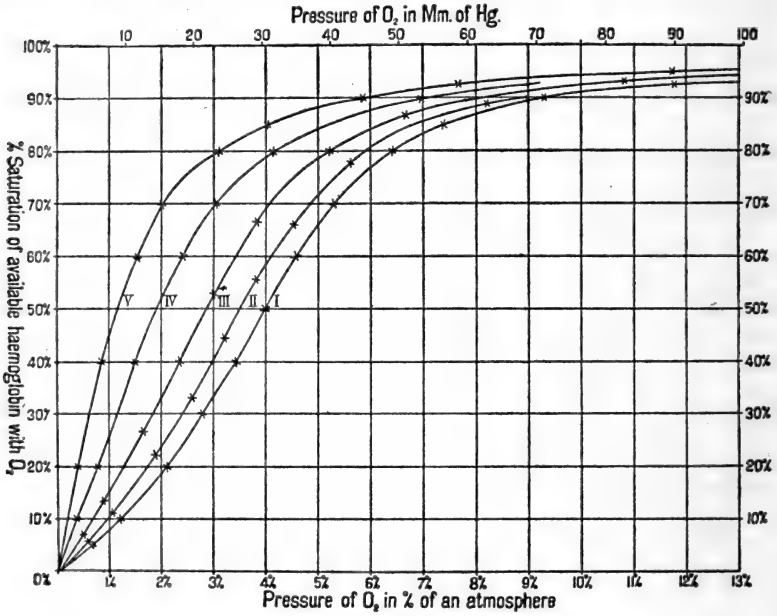

Figure 52.

Curve I, 0 per cent saturation with CO; II, 10 per cent; III, 25 per cent; IV, 50 per cent; V, 75 per cent.

with CO is practically helpless, as we have just seen; but a person whose haemoglobin percentage is simply diminished to half by anaemia may be going about his work as usual. Miners may be doing their ordinary work though their haemoglobin percentage is reduced to half or less by ankylostomiasis; and women may be going about their duties with their haemoglobin percentage reduced to a third by chlorosis. Even in the extremest "anaemia,"

with the haemoglobin below 20 per cent of its normal value, and the lips of extremest pallor, the patient is perfectly conscious, though hardly capable of any muscular exertion.

The key to this seeming paradox is furnished by the discovery[22] that the oxyhaemoglobin left in the arterial blood when it is partially saturated with CO has its dissociation curve altered in such a way that the haemoglobin holds on more tightly to the oxygen. The oxygen still present as oxyhaemoglobin is therefore less easily available, so that the oxygen pressure in the tissues must fall lower in order to get off the combined oxygen. With a given amount of available oxygen in the blood the physiological anoxaemia is thus increased. Figure 52, from a paper by J. B. S. Haldane,[23] shows the alterations in the dissociation curves of the oxyhaemoglobin with varying percentage saturations of the blood with CO. It will be seen, for instance, that with 50 per cent saturation of the blood with CO the oxygen pressure must fall to less than half the usual value, and with 75 per cent saturation to less than a third, in order to dissociate half the oxygen present in the arterial blood as oxyhaemoglobin. No wonder, therefore, that the symptoms of CO poisoning are much more severe than those of a corresponding simple deficiency of haemoglobin in the blood. It will be seen also that the shape of the dissociation curve is completely altered. The characteristic double bend (which, as already seen, is of such vital physiological importance) in the oxyhaemoglobin curve tends to disappear altogether, so that an enormous fall in oxygen pressure is needed to make the bulk of the oxygen in the oxyhaemoglobin dissociate.

In the investigations which Lorrain Smith and I made on the effects of continuously breathing a definite percentage of CO all the experiments were made on ourselves, and in a series which was more or less continuous from day to day. From the results of these experiments we estimated that it required about .05 per cent of CO in the air to produce the 30 per cent saturation of the blood which was necessary for any very noticeable symptoms of CO poisoning. In isolated experiments made later, however, we found the CO much more poisonous, so that it only required about .02 per cent to produce the required saturation. In the original experiments we had become "acclimatized" without knowing it. The great significance of this "acclimatization" will be discussed in succeeding chapters.

[22] Douglas, J. S. Haldane, and J. B. S. Haladne, *Journ. of Physiol.*, XLIV, p. 293, 1912.

[23] J. B. S. Haldane, *Journ. of Physiol.*, XLV, *Proc. Physiol. Soc.*, p. xxii, 1912.

The other gas, besides CO, which enters into molecular combination with haemoglobin is nitric oxide. But as free nitric oxide combines at once with the oxygen in air to form yellow "nitrous fumes," and these are intensely irritant and produce very dangerous inflammation, nitric oxide poisoning in the same sense as CO poisoning is impossible. Sir Humphrey Davy nearly killed himself when he attempted to breathe nitric oxide (NO) at the time when he discovered the effects of nitrous oxide, or "laughing gas" (N_2O). NO haemoglobin is, however, formed to some extent in the living body during poisoning by nitrites, as was discovered by Makgill, Mavrogordato, and myself;[24] and some time after death from nitrite poisoning the whole of the haemoglobin becomes combined with NO. Hence the body is red, just as in a fatal case of CO poisoning, so that the case might easily be mistaken for CO poisoning on mere spectroscopic examination of the blood. The condition can be distinguished at once by the fact that the blood and tissues remain red on boiling, just as in the case already alluded to of salted meat.

Another cause of an anoxaemia analogous to that of CO poisoning is present in the case of the action of poisons which produce methaemoglobin in the living body. The first of these to be discovered was chlorate of potash, which in former times, before the dangerous properties of chlorates were realized, used to be administered freely as an oxidizing agent, and has even been recommended as an antidote for the anoxaemia of high altitudes. The discovery that in a fatal case of diptheria treated with chlorate of potash the blood contained much methaemoglobin drew attention to the possible dangers from anoxaemia in poisoning by any of the numerous substances which are capable of producing methaemoglobin in the living body.

The possibilities of anoxaemia being produced were investigated by Makgill, Mavrogordato, and myself. As ferricyanide does not penetrate the walls of the red corpuscles, and chlorates do not do so in the animals we were using, we used chiefly nitrites for the experiments; and we did so for the reason, partly, that nitrites have other important physiological actions besides that of producing methaemoglobin (in reality a mixture of methaemoglobin with a certain proportion of NO haemoglobin). Having discovered the dose required to produce death we then, as soon as serious symptoms began to develop after administration of the dose, placed the animals in compressed oxygen. The result was

[24] Makgill, Mavrogordato, and Haldane, *Journ. of Physiol.*, XXI, p. 160, 1897.

that the serious symptoms disappeared and the animals recovered. If, however, they were removed into ordinary air, they died at once with anoxaemic convulsions. When kept in the oxygen for a sufficient time, however, they completely recovered and could be returned to ordinary air. Oxygen at ordinary atmospheric pressure was often sufficient to save the animals.

Having worked out a method for estimating colorimetrically the proportional extent to which the haemoglobin was altered by the poison, we then found that the dangerous symptoms depended, just as in CO poisoning, on the extent of the alteration. It was thus evident that the cause of death, and of the dangerous symptoms, was anoxaemia, just as in CO poisoning. We also found that the methaemoglobin and NO haemoglobin soon disappeared, leaving the blood quite normal, if death was averted. The methaemo-

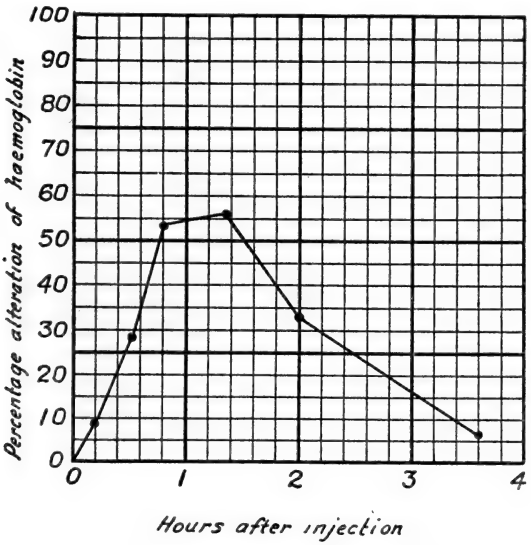

Figure 53.
Methaemoglobin due to sodium nitrate.

globin was simply reduced back again, just as on the addition of a reducing agent to a methaemoglobin solution outside the body. It was also evident that the reduction process was constantly going on and tending to neutralize the poison even while the relatively large amounts of it were still present in the blood. In proportion as the poison was destroyed or excreted the reduction process got the upper hand. There are, therefore, reducing agents of some

kind or another within the corpuscles. Figure 53 shows the percentage conversion to methaemoglobin in the blood of a rabbit at intervals after a non-poisonous dose of sodium nitrite. It will be seen that after four hours the blood had completely recovered.

The action of methaemoglobin-forming poisons is rendered evident at once by the marked cyanosis which they produce. The methaemoglobin has a dark color, and the arterial blood becomes therefore of a chocolate or coffee color. This form of cyanosis may become very marked indeed without serious real symptoms of anoxaemia being present. Thus in acute poisoning by dinitrobenzol (an ingredient of certain explosives) a man may become very blue in the face and yet be going about as usual, although he presents a most alarming appearance.

Many of the poisons which produce methaemoglobin cause, in addition, radical decomposition in the haemoglobin, and even breaking up of the red corpuscles. This is, for instance, the case, to a large extent, with dinitrobenzol, so that there are other colored decomposition products present as well as methaemoglobin; and for the present it is not possible to specify their nature. Their presence, or that of methaemoglobin, can, however, be detected at once on diluting a drop of the blood till the color begins to become yellowish, then saturating with coal gas or CO, and comparing the tint with that of normal blood diluted to a corresponding extent and similarly saturated. If any colored decomposition products are present the normal blood solution will be pinker, as the CO does not combine to give a pink color with these foreign substances.

When a poison causes solution of the red corpuscles (haemolysis), or decomposes the haemoglobin beyond the methaemoglobin stage, the haemoglobin is lost to the body, and "anaemia" is one result of this, as well as jaundice. Thus chronic poisoning by dinitrobenzol and similarly acting substances causes very serious anaemia. This also results from chronic poisoning by arseniuretted hydrogen, which has the peculiar action of injuring the walls of the red corpuscles and so causing haemolysis, with resulting haemoglobinuria, jaundice, and often nephritis. We are thus brought to the consideration of the anoxaemia caused by anaemia, the word "anaemia" being taken to mean simply a diminution in the percentage of haemoglobin in a given volume of blood, whether the blood volume itself is diminished, or normal, or increased. As a matter of fact the blood volume is usually much

increased in "anaemia," as was first shown by Lorrain Smith.[25]

It was found by Miss FitzGerald that in ordinary cases of anaemia there is no appreciable diminution in the alveolar CO_2 pressure.[26] As will be shown more fully in Chapter VIII, a chronic arterial anoxaemia, however slight, invariably lowers the alveolar CO_2 pressure if time is given, and if the anoxaemia continues during rest. The absence of a lowered alveolar CO_2 pressure in cases of anaemia is thus clear evidence of the absence of anoxaemia, in spite of greatly diminished oxygen-carrying capacity of the blood. It is evident, therefore, that the circulation rate is much increased in anaemia and this inference is confirmed by the absence of cyanosis. A little consideration will show that this increased circulation rate, while it serves to maintain the normal oxygen pressure of the blood in the systemic capillaries, will probably not reduce too much the pressure of CO_2 in the tissues. The CO_2 conveying power of the blood in the living body depends, as shown in Chapter V, on the concentration of haemoglobin present in the blood, and this concentration is greatly reduced in anaemia. Diminution in the actual CO_2-conveying power of the blood in the living body will therefore advance *pari passu* with the diminution of the oxygen-carrying power. Thus (as shown in Chapter X) an increased circulation rate is brought about by the combined stimulus of diminished oxygen pressure and increased CO_2 pressure. This is not so in the case of anoxaemia from defective saturation of the haemoglobin in the lungs; nor, for the special reason given above, in the anoxaemia of CO poisoning. The reason why imperfect saturation of the arterial blood causes such serious anoxaemia in the cerebrum and tissues elsewhere, while anaemia causes so little anoxaemia (during rest) unless it is very extreme, is probably bound up with this difference as regards effects on CO_2 pressure in the tissues. The matter will, however, be discussed more fully in Chapter X.

The last cause of anoxaemia to be considered is that due primarily to defective circulation; and it will be referred to very briefly here, as the relation of circulation to respiration will be discussed in Chapter X. When the blood pressure is very defective owing to failure of heart action or failing supply of venous blood to the heart, the inevitable result is failure in the general circulation rate, and failure also in the proper distribution of blood within the body. This must result in anoxaemia in the tissues, together with an

[25] Lorrain Smith, *Trans. Path. Soc. Lond.*, LII, p. 315.
[26] *Journ. of Pathol. and Bacter.*, XIV, p. 328, 1910.

undue rise in their CO_2 pressure. But owing to the combination of these two conditions the fall in oxygen pressure and rise in CO_2 pressure will both be moderate until the slowing of circulation is excessive: for the oxygen will fall along the steep part of the dotted curve in Figure 21, while the CO_2 pressure will rise along the thick line in Figure 26. This means that a great diminution in the charge of oxygen in the haemoglobin, and consequently a very considerable cyanosis, will be possible with a comparative small fall in the oxygen pressure or rise in the CO_2 pressure. Hence cyanosis due to slowing of the circulation is not in itself such a serious indication as cyanosis due to failing saturation of the blood with oxygen, although of course indicative of possible more serious failure of the circulation.

When fall of arterial blood pressure is due to defective filling of the large veins leading to the heart, benefit may be expected from the intravenous injection of suitable saline solution, as this will tend to fill up the veins, and to bring about adequate filling of the heart. A simple salt solution tends, however, to leak out again very quickly from the circulation. To remedy this defect Bayliss[27] has introduced the plan of adding gum to the salt solution, the gum fulfilling the same function in preventing leakage as the proteins normally present in blood plasma. This procedure has proved very successful, and avoids the risks and practical difficulties associated with transfusion of blood or liquids containing proteins. For the reasons already pointed out, the dilution of the blood by the saline injection does not cause anoxaemia.

As will be pointed out in Chapter X, failure in the venous return to the heart may be due to deficient pressure of CO_2 in the systemic capillaries, owing to excessive washing out of CO_2 in the lungs; and this excessive washing out may be secondary to arterial anoxaemia. Arterial anoxaemia and deficiency of CO_2 may also be the cause of failure of the heart muscle. It is probable, therefore, that in many cases the vicious circle may be more effectively broken by administration of oxygen or even CO_2 than by injection of gum-saline solution or transfusion of blood; but in other cases injection or transfusion would quite clearly be required.

[27] Bayliss, *Intravenous Injection in Wound Shock*, 1918.

CHAPTER VIII

Blood Reaction and Breathing.

It has been known for long that the reaction of blood to litmus paper is always slightly alkaline, while the living tissues are also alkaline, though they change to acid in dying. Knowledge as to the connection between the blood reaction and normal breathing is, however, mostly of very recent origin; and the same may be said of knowledge as to the extreme exactitude with which the reaction of the blood is regulated, and the physiological importance of the very slightest deviation from the normal reaction of the blood and tissues.

That the reaction within the body is physiologically regulated was originally indicated, not only by the reaction of the blood to litmus and other indicators being always the same, but also by the fact that on administration of sufficient doses of sodium bicarbonate or other alkalies the urine, which is normally acid in man, becomes alkaline. The same effect is produced by a vegetable diet, which contains a large amount of organic acids combined with alkali. The acids are mostly oxidized with formation of CO_2 within the body, thus leaving alkaline carbonates, so that the excess of alkali must be, and actually is, excreted in order that the reaction within the body may remain normal. In herbivorous animals the urine is always alkaline. On the other hand, in carnivorous animals, and in man with his usual mixed diet, the urine is acid. This is because there is an excess of non-volatile acid formed within the body by the oxidation of the sulphur, phosphorus, etc., in the food constituents and this excess is partly, at least, got rid of by the kidneys, and the normal alkalinity of the blood and tissues thus preserved.

More than forty years ago an important series of investigations bearing on the physiology of the blood reaction was carried out under Schmiedeberg's direction at Strassburg. The effect on rabbits of the administration of large doses of dilute hydrochloric acid was investigated by Walter,[1] and it was found, as one result, that the breathing of the animals was very greatly increased, becoming extremely deep as well as more frequent—the same sort of effect as is produced by excess of CO_2, as shown in Chapter II. The

[1] F. Walter, *Archiv f. exper. Pathol. Pharmakol.*, VII, p. 148, 1877.

animals also ultimately became comatose, just as is the case when CO_2 is in great excess; and finally there were signs of exhaustion of breathing, the breathing ceasing before the heart ceased to beat.

Another very important result reached in these investigations was that when the experiments were repeated on dogs it was much more difficult to produce the symptoms, and it was found that the amount of ammonia excreted (in combination with acid) in the urine was increased greatly. Under normal conditions the amount of nitrogen excreted as ammonia is small in proportion to the total excretion of nitrogen. Thus in man the amount of ammonia usually excreted in 24 hours is only about 0.7 gram (sufficient, however, to neutralize about 2 grams of H_2SO_4), so that only a small fraction of the total nitrogen is excreted as ammonia. In acid poisoning, however, the fraction becomes a very much larger one in carnivorous animals and in man. Walter found that in dogs the ammonia excretion could be pushed up to several times the normal by giving large doses of acid.

According to the existing evidence, which originated with Schmiedeberg and his pupils, ammonia is converted into urea in the liver. It appears, therefore, that when acid is administered to carnivorous animals or men, ammonia is not converted into urea, or else nitrogen which normally appears as urea is converted into ammonia and goes to neutralize the acid. If ammonia is administered by mouth as carbonate it is wholly converted into urea, and the excretion of ammonia by the urine may be actually diminished. If, on the other hand, the ammonia is administered in combination with a strong acid as a neutral salt, much of this ammonia appears as salts of ammonia in the urine. Some is, however, converted into urea in the liver, as was recently shown definitely by perfusion experiments.[2] It was found that during health the proportion of ammonia which escapes conversion into urea and consequently appears in the urine depends on the acid-forming or alkali-forming properties of the diet. Thus with a meat diet the proportion of ammonia is much higher than with a vegetable diet; and by administering alkalies ammonia may be made to disappear entirely from the urine.

The varying neutralization of acids by ammonia is therefore one of the means by which the reaction within the body is regulated in man and carnivorous animals, while variation in the excretion of acid or alkali in the urine is another. The former means hardly exists in herbivorous animals. But the significance

[2] Löffler, *Biochem. Zeitschr.*, LXXXV, p. 230, 1918.

of the most rapid and effective method of all—varying excretion of carbonic acid by the breathing—remained hidden till quite recently, although Walter's experiments showed that there is not only a great increase in the breathing, but the amount of carbonic acid present in the arterial blood is reduced in extreme case to about a twelfth of the normal.

It was discovered by von Jaksch[3] in 1882 that where acetone is present in the urine, as in bad cases of diabetes, verging on coma, or actually comatose, considerable quantities of aceto-acetic acid are also present; and soon afterwards Minkowski[4] found that oxybutyric acid, a closely allied substance, is likewise present. The excretion of ammonia had already been shown to be greatly increased, as well as the depth of the breathing and the acidity of the urine, just as in acid poisoning; and indeed it was this that led Minkowski, and Stadelmann before him, to the search for organic acids. Thus all the symptoms point to acid poisoning by the acids mentioned. Shortly after Priestley and I introduced our method of investigating alveolar air, Pembrey, Beddard, and Spriggs investigated the alveolar air in cases of diabetic coma at Guy's Hospital,[5] and found the alveolar CO_2 percentage as low as 1.1 per cent. It went up and down as the patient emerged from or relapsed into coma; and the administration of sodium bicarbonate warded off the attacks of coma, and at the same time kept the alveolar CO_2 percentage from falling. Investigation of the alveolar CO_2 pressure is now a well-recognized clinical method for estimating the gravity of symptoms in diabetic coma and other states of "acidosis," as well as for judging of the effects of treatment.

For a long time the degree of alkalinity of the blood was judged from the amount of acid which has to be added to a given volume of it or its serum before an indicator, such as litmus, gives the tint indicative of neutrality. By this method it was found that the blood in acid poisoning or diabetic coma is less alkaline than usual; and all sorts of similar supposed "acidoses" have been discovered, although the signs of physiological response to the presence in the body of too much acid might be more or less absent or even contradictory. A few years ago, however, it became evident that the amount of acid required for neutralization is no reliable

[3] Von Jaksch, *Berichte der deutschen Chem. Gesellsch.*, p. 1496, 1882.

[4] Minkowski, *Arch. f. exper. Pathol. u. Pharmak.*, XVIII, pp. 35 and 147, 1884.

[5] Beddard, Pembrey, and Spriggs, *Journ. of Physiol.*, XXXI, *Proc. Physiol. Soc.*, p. xliv, 1904; also XXXVII, p. xxxix, 1908.

measure of the blood alkalinity. Even a strong solution of sodium bicarbonate is but feebly alkaline; but the amount of acid which must be added to it to render it neutral is as great as if the sodium were present as caustic soda, and is thus no measure of the actual alkalinity of the solution. The carbonic acid united with the soda prevents it from being at all strongly alkaline, but at the same time does not completely neutralize it, and all weak acids have the same properties. They may thus be said to be "buffer" substances, since they prevent a strong acid from neutralizing at once a weakly alkaline solution. A great deal of the strong acid has to be added before the weak alkalinity is neutralized. The same applies to weak alkalies, *mutatis mutandis.*

Now the blood and tissues are full of buffer substances. In the first place, as already seen in Chapter V, carbonic acid is present in combination. Haemoglobin and various other proteins are also present; and it has been well known for a long time that proteins act as both acid and alkaline buffers, so that the neutral point in a solution containing proteins is very difficult to ascertain sharply by means of ordinary indicators. The color alters gradually in either direction as the neutral point for any particular indicator is approached. It was shown in Chapter V that in the alkaline blood haemoglobin and other proteins act as weak acids more than sufficient in amount to combine with the bases not already combined with strong acids, and that the presence of these proteins along with carbonic acid determines the manner in which the alkali in blood takes up and gives off CO_2 with varying partial pressures of this gas. The amount of acid required to produce neutrality is thus in itself no measure of the degree of alkalinity in blood, but depends on the amount of the various buffer substances, including carbonic acid in combination with alkali; and they may vary considerably in amount under different conditions. This has been pointed out very clearly by L. J. Henderson.[6]

It may be desirable at this point to remind the reader as to the conception of acidity and alkalinity to which chemical and physico-chemical investigation has led during the last thirty years. The phenomena of electrolysis revealed to Faraday the fact that the constituents of any "electrolyte," such as copper sulphate, are torn asunder during electrolysis into definite fragments, of which one kind travels toward the anode, and the other to the cathode. These fragments he called "ions," because it is their movement towards either anode or cathode, and the fact that each of them has

[6] L. J. Henderson, *Ergebn. der Physiol.*, VIII, p. 254, 1909.

a definite electrical charge, that determines the phenomena of electrolysis and the exact quantitative relationship between the current passed through a cell containing an electrolyte in solution and the splitting up of the electrolyte into its constituents. Van't Hoff and Arrhenius brought Faraday's conception into relation with osmotic pressure and various other phenomena connected with solutions.

Osmotic pressure was first measured accurately by the botanist Pfeffer.[7] He used a semi-permeable membrane (i.e., a membrane which allowed the solvent water, but not the dissolved substance, to pass) which had been originally discovered by Moritz Traube in 1867,[8] though Traube had not seen how to apply this membrane for measuring osmotic pressures. Some years later van't Hoff[9] made the brilliant discovery that in dilute solutions of sugar and other substances, the osmotic pressure is practically the same as the pressure which the solute would have if its molecules were present alone in the gaseous form at the same temperature. There must thus be a fundamental connection between molecular concentration, osmotic pressure, and gas pressure; also between molecular concentration and the vapor pressures, boiling points and freezing points of solutions, as had already been empirically shown by the investigations in particular of Raoult. Van't Hoff believed that osmotic pressure, etc., were due in some way to the molecular bombardment of the solute molecules, and therefore vary as their concentration per liter of solution; and this theory has served for the building up of the theory of solutions as it is still represented in current textbooks of physical chemistry. In reality this theoretical interpretation was not even justified by Pfeffer's data if concentration *per liter* is considered, and breaks down entirely for concentrated solutions. The theory is also quite unintelligible mechanically, since the bombardment pressure of the solute molecules would be in the wrong direction for explaining the phenomena. Hence many persons regarded van't Hoff's theory with the greatest suspicion; but the fact that it seemed to answer admirably as a means of prediction in the case of dilute solutions, and to cover an enormous mass of facts, has led to its very general acceptance, though other attempts have been made to substitute for it some more intelligible conception.

In 1918[10] I showed quite clearly, as I think, that van't Hoff's

[7] Pfeffer, *Osmotische Untersuchungen*, 1877.
[8] Traube, *Archiv f. (Anat. u.) Physiol.*, p. 87, 1867.
[9] Van't Hoff, *Zeitschr. f. physik. Chemie*, I, p. 481, 1887.
[10] Haldane, *Bio-Chemical Journal*, XII, p. 464, 1918.

conception of osmotic pressure was mistaken. It is neither the concentration per liter of the solute molecules, nor that of the solvent molecules, that determines osmosis, but the diffusion pressure of the solvent. Water passes through a semi-permeable membrane into a solution, because the diffusion pressure of pure water is greater than that of the diluted water in the solution. The osmotic pressure is not the excess of diffusion pressure of water outside the solution, but the external mechanical pressure required to equalize the two diffusion pressures, although in sufficiently dilute solutions this mechanical pressure is practically the same as the excess of diffusion pressure of water.

In a solution, just as in a gas mixture, the molecules are free to move about; and, just as in a gas mixture, the mean free space round each molecule is the same because the mean energy of external movement is the same for each molecule. Hence the free space in which water molecules are free to diffuse is in proportion to the total number per liter of molecules present. This space is of course greater per molecule of solvent in a solution than in the pure solvent. Hence the pure solvent diffuses into the solution unless the external pressure on the solution is raised sufficiently to equalize the two diffusion pressures.

When osmotic pressure, vapor pressures, boiling points, etc., are calculated in terms of this theory instead of van't Hoff's theory, the experimentally ascertained values agree with the theory, whereas this is not the case, as is now well known, with van't Hoff's theory, except in the case of very dilute solutions. Thus for solutions of cane sugar, and allowing for the fact that at temperatures near 0°C. cane sugar is present in solution as a pentahydrate, the osmotic pressures at 0°C. calculated from the concentrations on the new theory and the pressures actually observed by the Earl of Berkeley and Mr. Hartley at Oxford are as follows:

OSMOTIC PRESSURE IN ATMOSPHERES

Grams Cane Sugar per 100 cc.	*Observed*	*Calculated*	*Calculated on van't Hoff's theory*
3.32	2.23	2.24	2.17
9.59	6.85	6.85	6.29
18.26	14.21	14.17	11.95
25.81	21.87	21.80	16.90
28.13	24.55	24.44	18.41
54.24	67.74	67.66	35.48

The vapor pressures, boiling points, and freezing points of sugar solutions show a similar agreement between observations and the new theory, as pointed out in detail in my paper.

To physiologists the main advantage of the new theory is that, as will be pointed out in detail in later chapters, it enables us to utilize the kinetic theory of matter in unifying our conceptions of a great number of physiological phenomena.

The osmotic pressures observed by Pfeffer and others for dilute salt solutions were far greater than corresponded to van't Hoff's theory. This became quite intelligible when Arrhenius pointed out in 1887[11] that the discrepancy could be cleared up on the assumption that solutions of electrolytes are ionized to a greater or less extent. Their osmotic pressures are not merely due to the concentration (or, in terms of the new theory just referred to, the diffusion pressure) of complete molecules of the solute, but also to the concentrations of the ions present, as indicated by the varying electrical conductivities of different strengths of the solutions. This explanation of Arrhenius was received at first with some incredulity, but is now universally accepted, as the evidence in favor of it is overwhelming. A dilute solution of sodium chloride, for instance, is not now regarded as a solution of NaCl molecules, but, practically speaking, of sodium and chlorine ions. Similarly a dilute solution of hydrochloric acid is a solution of hydrogen and chlorine ions.

Ionization may be regarded as a tearing apart of the molecules of the electrolyte in solution on account of the molecular affinity of H_2O molecules for the atoms of the electrolyte molecules; and in accordance with this conception the ions are not stray atoms or other fragments of molecules, but molecular compounds with molecules of water. In pure water itself the molecules are also to a certain extent ionized, as indicated by, among other things, the conductivity of pure water. The products of this ionization are hydrogen and hydroxyl (HO) ions, combined with molecules of water.

The acidity of a solution is due to preponderance of hydrogen ions, and the alkalinity to preponderance of hydroxyl ions; and when the concentrations of hydrogen and hydroxyl ions are equal the solution is neutral. As, however, hydrogen and hydroxyl ions are constantly reacting with one another according to the equation

$$H + HO \rightleftarrows H_2O,$$

the product of the concentrations of hydrogen and hydroxyl ions

[11] Arrhenius, *Zeitschr. f. physik. Chemie*, I, p. 631, 1887.

remains the same, in accordance with the law of mass action, however acid or alkaline a solution may be. Hence the concentration of hydroxyl ions diminishes in proportion as that of hydrogen ions increases, and vice versa.

All acids and bases combine with one another in chemically equivalent proportions, but different acids and alkalies vary very greatly in the extent to which they are ionized. The "strengths" of different acids and alkalies were found by the electrical conductivity method to depend upon the extent of their ionization. The "strong" acid HCl is, for instance, very completely ionized into hydrogen and chlorine ions, and the "strong" base NaHO is similarly ionized into sodium and hydroxyl ions; while "weak" acids, such as carbonic acid, or weak bases, such as ammonia, are very slightly ionized.

Water itself is slightly ionized into hydrogen and hydroxyl ions, and can thus act as either a very weak acid towards bases or a weak base towards acids. In the case of strong or highly ionized acids and bases this property of water is practically of no account, as the ionization of water is so very small; but in the case of weak acids or bases the water competes appreciably with the acid or base. For instance in the case of potassium cyanide, a compound of an extremely weak acid with a very strong base, the following reaction occurs:

$$KCN + H_2O \rightleftarrows KOH + HCN.$$

Thus free KOH and free HCN are both present in a solution of this salt. But the KOH is highly ionized into K and HO ions, while the HCN is hardly ionized at all. Hence HO ions predominate, and the solution is alkaline. Carbonic acid is not such a weak acid as hydrocyanic acid; but the same relations hold, so that both carbonates and bicarbonates form solutions which are distinctly alkaline; and bicarbonate solutions are still slightly alkaline, even though much free carbonic acid is present, as in the case of blood in the living body.

The ordinary indicators appear to be extremely weak acids or bases which change color on combination. When the only other acids or bases present are strong ones, the change of color is of course very sharp; but with other weak acids or bases present, the change is gradual and the complete color change does not occur until the solution is distinctly alkaline or acid. This is because the indicator competes with other weak acids for the base; and different indicators compete in varying degrees. Thus different indicators turn with different degrees of slight variation

from the true neutrality point where hydrogen and hydroxyl ions are equal in concentration, as in pure water.

The relative diffusion pressures, or (to use the incorrect language of the still generally accepted van't Hoff's theory of osmotic pressure, etc.) the relative concentrations of any particular sort of ion, in different solutions, can be measured by the differences of potential communicated to a suitable electrode dipped in the solutions. Thus with a hydrogen electrode hydrogen ion concentration can be measured directly; and this method was applied, soon after its discovery, to the measurement of the hydrogen ion concentration (and therefore indirectly also of the hydroxyl ion concentration) of blood. The earlier attempts gave the result that the blood was neutral in reaction, and remained neutral even in acidosis. The physiological signs of acidosis were, however, very clear, as already explained. The electrometric method in its earlier form was thus far too rough for physiological work.

It was mentioned in Chapter I that the experiments of Geppert and Zuntz on the hyperpnoea following muscular contractions in animals showed a great diminution in CO_2 and a slight excess of oxygen in the arterial blood during the hyperpnoea. They therefore concluded that neither excess of CO_2 nor want of oxygen can be the cause of the hyperpnoea; and they sought for the cause in some acid substance present in the blood, since acids were known to stimulate the breathing. The search made for the acid substance did not, however, lead to any definite result; and the experiments of Priestley and myself on man brought us back to CO_2 as the stimulus to the increased breathing. The improbability of any organic acid being the stimulus to the breathing seemed to us to be in any case very great. No acid other than CO_2 is given off in the expired air, and organic acids, etc., are not appreciably oxidized in the blood itself. It did not therefore seem possible to understand how the air hunger of muscular exertion could be relieved, as it undoubtedly is, by increased breathing. In any case the diminished proportion of CO_2 in the arterial blood in these experiments was entirely discounted by the fact that this diminished proportion continued to exist for at least an hour after the hyperpnoea had passed off. We thought that in Geppert and Zuntz's experiments owing to defective circulation in the artificially stimulated muscles of the animal some lactic acid had been produced and thrown into the blood, thus greatly reducing its power of combining with CO_2. Thus, although the pressure of CO_2 was perhaps actually higher in the arterial blood and caused

hyperpnoea, the amount of CO_2 contained in the blood was much less. We also thought that owing to the diminished CO_2 carrying power of the blood there might be an increased rise of CO_2 pressure in the tissues. This explanation was, however, somewhat strained and unsatisfactory, as was pointed out in Chapter II. We had correctly divined the main cause of the greatly diminished proportion of CO_2 in the arterial blood in those experiments, but not the whole cause.

In a series of experiments by Boycott and myself on the effects of low atmospheric pressure in a steel chamber on the alveolar CO_2 pressure[12] we found that on returning from low pressure the alveolar CO_2 pressure, which had been lowered by the hyperpnoea caused by the low atmospheric pressure, did not return at once to normal, but remained low for some time. Ogier Ward, who was working in conjunction with us, found the same thing and in much more marked and persistent degree, on returning to ordinary pressure after a stay on Monte Rosa.[13] Galleotti,[14] and also Aggazotti,[15] had already found that the titration alkalinity of the blood is diminished by exposure to low pressure in a steel chamber or at high altitudes. It was also known from older experiments made in Hoppe-Seyler's laboratory by Araki[16] that in conditions of acute want of oxygen (CO poisoning, etc.) large quantities of lactic acid are produced in the body. Putting together all these facts, and the results of Walter's experiments on acid poisoning, we drew the conclusion that what the respiratory center responds to is the combined effect of carbonic acid and other acids on the reaction of the blood. It seemed no longer possible to maintain the hypothesis that CO_2 acts specifically in exciting the respiratory center. The long duration of the lowering of alveolar CO_2 pressure after exposure to want of oxygen seemed intelligible on the theory that excess of lactic acid had been produced owing to the anoxaemia, and that the sodium or potassium lactate thus formed had been excreted by the kidneys, thus robbing the body of alkali and leaving the blood correspondingly less alkaline—a deficiency which it required some time to make up.

This conclusion was further strengthened by the observation of Douglas and myself, that after an excessive muscular exertion

[12] Boycott and Haldane, *Journ. of Physiol.*, XXXVII, p. 355, 1908.
[13] Ogier Ward, *Journ. of Physiol.*, XXXVII, p. 378, 1908.
[14] Galleotti, *Arch. Ital. de Biol.*, XLI, p. 80, 1904.
[15] Aggazotti, *Ibid.*, XLIV, 1905.
[16] Araki, *Zeitschr. f. physiol. Chemie*, XV, p. 335, 1908; also XVI, p. 425; XVII, p. 311; XVIII, p. 422.

the alveolar CO_2 pressure remains low for about an hour.[17] We attributed this to the effect on the respiratory center of lactic acid

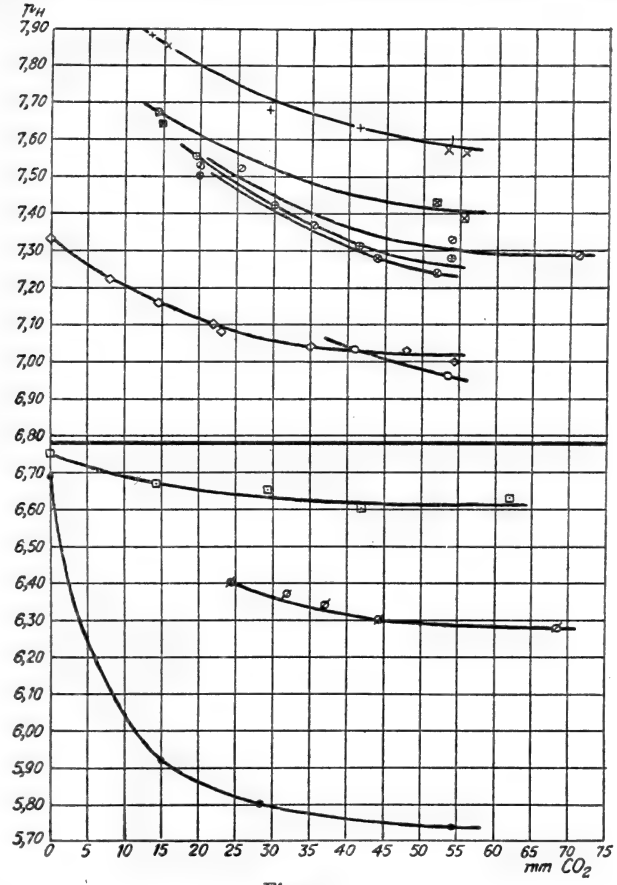

Figure 54.

⊕ Blood, + Serum, ○ Corpuscles of same sample. ⊠ Blood, X Serum of another sample. / Blood of another sample. ⓘ Another sample of blood. Ø Same sample with acetic acid added. ◇ 8 parts $\frac{M}{15}$ Na_2HPO_4 and 2 parts $\frac{M}{15}$ KH_2PO_4. ⊡ Equal parts $\frac{N}{15}$ Na_2HPO_4 and KH_2PO_4. ● $\frac{N}{10}$ KCl solution.

given off into the blood by muscles in which the work had been far in excess of the possible oxygen supply. The correctness of

[17] Douglas and Haldane, *Journ. of Physiol.*, XXXVIII, p. 431, 1909.

this inference was shortly afterwards established by Ryffel,[18] who had meanwhile worked out a new and very convenient method of determining small amounts of lactic acid in blood and urine.

The methods of determining hydrogen ion concentration in the blood were at that time still too crude to permit of testing these inferences by direct determinations, but shortly afterwards the electrometric method was greatly improved by Sörensen and particularly by Hasselbalch of Copenhagen. In 1912 Hasselbalch and Lundsgaard[19] published curves showing the variations of hydrogen ion concentration with variations in CO_2 pressure at body temperature in ox blood, and Lundsgaard[20] repeated the experiments with human blood. Figure 54 shows graphically their results for blood and other liquids. For convenience' sake the results for hydrogen ion concentration are plotted, not directly in terms of gram molecules per liter, but in terms of the negative *power* of 10 representing this value. This mode of notation, introduced by Sörensen, is represented by the symbol PH, and since the negative power increases with diminution of hydrogen ion, or increase of hydroxyl ion concentration, the curve rises with diminution of hydrogen ion concentration.

At body temperature the point of neutrality corresponds to a PH about 6.78, as indicated by the thick line in the figure. It will be seen from the curves that even with a far higher pressure of CO_2 than exists in the living body the neutral point is not reached. This is partly due to the fact that the proportional ionization of carbonic acid becomes less and less with increasing concentration, just as is the case with other acids, including even strong ones. The lower curve (for neutral potassium chloride solution) shows this clearly. Thus sulphuric acid when pure is quite devoid of acid properties and does not attack metals, because it is practically not ionized at all. This can be understood on the theory, already alluded to, that ionization in aqueous solutions is brought about through a reversible reaction with the water molecules.

The influence of a buffer substance (disodium phosphate) in hindering changes of hydrogen ion concentration is shown very strikingly in the two curves for phosphate solutions. In blood, as already pointed out, various buffer substances, including haemoglobin with other proteins, and the phosphate in the corpuscles, are present. The curve for acidified blood shows that even when

[18] Ryffel, *Journ. of Physiol.*, XXXIX, *Proc. Physiol. Soc.*, p. xxix, 1910.
[19] Hasselbalch and Lundsgaard, *Biochem. Zeitschr.*, XXXVIII, p. 77, 1912.
[20] Lundsgaard, *Biochem. Zeitschr.*, XLI, p. 247, 1912.

blood is rendered distinctly acid these buffer substances still act very efficiently. The haemoglobin acts as an alkali, whereas it always acts as an acid in blood within the living body.

In order to test whether it is really to difference in PH that the respiratory center normally reacts, Hasselbalch made the experiment of altering the resting alveolar CO_2 pressure by changing the diet. A meat diet, consisting largely of proteins containing sulphur and phosphorus which break down into free sulphuric and phosphoric acid, is evidently an acid-forming diet as compared with a vegetable diet, which contains less protein and a relative abundance of salts of organic acids which break up in the body so as to yield carbonates. Hasselbalch found that with the acid meat diet the resting alveolar CO_2 pressure was 4.4 mm. lower, and then proceeded to compare the PH of the blood in the two conditions. The results were as follows:[21]

	Alv. CO_2 Pressure mm. Hg.	PH of blood at 40 mm. CO_2 pressure	PH of blood at existing alveolar CO_2 pressure
Meat Diet	38.9	7.33	7.34
Vegetable Diet	43.3	7.42	7.36

It will be seen that at 40 mm. CO_2 pressure the blood sample taken with the meat diet was distinctly more acid than with the vegetable diet, but that at the existing alveolar CO_2 pressure the two values for PH were identical, at least within the limit of accuracy of the method of measurement. Hence the respiratory center had regulated the alveolar CO_2 pressure in such a manner as to keep the PH of the blood almost constant.

There is other evidence pointing in the same direction. Barcroft found that on the Peak of Teneriffe the dissociation curve of human blood appeared to be normal, provided that the curve was investigated, not at the normal sea level alveolar CO_2 pressure of about 40 mm., but at the existing resting alveolar CO_2 pressure.[22] We got a similar result at a greater height on Pike's Peak,[23] as did also Barcroft and his co-workers on Monte Rosa.[24]

[21] Hasselbalch, *Biochem. Zeitschr.*, XLVI, p. 416, 1912.
[22] Barcroft, *Journ. of Physiol.*, XLII, p. 44, 1911.
[23] Douglas, Haldane, Henderson, and Schneider, *Phil. Trans. Roy. Soc.*, (B) 203, p. 201, 1913.
[24] See Chapter XVII, of Barcroft, *The Respiratory Function of the Blood*, 1913.

As already pointed out this curve is shifted to the right or left with varying alkalinity, and the shifting is a moderately delicate index of the variation (Chapter III). Peters,[25] working with Barcroft, has shown that the shifting with variations in CO_2 pressure depends on the shifting of PH. Hence the constancy of the dissociation curve appeared to be a direct index of the constancy in PH of the blood. The lowering of alveolar CO_2 pressure at high altitudes seemed therefore to be just sufficient to keep the PH of the blood steady in so far as direct methods enable us to measure the degree of steadiness. As will be seen below, however, there is physiological evidence that the blood is actually more alkaline at high altitudes. More recently Hasselbalch and Lindhard have made direct electrometric measurement of PH in a steel chamber after exposure of sufficient duration to the low pressure, and their measurements give practically the same result.[26] The resting alveolar CO_2 pressure on Pike's Peak was about 27 mm., or 13 mm. below that at sea level. Raising the alveolar CO_2 pressure on Pike's Peak to 40 mm. would have caused the extremest panting.

As soon as the results of Hasselbalch and Lundsgaard were published, it was possible to estimate quantitatively the delicacy with which the respiratory center responds to variations in the reaction of the blood: for the delicacy of the reaction of the center to variations of CO_2 pressure was known from our previous experiments, while the curves of Hasselbalch and Lundsgaard made it possible to convert variations of CO_2 pressure into variations of PH in the blood. Some confusion arose, however, owing to the fact that Lindhard,[27] and Hasselbalch and Lindhard,[28] had meanwhile published experiments which seemed to indicate that the respiratory center in man is commonly far less sensitive to CO_2 than Priestley and I had found. The matter was therefore reinvestigated by Campbell, Douglas, Hobson, and myself.[29] We found that the Danish observers had been deceived, owing to a faulty modification of the method of sampling the alveolar air. The fresh experiments gave practically the same results as Priestley and I had obtained, so we could make the calculation accordingly.

A rise of 0.2 per cent or 1.5 mm. in the CO_2 pressure of the

[25] Barcroft, *The Respiratory Function of the Blood*, p. 316, 1913.
[26] Hasselbalch and Lindhard, *Biochem. Zeitschr.*, 68, p. 293, 1915.
[27] Lindhard, *Journ. of Physiol.*, XLII, p. 337, 1911.
[28] Hasselbalch and Lindhard, *Skand. Arch. f. Physiol.*, XXVIII, 1911.
[29] Campbell, Douglas, Haldane, and Hobson, *Journ. of Physiol.*, XLVI, p. 301, 1913.

alveolar air and arterial blood causes an increase of about 100 per cent in the resting alveolar ventilation, and from Figure 54 it will be seen that this corresponds to a difference of .012 in PH. This difference, large as its physiological effect is, cannot be detected with certainty by the electrometric method, or by indicators, and is quite undetectable by the shifting of the dissociation curve of oxyhaemoglobin. Nevertheless a twentieth of this difference would produce an easily measurable effect on the breathing or alveolar CO_2 pressure. The astounding delicacy of the regulation of blood reaction is thus evident. No existing physical or chemical method of discriminating differences in reaction approaches in delicacy the physiological reaction. Unfortunately, however, the quantitative significance of our calculation has not yet been appreciated. The blood within the living body is still treated as if its reaction were not only variable, during rest, as it is, but capable of showing the variations by the existing very rough chemical and physical reactions. One might as well try to cut delicate histological sections with a blunt carving knife, as try to demonstrate ordinary very minute changes in blood reaction by the existing physical and chemical methods.

It was discovered by Christiansen, Douglas, and myself, as previously set forth, that the reduction of oxyhaemoglobin, as this occurs in the course of the circulation, has an effect resembling that of the addition of alkali to the blood. Thus the CO_2 pressure of the blood in the systemic capillaries is prevented from rising nearly as high as it would otherwise do. The hydrogen ion concentration of the blood is also prevented from rising in correspondence with the actual greatly restricted increase in CO_2 pressure. Accordingly the actual increase of hydrogen ion concentration in mixed venous as compared with arterial blood must be very small. In this way the extraordinarily delicate regulation of the reaction of arterial blood becomes much more intelligible, as venous blood must be very little less alkaline than arterial blood. In determining the hydrogen ion concentration of blood by the ordinary electrometrical method it is necessary to reduce the blood first, as the presence of oxygen interferes with the action of the hydrogen electrode.[30] Thus the determination is made on reduced, or by Barcroft's method on partially reduced, blood, but with a CO_2 pressure corresponding to that of arterial blood. It is

[30] Peters, *Journ. of Physiol.*, 48, *Proc. Phys. Soc.*, p. vii, 1914. It is probable that owing to incomplete reduction the values obtained by Hasselbalch have been slightly too low.

evident, therefore, that the value obtained for the hydrogen ion concentration is lower than that which exists in either arterial or venous blood in the living body. To investigate the amount of this difference Parsons[31] adopted the method of determining the hydrogen ion concentration, not in whole blood, but in its serum, of which the hydrogen ion concentration is not altered when free oxygen is removed. Using this method, he found that with normal blood the PH at a constant pressure of CO_2 at anywhere near the alveolar CO_2 pressure is greater by .038 in the oxygenated than the reduced blood. Figure 55 show his results. From them and

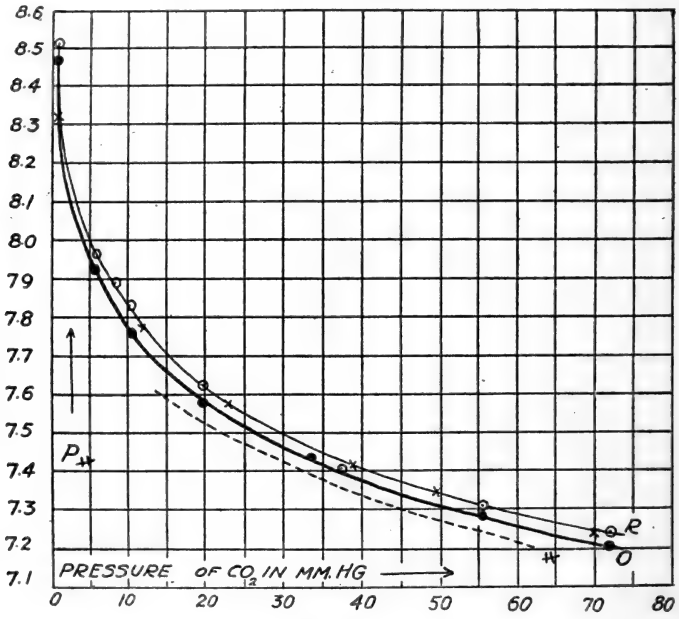

Figure 55.

Curve R, completely reduced blood. Curve O, fully oxygenated blood. X, direct measurements on reduced blood without removal of corpuscles. H, Hasselbalch's curve.

from Figure 26 (Chapter V) it is possible to calculate what the difference for normal blood between the PH of arterial and mixed venous blood is, assuming that the venous blood has lost a certain proportion of its oxygen and simply gained a corresponding proportion of CO_2. If the venous blood had lost all its

[31] Parsons, *Journ. of Physiol.*, LI, p. 440, 1917.

oxygen the difference would be .07, as shown in Figure 56 from Parsons's paper. Assuming, however, that the mixed venous blood loses normally a fourth of its combined oxygen (see Chapter X), the difference is only .0175—a difference which can hardly be detected except by physiological methods, and which corresponds to a rise of only 0.3 per cent in the alveolar CO_2 percentage.

It might be supposed that in order to obtain the true PH of arterial blood under abnormal conditions all that is necessary is to add a constant to the value obtained for reduced blood; and that consequently the ordinary methods of determining PH (whether electrometrically or from indications given by the dissociation

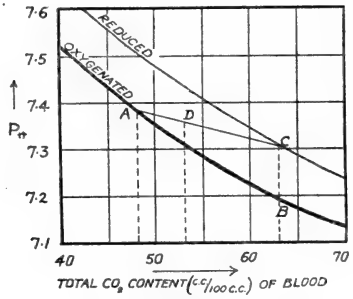

Figure 56.

The slope of the line AC shows the rate at which the PH of blood increases as its content of CO_2 increases in the capillaries.

curve of oxyhaemoglobin) give reliable indications of any alteration in the PH of the arterial blood. There is, however, no evidence at present that this is the case, and there is in fact other evidence pointing in the opposite direction.

If, in the first place, the proportion of haemoglobin in the blood is altered, there will presumably be an alteration in the difference between the PH of fully oxygenated and of reduced blood. Apart altogether from this, however, there may be another kind of alteration in this difference. In the paper by Christiansen, Douglas, and myself, it was pointed out that the probable reason why reduced blood appears to be more alkaline than oxygenated blood is that on reduction the haemoglobin becomes more aggregated and therefore acts less strongly as an acid. In abnormal blood the degree of increased aggregation may be either increased or diminished. This will alter the difference in PH between oxygenated and reduced blood, and will also, if our theory as to the cause of

the peculiar shape of the dissociation curve of the oxyhaemoglobin in blood is correct, alter the shape of the dissociation curve.

In a quite recent paper Lovatt Evans[32] has shown that the PH of blood as determined colorimetrically by an indicator method is as much as 0.2 higher than when determined electrometrically. He has also shown pretty conclusively that the electrometric method has an error owing to the formation of formate from carbonate by catalytic action at the electrode, so that the PH of blood is higher by 0.2 than appears from the electrometric determinations. The new colorimetric method of Dale and Evans[33] seems to avoid several defects inherent in the electrometric method as applied to blood.

On the existing evidence, and allowing for mistaken inferences which have been drawn in ignorance of the peculiar properties of haemoglobin (as it exists in the red corpuscles) in regulating the PH of blood, it seems evident that during health the regulation of the reaction of the arterial blood is carried out with a delicacy and constancy of which we can at present only obtain a real conception by physiological observations. The foregoing discussions show that there are at least three regulators of the reaction—the lungs, the kidneys, and the liver. We can also now form a general conception of how these regulators act under ordinary conditions.

The part played by the lungs in this regulation is, quite clearly, to deal rapidly with variations in reaction due to varying production of CO_2, and particularly to the rapid variation caused by varying muscular exertion. By keeping the alveolar CO_2 pressure approximately normal, the action of the lungs keeps the arterial CO_2 pressure approximately normal; and so long as the dissociation curve for CO_2 in the blood is also kept normal by other means the reaction of the arterial blood is also kept almost exactly normal. If, however, owing to rapid production of lactic acid in muscles, rapid secretion of gastric or pancreatic juice, or other causes, the dissociation curve for CO_2 is temporarily disturbed, the breathing compensates approximately at once for the disturbance in blood reaction.

The part played by the kidneys seems also clear. They not only respond to the minutest variations in blood alkalinity by secreting more acid or more alkaline urine, but also tend to keep normal the proportion of soda and potash and other crystalloid substances existing in the blood. In this way the dissociation curve of the CO_2

[32] Lovatt Evans, *Journ. of Physiol.*, LIV, p. 353, 1921.
[33] Dale and Evans, *Journ. of Physiol.*, LIV, p. 167, 1920.

in blood is kept normal; and no physiological phenomenon is more striking than the constancy of this curve under normal conditions. If the proportion of available alkali is temporarily diminished by acid poured out into the blood, the kidneys help to restore it to normal again; and similarly with excess of alkali. The action of the kidneys is slow compared with that of the lungs; but is apparently still more delicate. As L. J. Henderson was the first to point out clearly[34] the PH of urine is no measure of the total acid excreted in it, since urine, like blood, contains buffer substances. Among these phosphoric acid plays the main part in acid urine, and carbonic acid in alkaline urine. To measure the acid excreted titration must be employed, and in titrating alkaline urine the combining CO_2 must be allowed to escape.[35]

The part played by the liver is to neutralize as far as possible the disturbing effect of any excess of acid or of alkali introduced into the body through the intestines, or formed in the tissues. By allowing more, or less, ammonia to enter the circulation the liver regulates the reaction of the blood; and the neutral ammonia salts are afterwards eliminated by the kidneys as being foreign substances. The importance of the part played by the liver under normal conditions is evident enough in view of the fact that in man the ammonia excreted daily would just about suffice to neutralize all the sulphuric acid formed daily. Like that of the kidneys, the action of the liver is slow and delicate as compared with that of the lungs.

Possibly the intestines also play an active part in regulating the blood reaction. It is known, at any rate, that alkali may be eliminated from them in the form of insoluble alkaline phosphates.

We have now to consider how this joint regulation behaves when the action of one of the regulators is interfered with; and the case of interference with the lung regulation will be considered first. This regulation may be disturbed in various ways, but perhaps most is known at present as to its disturbance owing to the fact that under abnormal conditions the stimulus of anoxaemia increases the breathing, and thus disturbs the normal relation between the lung ventilation and the degree of stimulus of the respiratory center owing to varying reaction of the arterial blood. The history of the development of knowledge on this point is very instructive.

[34] L. J. Henderson, *Amer. Journ. of Physiol.*, 21, p. 427, 1908.

[35] Davies, J. B. S. Haldane, and Kennaway, *Journ. of Physiol.*, LIV, p. 32, 1920.

It has already been shown in Chapters VI and VII that until the oxygen pressure of the inspired air is lowered by about a third, or that of the alveolar air to about half (i.e., from about 100 mm. to 50 mm.) there is no marked immediate increase in the breathing. The effect on the respiratory center of the very distinct degree

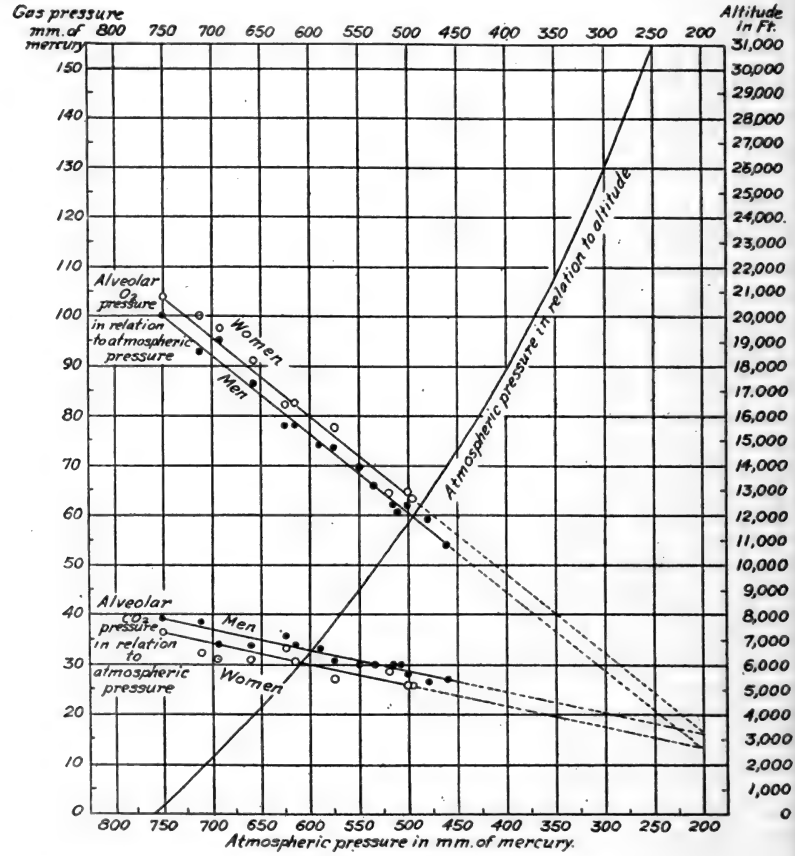

Figure 57.
Alveolar gas pressures in relation to barometric pressure or altitude.

of anoxaemia which is undoubtedly produced, in the manner explained in Chapter VII, is almost entirely masked by the contrary effect due to extra washing out of CO_2 and consequent lowering of the PH in the arterial blood. But if exposure to the lowered oxygen pressure is continued, not merely for perhaps an hour, but for days or weeks, there is a quite marked increase in

the breathing, as shown by a fall in the alveolar CO_2 pressure. This fact, already referred to in connection with the historical development of the theory of regulation of the breathing by the blood reaction, was brought out in full clearness by the investigations carried out in connection with the Pike's Peak expedition by Miss FitzGerald on persons fully acclimatized at different altitudes.[36] Figure 57 represents graphically her results on this subject. It will be seen that in such persons the alveolar CO_2 pressure falls regularly with increase of altitude. In other words the breathing increases in a regular ratio with diminution in the oxygen pressure of the inspired air.

What is the cause of this increase? Since the experiments, already referred to, of Boycott, Ogier Ward, and myself, it has been pretty generally assumed that in response to the stimulus of anoxaemia a slight acidosis, sufficient to account for the increased breathing, develops in the blood. This explanation received strong confirmation from the discovery by Barcroft in the Teneriffe experiments that the dissociation curve of the oxyhaemoglobin of the blood at high altitudes is sensibly the same in presence of the existing alveolar CO_2 pressure as at sea level in presence of the alveolar CO_2 pressure existing there. The extra acid, or diminished available alkali, present in the blood seemed just to compensate for what would otherwise be increased alkalinity due to the lowered CO_2 pressure. The physiological facts, however, do not correspond with the lactic acid theory. Moreover no excess of lactic acid could be discovered by Ryffel in the urine and hardly any in the blood, of persons exposed to low pressures in a respiration chamber or steel chamber,[37] or indeed in persons at high altitudes;[38] and no other abnormal acid could be discovered in the blood. Hence the theory of an acidosis due to formation of abnormal acids cannot be substantiated. In the report of the Pike's Peak Expedition we adopted the theory that the anoxaemia alters the activity of the kidneys in such a way that they regulate the blood to a lower level of alkalinity.

Another, and essentially similar, theory was adopted by Hasselbalch and Lindhard as the result of experiments in a steel chamber.[39] They found that the excretion of ammonia is markedly

[36] FitzGerald, *Phil. Trans. Roy. Soc.*, 203 (B), p. 351, 1913; and *Proc. Roy. Soc.*, 88 (B), p. 248, 1914. See also, Yandell Henderson, *Journ. of Biol. Chem.*, 1920.

[37] Ryffel, *Journ. of Physiol.*, XXXIX *(Proc. Physiol. Soc.)*, p. xxix, 1910.

[38] See Barcroft, *The Respiratory Function of the Blood*, p. 260.

[39] Hasselbalch and Lindhard, *Biochem. Zeitschr.*, 68, p. 295, 1915.

diminished at the lowered pressure, and were thus led to the theory that the acidosis of high altitudes is due to diminished formation of ammonia by the liver as a consequence of anoxaemia.

The question was again taken up in a series of experiments in steel chambers by Kellas, Kennaway, and myself, in which careful measurements were made of the excretion of acid and ammonia.[40] We found that even with a comparatively slight diminution of pressure there was a great diminution in the excretion of acid and ammonia, and the urine passed to the alkaline side of neutrality. The true explanation of the supposed acidosis then revealed itself to us. The kidneys and liver were responding quite normally, but to an alkalosis, this alkalosis being produced by the increase (largely masked) of breathing caused by the anoxaemia. A similar view of the supposed acidosis of high altitudes was reached, on independent grounds which will be discussed below, by Yandell Henderson.[41]

The increased excretion of alkali and diminished formation of ammonia lead gradually towards a compensation of the alkalosis and simultaneous relief of the anoxaemia, this relief being due to the increased oxygen supply to the lung alveoli, and to other causes discussed in Chapters IX and X. But the final result is a compromise. A certain small degree of anoxaemia and consequent alkalosis still remains, as evidenced by a continued low excretion of ammonia and other physiological symptoms and by the fact that on removal of the anoxaemia there is a quite appreciable *immediate* rise in the alveolar CO_2 pressure, as was shown for instance, when we breathed air enriched with oxygen after we had become acclimatized on Pike's Peak. The extra excretion of alkali comes to an end, however, as the kidneys cannot reduce the blood alkali further without very serious alteration of the normal balance of salts in the blood.

The supposed acidosis is thus not an acidosis at all, but the incomplete compensation of an alkalosis. The "adaptation" of the blood so as to relieve the alkalosis and anoxaemia is also nothing but an extension of the everyday adaptations by which alkalosis and anoxaemia are continuously being prevented. The reason why the adaptation takes so long at low atmospheric pressures is simply that it takes a long time for the kidneys and liver to get level with the very prolonged and considerable work thrown on them by progressive increase in the breathing. They are, as it were, pursu-

[40] Kellas, Kennaway, and Haldane, *Journ. of Physiol.*, LIII, p. 181, 1919.

[41] Yandell Henderson, *Science* (N. S.), XLIX, p. 431, 1910; see also the series of papers by Henderson and Haggard, *Journ. of Biol. Chem.*, 1919-1921 incl.

ing in a leisurely manner a goal which is constantly receding from them, so that it is a long time before they finally reach it. The quantity of alkali which has to be removed from the blood and tissues is very large, as a simple calculation will show.

With the compensation of the alkalosis there also comes compensation of any secondary anoxaemia caused by the alkalosis as a consequence of the Bohr effect discussed so fully in Chapters IV and VI. Owing to the increased breathing the percentage saturation of the arterial blood is (without any allowance for increased oxygen secretion) as high as at first, while the oxygen pressure in the systemic capillaries is higher (i.e., nearer normal) on account of the decreased alkalosis. Cyanosis may be, however, quite as marked as before. By the administration of acid the adaptation to a lowered oxygenation of the arterial blood could doubtless be hastened.

The study of responses to the anoxaemia and alkalosis of high altitudes is of great medical interest, since, as already explained in the two preceding chapters, anoxaemia is a very common and often extremely dangerous clinical condition. There can be no doubt that the same responses as occur in healthy persons at high altitudes occur also in patients suffering from anoxaemia. It is therefore important not to misunderstand these responses. During the war, for instance, the intensely dangerous anoxaemia of acute gas poisoning and "shock" was sometimes treated by the administration of alkalies, on the theory, based on nothing but the unintelligent use of a new method of blood examination, that the patients were suffering from "acidosis." Physiological knowledge as to the deadly significance of serious anoxaemia, and the (supposed) acidosis as an adaptive change tending towards its compensation, was ignored. It is also important to understand that the adaptive changes require time, and that so-called palliative treatment, by giving this time, may in reality be curative.

Another cause of interference with the lung regulation of blood reaction is to place an animal or man in an atmosphere in which the percentage or pressure of CO_2 is so high that the regulation breaks down completely and there is in consequence an excessive and lasting fall in the PH of the blood. This condition was studied recently in animals by Yandell Henderson and Haggard.[42] They made the very important and significant discovery that the acidosis thus produced gradually brings about a marked increase in the

[42] Yandell Henderson and Haggard, *Journ. of Biol. Chem.*, XXXIII, p. 333, 1918.

capacity of the blood for combining with CO_2. In other words the dissociation curve of the CO_2 in blood, if plotted as in Figure 25, would occupy a higher position. This is evidently a change tending to counteract the diminished blood alkalinity produced by the excess of CO_2.

The same observers found that on prolonged and forced artificial ventilation of the lungs, so as to produce a condition of alkalosis, there is a corresponding diminution in the capacity of the blood for combining with CO_2. This is also a change towards the normal alkalinity. Thus in an alkalosis produced by excessive removal of CO_2 the available alkali in the blood diminished, while in an acidosis produced by excess of CO_2 the available alkali increased. It is clear that in either case the change is of a character tending to neutralize the change in blood reaction.

What is the significance of this change? It occurs much too quickly to be capable of explanation as due to an adaptive response by the kidneys and liver. The probability is, therefore, that it is due to exchange of anions between the tissues and blood in the manner discussed in Chapter IV (Addendum), and is indicative, therefore, of very severe alkalosis or acidosis of the tissues. This would help to account for the very dangerous symptoms which Henderson and Haggard found to be an accompaniment of any considerable diminution of the available alkali of the blood, when the diminution was produced by excessive artificial respiration. Thus a diminution of about 40 per cent in the capacity of the blood for combining with CO_2 was fatal to the animal. A similar diminution due to the acidosis caused by running quickly up a stair is hardly felt at all. In the latter case the diminution in available alkali in the blood indicates a quite trifling acidosis, while in the former a similar change in the blood indicates a severe and fatal alkalosis.

These and other experiments[43] of these investigators brought out in a striking manner that it is a complete mistake to regard diminution of the available alkali (or so-called "alkaline reserve") of the blood as a definite sign of acidosis in the living body. The "alkaline reserve" of the blood and whole body is only another name for its "titration alkalinity"; and it has already been shown above that titration alkalinity is no measure, and not even a sure qualitative indication, of the real alkalinity of the blood. In the experiments of Yandell Henderson and Haggard the animals were

[43] Haggard and Henderson, *Journ. of Biol. Chem.*, XXXIX, p. 163, 1919; and XLIII, pp. 3, 15, and 29, 1920.

suffering from severe alkalosis although the "alkaline reserve" or titration alkalinity of their blood was greatly diminished; and similarly they were suffering from severe acidosis although the "alkaline reserve" of their blood was greatly increased.

It was these observations that led Yandell Henderson to the same conclusion which we reached—namely, that in the anoxaemia of high altitudes there is a condition of alkalosis, and not of acidosis, in spite of the greatly reduced titration alkalinity or "alkaline reserve" of the blood.

A ready method of interfering temporarily with the regulation of blood reaction by the lungs is forced breathing. This can be continued for a considerable time if it is employed in moderation. Leathes[44] found that if forced breathing is continued for some time the urine becomes alkaline to litmus, and the titration alkalinity has still more recently been investigated by Davies, J. B. S. Haldane, and Kennaway.[45] The titration alkalinity is, however, not so striking as after a large dose of sodium bicarbonate has been taken. The same observers found that after a large dose of sodium bicarbonate there was not only a rise of as much as 1 per cent in the alveolar CO_2 pressure for some hours, but the available alkali in the blood (as shown by the dissociation curve for CO_2) was markedly increased, while there was also a great increase in the titration alkalinity of the urine. Large quantities of bicarbonate (readily determined by the blood-gas apparatus) were present in the urine, which effervesced briskly on the addition of acid, though the actual alkalinity of the urine was of course only feeble, since the CO_2 acted as a buffer. The *titration* alkalinity (after removal of liberated CO_2) was equivalent to nearly 1 per cent of HCl. The ammonia had completely disappeared from the urine, and this was also the case after forced breathing, although such a degree of forced breathing as was practicable did not appreciably diminish the available alkali in the blood within one and one-half hours. A stay of several hours in air containing 5 to 6 per cent of CO_2 was also not sufficient to increase appreciably the available alkali of the blood, although the titration acidity of the urine was increased, along with increased excretion of ammonia. Collip has, however, found that, as might be expected from the change in distribution of acid and alkali between plasma and corpuscles

[44] Leathes, *Brit. Med. Journ.*, Aug. 9, 1919.

[45] Davies, J. B. S. Haldane, and Kennaway, *Journ. of Physiol.*, LIV, p. 32, 1920.

when the PH of blood is altered, the alkaline reserve of the plasma was distinctly diminished by forced breathing.[46]

The blood reaction may, of course, be disturbed in other ways than by interference with respiration. One of these ways is by ingestion of acids or by production within the body of great excess of some organic acid. Walter's experiments, interpreted in the light of our present knowledge, showed the effects of acid poisoning in stimulating to the utmost all the means of diminishing acidosis, including excessive breathing, greatly increased formation of ammonia, and secretion, presumably, of an abnormally acid urine. The titration alkalinity or "alkaline reserve" of the blood and doubtless also of the whole body was evidently diminished very greatly.

Christiansen, Douglas, and Haldane produced a temporary true acidosis by flooding the blood with lactic acid produced by muscular anoxaemia during the heavy exertion of running several times upstairs. In this case two results followed. In the first place there was a fall in the resting alveolar CO_2 pressure, which was, in several experiments, about 39 mm. before the exertion, and 30.5 mm. about 10 minutes after the exertion. The blood absorbed about 49 volumes of CO_2 per 100 of blood before the exertion in presence of the existing alveolar CO_2 pressure, and only about 28 afterwards. After one and one-half hours both the resting alveolar CO_2 pressure and the absorbing power of the blood for CO_2 had returned to normal.

In these experiments the capacity of the blood for absorbing CO_2 at a CO_2 pressure of 40 mm. had been reduced by about 40 per cent, and the resting alveolar CO_2 pressure by about 20 per cent, corresponding to an increase of about 25 per cent in the lung ventilation. There was thus a very distinct acidosis; but reference to the calculations already made will show that the acidosis could not have been detected by any existing method of directly estimating hydrogen ion concentration.

The great drop in the capacity of the blood for combining with CO_2 suggests at first that the blood had become correspondingly inefficient as a carrier of CO_2 from the tissues to the lungs, and that this deficiency could only be made up by a greatly increased circulation rate, if it was made up at all. The truth, however, is that the main difference produced was that the dead weight of CO_2 always carried round by the blood was greatly diminished. As a carrier of CO_2 from the tissues to the lungs, the blood was

[46] *Amer. Journ. of Physiol.*, LI, p. 568, 1920.

nearly as efficient as normal blood. This is due to the fact that, as already explained in Chapter V, the haemoglobin and other proteins play the essential part in the actual conveyance of CO_2 from the tissues to the lungs, and can still play this part in spite of what, in a physiological sense, is extreme acidosis.

The experiments were practically a replica in man of the experiments of Geppert and Zuntz on muscular activity in dogs (Chapter I). In discussing these experiments Priestley and I were not aware that a very great diminution of the CO_2 content of the blood may be caused by acidosis without any serious diminution in the capacity of the blood for conveying CO_2 from the tissues to the lungs. The discovery made in 1914 by Christiansen, Douglas, and myself has greatly altered the previously existing ideas as to the conveyance of CO_2 from the tissues.

The comparatively rapid recovery of the blood after the flooding of the body with lactic acid was evidently due to the fact that lactic acid was rapidly oxidized before the slight acidosis actually produced had time to cause any considerable extra excretion of acid by the kidneys, or formation of ammonia by the liver. Had the acidosis been produced by a mineral acid it would probably have taken far longer to pass off.

Disturbance of the blood reaction may be artificially produced by the ingestion of acids or alkalies, or even, to a slight extent, by varying the character of the diet. It requires a very large amount of acid or alkali to produce any considerable disturbance. This is partly due to the abundance of buffer substances in the body, but still more to the effective means (variations in lung ventilation, ammonia formation, and excretion of acid or alkali by the kidneys) which the body possesses of active defence against disturbance of reaction. If the administration of acids or alkalies is used medicinally as a means of assistance in the regulation of the blood reaction, the large doses required must be borne in mind. Small doses cannot but be practically useless. The amelioration of the physiological symptoms of acidosis or alkalosis will form the safest guide to what is required; but it is evidently very important not to mistake alkalosis for acidosis, or the hyperpnoea of acidosis for the abnormal breathing caused by anoxaemia or an exhausted or "neurasthenic" respiratory center. There are no short cuts to decisions on such a subject. A physician must be a real physician, and must have learned to be one by study of how the living body behaves—of what its φύσις is, to use the old expression of Hippocrates.

As the kidneys are essentially concerned in the regulation of the reaction within the body, it is evident that failure of the kidneys may cause serious disturbance of reaction. As, moreover, normal human urine is acid, and presumably is so in all animals if food is not taken, the disturbance will naturally be in the direction of producing acidosis. Hyperpnoea and other symptoms suggestive of acidosis are commonly met with as an accompaniment of serious inflammation of the kidneys; and these symptoms are now commonly attributed to acidosis. One peculiarity of them is that there may be little or no increase in the ratio of ammonia to total nitrogen excreted.

Considerable new light is thrown on the causes of acidosis by quite recent experiments of J. B. S. Haldane.[47] The experiments consisted in taking large doses of NH_4Cl during two or three days, so that an abnormal percentage of ammonia was present in the blood. As a result there were very pronounced respiratory and other symptoms of acidosis, including a marked fall in the available alkali of the blood. Owing to the excess of ammonia in the blood part of the ammonia of the NH_4Cl had been converted into urea, setting free much HCl into the blood. The normal response in which the liver sets free ammonia into the blood on the approach of acidosis was of course reversed, and though the urine was very acid the kidneys were unable by themselves to cope effectively with the HCl, so that acidosis resulted.

A further result was that the supply of phosphate in the body began to run short, so that the kidneys could not excrete so much acid as usual for a corresponding acidosis. When neutralized sodium phosphate was taken the excretion of acid was much increased, and the acidosis passed off correspondingly more rapidly.

These experiments are of special interest, as they revealed a practicable method of artificially producing marked symptoms of acidosis in man. Previous attempts to do so by drinking large quantities of dilute HCl or acid sodium phosphate had failed owing to the efficacy of the physiological means of regulation. It seems likely that in the acidosis of Bright's disease the formation of ammonia by the liver is checked by the accumulation of ammonia in the blood owing to the inefficiency of the kidneys. Hence the ratio of ammonia to toal nitrogen in the urine is not increased.

It follows from the facts brought forward in this chapter that

[47] J. B. S. Haldane, *Journ. of Physiol.*, LV, 1921.

the regulation of alveolar and arterial CO_2 pressure resolves itself into regulation of the blood reaction, and that the blood reaction itself is a normal which is constantly being regulated within marvelously narrow limits—so narrow that the variations, evident though they are made by physiological reactions, cannot be followed adequately by existing physical and chemical methods.

At this point it seems desirable to consider and criticize some of the indirect means which have been used for estimating variations in the hydrogen ion concentration of the blood. In recent years the capacity of the blood, or of its serum, for combining with CO_2 has commonly been taken as an index of hydrogen ion concentration, this capacity being also alluded to as a measure of the "alkaline reserve" of the blood. It is evident that the "alkaline reserve" of the blood is only another name for the "titration alkalinity" when CO_2 is allowed to escape. It is also evident from facts described above that the alkaline reserve is increased in conditions of acute acidosis due to excess of CO_2, and diminished in conditions of acute alkalosis due to excessive lung ventilation caused by artificial respiration or anoxaemia. Hence although the alkaline reserve is diminished in acidosis due to the presence of abnormal acids in the blood, a diminution in alkaline reserve cannot be regarded as by itself an index of acidosis. There is, in fact, no necessary connection between diminution in alkaline reserve or titration alkalinity and diminution in blood alkalinity.

Another indirect method which has been used for estimating variations in alkalinity is observation of one or more points in the dissociation curve of the oxyhaemoglobin of the blood in presence of the existing alveolar CO_2 pressure. This method is due to Barcroft and his pupils, and is based on the following facts. (1) As was shown in Chapter IV, each point in the dissociation curve of oxy- or CO-haemoglobin in blood is simply displaced to a proportional distance to the right or left on varying within wide limits the partial pressure of CO_2. Thus only one constant in the equation expressing the curve is altered. (2) It was shown by Peters,[48] and this had been completely confirmed by Hasselbalch,[49] that the alteration in the constant depends, in cases where only the CO_2 pressure is varied, on alterations in the hydrogen ion concentration, and can thus be used as a measure of it. Barcroft and others have therefore used the alteration in the constant as a measure in all cases of variation of hydrogen ion concentration in the blood.

[48] Barcroft, *The Respiratory Functions of the Blood*, p. 316.
[49] Hasselbalch, *Biochem. Zeitschr.*, 78, p. 132, 1916.

In persons at high altitudes, for instance, the constant is apparently quite normal in presence of the existing alveolar CO_2 pressure; and from this fact it was inferred that the hydrogen ion concentration of the blood is also normal, as already mentioned. On the other hand, in persons who have shortly before undergone some excessive muscular exertion the constant is very markedly altered; and from this fact a corresponding increase of hydrogen ion concentration in the blood is inferred. The same method has been employed for estimating variations of hydrogen ion concentration in the blood of patients.

When, however, the facts are examined more closely it appears that there must be a flaw in the reasoning. In the case of persons who have completed some severe muscular exertion in a few minutes before, there is no physiological evidence of anything but a most trifling acidosis, such as could not possibly be detected by alterations in the constant of the dissociation curve. The breathing is only increased to such an extent as to reduce the alveolar CO_2 pressure by about a fifth. This only corresponds to an acidosis equivalent to what would be produced by a rise of 0.3 mm. in the alveolar CO_2 pressure; and such a rise would be entirely inappreciable in its effect on the dissociation curve of oxyhaemoglobin. The rise apparently indicated by the alteration in the constant is enormously greater. Hence it appears that there must be some other cause for the alteration than rise in hydrogen ion concentration. This other cause is probably operative in many cases of pathological acidosis.

Another indirect method of measuring hydrogen ion concentration has been proposed by Hasselbalch.[50] He showed quite clearly that when the pressure of CO_2 is varied in blood or even serum the hydrogen ion concentration, as separately determined, is proportional to the ratio of combined CO_2 (which, as already explained, is a measure of the bicarbonate present) to free CO_2 when allowance is made for the percentage ionization of the free CO_2 and bicarbonate. This corresponds with the fact that the blood behaves as if more alkali were constantly being added to it in proportion as its reaction approaches the neutral point. It is very remarkable how closely Hasselbalch's law holds for different kinds of blood and in blood serum, in spite of great differences in the dissociation curves for CO_2. Figure 58 from Hasselbalch's paper is also very interesting as showing (for fresh ox blood) the differences in the dissociation curves for serum, blood, and corpuscles.

[50] Hasselbalch, *Biochem. Zeitschr.*, 78, p. 112, 1916.

These differences are just what might be expected in view of the action of haemoglobin as a weak acid in alkaline solutions. In spite of the great differences in the dissociation curves of blood and serum Hasselbalch's law held good. He therefore applied it as a means of calculating the hydrogen ion concentration of corpuscles and of abnormal blood, and seemed justified in doing so.

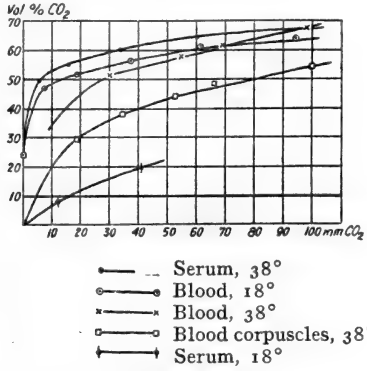

Figure 58.
CO_2 dissociation curves (from Hasselbalch loc. cit.)

Nevertheless this method, like that of Barcroft and Peters, seems to break down with abnormal blood. As an example of abnormal blood he took, from the paper already referred to by Christiansen, Douglas, and myself, experiments in which Douglas had flooded his blood with lactic acid by running quickly a number of times up and down the laboratory stairs at intervals during about a quarter of an hour. As a consequence his blood had lost about 40 per cent of its normal power of combining with CO_2, and his resting alveolar CO_2 pressure was diminished by about a fifth. The samples were taken about ten minutes after the last ascent of the stairs, and all sensible hyperpnoea had passed off. From the data given, Hasselbalch calculates, in accordance with the law he had discovered for the same blood at varying pressures of CO_2, that the PH of Douglas's arterial blood had fallen by .12. This would, in accordance with the data given above as to the effects of increase of PH on the breathing, suffice to increase the breathing to about ten times its resting value. Indeed Hasselbalch evidently believed that there must have been such an increase, since he speaks of the immensely increased breathing being unable to compensate for the decrease in PH. The breathing was, however, perfectly quiet and apparently normal, though the lowering of

the alveolar CO_2 pressure showed that it was about a fourth deeper than it otherwise would have been. On the physiological evidence, therefore, the fall in PH was only about .003, instead of .12, or only one-fortieth as much as calculated. From this example it would seem to follow that Hasselbalch's method, when extended to abnormal blood, is as unreliable as that of Barcroft and Peters. Further investigation as to methods of determining hydrogen ion concentration in abnormal blood seems to be much needed.

Except by observation of physiological reactions, there seems at present to be no method of estimating in a reliable manner the small variations in PH which are of so much physiological importance. Hasselbalch estimates that a difference of .03 can be detected in single determinations by the electrometrical method; but this is a very large difference, corresponding to an increase of 250 per cent in the breathing. The colorimetric method by means of indicators is equally rough. Time and effort will continue to be wasted on futile measurements until the extreme fineness of the physiological regulation of PH in the blood and tissues is more fully realized.

REACTION OF THE BLOOD IN EIGHT DIFFERENT WOMEN BEFORE AND AFTER CHILDBIRTH

	PH. at CO_2 pressure 40 mm.		Alveolar CO_2 pressure		PH at alveolar CO_2 pressure	
	Before	*After*	*Before*	*After*	*Before*	*After*
	7.40	7.44	31.0	42.2	7.44	7.43
	7.40	7.48	27.7	43.5	7.49	7.46
	7.45	7.45	35.6	39.8	7.48	7.45
	7.39	7.43	32.5	43.5	7.42	7.42
	7.39	7.44	32.7	37.7	7.43	7.45
	7.38	7.45	27.7	33.5	7.45	7.49
	7.38	7.43	30.3	38.3	7.41	7.44
	7.35	7.38	33.8	37.3	7.38	7.40
Mean	7.39	7.44	31.3	39.5	7.44	7.44

On account of various sources of error, already alluded to, in the electrometrical or other measurements of PH, we are still without much very exact information as to the permanent steadiness during health of the alkalinity of the blood under resting conditions. In this connection some very interesting observations have been made by Hasselbalch and Gammeltoft on the PH of the

blood during and after pregnancy.[51] It had already been found by Hasselbalch and others that the alveolar CO_2 pressure is much lower than normal during pregnancy. Taking advantage of this fact, they determined the PH of arterial blood before and after childbirth with the results shown in the accompanying table.

Allowing for the probable errors in determining the PH and alveolar CO_2 pressure, these figures seem to show that the fall in alveolar CO_2 pressure compensates within the limits of accuracy of the electrometric method for a fall in the PH of the blood which would otherwise occur. The mean of the first two columns shows that this fall in PH would have been 0.05, whereas the compensating fall in alveolar CO_2 pressure was 8.2 mm. as shown by the mean for the second two columns. Hence a difference of 0.01 in PH corresponds to a difference of 1.6 mm. of CO_2 pressure, or 0.23 per cent of CO_2 in alveolar air. We have already seen, however, that a change of about this amount in alveolar CO_2 pressure is sufficient to cause either apnoea or doubling of the alveolar ventilation according to its direction. Even under the most favorable conditions it is hardly possible at present to determine differences in PH within the body to within 0.03 in single observations; but by measuring the variations in lung ventilation as compared with production of CO_2 we have an index of change in PH which is at least 50 times as sensitive as the existing direct electrometric method, exact as this is in comparison with older methods.

Although the measurements of PH showed no change in the alkalinity of the blood during pregnancy, yet the fall in alveolar CO_2 pressure indicated that there was an increase of 25 per cent in the lung ventilation per unit of CO_2 given off. This, therefore, would correspond to an "acidosis" to the extent of a PH of 0.003—an amount far too small for direct measurement. That it was acidosis which caused the increase in the breathing was shown by the fact that the increase was accompanied by an increase of about 20 per cent in the proportion of nitrogen excreted as NH_3 to total nitrogen excreted in the urine. The authors conclude that there is an increased acid production in the body during pregnancy (or perhaps an increased drain of alkali from the body of the mother), but that it is compensated by increased breathing and formation of NH_3. It is true that relatively to the degree of accuracy at present attainable in determining the PH of blood the compensation is perfect. But if the compensation were really perfect we should be landed in the position of the vitalists of assuming effects

[51] Hasselbalch and Gammeltoft, *Biochem. Zeitschr.*, 68, p. 206, 1915.

produced without any measureable cause. In reality the acidosis is not completely compensated, and the incompleteness is only hidden by the extreme roughness of the method of measurement in comparison with the fineness of the physiological reaction.

The table seems to indicate that the normal PH is not quite the same, though very nearly the same, in different individuals. For the present, however, this conclusion is rather doubtful, in view of the fact that the measurements were for imperfectly reduced blood. We have seen already that in spite of the accuracy of regulation there are individual differences in the normal alveolar CO_2 pressure, the normal composition of haemoglobin, and the normal dissociation curve of blood for CO_2. As regards every detail of structure and function we may be certain of finding similar differences when the measurements are made with sufficient accuracy; and this doubtless applies also to even the PH of the blood.

We have already considered one cause which alters the PH to which the respiratory center regulates. This cause is anoxaemia. At high altitudes the body is in the long run protected to a large extent from the effects of the alkalosis thus produced, because the kidneys and liver still react almost true to the normal PH. There can be no doubt that other causes, such as the action of anaesthetics or poisons, or of other small changes in the composition of the blood, would have a similar effect in altering the standard to which the PH regulation of the arterial blood is set. This question, and the question how the PH is regulated, not merely in the arterial blood, but in the systemic capillaries, will be deferred to Chapters X and XIV.

We can now see much more clearly why it is that the resting alveolar CO_2 pressure is not quite steady in spite of the extreme sensitiveness of the respiratory center to the minutest variation in alveolar CO_2 pressure. There are various causes tending to disturb the constancy of the reaction of the blood; and the respiratory center, and not merely the kidneys and liver, must do its share in compensating for these disturbances. Hence the alveolar CO_2 pressure cannot remain completely steady during rest. One of these causes is the secretion of acid or alkaline digestive juices. On account of the secretion of acid gastric juices the alveolar CO_2 pressure rises distinctly very soon after a meal. The effects of a meal on alveolar CO_2 pressure have been investigated recently by Dodds.[52] He found that there is normally a sharp rise varying in different individuals, but usually amounting to about 4 mm. half

[52] Dodds, *Journ. of Physiol.*, LIV, p. 342, 1921.

an hour after the meal. This is rapidly followed by an equally marked fall below normal, culminating about one and one-half hours after the meal, with a subsequent rapid return to normal.

Bennett and Dodds[53] have found that the rise of alveolar CO_2 just after a meal is closely related to the concentration and rate of secretion of the gastric hydrochloric acid as indicated by samples taken from the stomach. In cases where there is little or no secretion of HCl the rise in alveolar CO_2 is absent, though the fall due to alkaline secretion into the intestine is still present. Another cause of variation in alveolar CO_2 pressure is the character of the diet. With an alkali-forming vegetable diet the alveolar CO_2 pressure is quite considerably higher than with an acid-forming meat diet. This was brought out very clearly in some of the experiments of Hasselbalch alluded to above; and he showed at the same time that the reaction of the urine varied in correspondence with the changes in alveolar CO_2 pressure.

During starvation the body is living on what amounts to an acid-forming diet, and Higgins[54] has shown that during starvation the alveolar CO_2 pressure falls. Perhaps the most striking effects are obtained with a carbohydrate-free diet. This leads to the formation within the body of a certain amount of aceto-acetic and oxybutyric acids, as in severe diabetes. Higgins, Peabody, and Fitz[55] showed that there is a striking fall in alveolar CO_2 pressure, together with a very large elimination of oxybutyric and aceto-acetic acid by the kidneys, and an accompanying large increase in ammonia excretion and excretion of acid.

All the available evidence points, therefore, to the conclusion that practically speaking the regulation of breathing in man during rest under normal conditions is regulation of the blood reaction. This very important conclusion is the outcome of the present chapter.

Addendum. Within the limits of the present book it is unfortunately impossible to deal in detail with the mass of quite recent literature bearing on the regulation of blood alkalinity. Some of this literature is based on assumptions with which, for the reasons already given, I am unable to agree: while other parts of it are concerned with details as to which it seems difficult for the present to form definite judgments. In general, however, it

[53] Bennett and Dodds, *Brit. Journ. of Exper. Pathol.*, II, p. 58, 1921.
[54] Higgins, Publication No. 203, *Carnegie Institution of Washington*, p. 168, 1915.
[55] Higgins, Peabody, and Fitz, *Journ. of Med. Research*, XXXIV, p. 263, 1916.

does not appear to me that anything which has recently been published, points to any important modification of the conclusions embodied in this chapter. In view of the great confusion which evidently exists as to the subject, it may, nevertheless, be useful to indicate more explicitly the reasons for regarding the words "acidosis" and "alkalosis" as denoting deviations towards the acid or alkaline side respectively of the normal reaction or hydrogen-ion concentration within the body.

Acidosis and alkalosis are now frequently regarded as conditions in which, whether or not there is an alteration in actual reaction, the "alkaline reserve" of the blood plasma is diminished or increased. This definition originated in a paper by Van Slyke and Cullen in which they pointed out the ease with which variations in the "alkaline reserve," or total capacity of the blood plasma for combining with CO_2 can be determined experimentally, and the advantages of using oxalated blood plasma in place of whole blood for the purpose.[56] Though they stated clearly that variations in alkaline reserve are no direct measure of the variations in actual reaction of the blood, they, very unfortunately as I think, proceeded to define "acidosis" as simply a condition in which the alkaline reserve of the blood is diminished. It is, however, to variations in reaction, and not in the conveniently measured alkaline reserve of the plasma that the body is reacting in conditions of acidosis or alkalosis; and to define acidosis or alkalosis as anything else than a deviation towards the acid or alkaline side of the normal reaction seems to me quite unjustifiable.

The confusion has been added to by the general failure to realize the extreme delicacy of physiological regulation of reaction, as compared with the comparative roughness of our present means of directly measuring changes in reaction. Thus in cases where there are all the physiological signs of acidosis, the available means of direct measurement may show no sign of the change; and hence it has been quite wrongly assumed that no change exists. This has contributed towards an acceptance of the definition of acidosis as a condition, not of increased hydrogen-ion concentration within the body, but of diminished alkaline reserve. The picturesque expression "alkaline reserve" is evidently an unfortunate one in so far as it suggests a reserve of alkali not in actual use. The alkali weakly combined in the body is in reality always in physiological use, and the most urgent symptoms of acidosis appear long before the alkaline reserve disappears.

[56] Van Slyke and Cullen, *Journ. of Biol. Chem.*, XXX, p. 289, 1917.

As was shown above, a difference of .012 in the PH of the blood is sufficient to double the resting breathing, or cause apnoea. This difference in PH corresponds to a difference of only about one part by weight of ionized hydrogen in a million million parts of blood. A continued difference of 0.1 in PH would in all probability cause danger to life. This is a much lower limit than has commonly been assumed. By forced breathing we can, it is true, produce a greater difference in the PH of arterial blood, and maintain this difference for an hour or more without loss of consciousness. The difference, however, applies only to the *arterial* blood. As will be shown in Chapter X, slowing of the circulation protects the tissues to a large extent from great rises in PH. It is possible, also, that active secretion of CO_2 by the lungs, as well as quickening of the circulation, protects similarly against fall in the PH of the tissues. Nevertheless, as Yandell Henderson has so clearly shown, when efficient forced respiration is kept up in animals for a sufficient time, not only do coma and progressive failure of circulation ensue, but so much damage is done that it is impossible to recover the animal on restoring the PH of the blood by administering CO_2, just as it is impossible to recover a patient who has suffered for a sufficient time from acute anoxaemia. That progressive and often irreparable damage ensues also during a condition of excessive acidosis is suggested by the phenomena of CO_2 poisoning and clinical acidosis. To what extent the damage during alkalosis is due directly to the rise in PH, or to the accompanying anoxaemia, we cannot at present say; and perhaps the question is at bottom merely academic. When the forced breathing is of oxygen instead of air the effects are much less marked, as mentioned above; but this may be because the circulation can be shut down more effectively when oxygen is breathed, and that hence the rise in PH in the tissues is diminished.

CHAPTER IX

Gas Secretion in the Lungs.

In the lungs the blood is separated from the alveolar air by two layers of living tissue, namely the capillary endothelium and the alveolar epithelium. What part in respiratory exchange is played by these very thin layers of living tissue? Is this part purely mechanical? In other words, do these layers behave towards the respiratory gases as any very thin non-living moist membrane would behave? Or do the living membranes play an active part in the process? We must now face this interesting, but also controversial subject.

There has been a tendency to assume that because these membranes are very thin they cannot play any active part. But it is not so long since even membranes consisting of cubical or columnar epithelial cells were supposed only to play a passive part in the separation of material; and the presumption that a thinner membrane of flattened cells cannot play an active part has come down to us from the time, about the middle of last century, when physico-chemical theories became dominant in physiology, and secretion in general was supposed to be a mere mechanical process like filtration or diffusion. Another prevalent presumption is that though liquids or dissolved solids may be actively secreted, gases probably pass through living membranes by simple diffusion.

So little information about gas secretion is usually to be found in physiological text books that it may be useful, before discussing gas secretion by the lungs, to give some account of gas secretion as it is now well known to exist in the swim bladder of fishes.

The swim bladder is morphologically a diverticulum of the alimentary canal, like the lungs. In some classes of fishes there is an open duct from the swim bladder into the alimentary canal, but in other classes this duct is closed. Quite evidently, the main function of the swim bladder is to make the specific gravity of the fish about equal to that of the water it displaces when the fish is at a certain depth. With a certain amount of gas in its swim bladder the fish will just float at a certain depth. It is, however, in a position of unstable equilibrium: for any movement upwards will cause expansion of the air, so that the fish will tend to rise with increasing velocity towards the surface; and any movement

downwards from the position of equilibrium will similarly tend to make the animal sink with increasing velocity to the bottom. When fishes are stunned by an explosion under water, about half of them float to the top, and the other half sink to the bottom. One has only to place a goldfish in a large and tall bottle of water provided with a perforated cork through which a thick walled tube containing water passes to another small bottle of water, in order to see how the fish deals with the situation. If the pressure in the large bottle is raised by raising the small bottle the fish will at first begin to sink, but will immediately turn its nose upwards and swim upwards, so as to reëstablish its position of unstable equilibrium; and conversely if the large bottle be lowered. It was formerly believed that a fish compresses or relaxes its swim bladder when it wishes to go downwards or upwards. That this is not the case was shown by Moreau[1] in a series of beautiful experiments. A fish is really confined temporarily to about a certain depth by its swim bladder; for if any cause tends to make it leave this depth the animal's response to the stimulus of expansion or contraction of its swim bladder soon brings it back to its proper depth.

The goldfish has an open duct to its swim bladder, so if the pressure is greatly diminished, as by connecting the large bottle to a filter pump, the air of the swim bladder comes bubbling out of the animal's mouth. If the pressure is now restored to normal the animal sinks to the bottom, and after a few fruitless efforts to swim upwards lies helpless on its side. If it is left there for some time, however, it gradually becomes more buoyant, and after a certain number of hours it will be swimming about as usual, with its swim bladder full of gas. If a fish has a closed swim bladder, and the gas from this is removed by means of a hypodermic syringe, the fish also sinks at first, but soon refills its swim bladder with gas. How is this gas produced, and what is it? It cannot have been swallowed as air, as the fish has been lying in water at the bottom all the time, or has a closed swim bladder. This brings us to gas secretion.

About the beginning of last century the eminent French physicist Biot was engaged in survey work in the Mediterranean, and was attracted by the observation that fishes caught with a line at great depths come to the surface and lie helpless with their swim bladders distended with gas and sometimes projecting out through the mouth. He determined to analyze the gas, and having intro-

[1] Moreau, *Mémoires de Physiologie*, Paris, 1877.

duced some of it, along with excess of hydrogen, into a glass "eudiometer" he passed a spark. Instead of the mild explosion usual in air analyses, there was a violent explosion which broke his instrument. He then knew that he had made a most significant discovery, as the gas he was analyzing must be nearly pure oxygen. He got another eudiometer and made a number of analyses of gas from the swim bladder. The results showed that while the gas taken from the swim bladder of a fish near the surface often contained less oxygen than ordinary air, that taken from fishes caught at great depths contained nearly pure oxygen.[2] Biot had discovered oxygen secretion.

To illustrate the real significance of his observations we may take an analysis made much more recently by Schloesing and Richard,[3] in connection with which the depth from which the fish was taken is definitely stated, and was 4,500 feet. They found that the gas contained 84.6 per cent of oxygen, together with 3.6 per cent of CO_2 and 11.8 per cent of nitrogen. The latter gases are, however, quite likely to have mostly got in by diffusion during the delay before the sample was taken. Now the pressure at 4,500 feet is 136 atmospheres. Therefore the oxygen pressure in the swim bladder was at least $136 \times \frac{84.6}{100} = 115$ atmospheres, while the oxygen pressure in the sea water was only about 21 per cent of an atmosphere, and, in the blood circulating in the capillaries round the swim bladder, certainly very much less. At a moderate estimate the oxygen pressure on the inside of the wall of the swim bladder was at least 1,000 times greater than in the capillaries outside.

In the monograph already referred to, Moreau described a number of experiments showing the conditions under which oxygen secretion into the swim bladder occurs. He found, for instance, that if a fish confined in an open cage was sunk to a considerable depth, so that its specific gravity became greater than that of the water, it gradually secreted oxygen so as to restore the balance; and similarly if its swim bladder had been emptied by puncturing. The simple experiment on the goldfish which I have just described is of the same nature. Moreau even found that if a weight was attached to one fish in an experimental tank, and a float to another fish, so that the first fish was for the time glued to the bottom, and the second to the surface, both fishes would soon be swimming

[2] Biot, *Mémoires de la Société d'Arcueil*, 1807.
[3] *Comptes rendus*, Vol. 122, p. 615, 1896.

about again quite unconcerned in the tank, their respective swim bladders having compensated by secretion or absorption of gas for the disturbance in equilibrium caused by the sinker or float.

Such facts as these pointed to the conclusion that the gas secretion is under the control of the nervous system; but this was not clearly demonstrated by Moreau. It was not till sixteen years later that Bohr showed that the secretion after emptying the swim bladder by puncture ceases after the branch of the vagus supplying the swim bladder is cut.[4] I well remember the interest with which I saw this experiment when Bohr showed it while he was staying with me in Oxford a few months before he published his paper on the subject. Dreser[5] had meanwhile already shown that the secretion of oxygen, like that of saliva, sweat, etc., is excited by the action of pilocarpine.

It is clear that a fish may require to get rid of gas from its swim bladder, as well as to secrete gas. If the duct is open, there is of course no difficulty in getting rid of gas; but it is different

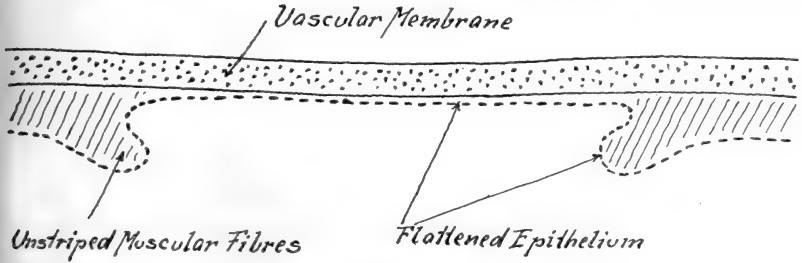

Figure 59.
Diagram of arrangement of "oval."

if the duct is closed. The oxygen might, conceivably, be secreted backwards; but often there is a large percentage of nitrogen in the gas, and there might be trouble about this. It was discovered by Jäger[6] that in fishes with a closed swim bladder there is an oval window-like area on the dorsal side of the swim bladder (Figure 59). Over this area there is nothing but a thin layer of flattened cells between the air of the swim bladder and an underlying layer containing a close network of capillaries. This thin layer seems to permit free diffusion outwards of the gas in the swim bladder. Assuming this to be the case, the oxygen will freely diffuse into the blood capillaries, where, as already seen,

[4] Bohr, *Journ. of Physiol.*, XV, p. 499, 1893.
[5] Dreser, *Arch. f. Exper. Pathologie*, XXX, p. 160.
[6] Jäger, *Pflüger's Archiv*, XCIV, p. 65, 1903.

the oxygen pressure is very low. Nitrogen and CO_2, on the other hand, will diffuse inwards if their partial pressure is less inside the swim bladder than in the blood, and outwards in the converse case. The pressure of nitrogen in the blood is doubtless about 79

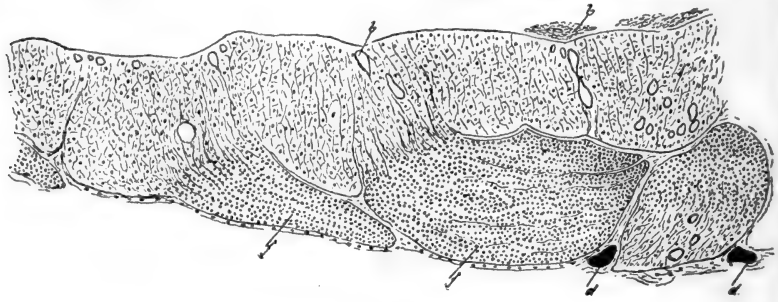

Figure 60.

Section through secreting gland of swim bladder of Sciaena aquila, showing the epithelial body and underlying layer of capillary network (f) with gas bubbles distending the gas ducts of the epithelial body (Jäger).

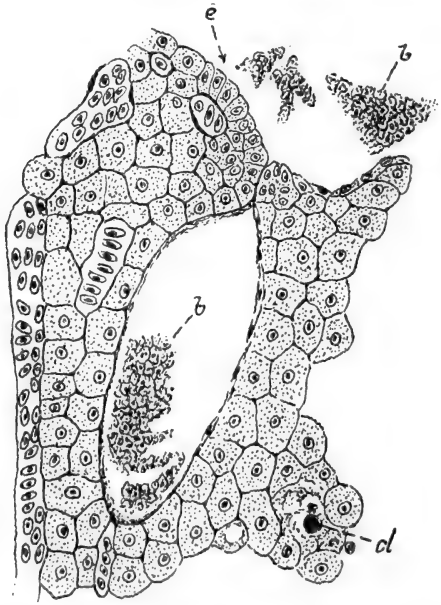

Figure 61.

More highly magnified portion of epithelial body shown in Figure 60. A distended gas duct, with surrounding secreting cells (Jäger).

per cent of an atmosphere, as it is in sea water; so whenever the oxygen percentage is sufficiently reduced by diffusion to make the nitrogen pressure in the swim bladder more than 79 per cent of an atmosphere, the nitrogen will follow the oxygen out through the "oval"; as will the CO_2, and from a similar cause. But Jäger found also that the "oval" can be opened or closed by the relaxa-

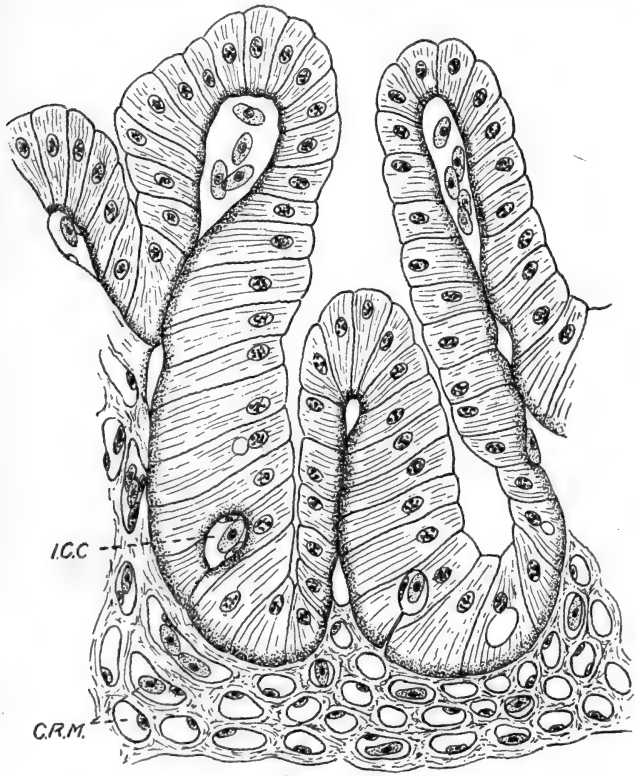

Figure 62.
(X 330) Folds of the swim bladder epithelium of *Gobius niger*. C.R.M., capillaries of the rete mirabile. I.C.C., intracellular capillary (Woodland).

tion or contraction of a ring of unstriped muscle surrounding its periphery. When this ring is contracted the "oval" is covered up by a layer of the ordinary lining membrane of the swim bladder. Thus not only secretion, but also absorption of gas from the swim bladder, is under complete physiological control.

On microscopic section of the wall of the swim bladder we find that at most parts it is lined by flattened epithelial cells similar in outward appearance to those covering the oval. At certain parts, however, this flattened epithelium passes into a layer consisting of cubical or columnar epithelial cells, and forming the so-called "epithelial body" (Figures 60, 61), or else a convoluted layer of columnar epithelium (Figure 62). In the glandular structure ducts containing gas may be seen (Figures 60 and 61) in certain species of fishes, and the gland is evidently an oxygen-secreting gland. The true glandular structure was one of Johannes Müller's many discoveries about glands.

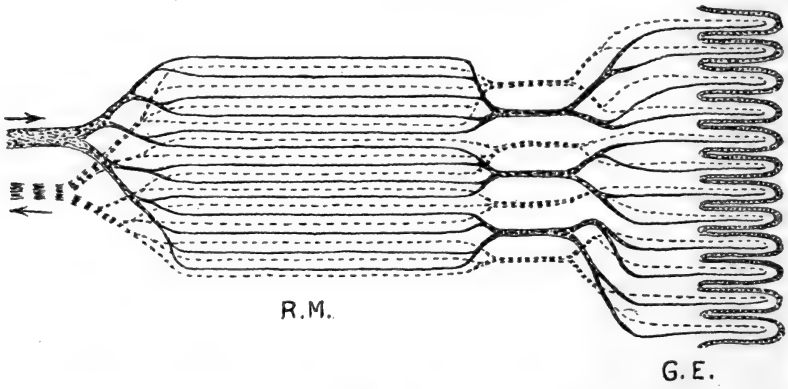

Figure 63.

Diagram of circulation in rete mirabile of eel. R.M. rete mirabile. G.E. gland epithelium. Arterioles and arterial capillaries continuous lines. Venules and venous capillaries interrupted lines (Woodland).

Beneath the glandular structure is a mass of red blood vessels, forming a structure which attracted the attention of anatomists hundreds of years ago[7] and came to be known as a *rete mirabile*. The arrangement of the blood vessels in this "red body" was recently studied by Woodland,[8] who established the fact that the *rete mirabile* is an arrangement in which the arterioles passing to the gland break up into capillaries which come into intimate contact with corresponding venous capillaries from the venules coming from it (Figure 63). What is the significance of this? The arrangement reminds us of that in a regenerating furnace, where the heat carried away in the waste gases is utilized to heat

[7] Redi, *Observations sur les animaux vivans contenus dans les animaux vivans.* Florence, 1684.

[8] Woodland, *Proc. Zoöl. Soc. of London,* p. 183, 1911.

the incoming air. Nevertheless it seems hardly probable that the arrangement is for heat regeneration. The blood passes to the gland with, presumably, the main physiological object of supplying oxygen, and venous blood in returning is already spent as regards its supply of oxygen. Nevertheless I think we can now suggest an explanation. It was discovered by Barcroft and King[9] that at low temperatures the influence of CO_2 in expelling oxygen from haemoglobin is much greater, relatively speaking, than at the temperature of warm-blooded animals. The difference is so great as to suggest that the dissociation of oxyhaemoglobin in the tissues of cold-blooded animals is practically dependent, not on fall

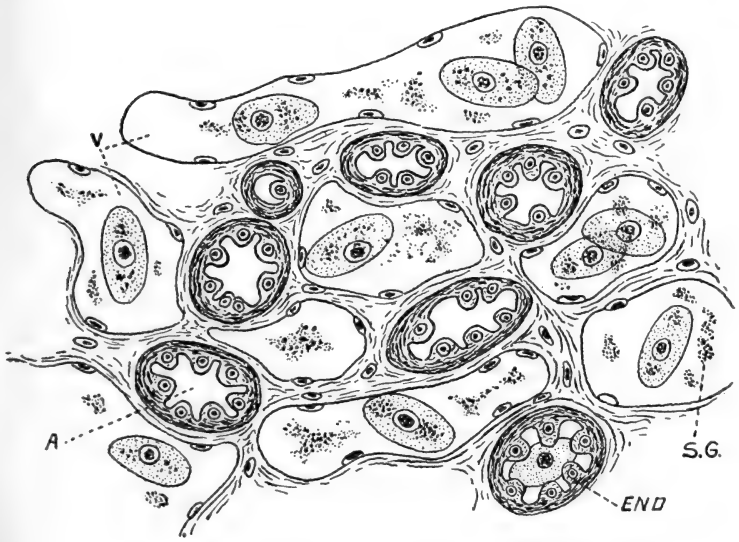

Figure 64.

(X 1000). Transverse section through anterior end of rete mirabile of Gobius niger, showing the peculiar endothelium (END) of the arterial capillaries (A) as compared with the venous capillaries. (V) (Woodland).

of oxygen pressure, but on rise of CO_2 pressure. It seems probable, therefore, that the function of the *rete mirabile* is to enable venous blood to communicate part of its CO_2 to the arterial blood. The effect of this will be to raise the CO_2 pressure of the blood supplied to the gland, and so raise the oxygen pressure. There may be active secretion of CO_2 into the arterial capillaries; and this

[9] Barcroft and King, *Journ. of Physiol.*, XXXIX, p. 374, 1909.

hypothesis is supported by the existence in the arterial capillaries of a very peculiar thickened endothelium figured clearly by Woodland (Figure 64).

Another very interesting case of gas secretion occurs in *Arcella discoides,* which is a microscopic unicellular organism found in rivers and ponds. It has a more or less transparent shell, shaped something like the top of a mushroom, with an opening where the stalk should come. Through this opening it protrudes delicate pseudopodia, by means of which it can creep about (Figure 65).

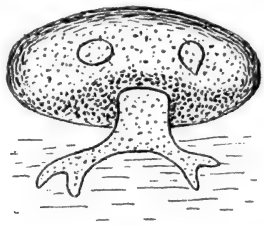

Figure 65.
Arcella raising itself by developing bubbles. Two bubbles visible through shell, and pseudopodia projecting through lower opening.

When a living and healthy arcella is examined in a drop of water under the microscope, the presence of one or more gas bubbles inside its protoplasm can at times be observed, particularly if by accident or design the animal has been turned on its back, with the opening of its shell upwards. The bubbles of course make the animal lighter, so that it rises towards the surface of the water, and also comes right-side up, after which they rapidly disappear again. The occurrence of these phenomena was described many years ago by Engelmann. Quite recently Dr. Bles took up the subject again at my suggestion, as it looked as if oxygen want was in some indirect way the real stimulus to the formation of the bubbles, just as it is (as we shall presently see) the stimulus to oxygen secretion in the lungs. He elicited the very interesting fact that a quite slight fall in the normal oxygen pressure of the surrounding water is sufficient to cause the immediate formation of gas bubbles in the arcella, and thus cause it to rise to where presumably there is more oxygen. It seems probable, also, from other observations made by him later, that the bubbles which are apt to develop when the animal is placed on its back are a consequence of stimuli produced by internal want of oxygen owing to

increased oxygen consumption during its efforts to right itself.

Before going further let us try to form some sort of conception as to what is occurring in a gland cell during the secretion of oxygen. On the side of the cell next the lumen of the duct we have a pressure of oxygen which may be 1,000 times as great as on the side next the capillaries; and yet oxygen may be passing inwards from the capillaries towards the duct. The cell is permeable to oxygen: for oxygen is passing through it. Yet the oxygen cannot be free to dissolve in the ordinary way in the "protoplasm" of the cell: for if this were the case the oxygen would run backwards through the cell like water through a sieve. At a pressure of 115 atmospheres, to go back to our concrete example, 100 volumes of water at 10°C would take up 430 volumes of oxygen (measured at 0° and 760 mm.); and if the oxygen were as freely soluble in the cell water as in ordinary water the swim bladder would leak outwards at a quite hopeless rate. If we start by looking upon "living protoplasm" as a mere solution and suspension of colloid and other material, we may as well give up the attempt to get any insight whatever into even the most rudimentary physiological processes.

When we take a broad general view of the phenomena of life, one of the most fundamental facts that appears is that the composition of each organism or part of an organism is distinctly specific. The percentage and nature of each of the substances which we can recover on disintegrating the living tissue are specific; and the more we learn about the nature of these substances the more clearly does this specific character emerge. It is evidently no mere accident that muscle yields so much potassium, so much phosphoric acid, so much water, and so much of various proteins. These substances must be present in some kind of combination in the living "substance"; and if so the living substance cannot be regarded as a mere solution of free molecules. The molecules are in some sense bound, as they are in a solid; and in so far as this is the case the living substance must in certain respects behave as a solid, impervious to the free passage of material by diffusion. The layer of thin flattened epethelium lining appears to be gas-tight (to oxygen at least) except where it covers the oval. At this point the layer allows gas to pass freely.

From this point of view we can understand why the living cells of the oxygen-secreting gland should be gas-tight, or nearly so, against diffusion backwards, but we have not yet considered how the gas passes forward through them during secretion; and if

"living material" behaved like an ordinary solid no such explanation would be forthcoming. But evidently a living cell does not behave like an ordinary solid: for it is constantly taking up and giving off material, not merely during secretion, but at every moment of its existence. This is evident from a general consideration of the phenomena of nutrition, and becomes still more evident if by altering the environment of a cell we disturb the labile balance between living cells and their surrounding liquids. In the secretion of oxygen and many other substances, such as urea, sugar, salts, etc., the substance taken up on one side of the cell is given off in the same form on the other side. In the processes of ordinary nutrition, on the other hand, the taking up and giving off may be on the same side of the cell, and the substance given off may be in a different chemical form from that taken up. We have no reason to believe, however, that there is any fundamental distinction between the taking up and giving off during ordinary nutrition and during secretion. Nearly a century ago Johannes Müller, at the end of his famous memoir on secreting glands,[10] after pointing out that his observations negatived the mechanical theories of secretion then current, suggested that secretion must be regarded as a process akin to growth, the only difference being that whereas in ordinary growth the material deposited tends to remain where it is, in secretion it is always being carried away and replaced. Johannes Müller's theory was bound up with his vitalistic physiology, and the clue which he was grasping at was swept from the hands of physiologists by the wave of mechanistic speculation which passed over physiology about the middle of last century. But now that we know from nearly a century of painful experimental investigation what to the genius of a great biologist like Müller was evident enough, that mechanical theories of secretion are impossible, we can take up the clue again.

When oxygen (or indeed any other substance entering into cell metabolism) is taken up on one side of the cell, we are led by the experimental facts to assume that the oxygen enters into easily dissociable chemical combination. Were this combination not easily dissociable we could not understand why a cell should be so enormously sensitive, as we shall see later that it is, to changes in the concentration of oxygen and other substances in its immediate environment. Now all we know about cell metabolism points to the conclusion that the balance of stability at any one part of the cell depends on the balance of stability at other

[10] Johannes Müller, *De Glandularum Secernentium Structura Penitiori*, 1830.

parts. The taking up of oxygen, for instance, depends on a host of conditions in the environment, such as the concentrations, or, more correctly, the diffusion pressures, of ions of different sorts, and of various other substances which are, or may be, passing into and out of the cell. A minute trace of pilocarpine, for instance, will set the oxygen-secreting cell violently taking up oxygen on one side, and giving it off on the other; and probably we could paralyze the oxygen secretion at once by reducing the concentration of calcium ions in the cell environment.

In a secreting cell the rate of secretion, other conditions being favorable, depends on the concentration of the dissolved material to be secreted. This we can see with the utmost clearness in the case of the kidney or intestinal epithelium. The rate of secretion also depends on the concentration of the dissolved material on the excretory side, as we can also see in the case of the kidney. Clear evidence on this point is summarized by Ambard in his book *La physiologie des reins,* Paris, 1920. We are thus led to the conclusion that the stability of the oxygen combination on one side of the oxygen-secreting cell depends, other things being equal, on the stability of the oxygen combination at the other side, and that in proportion as the oxygen combination at one surface becomes increased, the oxygen combination at the opposite surface becomes more ready to release oxygen towards the cell environment. It also seems probable that as we proceed from the absorbing to the secreting side of the cell, the tendency to give off oxygen becomes greater and greater. A cell of substantial thickness is therefore required to produce a large difference in oxygen pressure. The combination which dissociates itself on the excretory surface will, if the concentration of oxygen at that surface is not so high as to stop the dissociation, be constantly resaturating itself in part from the combination lying deeper in the cell. Thus oxygen will travel from the absorbing to the secreting side of the gland cell, just as urea, or sodium, or phosphoric acid, will travel from the absorbing to the secreting side of other kinds of secreting cells. We can also imagine how, in the course of their passage, chemical transformations may occur in the transported material, so that, for instance, an intestinal cell which takes up fatty acid may deliver fat on the other side, or a cell which takes up sugar may transform it into fat, or amino acids into proteins, or oxygen into CO_2 and water, or may perform any of the numerous other syntheses or disintegrations with which physiologists are familiar.

In the arcella, bubbles, probably consisting largely of oxygen, appear and disappear within the cell body, according to the existing physiological conditions. It seems probable that the bubbles, for the development of which a high internal oxygen pressure will be needed, occur in interstices of the living substance, due to the presence of inclosed liquid or solid substances. In these interstices the gas pressure can rise up to the point at which it produces disruption and bubble formation. Gas bubbles have not hitherto been observed in the cells of oxygen-secreting glands, although certain microscopic appearances have been taken for such bubbles.

The well-known transparent larva of Corethra possesses two gas floats: one near the anterior, and the other near the posterior end of the larva. The gas is enclosed in chitinous bladders developed from the tracheal system and partially rigid, with cells on their external walls. If the pressure of the water is increased the larva begins to sink owing to diminution in the capacity of the bladders, but regains its equilibrium in two or three minutes; and conversely if the pressure is diminished. This looks, therefore, like a case of gas secretion. Krogh showed, however, in a beautiful series of experiments[10A] that there is no gas secretion, but secretion of liquid out of or into the bladders, so as to compensate for the alteration in their capacity. The larva can equilibrate itself in this way since the bladders are partially rigid. In deep water, for instance, the gas pressure is kept the same as that of the atmosphere, and hence much less than that of the surrounding water. The gas pressures inside and outside the bladders are thus the same, and simple diffusion of gases is not modified by gas secretion.

Having to some extent cleared our ideas by the consideration of undoubted cases of gas secretion, we can now proceed to discuss the evidence as to gas secretion by the lungs. As mentioned already, Ludwig had the idea (in which he was right) that probably something occurs in the lungs to facilitate the escape of CO_2, and possibly the absorption of oxygen; and this idea appeared in the work of some of his pupils. It was a time when physiological research was very active in Germany; and friendly, or sometimes anything but friendly, shots were often exchanged between the leading laboratories. The Leipzig idea was accordingly put to the test by Pflüger and his pupils at Bonn, and for the purpose Pflüger devised an instrument which he called the aërotonometer, its object being to measure the partial pressures or tensions of the

[10A] Krogh, *Skand. Archiv. f. Physiol.*, XXV. p. 183, 1911.

gases contained in venous and arterial blood, so that these pressures could be compared with one another and with the corresponding pressures in the air of the lungs. The aërotonometer consisted of two tubes immersed in a water bath at body temperature, and closed below by a mercury seal. In one tube was placed a mixture containing a smaller percentage of CO_2 and greater percentage of oxygen than corresponded to the partial pressures expected in the blood; and in the other tube a mixture containing a higher percentage of CO_2 and a lower percentage of oxygen. The blood from the animal was then allowed to trickle down the inside of the tubes, so that it should as far as possible equalize its gas tensions with those in the tubes, either by taking up or giving off CO_2 or oxygen. In a successful experiment the blood gave off CO_2 and absorbed oxygen in one tube, and vice versa in the other, so that the gas pressures of the blood were defined within narrow limits on the analyses of the gases in the two tubes. The sample of lung air was obtained by another ingenious instrument, the "lung catheter," by means of which a bronchus could be blocked off and a sample of the gas in the lungs drawn off as soon as the air thus confined had reached a constant composition.

The conclusion drawn from the actual experiments by Pflüger and his pupils was that there was no average difference in gas pressures between the venous blood and the air inclosed beyond the blocked bronchus; and therefore no evidence of any giving off of CO_2 or absorption of oxygen except by simple diffusion.[11]

The question was taken up again by the late Professor Bohr of Copenhagen, one of Ludwig's pupils.[12] Bohr improved the aërotonometer, so that a large stream of arterial blood could be run through it and back to the animal, the blood of which had first been rendered incoagulable by injecting peptone or leech extract. He obtained the result that while usually the CO_2 pressure in the arterial blood is not less than in the alveolar air, and the oxygen pressure not greater, yet sometimes this relation is reversed. From these results he concluded that active secretion of oxygen from the lung air into the blood, and of CO_2 from the blood into the lung air, may both occur. Owing to the many possibilities of error the results were not very convincing, however; and Fredericq[13] of Liége soon afterwards made a further series of experiments, all of which seemed to tell in favor of Pflüger's interpretation.

[11] *Pflüger's Archiv*, IV, p. 465; VI, p. 65; VII, p. 23, 1871–1873.
[12] Bohr, *Skand. Arch. of Physiol.*, p. 236, 1891.
[13] Fredericq, *Arch. de Biol.*, XIV, p. 105, 1896.

About fifteen years later the aërotonometer was greatly improved by Krogh, who was then Bohr's assistant. He very greatly diminished the volume of air exposed to the blood in the aërotonometer, thus rendering it far quicker in its action; and ultimately he succeeded in working with a single bubble of air, round which a stream of blood could play, the bubble being afterwards analyzed with the help of a graduated capillary tube into which it could be sucked up and measured before and after its CO_2 and oxygen had been removed by suitable reagents.

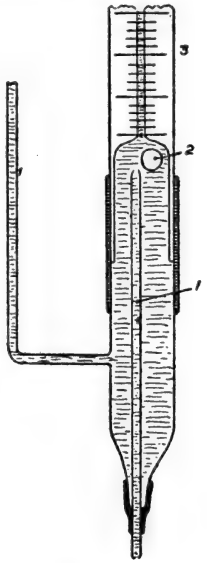

Figure 66.
Krogh's micro-aërotonometer, showing inlet and outlet for blood, lower part of measuring tube, and air bubble.

Before his death Bohr published some experiments made with Krogh's aërotonometer, and apparently showing distinctly that the pressure of CO_2 in the venous blood could be less than in the expired air, although CO_2 was being given off in the lungs; and that the arterial CO_2 pressure could also be less than that of the expired air. Krogh himself, however, took the view that there were errors in these experiments, and published, along with M. Krogh, the results of a careful series of experiments on animals under conditions which were much more nearly normal than in any previous experiments.[14] The arterial oxygen pressures were

[14] A. and M. Krogh, *Skand. Arch. f. Physiol.*, XXXII, p. 179, 1910.

always very distinctly below the oxygen pressures at the same time in the alveolar air; while the arterial CO_2 pressures were sensibly equal to those in the alveolar air. There was never any approach to excess of arterial over alveolar oxygen pressure, or of alveolar over arterial CO_2 pressure, even when these pressures were varied considerably by altering the composition of the inspired air. Krogh, therefore, rejected Bohr's conclusions that there is active secretion of oxygen or CO_2 in the lungs, and concluded in favor of Pflüger's view that the exchange of gases in the lungs is entirely due to diffusion. The following table shows the results of a typical experiment in which the alveolar oxygen pressure was varied during the experiment, the alveolar air and blood samples being taken nearly simultaneously.

TIME	TENSION OF CO_2 IN		TENSION OF OXYGEN IN	
	Alveoli	*Blood*	*Alveoli*	*Blood*
1.36–43	3.6	3.7	12.0	10.0
2.10–12	3.0	3.5	18.0	15.0
3.03– 3.07	2.5	2.5	12.0	11.5

Before following this long controversy further, I should like to point out a fallacy in the interpretation of the aërotonometer results. The conclusion of Pflüger that diffusion alone explains the giving off of CO_2 in the lungs was wholly fallacious, as has already been shown in Chapter V. The oxygen reaching the blood in the lungs helps to drive out CO_2; and under certain conditions which are very apt to occur during physiological experiments on animals, and may easily be produced in man, the venous CO_2 pressure may be lower than that of the alveolar air, although no secretion at all may be occurring. In the lung-catheter experiments the oxygen supply to the lungs was blocked off, so that the blood could not take up oxygen. As a consequence the CO_2 pressure in the confined air must have been considerably lower than if oxygen had been present. In reality Ludwig was right, and Pflüger was wrong. This source of fallacy does not in any way invalidate Krogh's conclusion that the arterial CO_2 pressure is not, under normal conditions, lower than the alveolar CO_2 pressure. I think this conclusion is correct; and it agrees, as he points out, with all the indications given by the work of Priestley and myself on the regulation of breathing in accordance with the alveolar CO_2 pressure.

When Bohr's original experiments on the question of secretion by the lungs were published in 1891, I was just beginning the serious study of mine gases and the physiological effects of vitiated air; and his results interested me greatly. A year or two later Lorrain Smith and I made a visit of several weeks to Copenhagen, and carried out some research work in the laboratory under Bohr's direction, thus learning a great deal which we could not have learned in England about existing methods of blood-gas investigation, and, far more important, getting into personal touch with Bohr himself. I should like to take this opportunity of saying how much we, and indirectly other physiologists in Great Britain and America, have owed to Bohr and the Copenhagen School of physiologists.

The difficulties of the aërotonometer method of determining the oxygen pressure of arterial blood were very evident, and I cast about in my mind for some better method. Soon afterwards I began investigating the action of carbon monoxide in mines, and the results of this investigation, and the colorimetric method of blood examination, which I worked out during the investigation, suggested a new means of attacking the problem which Ludwig had originally suggested.

The general principle of this method has already been explained in Chapter IV, and depends on the fact that within wide limits the relative proportions in which haemoglobin is shared between oxygen and CO are proportional to the relative partial pressures of the two gases when allowance is made for their relative affinities for the haemoglobin. Hence if the proportions in which oxygen and CO are shared in the haemoglobin of the blood when equilibrium is established are known, as well as the pressure of CO, the pressure of oxygen can be calculated. To measure the oxygen pressure in the arterial blood it is therefore only necessary to allow a man or animal to breathe a constant small percentage of CO until absorption of CO stops, owing to a balance having been struck between oxygen pressure and CO pressure in the blood passing through the lung alveoli. The percentage saturation of the haemoglobin with CO is then determined, and the arterial oxygen calculated from a knowledge of the relative affinities of the two gases for haemoglobin, as determined outside the body.

The method seemed simple in principle, but it turned out to be as full of pitfalls in practice as the use of the blood pump, aërotonometer, or spectrophotometer. What misled us most were:

(1) the assumption that Hüfner's oxyhaemoglobin dissociation curve, then and for many years later quoted in every textbook, was at least approximately correct; (2) the assumption that all haemoglobin is alike as regards its relative affinities for oxygen and CO; (3) ignorance at first of the powerful action of bright light on the dissociation of CO haemoglobin, and of the influence of temperature; (4) failure at first to realize how long it takes to saturate blood or blood solution outside the body with air containing low percentages of CO. There were probably also some errors in the colorimetric titrations, owing chiefly to our not taking precautions which subsequent experience showed to be necessary, against decomposition of blood solutions during long experiments.

The first experiments were made by Lorrain Smith and myself[15] on men, the subject of the experiment going through the lengthy process of breathing air containing a definite small percentage of CO, until absorption of CO ceased, as shown by the analyses of blood samples. The results led us to the conclusion that the normal resting arterial oxygen pressure was considerably above that of the alveolar air; and corrections, made afterwards for the causes of error just referred to caused this conclusion to stand out still more clearly. Subsequent experience leads me to the conclusion that we had become acclimatized more or less to want of oxygen by frequently breathing CO, so that at the time we were no longer ordinary normal subjects. We were at any rate breathing with complete impunity a percentage of CO which would under ordinary circumstances cause very unpleasant symptoms. On trying the next year and once or twice subsequently to repeat one of the experiments, we were surprised to find that the former percentages were too high for us, and we suspected that there must have been some error about the percentages breathed in the first series of experiments. On reconsidering the matter I cannot see how there could have been an error about the percentages breathed. It now seems practically certain that we had become acclimatized, and had consequently developed during the experiments a considerably higher arterial oxygen pressure than normal persons would have had, or than we ourselves would have had, if we had not absorbed so much carbon monoxide as in the experiments, and thus become somewhat short of oxygen.

Our next experiments[16] were on various small animals—chiefly mice. Small animals are specially convenient, as their

[15] Haldane and Lorrain Smith, *Journ. of Physiol.*, XX, p. 497, 1896.
[16] Haldane and Lorrain Smith, *Journ. of Physiol.*, XXII, p. 231, 1897.

blood becomes saturated within a few minutes to its maximum extent for any percentage of CO in the air. These experiments again gave an apparently higher oxygen pressure in the arterial blood than in the alveolar air. When the percentage of CO was increased, so that the animals began to show symptoms of considerable oxygen want, the difference between arterial and alveolar oxygen pressure became much greater. On the other hand, when the animals were breathing a mixture of oxygen and CO there was still a large apparent excess of arterial over alveolar oxygen pressure. This result was a great disappointment to us, as we had hoped that when oxygen was breathed, active secretion of oxygen inwards would cease. The fact that it apparently did not do so ought to have aroused our suspicions of the correctness of the measurements. The phenomena observed when the oxygen percentage, or the barometric pressure, was diminished, led us, apart from the measurements, to conclude that secretion of oxygen inwards became more active; but in our measurements of oxygen pressure we were depending on the substantial correctness of Hüfner's dissociation curve; and when this curve was subsequently found to be totally incorrect our measurements had also to be abandoned as incorrect.

During the next few years knowledge as regards the dissociation of haemoglobin had greatly increased, thanks to the work of Bohr, Zuntz and Loewy, Barcroft, and others, as well as our own work, as described in Chapter IV. Douglas and I now took up the old subject again, but with far more complete knowledge of the material we were dealing with.[17] Dr. Krogh had also kindly informed me in a letter of some experiments he had made (subsequently published)[18] showing that in the blood of a rabbit the relative affinities for haemoglobin of oxygen and CO were different from those in the ox; and we found, as already mentioned in Chapter IV, that this is not only so for different classes of animals, but also, and in a most marked degree, for different individuals of the same species.

We therefore had to modify the method. Each animal was exposed for a sufficient time to a definite percentage of CO in a bottle, and then drowned *in situ*. Some of its blood was then placed, undiluted and at body temperature, in the saturator, and thoroughly saturated in presence of some of the same mixture of air and CO that the animal had been breathing. The percentage

[17] Douglas and Haldane, *Journ. of Physiol.*, XLIV, p. 305, 1912.
[18] Krogh, *Skand. Arch. f. Physiol.*, XXXII, p. 255, 1910.

saturations with CO of the haemoglobin in the blood taken straight from the animal, and in that from the saturator, were then determined, and the arterial oxygen pressure calculated in the usual way. The following table shows the results.

Animal used	*Percentage of CO*	*Duration of exp. in minutes*	Percentage saturation of haemoglobin with CO		*Arterial oxygen pressure in percentage of the existing atmosphere**
			In vivo	*In vitro*	
Mouse	.016	60	26.2	17.2	12.2
"	.0165	50	26.7	19.5	13.9
"	.018	45	26.0	18.5	13.5
"	.019	33	19.7	12.5	12.1
"	.025	43	25.6	17.6	13.0
"	.046	40	29.1	22.7	15.0
"	.053	40	37.7	30.2	16.2
"	.100	32	45.0	43.0	19.3
"	.129	31	56.4	56.3	20.8
"	.198	—	57.6	56.5	20.0
"	.213	13	59.1	75.5	44.7†
"	.244	12	67.3	71.7	25.7†
"	.255	60	60.1	62.8	23.3
"	.260	25	67.0	64.7	18.9
"	.262	20	66.4	73.7	28.2
"	.275	25	66.5	76.9	35.9
Rabbit	.029	140	28.0	18.7	12.4
Same rabbit	.191	150	58.2	56.0	19.1

* Calculated without reduction for aqueous vapor in the alveolar air.
† Mouse died.

On looking down this table it will be seen that as long as the percentage of CO did not exceed about .03 per cent, or the percentage saturation of the blood did not go over about 28 per cent, the arterial oxygen pressure was only about that of the alveolar air, assuming that the alveolar air of a mouse has about the same composition as human alveolar air. But as the percentage of CO in the air, or the percentage saturation of the blood, rose, the arterial oxygen pressure rose, first to about that of the inspired air, and then, in most cases, far above it—sometimes to double.

We then repeated the old experiments with oxygen which had disappointed Lorrain Smith and me so much. The results were as follows:

EXPERIMENTS WITH MIXTURES OF OXYGEN AND CO ON MICE

Percentage of CO	*Duration of exp. in minutes*	Percentage saturation of haemoglobin with CO		Oxygen pressure in percentage of the existing atmosphere*	
		In vivo	*In vitro*	*Arterial blood*	*Inspired air*
0.16	30	31.3	29.6	77.4	83.9
0.61	30	57.0	54.6	66.6	73.5
1.15	30	71.4	70.8	83.1	85.6
1.47	30	69.0	75.0	96.3	71.5

* Calculated without reduction for aqueous vapor.

It will be seen that as long as the saturation of the blood with CO did not exceed about 60 per cent, the arterial oxygen pressure was about 7 per cent below that of the inspired air, just as the alveolar oxygen pressure would be. With over 60 per cent saturation, however, the animals began to suffer from oxygen want, and the arterial oxygen pressure went just as high above that of the inspired air as in animals breathing ordinary atmospheric air. The old experiments were wrongly calculated, because the relative affinities of haemoglobin for oxygen and CO are on an average different in mouse blood from what they are in human blood or in the ox blood which we then took as a fixed standard. This led us to calculate the arterial oxygen pressure about 50 per cent too high in both the "normal" and the oxygen experiments. Moreover the "normal" experiments were not normal, since the percentage saturations of the blood were about 40 per cent, and therefore too high to give normal results such as those of the first five experiments in the previous table. If one recalculates the average results of the old experiments in the light of this new knowledge they give just the same result as the new experiments.

The general, and absolutely sharp and definite, result of these experiments is that with very low percentages of CO there was no evidence of active secretion of oxygen inwards, but that with higher percentages of CO there was perfectly clear evidence of active secretion. This active secretion began to show itself as soon as the CO percentage was sufficient to cause symptoms of CO poisoning, which symptoms, as shown in Chapter VII, are simply those of oxygen want: moreover the secretion did not appear if oxygen was breathed along with the CO, until a much higher saturation of the blood with CO was reached. Pure oxygen, as

already shown in Chapter VII, provides a certain supply of dissolved oxygen to the blood independently of the oxygen carried by the haemoglobin, and thus prevents, to a large extent, the oxygen want which would otherwise be caused by the CO.

Now the oxygen want is in the tissues, and not in the lungs. Hence the stimulus to secretion originates in the tissues. This stimulus is almost certainly something carried by the blood from the oxygen-starved tissues to the lungs or central nervous system. One might perhaps suppose that whenever the respiratory center is excited, nervous impulses pass down secretory fibers in the vagus nerve and excite secretion in the lungs. Lorrain Smith and I tested this hypothesis, and found that when the respiratory center was excited by excess of CO_2 there was not the slightest rise in the arterial oxygen pressure. Hence the secretion has no direct connection with the ordinary activity of the center in producing respiratory movements; and the stimulus to secretion is not a hydrogen ion stimulus.

We also made a series of determinations on man. In view of the results of the mouse experiments we were anxious to work with low percentages of CO; but if we had used the old method which Lorrain Smith and I had employed, it would have taken so long before equilibrium was reached between the CO in the air and that in the blood that our experiment could hardly have been completed during winter daylight. We therefore adopted the course of quickly absorbing as much CO as would saturate the blood to the desired extent, and then breathing in and out of a small air space, in which the oxygen and CO_2 percentage was kept constant. Under these conditions CO must, of course, be given off into the air of the space, and as this air is breathed again and again, equilibrium between the CO in the air and that in the blood must establish itself very quickly. The method finally adopted was as follows (see Figure 67).

The subject, wearing a nose clip, breathes through the mouthpiece A, inhaling through the inspiratory valve B, and expiring through the valve C. The expired air passes through a rubber pipe of large caliber to the tin vessel D, which is filled with small fragments of solid caustic soda, and is made of such a size (diameter 23 cms., depth 12 cms.) that the whole of the carbonic acid in the expired air is effectively removed. Another rubber pipe leads the outgoing air current from D to the bottle E of 12 liters capacity, which is connected by another pipe with the inspiratory valve B. The entrance and exit pipes of E are so ar-

ranged that the incoming air current is directed to the bottom of the bottle, while the subject inhales air from the top. The arrows indicate the direction of the air current caused by the subject's respiration in the main circuit. Two side pipes lead into the rubber pipe connecting D with E. One of these, G, is of large bore and

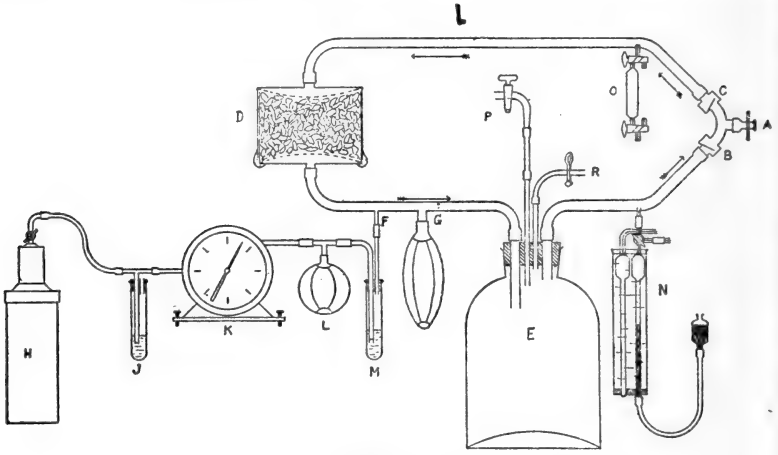

Figure 67.
Apparatus for determining the arterial oxygen pressure in man.

short, and is connected with a vulcanized rubber gas bag of considerable size, such as is utilized on Clover's ether apparatus. This bag serves only to accommodate each expiration, as the rest of the apparatus is indistensible, and at the end of inspiration the bag collapses entirely. The other side pipe F serves for the admission of oxygen. The oxygen supply is so arranged that oxygen enters the main air circuit automatically to fill up the deficiency caused by the absorption of oxygen by the subject at each breath. It is essential in a closed system of small size that the oxygen supplied shall be pure; the small amount of nitrogen contained in ordinary cylinder oxygen renders its use inadmissible. We therefore in all the later experiments used oxygen made by the action of water on "oxylith" in the generator H. The current of oxygen is controlled by the tap at the top of the generator, and passes along a pipe past a blow-off valve to air J, through a small gas meter K and thence through a water valve M to enter the main air circuit at F. The height of the water above the orifice of the pipe in M is about 2 mm. greater than in J, and the oxygen therefore passes out to air through the valve J unless

a slight negative pressure is set up in the main air circuit, when it will pass by preference through M. Such a negative pressure obtains in the main air circuit only at the end of an inspiration, and depends upon the fact that the whole volume of air in the circuit is diminished by the amount of oxygen absorbed at the last breath of the subject, as the carbonic acid expired is removed. The meter records, therefore, the actual oxygen consumption by the individual. Interposed between the meter and the valve M is a small rubber bag L, such as is used in a small sized football. This serves as a reservoir for the oxygen, and enables a free and sudden supply to be drawn into the air circuit. Without this it would be necessary to run the oxygen from the generator at an excessive and wasteful rate, and the slight resistance of the meter might be felt. In practice the oxygen supply is so adjusted that it is just escaping continuously to air through J, so as to insure that the bag L is filled to constant pressure; otherwise the readings of the meter will not accurately represent the oxygen consumption.

A Haldane gas analysis apparatus N is attached directly to the air pipe leading from the bottle E to the inspiratory valve, so that samples of the inspired air may be withdrawn at intervals during the experiment for analysis. The extremity of a vacuous gas sampling tube O is inserted into the pipe between the expiratory valve and the caustic soda tin, not far from the former, for the purpose of obtaining a sample of alveolar air by Haldane and Priestley's method. By means of the tap P, connected with the laboratory water supply, a large volume of air can be displaced from the bottle E through the pipe R, and used for filling saturating vessels, etc. Before each experiment the apparatus is tested for air-tightness by disconnecting the oxygen supply pipe at F and substituting a water manometer for it, and then producing a positive or negative pressure by blowing in air or sucking it out through the mouthpiece. The whole apparatus is readily blown out with fresh air by disconnecting the return air pipe from the inspiratory valve and blowing through the mouthpiece with a pair of bellows.

We found that the percentage of oxygen in the air in the apparatus falls by about 0.8 per cent during the first five minutes of an experiment, doubtless owing to the rise of temperature caused by the breathing, which will hinder the entrance of oxygen. After this the oxygen percentage shows oscillations, which however do not exceed 1 per cent. Such oscillations are unavoidable, seeing that the oxygen supply must be influenced in this method by the

depth of the individual breaths: the percentage could only remain absolutely constant if the depth of breathing was itself constant. For the same reason the oxygen consumption should not be determined over a shorter period than five minutes.

One great advantage of this apparatus is that it is very easy to subject oneself to atmospheres containing different percentages of oxygen by means of it. To obtain an atmosphere poor in oxygen all that is necessary is to uncouple the oxygen supply from the valve M and breathe into the apparatus. Air now enters through F instead of oxygen, and breathing is continued until analysis of the inspired air shows that the required degree of oxygen deficiency has been produced. If the oxygen supply is now reëstablished the artificial atmosphere produced will remain constant. To obtain an atmosphere rich in oxygen, the gas may be blown in through the orifice for the alveolar air sampling tube, leaving the mouthpiece free for the escape of the displaced air from the return air pipe.

The total volume of the air in our apparatus is about 15 liters, and we may therefore presume that the whole of it goes through the alveoli of a resting adult subject in three minutes. We have on a number of occasions breathed into the apparatus for an hour with the greatest comfort, the percentage of oxygen meanwhile varying only within the limits mentioned above.

The time during which the subject breathed into the respiration apparatus in our experiments has varied on different occasions from twenty minutes to one hour. So far as we could ascertain the shorter time was sufficient to establish equilibrium of concentration of the carbon monoxide in the blood and in the air breathed, though we have as a rule adopted a period in excess of this as a matter of precaution. In our earlier experiments we passed about 2 cc. of CO into the air in the respiration apparatus before beginning to breathe into it, in order that the percentage of this gas present at the start might approximate to its final value. As this procedure had no influence on the result of the experiment we gave it up, and the respiration apparatus thereafter always contained air free from CO at the commencement of the experiment.

Analyses of the inspired air were made several times during the course of the experiment, as it was naturally important for our purpose that the composition of the inspired air should show none but minimal variations. Shortly before the close of the experiment a sample of blood was withdrawn from the subject's finger into a capsule, and defibrinated with a platinum wire. Five-hun-

dredths cc. of this blood was then introduced into the saturating vessel in the manner described in our paper. Immediately afterwards two further small samples of blood were taken from the subject's fingers—as a rule one from each hand—the blood being received into small test tubes quite full of water, which were immediately corked. These samples served for the colorimetric determination of the degree of saturation of the blood with carbon monoxide. A last sample of the inspired air was then taken, and a sample of the alveolar air. Breathing into the apparatus was continued for about two minutes in case the composition of the air in the respiration apparatus had been altered by the deep expiration necessary to afford the alveolar air sample: some carbonic acid, for instance, might have got through the caustic soda tin. The experiment then terminated, and the mouthpiece of the respiration apparatus was at once closed. The saturating vessel containing the blood was as soon as possible filled by displacement with some of the air remaining in the respiration apparatus, which was expelled for this purpose from the bottle E by the arrangement indicated at P and R. While the saturating vessel was being rotated in the water bath at 38° the determination of the degree of saturation with carbon monoxide of the samples taken from the fingers was proceeded with. During this time also the analyses of the alveolar air, and air from the respiration apparatus, were completed and when necessary the analysis of a sample from the saturating vessel. After the saturating vessel had been rotated for half an hour or more, it was removed from the water bath and the degree of saturation with carbon monoxide of the blood contained in it was determined. All the data for calculating the oxygen pressure of the arterial blood and contrasting it with that of the alveolar or of the inspired air were then at our disposal.

Our first experiments on man were taken up with determining the arterial oxygen pressure under as normal conditions as possible, and we especially wished to guard against the effects of deficiency of oxygen. We therefore employed a low saturation (23 per cent) of the blood with CO and made sure that the respiration apparatus contained a normal atmosphere by ventilating it freely with fresh air before the experiment. All the experiments were made with the subject sitting at rest.

The results of these experiments are collected in the accompanying table.

The figures show quite distinctly that under normal circumstances when the subject is at rest the arterial oxygen pressure in

man corresponds exceedingly closely to the pressure of oxygen in the alveolar air. In fact in no single instance does the value of the arterial oxygen pressure differ from the alveolar by a greater amount than can be accounted for by the experimental error of the method.

We then tested the effect of raising the alveolar oxygen pressure considerably above the normal value by filling the respiration apparatus with an atmosphere rich in oxygen. The results of the experiments are also given in the table. Here again the figures show that the arterial and alveolar oxygen pressures have practically identical values. In these experiments on man we were content to use only a moderate increase of the alveolar oxygen pressure, for the higher the oxygen pressure is raised the less proportional difference is there between the inspired air and the alveolar air. A point will therefore eventually be reached when the determination of the difference of tint between the blood withdrawn from the body and that saturated with the inspired air in vitro will fall almost within the experimental errors of the method. It should be noted that in these experiments the carbonic acid in the alveolar air had precisely its normal value, namely 5.6 per cent when measured dry, and we have therefore no reason to suppose that the alveolar air samples were other than normal.

Having obtained thus results which indicated that during rest under normal conditions the transference of oxygen through the pulmonary epithelium occurs without active secretory intervention of the alveolar epithelium, we were naturally anxious to test the matter further under conditions in which some amount of deficiency of oxygen might affect the subject. The necessary deficiency of oxygen was obtained by exposing the subject to an atmosphere containing a considerably lower percentage of oxygen than the normal. The experimental procedure was precisely the same as before, save that we filled the respiration apparatus before the start with an appropriate atmosphere by the method described above. The results of these experiments are collected in the middle part of the table.

The partial pressure of oxygen in the air breathed corresponded to an altitude of 15,000 feet or over; yet we noted that a 23 per cent saturation of the blood with carbon monoxide was tolerated without inconvenience. One of the subjects was liable to headache when his blood was saturated to 25 per cent or more with carbon monoxide, but this was in no wise accentuated in these

experiments. That deficiency of oxygen was exerting its customary effect on the respiration is indicated by the low value of the alveolar carbonic acid percentage. Both the subjects noticed distinct hyperpnoea for some time after commencing to breathe into the respiration apparatus, and that this was accentuated on the slightest movement. The face remained of a distinctly bluish color throughout the experiment, but the blueness passed away if the hyperpnoea became exaggerated for a short time by muscular movement. On rebreathing normal air at the close of the experiment well-marked Cheyne-Stokes breathing was once or twice observed, indicating that the want of oxygen had induced a real hyperpnoea which had lowered the general carbonic acid pressure in the body considerably.

In calculating the arterial oxygen pressures from the experimental data of these experiments, it was necessary to make allowance for the fact that the arterial blood was not fully saturated with oxygen and CO, while the blood from the saturator must have been almost completely saturated, as the oxygen pressure in the air of the saturator was considerably higher, and hardly any CO_2 was present. For the correction required under these circumstances I must refer to our original paper.

On looking at the results of the four experiments it will be seen that in every case the arterial was above the alveolar oxygen pressure. The mean difference seems to be outside the limits of experimental error, but only amounts to 8 mm.

A further series of experiments was made with the subject doing muscular work. Preliminary experiments made with the work done on a tricycle ergometer had shown that when the breathing was greatly increased difficulties arose with the apparatus. We therefore decided to make use of work with only one arm. This enabled us to push the work to the point of fatigue, when want of oxygen would be produced in the muscles, with formation of lactic acid. That lactic acid was actually formed is indicated by the low alveolar CO_2 percentages. The work apparatus which we employed was of the simplest description. It consisted of a lever which could be moved backwards and forwards, and transmitted its motion by means of a connecting rod to a small table carrying a weight which slid to and fro upon a smooth plank, to one end of which the lever was pivoted.

The work apparatus was placed upon the ground adjacent to the chair on which the subject sat, so that he could move the lever and yet breathe comfortably into the respiratory apparatus. By

increasing the weight the amount of work done by the subject could be raised. It was not possible to measure the actual work done in mechanical units, but we could do so in physiological units by observing, by means of the small gas meter, the effect on the oxygen consumption of the subject per minute. What we term "moderate work" in the tables below was sufficient to raise the total oxygen consumption to one and a half times its resting value, while "severe work" doubled the resting oxygen consumption. Work which doubles the resting oxygen consumption is only equivalent to walking on the flat at two miles per hour, and does not sound particularly severe, but we found it sufficiently tiring when it was performed by one arm only, and kept up for half an hour at a time.

The lower part of Table III shows the results of the work experiments. These results are very striking: for the arterial oxygen pressure was on an average 4.4 per cent, or 32 mm. of mercury, above the alveolar oxygen pressure, and in two experiments was 8.5 and 15.6 mm. above the oxygen pressure of the inspired air (allowing for aqueous vapor).

In the last experiment on the table the effects of muscular work and low oxygen in the inspired air were combined. It will be seen that the arterial was 33.5 mm. above the alveolar oxygen pressure, whereas with a low oxygen in the inspired air and no work the arterial never exceeded the alveolar oxygen pressure by more than 13 mm. As already mentioned, it was noticed that when work was done while a low oxygen percentage was being breathed the lips and face lost the bluish color due to the low oxygen, and became of a normal red color. It was also noticed many years ago by Loewy[25] that even a slight muscular exertion produced a marked improvement in the subjective symptoms of want of oxygen in a steel chamber at low atmospheric pressure. Our results on the arterial oxygen pressure during muscular exertion furnish an evident clue to these observations.

In a former chapter I have referred to some of the results of the expedition to Pike's Peak undertaken in 1911 by Professors Yandell Henderson and Schneider, Dr. Douglas, and myself.[26] Part of our object was to determine whether the want of oxygen

[25] Loewy. *Untersuchungen u. d. Respiration und Circulation,* Berlin, 1895, p. 16. The fact that Geppert and Zuntz (*Pflüger's Archiv,* XLII, p. 189, 1888) found a little more oxygen in arterial blood during work than during rest may point also in the same direction.

[26] Douglas, Haldane, Yandell Henderson, and Schneider, *Phil. Trans. Roy. Soc.,* (B) 299, p. 195, 1913.

due to the rarefied air at 14,000 feet did not produce active secretion of oxygen inwards. We used the same method as at Oxford, taking every precaution against errors. The results were quite unmistakable. We found that as soon as acclimatization to the air was established the arterial oxygen pressure became considerably higher than that of the alveolar air. The next table shows our results. In ordinary resting experiments on acclimatized persons, the arterial oxygen pressure was on an average about 70 per cent above the alveolar oxygen pressure. When, however, air extra rich in oxygen was breathed, so that the alveolar oxygen pressure rose to about what it is at sea level, the difference between arterial and alveolar oxygen pressure fell to 8 or 10 per cent, even during the short period of an experiment. In a subject investigated immediately on arrival at the summit by the cogwheel railway the arterial was only about 15 per cent above the alveolar oxygen pressure, whereas three days later, after acclimatization, the excess was 100 per cent.

The Pike's Peak results threw much new light on oxygen secretion by the lungs, and on the former experiments at Oxford. It was evident, that not only is oxygen want a stimulus to active oxygen secretion by the lungs, but that the response to the stimulus improves greatly with practice or "acclimatization," just as is the case with other physiological responses. We can now see why some experiments—for instance those which Lorrain Smith and I made jointly on ourselves, indicated oxygen secretion, while other experiments in which the physical and chemical conditions seemed to be the same gave negative results. It was the physiological conditions which were different. In the latter experiments we were not acclimatized against anoxaemia.

It is easy to see the physiological advantage of oxygen secretion as a defense against the anoxaemia of high altitudes and similar conditions, or against carbon monoxide poisoning; but its uses under ordinary conditions, where nothing but pure air at about ordinary atmospheric pressure is breathed, are not so obvious. It is clear that as the arterial haemoglobin is nearly saturated with oxygen, during rest, at any rate, without any active secretion, hardly anything could be gained by secretion, since any additional oxygen which could be added to the blood would be trifling in amount unless with an enormous secretory pressure such as has never been found experimentally. We can thus readily understand why there is no secretion during rest under normal conditions, as our experiments clearly showed to be the case. It was

PIKE'S PEAK—ARTERIAL OXYGEN TENSION

Date	*Subject*	*Alveolar air Gases per cent*		*Percentage saturation of blood with CO*		*O_2 tension of arterial blood in percentage of the existing atmosphere without allowing for aqueous vapor*	*O_2 tension of alveolar air in mm. Hg (at 37° moist)*	*O_2 tension of arterial blood in mm. Hg (at 37° moist)*	
		O_2	*CO_2*	*In vivo*	*In vitro*				
July 19	C. G. D.	13.03	6.91	21.0	22.5	21.9	53.4	89.8	
20	"	11.96	6.82	20.5	22.7	20.9	49.0	85.6	
24	"	21.13	7.09	19.2	17.5	25.1	88.0	103.6	High O_2 insp.
26	"	24.23	7.40	18.15	16.0	26.8	99.3	109.9	High O_2 insp.
Aug. 2	"	15.80	6.58	17.5	20.75	24.0	64.6	98.1	Work.
July 21	J. S. H.	16.20	6.28	19.35	20.4	24.9	66.8	102.4	
28	"	14.81	6.41	19.45	21.4	22.7	60.5	92.8	
Aug. 1	"	8.13	4.76	18.3	19.4	13.5	33.2	55.2	Low O_2 insp.
13	"	29.20	7.40	19.0	17.3	31.7	120.6	131.0	High O_2 insp.
July 29	Y. H.	13.77	6.67	18.0	16.7	18.8	56.9	77.7	
Aug. 9	"	16.56	5.86	16.3	18.4	25.3	68.4	104.4	
July 31	E. C. S.	10.61	7.61	19.2	21.6	20.3	43.4	83.0	
Aug. 8	"	12.70	7.63	18.6	20.8	23.4	52.3	96.4	
Aug. 4	J. E. F.	11.16	7.93	12.8	9.5	12.9	45.6	52.7	On arrival.
7	"	9.86	7.62	16.75	19.7	19.75	40.7	81.4	

only during work that the experimental results showed secretion; but as a matter of fact the increase found in the arterial oxygen pressure above the alveolar oxygen pressure would be of very little service in charging the blood further with oxygen; and this brings us back to the original question.

In the first place it must be pointed out that the experiments which Douglas and I made on oxygen secretion during muscular work were carefully arranged in such a way as to demonstrate the existence of secretion if any secretion occurred during muscular work. We knew already that the stimulus to oxygen secretion came from anoxaemia of the tissues. We knew, also, that the only probable function of oxygen secretion was, not to raise the arterial oxygen above that of the alveolar air, but to prevent a serious fall, such as otherwise might take place during work sufficient to increase very greatly the oxygen requirements of the body. But we had no index of what the fall might be in the absence of secretion. We therefore made the experiments in such a way that tiring work, such as would presumably furnish the stimulant to oxygen secretion, was done with one arm only. The oxygen requirements of the body were in this way only increased to a very moderate extent, so that oxygen secretion would have every chance to raise the arterial oxygen pressure above the alveolar oxygen pressure, just as in CO poisoning or at high altitudes during rest. It was also much easier to make the experiments accurately when the oxygen intake was not greatly increased.

Since our original experiments, and those on Pike's Peak, were carried out, a good deal of both direct and indirect evidence has accumulated in confirmation of our conclusions, and must now be referred to. In Chapter VII the very clear physiological evidence was summarized, showing that there is, in persons who are not in good physical training, considerable anoxaemia during hard muscular exertion. This is not merely local anoxaemia in the muscles with the associated formation of lactic acid described in Chapter VIII: for if the work is not too hard the respiratory symptoms indicating anoxaemia are still present during the work, but there is no trace of a subsequent fall in the resting alveolar CO_2 pressure. This fall is the physiological indication of lactic acid, and runs parallel, as already mentioned, with the presence of much lactic acid in the blood and urine. As Douglas and his pupils have found,[27] there is, as a matter of fact, practically no increase in

[27] Campbell, Douglas, and Hobson, *Phil. Trans. Roy. Soc.*, (B), Vol. 210, p. 1, 1920.

the lactic acid present in the urine during moderate work. Thus the anoxaemia cannot well be due to anything else but imperfect saturation of the arterial blood with oxygen; and that this is the actual cause is directly shown by the fact that a very moderate increase in the oxygen percentage of the air breathed relieves the symptoms.

In ordinary persons not in good physical training a very moderate diminution in atmospheric pressure is quite sufficient to cause a noticeable excess of hyperpnoea on any considerable exertion, such as climbing or walking fast. This is very evident on going by train to some place four or five thousand feet above sea level; and the cause is, without a shadow of doubt, imperfect oxygenation of the arterial blood. At ordinary atmospheric pressure we are accustomed to a certain degree of hyperpnoea and exhaustion with a given degree of muscular exertion. That this is in part dependent on imperfect saturation of the arterial blood is only revealed by the fact that in air at a higher atmospheric pressure (as in the case of workers in compressed air, and probably in deep mines), or when air enriched with oxygen is breathed, the same work becomes much easier, at any rate to many persons.

The observations of Dr. Henry Briggs, described in Chapter VII, show that there is a striking difference in this respect between men in good physical training and ordinary persons, as the former class get no benefit from air enriched with oxygen unless the work is excessively hard, while the latter get great benefit, shown, not only by the much greater ease and comfort with which they perform the work, but by the smaller amount of air which they require to breathe. The corresponding difference at high altitudes is perfectly familiar to mountaineers. The man who is in good training is free from the hyperpnoea, mountain sickness, and other effects of high altitudes to a far greater extent than the man who is not in training; and this evident fact has often led mountaineers to the mistaken conclusion that mountain sickness has nothing to do with altitude or anoxaemia, but is simply a sign of imperfect training.

All the facts just mentioned confirm the direct evidence in favor of oxygen secretion in the lungs. Part of the exhaustion of hard physical work is due to imperfect saturation of the arterial blood with oxygen and the consequent effects on the respiratory center and central nervous system as already described in Chapters VI and VII. In persons who are in good physical training

these effects are in abeyance because as one part of physical training the lung epithelium has become much more capable of responding to the stimulus calling forth increased secretion of oxygen, just as in the case of a man who has become acclimatized to a high altitude, or to breathing air containing a small percentage of CO. It is the training of the lung epithelium, and not anything else, that makes the specific difference. This is shown at once by the fact that acclimatization to high altitudes or CO poisoning takes place whether a man takes exercise or not.

In this connection I may mention the result of an experiment which I made for a specific object during the war. It seemed desirable to find out how soon the fall in oxygen percentage in the air of a submarine would begin to have serious effects. I therefore shut myself in an air-tight respiration chamber which was provided with the same sort of purifier for absorbing the CO_2 produced by respiration as was used in British submarines. The oxygen percentage was also allowed to fall at the same slow rate as that at which it had been found to fall in the most crowded submarines then in use. After a few hours a light would no longer burn in the air, and in a few more hours even a lighted pipe handed in through a small air lock would no longer keep alight. After 56 hours the oxygen percentage had fallen below 10. I then terminated the experiment as the purifier was failing, and the immediate object of the experiment, which was to find out whether the air in a submarine would last easily for 48 hours without any addition of oxygen, had been attained. I had no trace of mountain sickness or any other symptom of anoxaemia, and my lips were just as red as usual, though from other experiments described in Chapter VII, I knew that without acclimatization I should have broken down hopelessly in the existing atmosphere. A laboratory attendant who afterwards went into the chamber along with me became blue and uncomfortable, and finally collapsed and had to be pulled out hurriedly.

In this experiment the fall in oxygen percentage had been so slow that acclimatization had kept pace in me with the fall in oxygen percentage, just as when a man ascends only very gradually to a high altitude. There is, however, much more in this acclimatization than mere increase in the power of oxygen secretion, since there is also the gradual adjustment of blood reaction to increased breathing, as explained fully in Chapter VIII.

In a more recent series of experiments by Kellas, Kennaway,

and myself[28] these two effects were separated. One of our objects was to see how far acclimatization to high altitudes could be obtained by discontinuous exposures to low barometric pressures. This question is of course of considerable importance to airmen, in whom the exposures are discontinuous. The effects produced before acclimatization on Dr. Kellas, myself, and others, by an exposure to 320 or 330 mm. barometric pressure, are described in Chapter VI. To obtain acclimatization we used the method of exposing ourselves for six to eight hours to atmospheric pressures of 500, 430, and 360 mm. on three successive days. We found, however, that our resting alveolar CO_2 pressure had always returned to normal before the morning after each successive exposure. Thus there was no lasting adjustment of blood reaction to increased breathing, as any change in this direction had disappeared by the morning. There was also no lasting increase in our haemoglobin percentages. Any acclimatization obtained must therefore, apparently, be due to increased power of oxygen secretion.

The result of the experiment was that there was marked acclimatization, but limited in amount. When unacclimatized I had been totally disabled, and had lost all memory, at a pressure of 320 mm., as already described. But on the last day of the acclimatization we stayed at 315 mm. for a considerable time, during which, though we were distinctly blue, I could quite easily continue to do gas analyses and other operations, and move about as usual, with no loss of memory afterwards of what had occurred. In this experiment my son, Captain J. B. S. Haldane, acted as an unacclimatized control. He came in with us and stayed for some time at 366 mm.; but after two hours he was so much affected that we had to let him out. His breathing had become increasingly rapid and shallow, and he had gradually sunk into a stupified condition. After coming out he could remember hardly anything of the last hour in the chamber.

It is clear from this experiment that airmen, so long as they retain their health, and remain at high altitudes pretty frequently, must be capable of acquiring a considerable degree of acclimatization. This acclimatization was long ago noted by Glaisher in connection with his occasional high balloon ascents. An equal degree of acclimatization can undoubtedly be maintained in a simpler manner by good physical training; and at heights of less than about 20,000 feet an airman in good physical

[28] Haldane, Kellas, and Kennaway, *Journ. of Physiol.*, LIII, p. 181, 1919.

training should have little difficulty from anoxaemia. It must be noted, however, that even a small degree of the neurasthenia with shallow breathing described in Chapter III renders an airman totally incapable of going to any considerable height without an oxygen apparatus.

Our acclimatization experiment indicated that with complete acclimatization, including adjustment of the blood reaction to the increased breathing, and increase in the haemoglobin percentage, a man could probably, if the mere physical difficulties were not too great, reach the summit of Mount Everest without breathing anything else than ordinary air, though he would quite certainly die at this altitude if he were not acclimatized.

It was pointed out in Chapters III and VII that, on account of the imperfect distribution of air in the lungs, the average alveolar oxygen pressure is, even during rest under normal healthy conditions, no certain guide to the oxygen pressure of the mixed arterial blood. During heavy work this must be so to an increased degree, since, although the expansion of the lungs is much better, the rate at which oxygen is absorbed is enormously greater. Meakins and Davies[29] have recently made exact determinations of the percentage saturation with oxygen of the haemoglobin in the arterial blood of a number of healthy persons, and found it to vary from 94 to 96 per cent in different persons, the variation depending probably on the differences in the oxyhaemoglobin curves which Barcroft discovered (Chapter IV). In my own case the saturation was 94.3 per cent. This is not much lower than 96 per cent, the saturation which would be expected if my arterial blood were fully saturated to the oxygen pressure of the mixed alveolar air. If, however, we look at the dissociation curve of the oxyhaemoglobin of human blood, we see that 94.3 per cent saturation corresponds to an oxygen pressure of only 11.2 per cent of an atmosphere, as compared with 13.2 per cent in the alveolar air. Thus the oxygen pressure in the mixed arterial blood is very distinctly less than in the alveolar air; and this is the sort of result which the aërotonometer gives, as already explained.

On the other hand the carbon monoxide method gives, during rest under normal conditions, exactly the same oxygen pressure in the arterial blood as in the alveolar air. This difference in the results by the two methods used to be rather a puzzle, and was explained by me as probably due, either to a process of rapid but

[29] Meakins and Davies, *Journ. of Pathol. and Bacter.*, XXIII, p. 453, 1920.

slight oxidation in the blood itself, or to a little blood getting through the lungs without exposure to alveolar air. Our shallow breathing experiments, and the neurasthenia cases, showed clearly enough why the mixed arterial blood is not fully saturated to the alveolar pressure; but why does the carbon monoxide method not show this? A little consideration will show the reason. The carbon monoxide method gives the average arterial oxygen pressure of all the portions of arterial blood leaving the lung alveoli, just as the "alveolar air" gives the average oxygen pressure of all the portions of air in the alveoli of the air-sac system. But the oxygen pressure of the mixed arterial blood cannot be deduced, as fully explained in Chapter IV, from the average of the oxygen pressures in the blood leaving the alveoli. It is this average that the carbon monoxide method gives. Hence for the purpose of deducing the oxygen pressure of the mixed arterial blood the carbon monoxide method has exactly the same defects as the method of inferring this value from the oxygen pressure of the alveolar air on the assumption (perfectly valid for resting conditions at ordinary atmospheric pressure when pure air is breathed) that diffusion equilibrium is established between alveolar air and blood. For the purpose, however, of deciding whether or not active secretion of oxygen is occurring, the carbon monoxide method is perfectly valid. It gives just the information needed; and for this purpose it is far more reliable than the aërotonometer method, which has always given misleading information on the question of diffusion equilibrium for oxygen, and made it appear as if diffusion equilibrium is never attained, even during complete rest.

To those who pin their faith, as regards the secretion question, to the aërotonometer results, I may perhaps point out that if they were accepted as evidence they would completely wreck the diffusion theory. For if diffusion equilibrium is not even obtained under resting conditions under normal barometric pressure it would be quite inconceivable on the diffusion theory that anything approaching to diffusion equilibrium would be obtained during muscular work, and particularly at high altitudes. Yet on Pike's Peak is was possible to do hard muscular work with the lips remaining quite red.

It will easily be seen on consideration that as the barometric pressure, or the oxygen percentage of the inspired air, is progressively reduced, the difference in percentage saturation between the mixed arterial blood and blood completely saturated at

the existing alveolar oxygen pressure will increase more and more if diffusion alone determines the saturation of the blood in the lungs, and will tend in the same direction even if active secretion assists diffusion. We can thus easily explain why some of the persons who ascended Pike's Peak were very blue in the face, and why fainting or partial loss of consciousness were common occurrences. We can also understand why some persons become more or less unwell at first on going to an altitude of only four or five thousand feet, and why in all persons there is a distinct physiological reaction to anoxaemia, as shown by lowering of the alveolar CO_2 pressure and rise in the haemoglobin percentage. This physiological reaction would be difficult to understand if there was uniform saturation of the haemoglobin in all the alveoli. We must conclude that whether or not a person is acclimatized to a low barometric pressure the percentage saturation of the mixed arterial haemoglobin with oxygen is distinctly diminished, though the amount of the diminution is not indicated by the carbon monoxide method.

In the process of oxygenation of the blood in the lungs, the oxygen has to pass from the alveolar air through a thin layer of living tissue into the blood and into the corpuscles. This process must take some time. To the genius of Christian Bohr we owe the principle of a method by which the time may be estimated, in so far as the process is one of diffusion. In connection with the absorption of oxygen by the lungs it is not possible to measure the rate at which, with a given diffusion pressure, oxygen passes inwards, because we do not know the mean diffusion pressure. We can, as will be shown later, measure the oxygen pressure of the venous blood, as well as that of the alveolar air and arterial blood; but we do not know how quickly the blood becomes saturated in its passage along the alveolar capillaries. Hence we cannot estimate the mean difference in oxygen pressure required for the diffusion inwards of a given quantity of oxygen in a given time. In the case of absorption of CO present in the air in a low proportion the conditions are quite different, however: for we can determine the percentage of CO in the alveolar air, and the rate at which the gas is absorbed, while, for short experiments, the difference in CO pressure between the alveolar air and the blood is constant. In this way we can tell how much CO is absorbed per minute with a given pressure difference; and from this, allowing for the greater solubility and slightly lower diffusibility of oxygen, we can calculate the rate at which oxygen diffuses in with the same pressure difference.

Bohr's original calculations (based on rather rough experiments made by myself for another purpose) were not very accurate; but the matter was reinvestigated by A. and M. Krogh,[30] and still more recently by M. Krogh.[31] A. and M. Krogh found that for adults about 25 cc. of oxygen will diffuse inwards per minute for every 1 mm. of difference in oxygen pressure during rest, and about 35 cc. during work. The estimate of M. Krogh is considerably higher; but I do not think that the method which she used was at all reliable, for the following reasons. The method consisted in taking in a deep breath of air containing a small percentage of CO. Part of this breath was then breathed out, and a sample of the alveolar air taken. The rest of the breath was held for a measured interval of time, after which a second sample of alveolar air was taken, and the percentages of CO in the two samples very accurately determined. From the fall in the percentage of CO between the two samples the rate of absorption of the CO was then calculated.

If the difference between the percentages of CO in the two samples represented absorption of CO, the method would be a correct one. Actually, however, it is quite impossible, as I have convinced myself by repeated experiments with various gas mixtures, to secure an even distribution of a gas through the lung air by taking in a single deep breath. The first alveolar sample contains an undue proportion of the atrial air containing a higher initial percentage of CO, while the second sample comes exclusively from the alveoli of the air-sac system, in which the percentage of CO was never nearly so high as in the atria. Thus the apparent absorption of CO during the interval of holding the breath is much greater than the actual absorption. The method is thus fallacious; and the same criticism applies to a number of other Copenhagen experiments with regard to alveolar air, the dead space in breathing, etc.

Taking, however, the earlier estimate of A. and M. Krogh, it can be calculated[32] that during rest at normal atmospheric pressure, the arterial blood passing through an average alveolus would easily be saturated by simple diffusion to the oxygen pressure of the air in the alveolus. During considerable muscular work, however, this would not be the case; and the arterial blood would emerge incompletely saturated. That there should be some an-

[30] A. and M. Krogh, *Skand. Arch. f. Physiol.*, XXIII, p. 236, 1910.
[31] M. Krogh, *Journ. of Physiol.*, XLIX, p. 271, 1915.
[32] Douglas and Haldane, *Journ. of Physiol.*, XLIV, p. 337, 1913.

oxaemia during considerable exertion is therefore exactly what might be anticipated on the diffusion theory, even without any allowance for the effects of uneven distribution of air and blood among different alveoli. When allowance is also made for this factor, the presence of anoxaemia during even very moderate exertion at ordinary atmospheric pressure in persons not physically fit is just what might be expected; and at high altitudes the anoxaemia would be so serious as to make any considerable exertion impossible but for active secretion.

All the facts, therefore, and not merely our direct measurements, go towards showing that oxygen secretion is a most important physiological factor, not merely under exceptional circumstances, but during ordinary life at sea level. It is probably also an important factor under pathological conditions, though on this subject our knowledge is still almost a blank, owing to lack of observations. The only relevant observations are those of Lorrain Smith.[33] His experiments, when due allowance is made for the errors already referred to in our calculations, showed that either a rise of body temperature or a severe infection paralyzed the power of oxygen secretion in response to CO poisoning. When lung inflammation was produced by exposing the animals to a high pressure of oxygen (see Chapter XII) the arterial oxygen pressure fell to values which, when corrected, are much below that of the alveolar air. In this case it is evident that not only active secretion, but also diffusion of oxygen inwards, was interfered with. The animals were incapable of muscular exertion and thus showed symptoms similar to those of phosgene poisoning, as described in Chapter VII.

A significant determination has quite recently been published by Harrop[34] of the percentage saturation of human arterial blood with oxygen, first during rest, and then just after exhausting work. The results were 95.6 per cent during rest, and 85.5 per cent just after the exertion. The deficiency found in the blood just after exertion is far greater than could be accounted for by experimental errors.

As already mentioned, the aërotonometer experiments of Krogh indicated that the arterial CO_2 pressure is the same as that of the alveolar air. The manner in which the respiratory center responds to the slightest increase or diminution in the alveolar CO_2 pressure, and the quantitative correspondence between rise in alveolar

[33] Lorrain Smith, *Journ. of Physiol.*, XXII, p. 307, 1898.
[34] Harrop, *Journ. of Exper. Med.*, XXX, p. 246, 1919.

CO_2 pressure and response of the respiratory center, point most clearly to the conclusion that within pretty wide limits there is no active secretion of CO_2 outwards in the lung, or active retention of CO_2 when the lungs are over-ventilated. In individual experiments Bohr obtained results which seemed to point to active secretion of CO_2 outwards. The latest of these were made with Krogh's small aërotonometer; but Krogh has pointed out how easily errors may arise with this instrument; and in view of all the facts I think his criticism of Bohr's experiments is probably correct.

If we calculate, by Bohr's method, the rate of diffusion of CO_2 from the alveolar air into the blood, the result is that for the same difference in partial pressure CO_2, in consequence of its much greater solubility, must diffuse outwards about 20 times as rapidly as oxygen diffuses inwards. Against this, however, must be set the fact that the initial difference in CO_2 pressure between the venous blood and alveolar air is only about a tenth of the corresponding difference in oxygen pressure. On balance, however, there is probably little hindrance, even during hard work, to the establishment by diffusion of practical equilibrium in CO_2 pressure between the alveolar air and arterial blood. We have already seen that the giving off of CO_2 in the lungs is dependent in great part on the saturation of the haemoglobin with oxygen. Hence the giving off of CO_2 is to a large extent under the control of oxygen absorption, and so of oxygen secretion when this occurs.

Apart from this there seem to me to be strong reasons for suspecting that although active secretion of CO_2, like active secretion of oxygen, does not occur under ordinary conditions, it does occur when high pressures of CO_2 exist in the arterial blood, and the body is threatened by the excess of CO_2. As yet there is no direct evidence on this subject; but the reasons are as follows: (1) When a small volume of oxygen is rebreathed as long as possible, or even when the breath is held as long as possible after filling the lungs with oxygen, the percentage of CO_2 in the alveolar air mounts up much higher and more rapidly than can well be accounted for from any probable rise in the pressure of CO_2 in the venous blood. Examples of experiments in this direction are given in the paper by Christiansen, Douglas, and myself. (2) It appears that men in good training and with the power of oxygen secretion well developed are capable of standing a much higher percentage of CO_2 in the inspired and alveolar air than other men. In my experience with self-contained mine-rescue apparatus,

and similar devices, I have often been struck with the greater sensitiveness to CO_2 of myself and other sedentary workers in comparison with men in good physical training, although nearly pure oxygen was being breathed. These observations suggest very strongly that along with the power of oxygen secretion the power of secretion of CO_2 is developed by muscular exertion. (3) In the experiments of Paul Bert[35] on the blood gases when increasingly high percentages of CO_2 were breathed by animals, it appeared that with increase in the CO_2 percentage the CO_2 in the arterial blood often showed little or no increase. It seems very difficult to explain these results apart from active secretion of CO_2 coming into play progressively, and particularly in view of the experiments of Henderson and Haggard on the increased CO_2-absorbing capacity of the blood when excess of CO_2 is breathed (Chapter VIII).

In view of the absence, as yet, of direct measurements, it seems unnecessary to discuss this question further; but I may point out that just as the opponents of the oxygen-secretion theory have been mistaken in drawing general conclusions from experiments in which oxygen secretion was either absent or could not be demonstrated, it is very probable that they have been equally mistaken over secretion of CO_2. Bearing in mind Johannes Müller's argument as to the analogy between secretory activity and ordinary metabolic processes, it seems quite likely that the active transport, not only of oxygen, but also of CO_2, is a phenomenon which occurs in all living cells.

Not only do oxygen and CO_2 diffuse through the lung epithelium into or out of the blood, but also other gases, such as nitrogen, hydrogen, methane, carbon monoxide, etc., so that their partial pressures become exactly equal in the body and the alveolar air. But how is it that oxygen is sometimes actively secreted inwards, and that the oxygen pressure may be greater in the blood without the oxygen leaking back by diffusion into the alveolar air just as other gases leak in or out? We must, I think, suppose that the structure of the alveolar epithelium is not homogeneous but may be divided into a reticulum of living structure and a plasma filling the interstices, just as is the case with the body as a whole. The diffusion will take place through the plasma, while the living substance behaves as a solid towards diffusion, as in the case of the secreting cells of the swim bladder. Not only oxygen but also

[35] Paul Bert, *La Pression barométrique*, p. 985.

other gases will diffuse through the plasma; but during secretion of oxygen the living substance behaves like the protoplasm of the swim bladder, taking up oxygen on one side of the cell, and giving it off at a higher pressure on the other. The oxygen will tend to diffuse backwards if, as in experiments with a high percentage of CO, the oxygen pressure becomes higher in the blood than in the alveolar air; but some, at least, of this oxygen will be caught on its way and returned.

This general conception throws light in other directions. For let us suppose the direction of the oxygen secretion to be reversed, so that the lung epithelium, instead of absorbing oxygen, hinders its passage. Nitrogen and other inert gases will still be able to pass inwards freely by diffusion. We shall thus have nitrogen going through, without oxygen. Now let us suppose that the epithelium has an excretory function; and let us apply the general conceptions, above set forth, to the glomerular epithelium of the kidney. We can imagine the living substance of this epithelium holding back, by an active process, all the normal constituents of blood, particularly water, if their normal diffusion pressures are not exceeded, but otherwise letting them through. All the known facts seem to confirm Bowman's original conclusion that the water of the urine is usually almost entirely separated in the glomeruli. It seems also clear that as shown by Ludwig and his pupils, the process of separation is dependent on blood pressure, like a filtration process. If we suppose that the passages through which the liquid is filtered are not permeable by the proteins of the blood, we have an explanation, as pointed out by Starling, of why a certain minimum blood pressure is needed. The liquid separated might be little different from pure water, whereas the blood plasma contains salts in considerable amount. Such a liquid could not be separated by simple filtration, and numerous other facts are against the simple filtration theory. I think that all the facts conform with the theory that the glomerulus is a filter, but with a living framework, and that the action of this living framework, is to pick out and return to the blood what belongs to its normal composition, the rest being allowed to pass. In this process the glomerular epithelium will of course be doing work; but every living tissue seems to be always doing work, even when it is "resting." During a glomerular diuresis there may be no extra work for the epithelium to do, and it will simply act as a filter, just as the lung epithelium during rest under normal conditions acts like a nonliving membrane. Barcroft and Straub have shown that during

certain kinds of diuresis there is no increased consumption of oxygen by the kidney, and therefore presumably no work done by the kidney in the process of separation of the extra urine formed.[36] It is probable that under normal conditions a pure filtration diuresis of this type never occurs at all; but the possibility of producing it experimentally throws much light on the mode of action of the glomeruli and also of the lung epithelium. Possibly the substances carried to the lungs during anoxaemia act in the same way as a diuretic drug acts on the kidneys.

In concluding this long chapter I must make some reference to criticisms which have been made on our experiments. Part of these criticisms are the evident outcome of a natural conservative desire to save some remnant of the old mechanistic theory of glandular secretion. The lungs and the kidney glomeruli were the last remaining strongholds that there seemed much hope of defending, and I can admire the spirit which has animated the defenders. It is different, however, with the criticisms made by my friend Mr. Barcroft in his recent book,[37] as he fully acknowledges the difficulties of the diffusion theory and the inherent probability of secretory activity in the lungs.

He bases these criticisms on the work of his pupil, Mr. Hartridge. The latter devised a new and thoroughly sound method of determining the percentage saturation of the blood with CO by delicate measurements of the shifting in position of the absorption bands of oxy- and CO-haemoglobin; and he showed clearly that his method, although it requires elaborate apparatus, is capable of giving accurate results. Armed with this method he proceeded to repeat, as he thought, some of the experiments (not yet published except in a short abstract) of Douglas and myself on man. Unfortunately he modified the method in essential respects, neither taking precautions that the subject was breathing a constant percentage of oxygen, nor using whole blood in the saturator, nor experimenting in a way calculated to elicit any evidence of active secretion during work. His experiments did not appear to show any active secretion, and it would have been extraordinary if they had.

I now come to the main point of Barcroft's criticisms. Hartridge had at first calibrated his instrument by ascertaining its readings with what he believed to be known mixtures of oxyhaemoglobin and CO haemoglobin. He subsequently found that his calibrations

[36] Barcroft and Straub, *Journ. of Physiol.*, XLI, p. 145, 1911.
[37] Barcroft, *The Respiratory Function of the Blood*, p. 204.

had been quite incorrect; and in order to secure correct calibration he finally had recourse to the very tedious method of pumping out the CO and oxygen from the blood mixture after adding ferricyanide, and determining the CO and oxygen by analysis, using the general method which I followed in originally testing the accuracy of the ferricyanide method for blood gases. In his paper[38] Hartridge says of his first method that "experiments made since to discover the cause of the error have shown that with the method of mixture employed complex interactions take place between the two portions of solvent." Let us expand this somewhat mystic statement. He was working with blood diluted with water to about a twentieth. One portion of this he saturated with CO, and another portion with air. These were then mixed. It was apparently expected that the result would be a mixture containing half the haemoglobin saturated with CO and the other half with oxygen. Now if one dilutes blood to a twentieth and saturates with CO, the solution will contain about one volume of CO in combination with haemoglobin to two and one-half in simple solution; and when this is mixed with an equal proportion of the solution saturated with air the CO in simple solution in the first part will straightway combine with the haemoglobin in the second part, and turn out the oxygen, the result being that practically the whole of the haemoglobin combines with CO. With the method first adopted by Hartridge it was clearly impossible for him to calibrate his instrument.

Our colorimetric method of determining the saturation of haemoglobin with CO had repeatedly been tested against mixtures previously prepared, the most scrupulous precautions (described in three different papers) being, however, taken to avoid errors arising from the solubility of CO. Barcroft, however, infers that because Hartridge's calibration failed with the method of mixtures, ours was presumably also inaccurate: whereas Hartridge's final calibrations were made with the blood pump, which is an "objective method," and therefore the only trustworthy one. Hence, Barcroft argues, Hartridge's experiments, so far as they go, furnish the only reliable evidence about oxygen secretion, as to which they give a negative result. As a matter of fact there is not a shadow of doubt that our method of testing the colorimetric method was at least as exact as the final method used by Hartridge.

[38] Hartridge, *Journ. of Physiol.*, XLIV, p. 9, 1912.

Barcroft's reference to objective methods recalls to my mind what happened when Hartridge came to Oxford to demonstrate his method. It was apparently an "objective method," dependent, like Hüfner's spectrophotometric method, on the exact positions of absorption bands in the spectra of oxyhaemoglobin and CO haemoglobin—bands of which the "exact positions" can be quite easily photographed. A solution of blood was prepared for demonstration; and Hartridge, the late Professor Gotch, and I went into a dark room and proceeded first to determine the zero point on the scale of the apparatus. First one, and then the others of us determined the zero point. But the results were all different, though each one of us always got the same result. We stood there in the dark, each suspecting the others of want of accuracy, but afraid to say so. Suddenly the truth dawned on us. Even the position of an absorption band is subjective!

And then, if our ears could have caught it, we might have heard a gentle but kindly laugh. It came from a Spirit that flits round old university walls and even wanders sometimes into laboratories. It was the Spirit of Humanism that laughed, and it always laughs when men find out with Socrates that what is objective is also subjective.

Addendum. Barcroft and his associates[39] have recently made a very carefully planned attempt to see whether any evidence of oxygen secretion could be obtained by analyses of the arterial blood. Barcroft himself was the subject of the experiment, and he remained for a week in a respiration chamber in which the oxygen percentage was gradually lowered, until on the last day there was only about 11 per cent of oxygen in the air, corresponding to an altitude of 18,000 feet, or about 17,000 if allowance is made for the presence in the air of about 0.5 per cent of CO_2. There was thus apparently every chance of acclimatization occurring. On the other hand very little acclimatization seems to have actually occurred, as the subject was very unwell, with slight rise of temperature, on the last day or two, and was in a fainting condition at the end, just before the samples of arterial blood were taken.

Samples of arterial blood were taken, firstly during rest, and later during work on a bicycle ergometer of about 380 kilogrammeters per minute, which would increase the respiratory exchange about three or four times. The haemoglobin of the sample during rest was found to be 88.1 per cent saturated with oxygen. Analyses

[39] Barcroft, Cooke, Hartridge, T. and W. Parsons, *Journ. of Physiol.*, LIII, p. 450, 1920.

of the arterial blood were made, both by the ferricyanide method and with the pump, and agreed closely. Samples of alveolar air were also taken, and part of the arterial blood saturated with air of about the same composition. The saturation of the haemoglobin of this blood, when corrected for the slight difference in oxygen pressure between the air in the saturator and the sample of alveolar air, was found to be 91 to 92 per cent, which is distinctly higher than the saturation of the arterial blood. The oxygen pressure of the sample of alveolar air was, however, quite unaccountably high. It was 68 mm., instead of about 45 mm. which was the value actually found in a determination made a few hours previously, and was also the value to be expected from the curve shown in Figure 98 of this book. Had the actual alveolar gas pressures corresponded with those of the sample, the respiratory quotient would have been about 2; and such a quotient occurs only during forced breathing, which could not have occurred. It seems, therefore, that there must have been some mistake about the alveolar sample; but what this was is far from clear. If the actual alveolar oxygen pressure had been about 45 mm., as would correspond to the alveolar CO_2 pressure, the oxygen saturation of the blood from the saturator would have been considerably lower than that of the arterial blood. The experiment is thus inconclusive, apart altogether from the question as to whether the subject was acclimatized at all, or to what extent.

The experiment during work is much more consistent. The arterial haemoglobin was found to be only 83.5 per cent saturated with oxygen. A lower saturation during work of the character chosen corresponds well with all our observations on Pike's Peak and at Oxford. Unacclimatized persons became very blue in the face on Pike's Peak with comparable work; and even after acclimatization there were clear indications of some anoxaemia. In me, for instance, the alveolar oxygen pressure rose about 8 mm., and the alveolar CO_2 pressure fell, on walking at 4 miles an hour; and this, as we pointed out, indicated arterial anoxaemia. The haemoglobin of the blood exposed to the alveolar air in the saturator gave a saturation of 89.2 per cent, which is 5.7 per cent higher than the saturation of the arterial blood. This result furnishes no evidence of secretion, but to show that there was actually no secretion it would, I think, be necessary to make a control experiment on a person who had spent only a short period in the chamber, and was undoubtedly unacclimatized.

Barcroft and his associates consider that the results of the

experiments were against the secretion theory. In this I cannot agree with them. It seems to me evident that if there was any acclimatization in these experiments it was very imperfect, and not comparable to the acclimatization commonly observed at high altitudes, and closely studied by us on Pike's Peak. Acclimatization occurs much more readily in certain persons than in others, and seems also to be greatly affected by accompanying conditions. An experiment in which marked acclimatization occurred in myself in a respiration chamber was referred to above. On endeavoring to repeat this experiment in the summer of 1920 there was no effective acclimatization, and on account of severe symptoms of anoxaemia, accompanied by blueness of the lips, etc., I had to stop before the oxygen pressure had fallen to quite as low a point as on Pike's Peak, or to nearly as low a point as in the previous experiment where no pathological signs of anoxaemia were produced. It was about a week before I recovered from the effects of this unsuccessful experiment. The weather was hot, and the chamber correspondingly uncomfortable. I was also several years older. In this experiment my arterial blood was analysed by Professor Meakins, who found the haemoglobin to be considerably below its normal saturation with oxygen. There was evidently little or no acclimatization.

I should like to correct here one or two misunderstandings which occur in the paper of Barcroft and his associates. Through a misreading of the paper by Douglas and myself he concluded that on lowering the oxygen pressure of the inspired air to what corresponded to about the oxygen pressure on Pike's Peak we found in a short experiment at Oxford that by the carbon monoxide method the arterial oxygen pressure was 70 mm. above the alveolar oxygen pressure. The actual difference was only trifling (about 8 mm.), as shown in the table reproduced above. It required prolonged acclimatization to produce as great a difference as even 35 mm. There is also a misunderstanding as to our experiments on the effects of work. Though we made no observations by the carbon monoxide method on the effects of work such as was employed by Barcroft, all the other observations referred to in the present chapter tend to show that except, perhaps, when physical training or acclimatization is very effective, the arterial oxygen saturation during such work is lower than during rest.

Clear evidence is brought forward by Barcroft and his associates that no appreciable loss of dissociable oxygen occurs in arterial blood which is allowed to stand for a short time. In the

Pike's Peak report we concluded that such a loss probably occurs. The chief reason for this conclusion was that the aërotonometer always gives a lower oxygen pressure than that deduced on the diffusion theory from the alveolar oxygen pressure, or indicated by the carbon monoxide method during rest under ordinary barometric pressure. As explained above, however, there is now another and very clear explanation for this; and since the investigation by Meakins, Priestley, and myself on the effects of shallow breathing I have altogether ceased to believe in the presence, to any extent which would upset a blood-gas or aërotonometer determination, of "reducing substances" in blood. I am in entire agreement with Barcroft's criticism of the old experiments by which Pflüger believed that he had demonstrated the existence of reducing substances in fresh arterial blood. It may also be mentioned here that in some unpublished experiments Douglas and I were unable to obtain any evidence by blood-gas analysis of the presence of reducing substances, even in blood which was completely reduced by prolonged stoppage of the circulation in the arm.

CHAPTER X

Blood Circulation and Breathing.

ALTHOUGH it does not fall within the scope of this book to deal in detail with the physiology of the circulation, yet the connection between breathing and circulation is so specially intimate that a chapter must be devoted to this subject. Physiology is most emphatically not a subject which can be divided off into water-tight compartments.

We have seen that it is with the composition of the arterial blood that breathing is essentially correlated; but it has also been shown in successive chapters that the amount and composition of the blood returning from the tissues to the lungs play a most essential part in determining the composition of the arterial blood, and are thus intimately correlated with breathing. If, moreover, the blood supply to the brain and other tissues is insufficient, or the blood is abnormal in composition, the breathing is affected in various ways. On the other hand circulation is intimately dependent on breathing. If the breathing is hindered the circulation is quickly affected; and, as Yandell Henderson was the first to show, excessive breathing brings about failure of the circulation. Thus we cannot at all fully understand how the breathing is regulated and what part it is playing unless we understand the distribution of the circulating blood and the means by which its composition in the tissue capillaries is regulated.

It seems evident that the most urgent and immediate need for an adequate blood supply to any part of the body arises from the necessity for a continuous supply of fresh oxygen. If the supply of oxygen to the arterial blood is cut off in a warm-blooded animal by placing it in nitrogen or hydrogen, loss of consciousness occurs as soon as the store of oxygen in the lungs and venous blood is washed out. In man eight or ten breaths suffice for this during rest, and still fewer breaths during exertion. In very small animals, with their rapid breathing and circulation, two or three seconds are sufficient; and a few seconds afterwards the heart is paralyzed also. The important effects of even a slight diminution in the pressure of oxygen in the arterial blood have been made clear in preceding chapters.

A second, but somewhat less urgent, need is for a continuous removal of carbonic acid or any other acid product formed in the tissues. We can probably express this generally as a need for preventing an abnormal proportion of hydrogen ions to hydroxyl ions. The effect on the central nervous system of a sudden flooding with CO_2, without deficiency of oxygen, is almost as striking, though not so immediately dangerous to life, as the effect of deprivation of oxygen. The results of even a slight variation in arterial CO_2 pressure have often been referred to already.

Other conditions in the blood besides the diffusion pressures of oxygen and CO_2 or other acid products are just as important to life. For instance there are the diffusion pressure of water (inaccurately identified with osmotic pressure) and the diffusion pressures of the ions of various inorganic salts, on the importance of which the investigations of Ringer and many others have thrown much light. But none of these values vary in the same rapid manner as the diffusion pressures of oxygen and CO_2 do; and of ordinary nutrient substances present in blood, the tissues themselves appear to possess a store which can be drawn on if the supply from the blood fails for a time. The results of perfusion experiments continued with the same blood indicate that if only the blood is properly aërated it continues for a very long time to support life in the tissues.

It would seem, therefore, that the regulation of circulation through the tissues must in the main be determined in correlation with the need for supplying oxygen and removing CO_2. There are evidently, however, cases where some other factor determines the circulation rate. For instance, the skin circulation is determined to a large extent in relation to the regulation of body temperature; and the circulation through an actively secreting gland is probably determined to a considerable extent in correlation with local excess or deficiency of water or dissolved solids.

We can form a general idea as to what changes in gaseous composition determine the circulation rate through the tissues if we compare the arterial blood with the mixed venous blood returning to the lungs. As regards this point, analyses showing the difference in composition have already been quoted in Chapter V, and indicate that, in the animals experimented on, the blood in its passage through the tissues had lost about a third of its available oxygen, and gained the amount of CO_2 which would correspond to the loss of oxygen when allowance is made for the existing respiratory quotient of the animal. If we applied these

results to man, and interpreted them in the light of the thin line in the dissociation curves of oxyhaemoglobin shown in Figure 28 (assuming that the haemoglobin of arterial blood is 95 per cent saturated) and the thick line in the corresponding curve for CO_2 (Figure 26) it would appear that the average pressure of oxygen in the venous blood is about 5.2 per cent of an atmosphere, or 40 mm. of mercury, and the average pressure of CO_2 about 47 mm. The experiments were, however, made on animals, while the dissociation curves (the only accurately determined ones) are for human blood. Moreover the animals, owing to operative disturbances, anaesthetics, etc., were more or less under abnormal conditions. Hence the inferences just drawn are mere approximations. The very great variability in the CO_2 content of the samples of arterial blood from animals of the same species, as compared with the constancy of CO_2 content in the case of man under normal resting conditions, is in itself very significant. The history of the investigations detailed in the preceding chapters is sufficient to warn us of the necessity for reaching more than rough approximations in physiological investigation, and for expecting that physiological regulation of the circulation may turn out to be something just as delicate and definite as regulation of respiration. It is to measurements in man, rather than in animals, that we must look for information of sufficient physiological accuracy, just as it has been through measurements in man that our definite information as to the regulation of breathing has been obtained.

The difficulty as regards human experiments has till quite recently been that of suitable methods. We can easily measure the blood pressure, pulse rate, etc., in man; but the information thus obtained is extremely limited in value and almost impossible to interpret satisfactorily in the absence of information as to the rate of blood flow. Direct measurements of the rate of blood flow in animals have been carried out by means of the Ludwig "Strohmuhr" and the improved forms of it which have been applied to measuring the blood flow through the aorta; but the operative disturbance is far too serious to allow of sufficiently definite results being obtained. Valuable information of a rough kind was obtained by Zuntz and Hagemann[1] in experiments in which the gases of the venous and arterial blood were determined in horses, along with the total respiratory exchange, during rest and work. These experiments seemed to show clearly that the

[1] Zuntz and Hagemann, *Landwirtsch. Jahrb.*, 27, Supplem. Bd. III, 1898.

general circulation rate is considerably increased during muscular work, so that, in spite of the enormous increase in consumption of oxygen and production of CO_2 in the body, there is still a good deal of oxygen in the venous blood.

Other very interesting experiments were made on man by Loewy and von Schrötter.[2] They succeeded in introducing a modified Pflüger lung catheter (Figure 68) into a branch bronchus or one of the two main bronchi in man. The supply of fresh

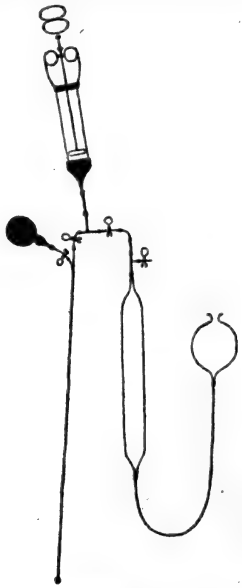

Figure 68.

Lung-catheter as used by Loewy and von Schrötter. The lung-catheter consists of a central inner tube open at the lower end, and an outer tube ending below in a distensible bulb which can be blown up by the rubber bag when the end of the catheter is placed in position in a bronchus. By means of the syringe and glass sampling tube a sample of gas from beyond the bulb can be collected over mercury free of air.

air to the corresponding part of a lung, or whole lung, was thus completely cut off and remained so for long periods. The breathing, however, went on quite quietly and naturally, just as before, even though all the air usually distributed to the two lungs was going to only one lung. It is very significant that so little disturbance in breathing, etc., was produced; but the fact is quite easily intelligible now in the light of the preceding chapters. The

[2] Loewy and von Schrötter, *Die Blutcirculation beim Menschen*, 1905.

lung which remained connected with fresh air was receiving much more fresh air than usual, so that the proportion of CO_2 in the arterial blood from this lung would be reduced practically in proportion to its increased ventilation. This blood would mix with the venous blood from the other lung, and in this way form a mixture in which the proportion of CO_2 was about normal. The arterial blood from the ventilated lung would, in virtue of the higher pressure of oxygen and lower pressure of CO_2, contain slightly more oxygen than usual, while the blood from the unventilated lung would contain considerably less. The result would be a mixture containing an abnormally low proportion of oxygen, but not sufficiently low to cause any marked immediate disturbance. Even with a whole lung blocked off, the haemoglobin of the mixed arterial blood would be at least 85 per cent saturated with oxygen instead of 95 per cent, so that the effect on the breathing would be no greater than the probable effect, hardly noticeable at the time, of breathing air containing 14 per cent of oxygen, or ordinary air at a height of about 11,000 feet.

Analyses of the air in the blocked lung showed that after a comparatively short interval of time the percentages of oxygen and CO_2 became steady, and were, in different individuals, about 5.3 per cent of oxygen and 6.0 per cent of CO_2, corresponding respectively to 37.5 mm. and 42 mm. These values are evidently the pressures of oxygen and CO_2 in the venous blood. The low value of the venous CO_2 pressure was quite unintelligible at the time, since the average arterial CO_2 pressure is about 40 mm. as shown above. The experiments of Christiansen, Douglas, and myself (Chapter V) showed, however, that the true venous CO_2 pressure is in reality only a little higher than the arterial CO_2 pressure; and if we allow for the fact that the breathing was presumably slightly increased by the stimulus of want of oxygen the result is just what might be expected. The venous oxygen pressure would be somewhat lower than usual, since the arterial blood was incompletely saturated with oxygen. Hence both the oxygen pressure and the CO_2 pressure would be below normal. The results of these experiments were nevertheless of the highest interest.

It is evident that if by any means we can measure the rate of blood flow through the lungs, and at the same time measure the intake of oxygen and discharge of CO_2 from the blood, we can calculate how much oxygen a given volume of the blood gains, and how much CO_2 it loses, in the lungs; and in this way we can

indirectly calculate how far the gain and loss vary under different conditions. A rough method devised by Yandell Henderson for measuring the relative rates of the blood flow was used in the Pike's Peak expedition, and served to indicate that the rate of blood flow remained practically normal in spite of the great altitude. Another method, the principle of which was tried, though without success, by Henderson on Pike's Peak, was about the same time independently worked out and extensively used by Krogh and Lindhard at Copenhagen.[3] This method gives absolute and not merely relative results. The principle of the method is that the lungs are filled by a very deep breath with a mixture containing a considerable percentage of nitrous oxide, a gas which is very soluble in blood. A sample of alveolar air is taken after an interval of five seconds to allow the lung tissue to become saturated with the nitrous oxide, and after a further interval during which the breath is held, another alveolar sample. By determining the nitrous oxide in the two samples, and also the total volume of gas in the lungs, we find out how much nitrous oxide has been absorbed. Knowing the solubility of nitrous oxide in blood, and assuming also that the blood leaving the lungs is fully saturated with nitrous oxide to the existing partial pressure of the gas, we can calculate from the loss of nitrous oxide how much blood has passed through the lungs in the given time interval. The experiment must be carried out so rapidly that the venous blood continues to be free of nitrous oxide.

There are various sources of probable error in this method, but in the hands of Krogh and Lindhard it gave fairly consistent results. They found that during rest the amount of blood circulating through the lungs of an adult man varies from about 2.8 to 5 liters per minute, and that the arterial blood loses about 30 to 60 per cent of its available oxygen on an average, and during considerable work about 50 to 70 per cent. The following table gives calculated volumes of blood passing through the lungs, and calculated percentage losses in the available oxygen of the blood as it passes round the tissues.

It will be seen that, allowing for the fact that the haemoglobin of arterial blood is only 95 per cent saturated with oxygen, the haemoglobin of the venous blood was apparently only 38 per cent and 53 per cent saturated in the two resting experiments. The flow of blood through the lungs during work appeared to be as

[3] Krogh and Lindhard, *Skand. Arch. f. Physiol.*, XXVII, p. 100, 1912.

much as six times as great as during rest. As the pulse rate only went up to about double the normal, the volume of blood expelled from the heart at each systole must, if these results were reliable, have been trebled. This would be just as striking an increase as occurs in the depth of breathing during muscular work. The values for utilization of the available oxygen of the arterial blood are

Subject	*Work in kg.m. per minute*	*Calculated blood flow—Liters per minute*	*Percentage utilization of available O_2 of arterial blood*
J. L.	0	2.8	60
"	458	9.8	73
"	1 *minute after work*	4.45	44
A. K.	0	2.95	46
"	446	16.0	47
"	552	17.6	51

not very far from those obtained in the horse by Zuntz and Hagemann, but do not agree at all well with those of Loewy and von Schrötter in man. In the case of six experiments on different individuals where approximate data were available the latter observers calculated a utilization of rather less than 20 per cent during rest.

During or since the war several other observers have used the method of Krogh and Lindhard, and obtained more or less similar results. These observers include Boothby,[3A] as well as Newburgh and Means[3B] in America. Lindhard[3C] has also published a number of additional results, which give, on the whole, a distinctly higher rate of circulation, and lower percentage utilization of oxygen, during rest.

The subject had meanwhile been approached by a quite different method by Yandell Henderson.[4] He used dogs for his experiments, and placed a recording plethysmograph round the heart after removing the pericardium. By this method he found that the volume of blood discharged per heartbeat was approximately the same, whether the heart was beating faster or slower. Thus within wide limits the volume of blood discharged per minute

[3A] Boothby, *Amer. Journ. of Physiol.*, XXXVII, p. 383, 1915.
[3B] Newburgh and Means, *Journ. of Pharm. and Exp. Therap.*, VII, p. 4, 1915.
[3C] Lindhard, *Pflüger's Archiv.*
[4] Yandell Henderson, *Amer. Journ. of Physiol.*, XVI, p. 325, 1906.

appeared to depend almost entirely on the pulse rate. He concluded that under normal conditions the heart is, practically speaking, always adequately filled during diastole, although under abnormal conditions the filling may become inadequate—for instance when the carbon dioxide of the blood is greatly reduced by excessive artificial respiration. If we apply Henderson's conclusions to man it is evident that they cannot be reconciled with those of Krogh and Lindhard. On Henderson's theory the increased absorption of oxygen and discharge of CO_2 from the blood passing through the lungs during muscular exertion must be due to a very large extent to greater utilization of the oxygen in the blood passing round the body, and a corresponding increase in its charge of CO_2. The rate of circulation can only be increased in proportion to increased pulse rate, the discharge of blood per systole remaining about the same.

There is no question that the systolic discharge may, at least under abnormal conditions, vary enormously. This was very clearly shown by the experiments of Starling and Patterson,[5] with a "heart-lung preparation"—i.e., a preparation in which the only circulation was through the lungs and heart, the lungs being ventilated so as to insure full oxygenation of the blood. By varying the venous blood pressure, the systolic discharge could be varied tenfold, without any variation in the pulse rate. It does not follow, however, that there are corresponding variations in systolic discharge in normal men and animals with the organic regulation of circulation not thrown out as in the case of a heart-lung preparation.

In the nitrous oxide method there are various sources of possible very serious error which can hardly be discussed in detail here. In order to get a more direct and accurate insight into the venous gas pressures and their relation to blood flow, a new method was introduced by Christiansen, Douglas, and myself.[6] In the first application of this method we simply determined the CO_2 pressure of the venous blood after oxygenation but without its losing any CO_2. As we had already discovered (see Chapter V), this pressure is higher by an easily calculable amount than that for the unoxygenated venous blood. Mixtures containing about the required percentage of CO_2 were prepared by adding CO_2 to air. A deep breath of one of these mixtures was taken in

[5] Starling and Patterson, *Journ. of Physiol.*, XLVIII, p. 357, 1914.
[6] Christiansen, Douglas, and Haldane, *Journ. of Physiol.*, XLVIII, p. 244, 1914.

after previously expiring deeply. After two seconds part of the air in the lungs (about 1½ liters) was expired, so as to obtain a sample of alveolar air. The rest of the breath was held for five seconds and a second sample of alveolar air was then taken. If these two samples gave practically the same percentage of CO_2, the CO_2 in the alveolar air was evidently in pressure equilibrium with the CO_2 of the oxygenated venous blood. If too much CO_2 were present in the alveolar air the second sample would contain less CO_2 than the first, and if too little, more. We were thus using the whole of both lungs as an aërotonometer. For any particular person it was easy to find the mixture which gave equilibrium. With the help of Figure 26 (Chapter V) we could then calculate the CO_2 content of the venous blood and the true value of the venous CO_2 pressure. We could also calculate how much CO_2 the blood had taken up in passing round the body if we knew the normal alveolar CO_2 pressure. The following table shows the results obtained during complete rest in a sitting position with the four subjects investigated.

Subject	*Arterial CO_2 pressure in mm. Hg.*	*Venous CO_2 pressure in mm. Hg.*	*Difference*
J. C.	34.9	41.8	6.9
J. S. H.	40.6	45.6	5.0
C. G. D.	39.7	44.4	4.7
J. G. P.	40.4	45.1	4.7
Mean	38.9	44.2	5.3

Reference to Figure 26 shows that on an average the venous blood had only taken up about 24 per cent of the CO_2 which it would have taken up if all its available oxygen had been used up. Hence the blood had only lost about 24 per cent of its oxygen in passing round the circulation; and in the three male subjects the proportion lost was only about 21 to 22 per cent. This indicates a much faster circulation rate during rest than the nitrous oxide method had shown.

At the outbreak of war, Dr. Douglas and I were engaged in carrying these experiments further; but as he volunteered at once for active service they were interrupted; and owing to the disorganization following the war they are not yet completed, though I was able to carry them on up to a certain point with help from Dr. Mavrogardato, and to communicate a number of

results to the Physiological Society in 1915. We had been engaged in measuring directly both the true venous CO_2 pressure and oxygen pressure just after forced breathing, so as to discover the effects of lowered CO_2 pressure on the circulation. We found that the apparent venous oxygen pressures were incredibly high—70 mm. or even more. On further investigation it became evident that after a single deep expiration, followed by a single deep inspiration of the gas mixture, the air in the alveoli was not properly mixed. At the end of the forced breathing there would be nearly 20 per cent of oxygen in the alveolar air. With one deep inspiration of the mixture, the air in the air-sac system of alveoli was mingled with air from the inspired mixture, but an even mixture in all parts of the alveolar system was not obtained, so that the air-sac alveoli contained considerably more oxygen than the rest of the alveoli. As a consequence the second alveolar air sample, taken more exclusively from the air-sac alveoli, contained more oxygen than the first, in spite of the fact that it had remained longer in the lungs. It was evidently necessary, therefore, to take two or, in the case of forced breathing, three successive deep breaths of the mixture before holding the breath and taking the samples. When this was done the results were quite consistent, and showed that the venous CO_2 pressures as determined directly during rest confirmed the calculated values previously obtained; while the venous oxygen pressures, when interpreted in the light of the thin-line curve of Figure 28, corresponded very closely with the percentage oxygen loss of the blood as calculated indirectly from the venous CO_2 pressure. Moreover, not only the venous CO_2 pressure, but also the venous oxygen pressure, was considerably lower at the end of forced breathing.

The following are examples of two typical experiments carried out on myself at the end of ten minutes' rest on a chair.

No. 1, 26/2/15. Bar. 762 mm.

Mixture used contained 6.21 per cent of CO_2 and 5.73 per cent of oxygen.

First alveolar sample 2″ after last deep inspiration, 6.43 per cent of CO_2 and 6.18 per cent of oxygen.

Second alveolar sample 5″ after first sample, 6.47 per cent of CO_2 and 6.22 per cent of oxygen.

Therefore venous CO_2 pressure = 6.47 per cent = 46.16 mm. and oxygen pressure 6.22 per cent = 44.5 mm.

Normal alveolar CO_2 percentage (mean of inspiratory and expiratory samples) 5.64 per cent = 40.3 mm.

Metabolism (by Douglas Bag method) = 330 cc. of CO_2 and 379 cc. of oxygen (at 0° and 760 mm.) per minute.

As the venous CO_2 pressure was 6.0 mm. above the arterial, the blood (calculating from Figure 26) had gained 4.2 per cent by volume of CO_2. Hence the circulation rate calculated from CO_2 was $\frac{330}{42} = 7.9$ liters per minute. As the venous oxygen pressure was 44.5 mm. and this corresponds, calculating from Figure 28, to 73 per cent saturation of the haemoglobin, the blood had lost about 22 per cent of its combined oxygen. Adding the corresponding small amount of dissolved oxygen this corresponds to a loss of about 4.3 volumes per cent of oxygen. Hence the circulation rate, calculating from the oxygen, was $\frac{379}{43} = 8.8$ liters per minute.

No. 2. 27/2/15. Bar. 752 mm.

Mixture used contained 6.26 per cent of CO_2 and 5.26 per cent of oxygen.

First alveolar sample 2″ after last deep inspiration, $CO_2 = 6.26$ per cent and $O_2 = 6.25$ per cent.

Second alveolar sample 5″ after first sample, $CO_2 = 6.30$, $O_2 = 6.09$ per cent.

Therefore venous CO_2 pressure = 6.30 per cent = 44.4 mm.; and oxygen pressure 6.09 per cent = 42.9 mm.

Normal alveolar CO_2 pressure (mean) = 5.55 per cent = 39.1 mm.

Metabolism 332 cc. of CO_2 and 374 cc. of oxygen absorbed (at 0° and 760 mm.) per minute.

As the venous CO_2 pressure was 5.3 mm. above the arterial, the blood (calculating from Figure 26) had gained 3.7 volumes per cent of CO_2. Hence the circulation rate calculated from CO_2 was $\frac{332}{37} = 9.0$ liters per minute. As the venous oxygen pressure was 42.9 mm., and this corresponds (Figure 28) to 70 per cent saturation of the haemoglobin, the blood had lost about 25 per cent of combined oxygen or about 4.9 volumes per cent of oxygen. Hence the circulation rate, calculating from the oxygen, was $\frac{374}{47} = 8.0$ liters per minute.

If we take these two experiments together, the circulation rate determined from the CO_2 was 8.45 liters per minute, and from

the oxygen 8.40 liters, the general mean being 8.4 liters. As my pulse rate was 80 to 85 per minute this means that just about 100 cc. of blood were delivered at each heartbeat; and as my blood volume is about 4.8 liters (see p. 280 of the Pike's Peak Expedition's Report) a volume of blood equal to that in the whole body was passing round every 35 seconds.

This is a much higher rate than has usually been calculated in recent years, but not higher than what the data of Loewy and von Schrötter indicate. There are so many sources of probable error in the nitrous oxide method,[7] that I do not think that much stress can be laid on the lower estimates which this method has given during the resting condition. Nevertheless it is already evident from our experiments that considerable individual differences exist in the resting circulation rate in man; and it is probable that under abnormal conditions both the circulation rate and the delivery per beat vary considerably even in persons of the same weight.

At different times we have found very little difference in the resting venous gas pressures of the same individual. These gas pressures seem to be not much less steady during rest under normal conditions than the arterial gas pressures. It is very different, however, during exertion. The smallest muscular exertion raises the venous CO_2 pressure, and the rise is far more than corresponds to the comparatively slight rise in arterial CO_2 pressure as measured in the ordinary way in the alveolar air. Hence it is now perfectly certain that the general circulation rate does not increase in anything like direct proportion to increased metabolism. Even with moderate exertion (about a third the maximum possible) on a Martin's ergometer, the difference between arterial and venous CO_2 pressure became about two and one-half times as great as usual, so that the venous blood could not be more than about 45 per cent saturated with oxygen. So far as we can calculate there is sometimes more increase in circulation than can be accounted for by increased pulse rate; but the increase is seldom

[7] For instance, it seems very probable that while the breath is held in performing an experiment the blood flow to the heart, and consequently through the lungs, is temporarily diminished. Krogh and Lindhard, misled, as we believe, by the imperfect mixture of oxygen in the alveolar air in their experiments, estimated that there is a greatly increased absorption of oxygen, and a corresponding abnormal increase in circulation, while the breath is held; and their results are corrected accordingly. The correction, which is a large one, does not seem to us to be warranted, and without it their results come much closer to ours. This is especially true for Lindhard's later results.

great. Roughly speaking, therefore, our results confirm those obtained by Henderson on the dog.

Henderson and Prince have determined in a number of persons the oxygen consumption per beat of the heart, or what they call for brevity "the oxygen pulse."[8] This value is obtained by simply dividing the oxygen consumption per minute by the pulse rate. Figure 69 shows graphically a fairly typical example of their

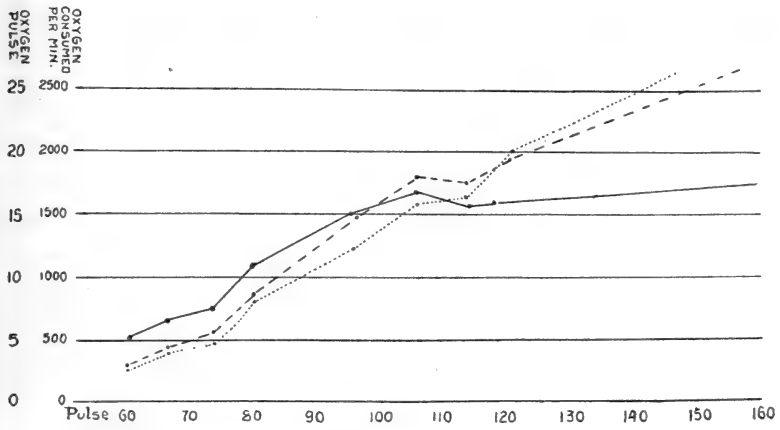

Figure 69.

Subject Y. H., Weight 75 kilos. Haemoglobin 107. In this diagram the broken line expresses the oxygen consumption per minute, the dotted line the CO_2 elimination, and the solid line the oxygen pulse. During the short periods of vigorous exertion and rapid heart rates, the CO_2 elimination was increased to a greater extent than the oxygen consumption, the respiratory quotient even rising above unity in some cases, and indicating an excessive blowing off of CO_2.

results. It will be seen that with low oxygen consumption per minute the oxygen consumption per beat is low, but increases rapidly up to a maximum as the oxygen consumption per minute increases owing to muscular exertion. When, however, this maximum is reached, further increase of the oxygen consumption per minute causes no increase in the oxygen consumption per beat. Interpreting these data in the light of our own experiments on man, and Henderson's former experiments on the heart of the dog, the increased oxygen consumption per beat is not due to any marked extent to increased output of blood per beat, but to increased utilization of the charge of oxygen in the arterial blood.

[8] Yandell Henderson and Prince, *Amer. Journ. of Physiol.*, XXXV, p. 106, 1914.

When this increased utilization reaches its physiological limit, further increase in the oxygen consumption per minute can only be obtained by increase in the rate of heartbeat.

The mixed venous blood returning to the heart comes from various parts of the body; but during muscular exertion a very greatly increased proportion must come from the muscles. Now there is evidence from a series of experiments by Leonard Hill and Nabarro that the venous blood returning from the muscles contains even during rest far less oxygen and more CO_2 than at any rate the venous blood returning from the brain.[9] Without obstructing the vessels they collected venous blood returning from muscles through the deep femoral vein, and from the brain through the torcular Herophili in the dog. The following table shows the average of about eight determinations in each case.

		OXYGEN, VOLUMES PER CENT			*Percentage loss of*
		Artery	*Vein*	*Difference*	*oxygen*
Rest	Muscle	18.10	5.12	—12.98	72
	Brain	16.81	13.39	— 3.42	20
Tonic fit	Muscle	17.05	3.30	—13.75	81
	Brain	15.17	10.22	— 4.95	32
Clonic fit	Muscle	18.66	6.03	—12.63	69
	Brain	15.77	11.46	— 4.31	27

It will be seen (1) that during rest the blood lost three and one-half times as much of its charge of oxygen in the muscles as in the brain; (2) that during the intense activity of a tonic or clonic fit (produced by absinthe) the percentage loss of oxygen by the blood was only slightly increased in either the brain or the muscles. The animals were anaesthetized with morphia or chloroform, so it is possible that the circulation was less active than in normal animals; but the difference between the brain circulation and that through muscles is none the less striking.

In the light of these experiments we can see what is presumably happening as regards the mixed venous blood during muscular

[9] Leonard Hill and Nabarro, *Journ. of Physiol.*, XVIII, p. 218, 1895.

activity. The chief reason why the oxygen diminishes and CO_2 increases so strikingly is that the mixed venous blood contains a much larger proportion of blood from muscles, and that this blood is very poor in oxygen whether the muscles are working or not. During rest the mixed venous blood will contain but little blood from the muscles, and a large proportion from the brain and probably other parts which furnish venous blood relatively rich in oxygen. As indicated by the size of its arteries, the brain has a very rich blood supply, going mainly to the gray matter. Its normal oxygen pressure is evidently very high; and this renders intelligible the fact that it is so sensitive to deficient saturation of the arterial blood with oxygen. The rapid circulation explains the promptness of its reaction to changes in quality of the arterial blood.

The fact that during muscular exertion the mixed venous blood contains much less oxygen and more CO_2 explains why, if the breath is voluntarily held during exertion, the alveolar CO_2 percentage shoots up much higher than if it is held for a far longer time during rest. It also explains what would otherwise be a very puzzling fact with regard to congenital heart affections ("morbus coeruleus"). In cases of morbus coeruleus the face becomes intensely blue on muscular exertion. Quite evidently the arterial blood is very imperfectly oxygenated; and Douglas and I found that the blueness continues even if the patient breathes pure oxygen during the exertion. The blueness is due to part of the venous blood short-circuiting through a congenital direct communication between the right and left sides of the heart, so that the mixed arterial blood always contains a certain proportion of unaërated venous blood. During rest this venous blood contains so much oxygen that the cyanosis is only slight; but during exertion, with much less oxygen in the venous blood, the cyanosis is of course far more marked, and the breathing of oxygen avails very little towards redressing the balance.

It is evident from the facts just referred to that the increase in blood flow through the lungs during exertion is very much less than the increase in air breathed. At first sight, therefore, it might seem that the regulation of circulation differs fundamentally from the regulation of breathing. A little consideration, however, shows that there are no real grounds for this conclusion. If we take as our measure, not the blood flow through the heart, but the blood flow through individual parts of the body, the facts so far discussed do not point to any other conclusion than that the blood flow, just

like the breathing, is delicately regulated in accordance with the local requirements for the supply of oxygen and removal of CO_2.

The idea that the local circulation is regulated in accordance with the local CO_2 pressure was brought forward in a very definite form by Yandell Henderson in a series of papers on "Acapnia and Shock."[10] He showed, firstly, that the local circulation and functional activity in the exposed intestines depends upon the maintenance in them of a sufficient pressure of CO_2, and secondly, that on the removal of an excessive quantity of CO_2 from the body by excessive artificial or natural respiration the circulation fails, whereas excessive ventilation with air to which sufficient CO_2 has been added produces no such effect. These are evidently facts of fundamental importance as regards the regulation of the circulation, and as showing the intimate connections between respiration and circulation. On these and other observations he also based the theory that the immediate cause of shock may be excessive respiratory activity.

The blood-gas changes caused by excessive artificial respiration were first investigated by Ewald in connection with apnoea.[11] He not only found that there is a slight excess of oxygen and very large deficiency of CO_2 in the arterial blood, but also (though of this he did not realize the significance) that there is great deficiency of both CO_2 and oxygen in the mixed venous blood. The changes in the arterial blood have already been discussed in earlier chapters, and it was pointed out in Chapter VII that owing to the deficiency of CO_2 a state of anoxaemia must, other things being equal, be produced by forced breathing. Ewald's analyses show, however, that there is something more to cause anoxaemia than mere deficiency of CO_2. The latter would not by itself account for the deficiency of oxygen combined with haemoglobin in the venous blood. In long experiments Ewald found this oxygen down to about a third of the normal, and the CO_2 down to half the normal. Taking into account both the direct effect of deficiency of CO_2 in diminishing the free oxygen present in the venous blood, and the effect in the same direction of the diminished proportion of oxyhaemoglobin present, the artificial respiration must have brought about a condition of very intense anoxaemia in the tissues. But the diminution in the proportion of oxyhaemoglobin

[10] Yandell Henderson, *Amer. Journ. of Physiol.*, XXI, p. 126, 1908; XXIII, p. 345, 1909; XXIV, p. 66, 1909; XXV, p. 310, 1910; XXV, p. 385, 1910; XXVI, p. 260, 1910; XXVII, p. 152, 1910; XLVI, p. 533, 1918.

[11] Ewald, *Pflüger's Archiv.*, VII, p. 575, 1873.

cannot have been due to any other cause than diminution in the circulation rate; and this diminution is shown far more directly by Yandell Henderson's experiments and numerous blood-gas analyses by the ferricyanide method. The diminution in circulation goes so far that the venous return to the heart becomes quite inadequate to fill the ventricles. Hence arterial as well as venous pressure finally falls, and the heart itself is inadequately supplied with free oxygen or CO_2, and gradually fails along with failure in the brain and other parts of the body.

Slowing of the circulation through the hands during forced breathing was clearly demonstrated by his calorimetric method by G. N. Stewart.[11A]

By means of the new method for determining venous gas pressures in man we found that though there is a considerable fall, after forced breathing for about three minutes, in the CO_2 content of the mixed venous blood, there is, relatively speaking, an even greater fall in the oxygen content. The experiments were difficult because of the mental state of the subject. I had to be watched very closely to see that I carried out the proper manipulations, and many experiments failed because of gross errors, such as taking in a deep breath of ordinary air from the room. The gas mixture used had to contain less than 4 per cent of oxygen and less than 5 per cent of CO_2. The fall in oxygen pressure was considerably more than could be accounted for as due to the fall in CO_2 pressure on account of the Bohr effect. Hence the circulation rate was diminished. The mental condition was apparently due to marked anoxaemia of the nervous centers; and it may be remarked that owing to the rapid normal circulation through the brain the effects of the forced breathing must be felt there sooner than elsewhere.

We also investigated the effect on the circulation of a moderate excess of CO_2, sufficient to increase the breathing to about five times the normal. This was easily accomplished in a respiration chamber in which the CO_2 percentage had been raised to a little over 5 per cent. Under this condition there was a slight rise in both my arterial and venous CO_2 pressure; but the difference between them was not diminished. Thus there had been no appreciable increase in the circulation rate. It was quite clear that the circulation does not increase with increased arterial CO_2 pressure in a manner corresponding to the increase of breathing. The

[11A] G. N. Stewart, *Amer. Journ. of Physiol.*, XXVIII, p. 190, 1911.

breathing had increased five times or more, but the circulation had apparently not increased at all. The pulse, etc., were also hardly affected. With a great excess of CO_2, however, the venous return to the right heart is evidently much increased. This was first definitely observed by Yandell Henderson, who also makes the, to me, interesting remark that he first noted the signs of increased circulation rate on myself, while I was nearly overcome by accumulation of CO_2 in a mine-rescue apparatus, without any deficiency of oxygen.[12] Similarly, great deficiency of CO_2, as in forced breathing or excessive artificial respiration, will diminish the circulation rate; and it seemed probable that great increase in the oxygen pressure in the tissues (though this is difficult to produce except under the high atmospheric pressures referred to in Chapter XII) would have a similar effect.

That this effect is actually produced in man is indicated by the results of quite recent experiments by Dautrebande and myself.[13] We found that when pure oxygen was breathed, particularly under a barometric pressure increased to two atmospheres, the breathing increases, as shown by a fall in alveolar CO_2 pressure, and there is a simultaneous slowing of the pulse. This indicated a slowing of circulation through the brain, such as would compensate for the high oxygen pressure of the arterial blood. The slowing would of course raise the pressure of CO_2 in the brain, and thus increase the breathing. It would also explain the fact that though oxygen at two atmospheres pressure has a rapid poisonous action on the lungs and other living tissues directly exposed to it (see Chapter XII), there are no evident cerebral symptoms until oxygen at much higher pressures is breathed.

The responses involved in the chemical control of the venous return to the right heart were found by Henderson and Harvey to be peripheral, but independent of the vasomotor nerves and nerve endings. In the "spinal" cat they found that slow injections of adrenalin, and other prolonged vasomotor stimulations, cause a maintained elevation of arterial pressure, but only an evanescent rise of venous pressure. Ventilating the lungs with air rich in CO_2 (with ample oxygen) has, on the contrary, in the absence of the medullary vasomotor center, no appreciable direct effect upon arterial pressure, but induces a gradual, sustained and large elevation of venous pressure. They note also that during this action

[12] Yandell Henderson and Harvey, *Amer. Journ. of Physiol.*, XLVI, p. 533, 1918.

[13] Dautrebande and Haldane, *Journ. of Physiol.*, LV, p. 296, 1921.

the veins are always relaxed, as well as distended; and they consider that the easier escape of the blood from the tissues, due to relaxation especially of venules, is the cause of the larger venous return and consequent rise of venous pressure. Recently Henderson, Haggard, and Coburn[14] have shown that inhalation of air containing 6 or 8 per cent of CO_2 has a powerful restorative effect upon the circulation, and particularly upon the venous pressure, in patients after prolonged anaesthesia and major surgical operations.

With great deficiency of oxygen there is also at first a very marked increase in the circulation rate. This is shown by the greatly increased pulse rate, deep blue flushing of the skin, etc., and great rise of venous blood pressure when air very deficient in oxygen is breathed. In rapid poisoning by CO there is the same flushing of the skin and distention of large veins, though the color is now red and not blue. The increased pressure in the great veins causes the distention of the right side of the heart and rapid production of oedema of the lungs so characteristic of acute asphyxia, although but for the fact that the heart muscle is lamed by the anoxaemia there would probably be no over-distention. As Starling and Knowlton found, oedema of the lungs and over-distention of the right side of the heart are very quickly produced by a quite moderate increase of the ordinary very low venous pressure at the entry to the heart.[15] With moderate oxygen deficiency, produced rapidly, there are, just at first, distinct signs of increased circulation as well as of increased respiration; but very soon the increased washing out of CO_2 from the blood moderates both the breathing and circulation, and after a short time the circulation, as well as the breathing, quiets down, so that unless the anoxaemia is considerable the increased pulse rate and other signs of increased circulation may have practically disappeared.

The circulation during and just after forced breathing in man was meanwhile investigated by a quite different method by Henderson, Prince, and Haggard.[16] They measured the venous pressure by observing the height of the column of blood in a vein of the arm when the subject was placed in a head down position on a sloping board (Figure 70), thus obtaining a measure of the venous

[14] Henderson, Haggard, and Coburn, *Journ. Amer. Med. Assn.*, LXXIV, p. 783, 1920.

[15] Starling and Knowlton, *Journ. of Physiol.*, XLIV, p. 206, 1914.

[16] Yandell Henderson, Prince, and Haggard, *Journ. of Pharmac. and Exper. Therapeutics*, XI, p. 203, 1918.

blood pressure at the entry to the heart. The effect of forced breathing was to cause a great diminution in venous blood pressure. Thus the supply of blood to the heart must have become inadequate to fill the right ventricle. Owing, however, to the diminished outflow of blood from the arterial system there was no fall in arterial blood pressure. It seems to be only when the anoxaemia of forced breathing becomes so intense as to affect the heart muscle seriously that the arterial blood pressure falls.

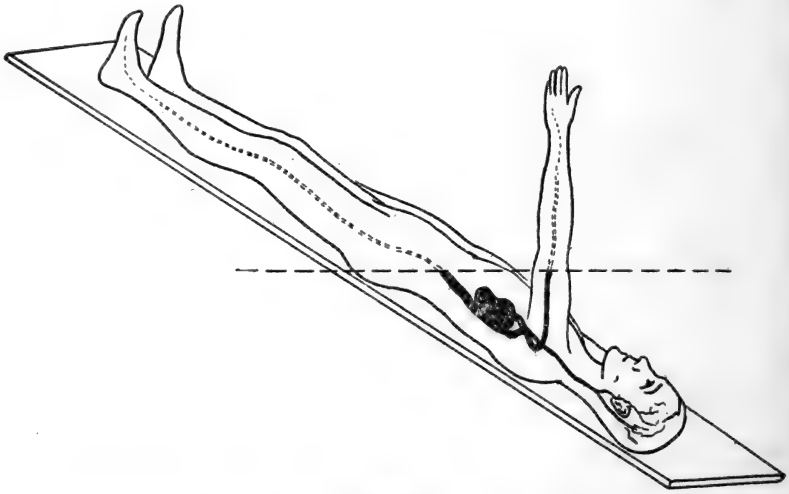

Figure 70.
Measurement of venous blood pressure by placing subject in a head-down position.

Putting all these facts together, it appears that in general the circulation is so regulated as to keep the pressures of both oxygen and CO_2 approximately steady in the venous blood from any particular organ. The regulation is evidently of a double kind, involving both oxygen and CO_2. If the oxygen pressure goes down and the CO_2 pressure also goes down, as in a pure anoxaemia, there is comparatively little effect on the circulation rate, because increase due to the lowered oxygen pressure is at once counteracted by the effect of diminution due to the lowered CO_2 pressure. Similarly, in an atmosphere containing simple excess of CO_2 increased circulation due to the excess of CO_2 pressure tends to be counteracted by decrease due to increased oxygen pressure. During muscular work, on the other hand, there is both a rise of CO_2 pressure and fall of oxygen pressure, and consequently a

great increase in blood flow through the muscles, with a corresponding increase in venous blood pressure, as Henderson and his colleagues found with the apparatus shown in Figure 70.[17]

The correspondence between blood flow and amount of work done by a muscle seems to appear clearly in data obtained by Markwalder and Starling for the coronary circulation with varying work of the heart in a heart-lung preparation.[17A] The amount of blood pumped by the heart, the aortic blood pressure, and the flow through the coronary vessels, were measured simultaneously. The data show that if the work done is estimated by the amount of blood pumped multiplied by the aortic pressure, the coronary blood flow varied within wide limits in proportion to the work done. The variations in coronary blood flow might, of course, be attributed to the variations in aortic blood pressure, but this interpretation does not seem to explain more than a small part of the facts.

At first sight the regulation of the circulation appears to be different from that of respiration, since in the case of the latter the influence of CO_2 predominates. This, however, is simply because when ordinary air is breathed the oxygen pressure in the tissues is not increased when the breathing increases. In reality, there is no fundamental difference. Whenever anoxaemia is present the respiratory regulation, as already shown in Chapter VII, works just like the local circulatory regulation. The breathing is not then free to increase in such a way as to compensate approximately for increasing anoxaemia, because increased breathing lowers the CO_2 pressure and this tends to diminish the breathing. Similarly the breathing cannot increase freely with increased CO_2 pressure, because the increased breathing would diminish the anoxaemia. Under deep anaesthesia, when the arterial blood becomes dark, CO_2 has very little effect on the breathing.

There can be little doubt that in the case of circulation, just as in that of respiration, increase in CO_2 pressure stands simply for increase in hydrogen ion concentration. Hence alkalosis due to deficiency of CO_2 in the systemic capillaries, or acidosis due to excess, will tend to be relieved by the slow acclimatization changes described in Chapter VIII.

When once the fundamental fact is grasped that the general flow of blood throughout the body is correlated with the gas pres-

[17] Yandell Henderson and Haggard, *Journ. of Pharmac. and Exper. Therap.*, XI, p. 197, 1918.

[17A] Markwalder and Starling, *Journ. of Physiol.*, XLVII, p. 279, 1913.

sures in the capillaries, the whole physiology of the circulation appears in a new light. It is not the heart nor the bulbar nervous centers which govern the circulation rate, but the tissues as a whole; and they govern it with an accuracy and delicacy comparable to the accuracy and delicacy with which they govern breathing. The heart and vaso-motor system are only the executive agents which carry out the bidding of the tissues, just as the lungs and nervous system do in the case of breathing.

It appears that the immediate function of the heart is not to regulate the circulation rate, but simply to pass on at a greatly increased pressure the blood supplied to it. The problem of the regulation of the circulation under normal conditions seems in the main to resolve itself into that of the regulation by the tissues of the amount of blood supplied to the heart; and this regulation depends, as we have just seen, to an overwhelming extent on a linked control by the oxygen pressure and hydrogen ion concentration in the systemic capillaries.

Just as in the case of regulation of breathing, so also in the case of regulation of the circulation, the dominant facts have been, and still are, obscured by masses of detail which, in their unconnected form, simply confuse the mind and lead to wholly mistaken judgments. It is difficult to pick a way through all these details, but the salient points concerning the immediate control of the heart's action must now be referred to.

We owe mainly to Gaskell the demonstration that the muscular fibers of the heart may continue to contract rhythmically apart from nervous control and even when they are separated from one another, just as the rhythmic activity of the respiratory center continues apart from peripheral nervous control. When, however, different parts of the heart are separated from one another, the frequency of the contractions in the different parts is different, the ventricular contracting less frequently than the auricular parts. In lower vertebrates the order of frequency in contractions is sinus venosus, auricle, ventricle, and bulbus arteriosus. Moreover the individual fibers in each separated part contract normally in unison with one another so long as they are not separated. In a normal intact heart, however, not only do the individual fibers in sinus venosus, auricles, ventricles, and bulbus arteriosus contract in unison, but so also do all the parts of the heart.

The explanation of this contraction in unison has been furnished by the physiological and clinical investigations of the last few years. As was shown by Lewis with the help of the string gal-

vanometer, each normal contraction starts in what is known as the Keith-Flack node, an island of primitive sinus venosus tissue in the right auricle. Thence it is conducted by primitive muscular tissue to the auricles, and by a bundle of similar muscular tissue, the bundle of Kent or His, to the ventricles. This primitive tissue is distributed (as the fibers of Purkinje) over the ventricles, and has a conduction rate far faster than the rest of the muscular tissue of the heart. Thus all parts of the ventricles contract almost simultaneously, and shortly after the almost simultaneous contraction of all parts of the auricles; while the pace of the whole heart is set by the contractions starting in the Keith-Flack node. Impairment or total failure in the conduction from auricle to ventricle, or from fiber to fiber in auricle or ventricle, explains many of the peculiarities met with in heart affections.

So long as the contractions of the ventricles are complete, the volume of blood discharged at each beat must depend on the extent to which the right ventricle fills in diastole. This, in turn, depends on the rate at which blood is let through from the arteries to the veins. The difference between arterial and venous pressure is so great that accessory factors such as the pumping movements of respiration can hardly have more than a very minute average influence on the circulation, though they have a marked temporary influence. It is therefore the rate at which the systemic blood is allowed to pass through the tissues into the venous system that determines the amount of blood pumped by the heart; and, as already pointed out, the rate at which blood is allowed to pass through the tissues is determined by their metabolic requirements, and particularly by the amount of blood required to keep the diffusion pressures in them of oxygen and carbonic acid approximately steady.

It is evident that in the carrying out of this regulation, both by the heart and the blood vessels, the nervous system plays a very important part, just as in the case of regulation of breathing; but the main fact must never be lost sight of that the primary factor in determining the rate of circulation is neither the heart nor the nervous centers specially connected with the circulation, but the metabolic activities of the tissues. At bottom the regulation of the circulation is a chemical regulation, just as in the case of the breathing.

The frequency and strength of the heartbeats are moderated through the central nervous system, first by the well-known inhibitory impulses passing to the heart through the vagus nerve,

and secondly by the equally well-known accelerator impulses passing to the heart through sympathetic branches. Increased liberation of inhibitory impulses has been found to be a direct result of rise of arterial blood pressure (so that the inhibition tends to prevent an excessive rise of arterial pressure and consequent fatigue of the heart or over-distention of arteries), but is certainly also a result of rise in oxygen pressure and diminution in CO_2 pressure in the blood passing through the brain. An increase of arterial blood pressure will, therefore, owing to the increased rate of circulation, slow the heart. When the arterial blood pressure is normal there is a considerable amount of vagus inhibition, so that on section of the vagi the heartbeats quicken. It appears also that this tonic nervous inhibition of the heart is itself reflexly inhibited, either directly or indirectly, by increase of pressure on the great veins opening into the heart. This was recently shown by Bainbridge,[18] who found that, even if the accelerator nerves are cut, increase in venous pressure causes marked quickening of the heartbeats provided that the vagi are still intact. He showed that any considerable increase in venous pressure causes quickening of the heartbeat, and that the quickening depends upon the integrity of the vagus nerves. Part, at any rate, of this effect is due to inhibition of the tonic inhibitory action of efferent vagus fibers. Another part is probably due to reflex excitation of accelerator nerves, but on this point the evidence was not so clear. The action of the heart is not subject to direct voluntary control, but the effects of emotional stimuli on the rate of heartbeat are well known and very evident.

There is no necessary connection between rate of heartbeat and circulation rate. This has been shown by various experiments, but most strikingly by the experiments of Starling and his pupils on the bodies of animals in which an artificial circulation through the heart and lungs alone had been established, the physiological connections with central nervous system and rest of the body being cut off. In such a "heart-lung preparation" the rate of heartbeat remains steady for long periods if the temperature is kept steady and artificial respiration is maintained; but the flow of blood can be varied within very wide limits by simply varying the rate at which blood is supplied to the right side of the heart. Thus Patterson and Starling found that with a pulse rate which was steady at 144 the circulation rate in a heart-lung preparation from the

[18] Bainbridge, *Journ. of Physiol.*, L, p. 65, 1915.

dog could be varied from 215 to 2,000 cc. per minute by simply regulating the supply of blood to the right side of the heart.[19]

The heart is thus a pump which is capable of adjusting its output without any variation in rate of stroke; and we might imagine a heart working quite efficiently on this principle, without any regulation by the nervous system. The circulation would adjust itself automatically in accordance with the rate at which blood was allowed to pass through the systemic capillaries; and the resistance in the arterioles and capillaries would automatically maintain a sufficient arterial blood pressure.

It is possible that in certain cases of heart disease, where the physiological connection between auricles and ventricles through the bundle of Kent and His is broken, the circulation is maintained in this way, since in these cases the pulse rate does not change during the very limited amount of muscular exertion which is possible. In normal persons or animals, however, the pulse rate increases very markedly during muscular exertion; and in persons in whom, owing to some nervous or cardiac abnormality this increase does not occur, the capacity for exertion is very small. We must infer, therefore, that under normal conditions the capacity of the heart for increasing the circulation rate without increase of the rate of heartbeat is very limited—far more so than might be inferred from study of a heart-lung preparation. In other words the output of the heart during systole is usually pretty constant under normal conditions, as Henderson was the first to point out.

We must now consider in more detail how the distribution of blood is regulated. It has been known since the discovery by Claude Bernard of vasomotor nerves that the distribution of blood in the body is regulated through the nervous system. Vasoconstrictor nerves are known to be widely distributed in all parts except the central nervous system, and vasodilator nerves have also been discovered at certain points. There is also a main vasomotor center in the medulla from which vasoconstrictor impulses radiate, and subsidiary vasomotor centers in the spinal cord. Another and much more direct means of regulating the distribution of blood has recently been discovered by Krogh.[20] He has found by microscopical examination of living capillaries, and by injection of Indian ink, that under resting conditions the great majority of capillaries in muscular and other tissues are firmly

[19] Patterson and Starling, *Journ. of Physiol.*, XLVIII, p. 357, 1914.
[20] Krogh, *Journ. of Physiol.*, LII, p. 457, 1919.

contracted and impermeable to blood, so that neither blood corpuscles nor even the finest particles of Indian ink can pass through them. Nor is the full arterial blood pressure capable of forcing them open. Whenever the tissue is stimulated to activity, however, these capillaries open wide, so that blood can pass through them freely. He found, for instance, that in muscle of the guinea pig about twenty times as many capillaries were open during activity of the muscle as during rest. The active contractility of capillaries had been directly observed by Roy and Graham Brown in 1880, but the real significance of this observation had not been realized.

Krogh's observations have thrown a flood of new light on the exchange of gases and other material between the blood and the living tissues: for the opening out of new capillary paths whenever a greater exchange of material is taking place must facilitate enormously the exchange, and thus furnish a means of keeping the gas pressures in the tissues approximately normal in spite of great variations in metabolism. During muscular work, for instance, the immense increase of capillary paths will greatly facilitate the exchange of oxygen and carbonic acid between the blood and the muscle fibers. There must be a great tendency to fall in the oxygen pressure of the blood passing through the muscle capillaries during muscular work. Unless this fall were approximately compensated for by the opening out of new capillaries, it is difficult to see how a sufficient oxygen supply could be maintained, as in all probability the oxygen consumption in a muscle during very hard work is twenty or thirty times as great as during rest. We can also now understand much better how it comes about, for instance, that when the skin circulation is cut down to the utmost by vasoconstriction in the prevention of unnecessary loss of heat from the body, the skin, though more or less blue from greatly diminished blood flow, may be still full of blood, as shown by the full blue color.

Probably it is the stimulus of the presence in excess of certain metabolic products, particularly carbonic acid, and the deficiency of others, particularly oxygen, that determines the relaxation of the capillary walls. There can also be little doubt that the same stimuli, acting reflexly, determine the activity of local vasomotor nerves. Temperature stimuli, or irritation stimuli, appear to act in a similar manner. Stimuli may also act centrally, however, as in the general regulation of body temperature by variations in the skin circulation, or in emotional vasomotor changes.

How very powerfully a local stimulus may act on local blood circulation is strikingly shown by a recent experiment of Meakins and Davies.[20A] They found that when the arm was immersed in cold water the returning venous blood was completely deprived of oxygen. On the other hand, when the arm was kept in hot water the haemoglobin of the venous blood was 94 per cent saturated with oxygen, as compared with 96 per cent for the arterial blood. The oxygen consumption was doubtless much greater in the warm than in the cold skin, so the difference in circulation rate must have been enormous.

If the regulation of blood distribution in the body were simply a matter of opening the proper sluice gates according to local requirements, the matter would be much more simple than it is. Actually, however, the contraction and dilatation of various arteries, veins, and capillary tracts must tend to have the effect of varying the total capacity of the blood vessels, with the result that the venous blood pressure at the heart inlet varies, and either too little, or too much, blood is supplied to the heart. As a consequence, the arterial blood pressure would either tend to fall too much to secure an adequate supply of blood to the brain and other parts, or else to rise too high.

There appears to be an elaborate nervous defense against such disturbances. Excessive rise of arterial blood pressure is guarded against, not only by the reflex vagus inhibition already referred to, but also by reflex vasomotor inhibition through the "depressor" branch from the cardiac vagus. Excitation of the depressor fibers causes inhibition of the vasomotor center in the medulla and consequent dilatation of arteries and probably veins in the splanchnic and other areas. Depressor action is brought about (whether directly or indirectly) by excessive arterial blood pressure, so that the pressure is relieved. Deficiency in arterial and venous pressure is guarded against by an opposite "pressor" action resulting in excitation of the vasomotor center and consequent rise in blood pressure. A normal stimulus to pressor action of the center is quite evidently deficiency of oxygen combined with excess of carbonic or other acids in the blood supplying the brain. Thus the arterial and venous blood pressures rise very markedly in response to deficiency of oxygen combined with excess of carbonic acid, whether produced by deficient aëration of the blood or circulatory failure. A very important effect of this rise of blood pressure is

[20A] Meakins and Davies, *Journ. of Path. and Bact.*, XXIII, p. 460, 1920.

to concentrate the available blood flow towards the brain. In muscular exertion there is also a rise of blood pressure, due partly to the effect on the vasomotor center of excess of CO_2 and deficiency of oxygen in the arterial blood, but perhaps partly also to a general pressor action complementary to a local depressor action on the arteries and veins concerned in supplying the muscles with blood.

We may compare the action of the bulbar centers controlling blood pressure and heart rate with that of the respiratory center in its linked responses to direct chemical and peripheral nervous stimuli; but data are not yet available for carrying the comparison into detail.

From this general survey of the experimental evidence relating to the regulation of the circulation, it will be seen that the deciding factor in determining the rate of circulation and local distribution of blood flow is local or general deficiency or excess in the diffusion pressures of the substances which enter into tissue metabolism, and particularly deficiency or excess in the diffusion pressures of oxygen and carbonic acid. Temperature is also a factor, but perhaps not a different one, since the diffusion pressure of a substance varies as its absolute temperature.

The regulation of the circulation may be abnormal in various ways, and the present chapter would be incomplete without some reference to this subject. The abnormality may arise from disease or congenital defect of the heart or from operative interference, but is very commonly due to disorder of the nervous regulation, whether or not any organic defect is also present. Another form of abnormal circulation is due to a deficient volume of blood, or to abnormality in its composition. In all these cases the abnormal circulation is reflected in abnormal breathing. Owing to the absence of adequate clinical or experimental investigations it is difficult as yet to deal with this subject in a satisfactory manner, and I can only attempt to discuss it tentatively in the light of what is already known.

The effect may first be considered of a valvular defect which either causes narrowing of valvular openings (stenosis) or makes a valve incompetent so that there is regurgitation. The effect of this is that, other things being equal, more work is thrown on one or another part of the heart. If this extra work is not serious it may be completely met, and partly by a true hypertrophy of the muscular substance on which the increased work is thrown; but if the extra work is serious the action of the heart as a pump will

be limited, so that the increased circulation required during muscular exertion cannot be produced. The arterial blood pressure will therefore fall during muscular work of more than a certain amount. In consequence of this the coronary circulation may also be impaired, with possibly dangerous consequences under the existing circumstances; and there will be faintness along with hyperpnoea, owing to slowed circulation and hence diminished oxygen pressure and increased CO_2 pressure in the capillaries of the brain. During rest, however, or such muscular exertion as is possible without abnormal symptoms, the circulation will be carried on in a normal manner.

The alveolar CO_2 pressure in a number of cases of valvular heart disease was investigated by Miss FitzGerald, and found to be normal except in cases confined to bed with serious symptoms.[21] The absence of any fall in the alveolar CO_2 pressure constituted good evidence of the absence of any impairment of the circulation during rest. In cases with serious symptoms even during rest there was a marked fall in the alveolar CO_2 pressure. This is also the case in congenital heart affections, when the alveolar CO_2 pressure may be as low as 20 mm.[22]

We can see what is happening in these cases. Owing to the impaired or short-circuited circulation the oxygen pressure in the tissues falls and the CO_2 pressure tends to rise. This, however, increases the breathing, and so prevents the rise of CO_2 pressure by abnormally diminishing the CO_2 pressure of the arterial blood leaving the lungs. The fall in oxygen pressure cannot, however, be prevented in this way, as the increased breathing will not materially increase the oxygen in the arterial blood. Some anoxaemia will therefore be present, and will probably show itself by the color of the skin and lips, as well as by more frequent, and possibly shallower, breathing, and other symptoms of anoxaemia. The alkalosis produced by the increased breathing due to anoxaemia will gradually be compensated for by increased excretion of alkali and diminished formation of ammonia, just as at a high altitude (see Chapter VII); and this will tend to diminish the real anoxaemia though without diminishing the cyanosis. Unless the breathing became shallow no material relief could be looked for owing to active secretion of oxygen inwards by the lung epithelium, as this would only slightly increase the oxygen in the

[21] FitzGerald, *Journ. of Pathol. and Bact.*, XIV, p. 328.

[22] French, Pembrey, and Ryffel, *Journ. of Physiol.*, XXIX, *Proc. Physiol. Soc.*, p. ix, 1909.

arterial blood; but some relief may come from compensatory increase in the percentage of haemoglobin in the blood. In a bad heart case the heart has usually broken down owing to either some more or less acute infection or to too much muscular exertion; and usually the main question is whether, and to what extent, the heart will recover with rest and the passing off of the infection.

In many heart affections the defect is in the nervous regulation of the heart, either without or with a valvular defect. The accelerator, inhibitory, depressor, or pressor reflexes may be acting excessively. Cases with evident defects of nervous control have been very common during the war, under such names as "soldier's heart," "disordered action of the heart," "neurasthenia," etc. In the commonest form of this defect there is very abnormal increase in pulse rate on slight exertion or emotional and other stimuli; and accompanying the increase there is pain and hyperalgesia in the areas where pain is usually felt in heart affections. The exaggerated cardiac reflexes seem to be similar to the exaggerated Hering-Breuer respiratory reflex in the same cases, and to be due to the same causes (see Chapter III). Reflexes and nervous or emotional responses of all kinds are exaggerated in these cases of neurasthenia; and the exaggeration of cardiac reflexes is frequently only one symptom of a condition of general neurasthenia. The pain is probably only an expression of fatigue produced by the over-frequent heartbeats.

A similar condition is very commonly present as an accompaniment of valvular defect; and the associated shallow breathing may cause very serious secondary anoxaemia in the manner already described in Chapter VII. This seems to be the explanation of the orthopnoea and Cheyne-Stokes breathing so often seen in bad heart cases, and also explains the marked effects of oxygen inhalation in relieving the symptoms. Continuous inhalation of air enriched with oxygen is likely to prove a very valuable remedy in promoting recovery where failure of the respiratory center is complicating defects of circulation.

A very interesting investigation demonstrating a relation between vasular disturbances in the lungs and the Hering-Breuer reflex has recently been published by J. S. Dunn,[22A] who was working at the time in conjunction with Barcroft. He produced multiple embolism of pulmonary arterioles by intra-venous injection of starch granules. When only a moderate degree of embolism was produced (so as not to cause immediate death) he observed

[22A] Dunn, *Quart. Journ. of Med.*, XIII, p. 129, 1920.

an extraordinary increase in frequency and diminution in depth (to half or even a fourth) of respiration. At the same time the rate of circulation (measured by a very perfect blood-gas method described in the same journal by Barcroft, Boycott, Dunn and Peters) was not diminished, nor was the venous blood pressure raised, or the arterial pressure disturbed: nor was there appreciable deficiency of oxygen or excess of CO_2 in the arterial blood. But when the vagi were cut the respirations slowed down and became normally deep at once. It appears, therefore, that the Hering-Breuer reflex (Chapter III) was enormously exaggerated as a result of the disturbed pulmonary circulation. Just at first the breathing was stopped, which suggests that the respiratory movements were jammed completely by the exaggerated reflex. These experiments throw a quite new light on the intense and exhausting dyspnoea caused by pulmonary embolism, and also in cardiac cases where there is rapid breathing without other cause. How the vagus nerve endings are excited is not yet clear. The discovery of a drug capable of controlling their action would evidently be an important advance in therapeutics.

In defective circulation owing to loss of blood the primary cause of breakdown appears to be that, in spite of contraction of arterioles and venules owing to pressor reaction of the vasomotor center, there is not sufficient blood to fill the large veins and adequately supply the right side of the heart. As a consequence the arterial blood pressure falls and the circulation slows down, with consequent anoxaemia acting most seriously on the brain, and affecting the breathing in the manner already explained in connection with valvular affections where compensation is imperfect. The natural remedy for this condition would appear at first sight to be a pressor excitation of the vasomotor center, just as the natural remedy for arterial anoxaemia due, say, to low atmospheric pressure, appears at first sight to be increased breathing and increased circulation rate. But just as the increased breathing and circulation rate in arterial anoxaemia is to a large extent prevented by the counter-balancing effect of the alkalosis thereby produced, so also is the full pressor response to anoxaemia due to fall in blood pressure. The breathing is already stimulated by the diminished blood circulation in the brain, so that the arterial blood is so alkaline as to quiet down the vasomotor center, in spite of the anoxaemia. Benefit may be expected from the administration of CO_2 or even of acids; but the main need is for increase in the volume of the blood. This increase comes naturally, provided

that fluid is supplied; and the great thirst which results from loss of blood is an expression of the need for fluid. But time is required for this natural process of recuperation, and meanwhile the patient may die.

Fluid may be supplied quickly by the intravenous injection of Ringer's Solution, but this plan is rather ineffective, since the injected liquid leaks out from the vessels quickly. Bayliss therefore introduced his now well-known gum-saline solution for use in cases of loss of blood and similar conditions.[23] The gum does not leak out at all readily from the vessels, and in virtue of the osmotic pressure which it produces it keeps the salt solution from leaking out. The gum thus plays the same part in this respect as the proteins of the blood plasma, but is free from the occasional toxic properties of the proteins in blood transfused from another person, although it seems to be sometimes not free from disadvantages. It might seem at first sight as if the injection of gum saline must, other things being equal, be very inferior in its effects to transfusion of blood, since there is no haemoglobin in the salt solution. But unless the loss of blood has been enormous there is no great need for haemoglobin. Increased rate of circulation will make up for diminished power of the blood to carry oxygen and CO_2, as explained more fully on page 293.

The conditions known as "wound-shock," "surgical shock," "anaesthetics shock," and shock from burns, have given rise to much discussion and investigation. When "shock" is fully developed, the arterial blood pressure is very low, the pulse feeble, the lips and skin leaden colored, and the breathing shallow and often rapid, or sometimes periodic. It appears at present as if this general condition can be brought about in several different ways; and Yandell Henderson's investigations have thrown a clear light on certain of the causes of shock. It will be convenient to consider these first.

He showed in the first place that a condition of shock can be brought about in animals by continued excessive ventilation of the lungs. This of course greatly reduces the CO_2 in the arterial blood, thus producing a state of alkalosis. The response to this is slowing of the circulation, and consequent great anoxaemia, as already explained. The slowing of the circulation tends, of course, to diminish the alkalosis in the tissues, but only at the expense of producing most formidable anoxaemia. The alkalosis is also com-

[23] Bayliss, *Intravenous Injection in Wound Shock*, 1918.

bated by the body in other ways, one being the prompt stoppage of ammonia formation and the excretion of alkaline urine, as already explained; and, whether in consequence of this or of other causes, the so-called "alkaline reserve" of the blood decreases greatly, as Henderson and Haggard showed (Chapter VIII). Nevertheless the anoxaemia and alkalosis cannot be overcome. The circulation rate steadily diminishes; the heart, in consequence, probably, of anoxaemia, begins to fail, apart altogether from its inadequate supply of venous blood; and finally there is complete failure of the heart. If, however, the forced breathing is stopped before cardiac failure has occurred, death may occur from prolonged apnoea and consequent acute asphyxia, as mentioned in Chapter II. When the condition of shock has developed sufficiently, the animal cannot be saved by adding CO_2 to the air breathed; but in the earlier stages this procedure is quite effective. The hopeless condition to which the animal is reduced by the forced artificial respiration is probably analogous to the condition produced in various ways by prolonged anoxaemia, as in very severe CO poisoning, or in a patient who has been allowed to suffer for long from severe arterial anoxaemia. It is probably the anoxaemia rather than the alkalosis that produces the serious effect, since, as already mentioned, forced breathing of oxygen is more easily tolerated than forced breathing of air.

A condition of shock produced by forced artificial respiration is, of course, not a natural occurrence; but Henderson showed that excessive respiration can be produced by natural means in two ways: firstly, by powerful afferent stimuli, as by electrical stimulation of the sciatic nerve, even in the presence of anaesthesia sufficient to abolish consciousness; and secondly, by the action of ether in doses not sufficient to anaesthetize an animal completely. The afferent stimuli, or the ether, increase the breathing to such an extent as to diminish greatly the CO_2 in the arterial blood, thus producing great alkalosis or acapnia, with concomitant anoxaemia. By these means, therefore, a condition of shock may easily be produced in a patient; and it seems probable that in this way the condition generally known as shock is frequently produced as a matter of fact.

Clinical evidence seems, nevertheless, to indicate that in many ordinary cases of wound shock there has been no excessive breathing. On the other hand there are many facts indicating that the symptoms are due to absorption from injured tissues of

harmful disintegration products,[24] and Dale and Laidlaw have shown that similar symptoms are caused by the action of histamine produced by tissue disintegration.[25] In "histamine shock" the venous return to the heart is inadequate, just as in acapnial shock, and blood appears to stagnate in dilated capillaries so that the rest of the vascular system is imperfectly filled with blood. Dale and Laidlaw regard the dilatation of capillaries as a primary action of the poison. The respiratory center seems, also, to be affected very quickly, so that artificial respiration is needed to keep the animal alive. How far the failure of the respiratory center is consequent on failure of the circulation, or vice versa, it seems difficult at present to say; but the shallow breathing and leaden cyanosis in shock are indicative of advancing failure of the respiratory center, and appear to be clear indications for early and continuous oxygen administration, if the condition cannot be dealt with by removing its cause or in other ways. To remedy the imperfect filling of the vessels and consequent failure of the circulation, there is an equally clear indication for the intravenous injection of gum-saline solution. Whether the administration of air containing CO_2 would be of service, as in shock due to simple alkalosis, is not yet known. If the respiratory center is injured by a poison from the injured tissues it may be unable to respond properly to the CO_2.

Dale found that the danger from histamine shock may be enormously increased by the administration of an anaesthetic. Many of Henderson's observations seem to point in the same direction as regards acapnic shock. These investigations throw much light on the fatal accidents of anaesthesia.

In connection with circulation and breathing it is important to consider the manner in which the volume and haemoglobin percentage of the blood adjust themselves under varying conditions. They are fairly constant within about five per cent under ordinary conditions for any individual, and the volume of blood in a mammal bears a pretty constant ratio to the body weight. This proportion does not depend upon size or ratio of body weight to surface, since it is about the same in large as in small mammals. Thus in the rat or mouse the proportion is about the same as in man.

In a small warm-blooded animal such as a mouse the metabolism per gram of body weight is enormously greater than in a large

[24] *Report No. VIII of Surgical Shock Committee* (Special Report No. 26 of Medical Research Committee), 1919.

[25] Dale and Laidlaw, *Journ. of Physiol.*, LII, p. 355, 1919.

animal such as a man, and roughly speaking is proportional to the ratio of external surface to body weight. As was shown by Dr. Florence Buchanan,[26] the pulse rate and respiration rate vary in about the same proportion. Thus in a canary the pulse rate, as recorded photographically by means of the capillary electrometer, was about 1,000 per minute, the rate, as compared with that in man, being greater in proportion to the more rapid metabolism. The circulation rate in a small animal is thus enormously greater than in a large animal, and indeed must be so; but the proportions

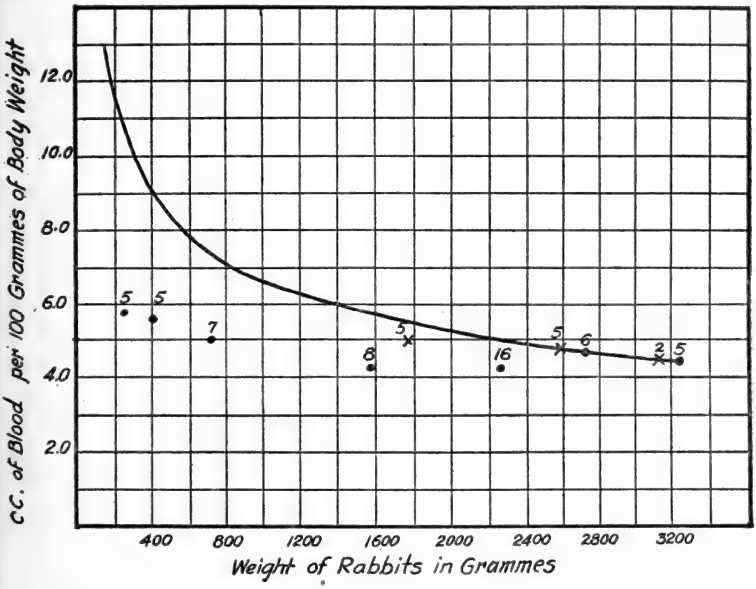

Figure 71.

Blood volumes of rabbits in cc. of blood per 100 grams of body weight. The curve shows what the blood volumes would be if they varied in the proportion of body surface to body weight. The dots and crosses show average results of actual determinations by the modified Welcker method. Dots represent results of Boycott: crosses of Dreyer and Ray. The numbers indicate number of determinations for each group of observations.

between the different parts of animals, including the blood, do not depend on differences in size of the animals. From a very limited number of experiments on animals, Professor Dreyer of Oxford[27] drew the extremely improbable conclusion that in ani-

[26] Buchanan, *Science Progress*, July, 1910.

[27] Dreyer and Ray, *Philos. Trans. Royal Society*, B, CCI, p. 138, 1910; also Dreyer, Ray, and Walker, *Skand. Arch. f. Physiol.*, 28, p. 299, 1913.

mals of the same species the blood volume is a function of the ratio of body surface to mass, and even inferred that the carbon monoxide method of determining blood volume (appendix) must be incorrect because it showed no such relation in experiments published by Douglas.[28] The matter was afterwards reinvestigated in rats by Chisolm,[29] and by Boycott.[30] Figure 71 shows the results of Boycott and of Dreyer (all obtained by the modified Welcker method) in rabbits of different sizes. It will be seen that there is no difference between them, and that, although young rabbits have usually a somewhat higher proportion of blood than older ones, the increased proportion does not vary with the proportion of body weight to surface. The circulation rate must, other things being equal, be faster in a smaller animal with its higher proportional metabolism, but an increased proportional dead weight of blood would be no advantage, but a disadvantage.

When the volume of blood is reduced by considerable bleeding, there is at first a fall in arterial, and doubtless also in venous, blood pressure; but soon the blood pressure is restored. The first effect of the bleeding is probably to evoke partial compensation by a pressor excitation of the vasomotor center. This is probably due to diminished circulation rate and consequent fall in oxygen pressure and increase of CO_2 pressure in the medulla. Very soon, however, the blood volume is more or less restored by taking up of liquid from the tissues and intestines. The blood is thus diluted; but the diluted blood fills up the blood vessels and completely restores the blood pressure. After a delay of many days or perhaps several weeks, the hydraemic blood is restored to normal by reproduction of the missing corpuscles.

Similarly when blood is transfused from another animal of the same species there is at first a rise of both venous and arterial blood pressure. Soon, however, the volume of blood is reduced by disappearance of most of the extra plasma. The remaining blood then contains an excess of red corpuscles, and these are only got rid of in the course of some days or weeks.

The changes which occur were followed by Boycott and Douglas with the help of the carbon monoxide method of determining the blood volume in living animals.[31] They found that on repeated

[28] Douglas, *Journ. of Physiol.*, XXXIII, p. 493, 1906.
[29] Chisolm, *Quart. Journ. of Exper. Physiol.*, IV, p. 208, 1911.
[30] Boycott, *Journ. of Pathol. and Bacter.*, XVI, p. 485, 1912.
[31] Boycott and Douglas, *Journ. of Pathol. and Bacter.*, XIII, p. 270, 1909.

bleeding the reproduction of the red corpuscles becomes more and more rapid, so that finally the animal can reproduce the lost corpuscles very rapidly. Similarly on repeated transfusion the animal can get rid of the transfused corpuscles more and more rapidly. It thus becomes adapted to either bleeding or transfusion.

In an animal in which as a result of bleeding or similar causes the proportion of haemoglobin in the blood is abnormally low the oxygen pressure must fall more rapidly than usual if the rate of circulation is unaltered, as the blood passes through the tissues. In accordance with what has been already said, this will naturally tend to be more or less compensated for by an increased rate of circulation. But this can occur freely without the opposing effect due to the production of alkalosis, since owing to the diminished percentage of haemoglobin the pressure of CO_2 would also be

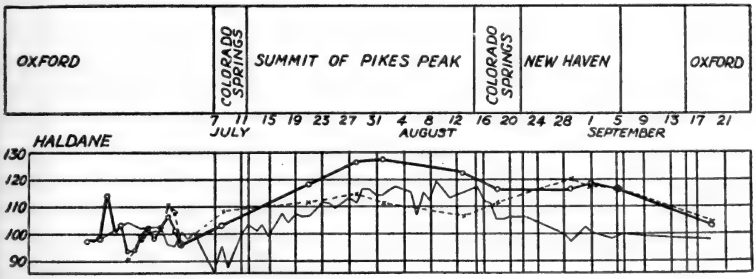

Figure 72.

Ordinates represent percentages of the average haemoglobin percentages obtained before ascending the Peak (Oxford and Colorado Springs) on the particular subject. Continuous thick line = total oxygen capacity or total amount of haemoglobin. Continuous thin line = percentage of haemoglobin. Interrupted line = blood volume. The values in Oxford before the start of the expedition are plotted without relation to time.

too high unless the circulation rate were increased. An increased circulation rate is thus the natural response to a diminished haemoglobin percentage.

We know from observations on persons living at high altitude that one result of the shortage of oxygen caused by the diminished barometric pressure is that the percentage of haemoglobin and of red corpuscles in the blood rises (see Chapter XIII). In different individuals the rise varies considerably. Thus in persons who had been living for some weeks on the summit of Pike's Peak we found that the haemoglobin percentage varied from 113 to 153 per cent of the normal. The rapidity with which the change occurs varies also greatly in different individuals. Figure 72 shows the rate

at which the change occurred and disappeared in one of the members of the Pike's Peak expedition, and Figure 73 shows the far faster rate of increase in haemoglobin in Mr. Richards, a mining engineer who kindly made for me a careful series of

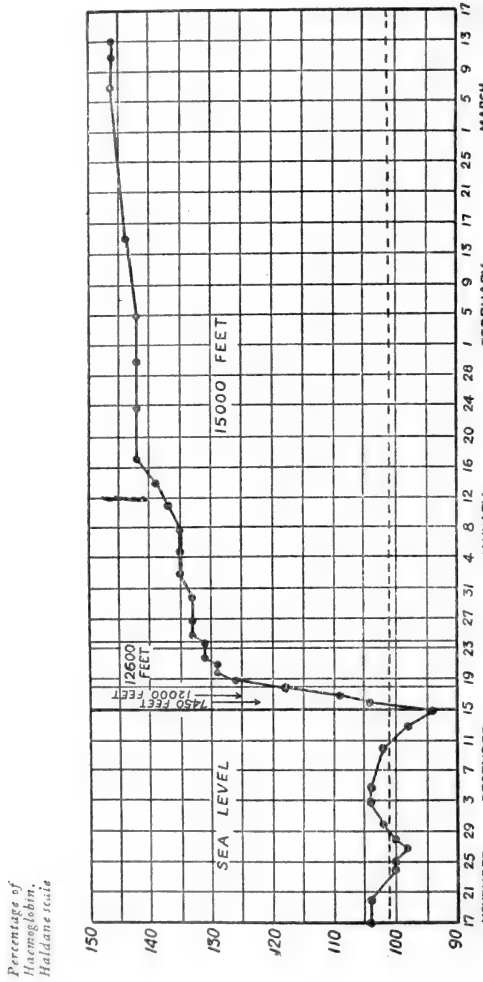

Figure 73.

Rise of haemoglobin percentage on going gradually to a height of 15,000 feet and staying there. The interrupted line represents the mean percentage of haemoglobin at sea-level.

observations on himself on going to a mine in Bolivia at a height of 15,000 feet. Figure 72 also shows the changes in blood volume and total haemoglobin in the body (total oxygen capacity). It will be seen that after the first few days the blood volume in-

creases, so that the total haemoglobin in the body increases more than the percentage of haemoglobin. Thus the corpuscles do not simply increase at the expense of the space occupied by plasma, but the total space occupied by the blood is increased. It seems probable, however, that when a rapid increase in the percentage of haemoglobin occurs, as shown in Figure 73, the increase is mainly brought about at first by disappearance of plasma owing to a pressor reaction of the vasomotor center, with consequent increased filling of the capillaries and resulting loss of liquid from the blood. In acute anoxaemia produced by asphyxial conditions there appears to be a rapid loss of fluid from the blood, and this is probably due to a pressor reaction. Schneider and his colleagues have recently observed that in a considerable proportion of airmen exposed for a quite short time to low pressures of oxygen there is a small but quite appreciable rise in the haemoglobin percentage.[32]

There appears to be no doubt that the cause of the increased total amount of haemoglobin and red corpuscles in the body at high altitudes is increased activity of the bone marrow in forming red corpuscles. On this point direct evidence was obtained by Zuntz and his colleagues.[33] They found that in dogs the blood-forming red marrow was markedly increased at a high altitude. The stimulus to this increase was undoubtedly fall in the oxygen pressure of the blood, and it is doubtless in the same way that increased formation of red corpuscles is brought about by loss of blood, especially if repeated. From the experiments of Boycott and Douglas on repeated blood transfusions, we can also infer with great probability that with increased oxygen pressure in the tissue capillaries, owing to an increased proportion of haemoglobin, there is a corresponding increase in the blood-destroying tissues. The proportion of haemoglobin in the blood appears, therefore, to be dependent on the oxygen pressure in tissue capillaries. This inference is confirmed by the fact that, as Nasmith and Graham showed,[34] the haemoglobin percentage rises markedly in animals which are kept exposed to a small percentage of CO.

In cases of chronic heart disease, and more particularly in cases of congenital heart defects accompanied by cyanosis, there is often a great increase in the total haemoglobin and also in the blood volume. Thus in a congenital case of "Morbus coeruleus," brought

[32] Gregg, Lutz, and Schneider, *Amer. Journ. of Physiol.*, L, p. 216, 1919.
[33] Zuntz, Loewy, Muller, and Caspari, *Höhenklima und Bergwanderungen*, Berlin, 1906.
[34] Nasmith and Graham, *Journ. of Physiol.*, XXXV, p. 32, 1906.

to us by Dr. Parkes Weber, Douglas and I found that the haemoglobin percentage was increased 80 per cent; the blood volume 100 per cent; and the total haemoglobin 260 per cent;[35] and we found similar increases in another case. Lorrain Smith had already found a considerable increase in a non-congenital heart case with chronic cyanosis.[36]

In some cases (so-called idiopathic polycythaemia) where there is neither exposure to a lowered oxygen pressure nor any heart or lung affection, the haemoglobin percentage and number of red corpuscles per unit volume is greatly increased. On determining the blood volume in two of these cases I found it greatly increased. Boycott and Douglas examined three other cases with a similar result.[37] In the most marked of these cases the haemoglobin percentage was 176 per cent of the normal, and the blood volume nearly three times the normal, so that the amount of haemoglobin in the body was about five times the normal. Idiopathic polycythaemia is accompanied by a bluish tint of the skin, and this suggests that from some cause there is slowing of the circulation and consequent anoxaemia of the tissues, to which the increased haemoglobin percentage is a natural response.

It is clear that increase in the haemoglobin percentage will tend to diminish the tissue anoxaemia at high altitudes or in cases of heart affections; for the blood can pass more slowly (or at a more normal rate at high altitudes) through the capillaries before a given fall in the oxygen pressure occurs. This compensation is never complete, however; for if it were there would be no stimulus to the increased concentration of haemoglobin. An undue rise of CO_2 pressure in the tissues is also prevented by the increased haemoglobin percentage.

When the red corpuscles and haemoglobin are increased 60 or 80 per cent the viscosity of the blood is very greatly increased, and a good deal of stress has been laid on this increased viscosity as a hindrance to circulation. Nevertheless persons with their haemoglobin percentage increased 50 per cent at high altitudes are capable of the severest muscular exertion; and there is no indication in them of any circulatory impairment. When we consider the manner in which the circulation is normally regulated, as

[35] The details of this case are given by Parkes Weber and Dorner, *Lancet*, Jan. 21, 1911.

[36] Lorrain Smith and McKisack, *Trans. Path. Soc. of London*, LIII, p. 136, 1902.

[37] Boycott and Douglas, *Guy's Hospital Reports*, LXII, p. 157.

explained above, it seems evident that anything but a very extreme increase in viscosity will at once be compensated for by more free opening of arterioles and capillaries. The resistance to flow of blood in the living body is regulated physiologically, and cannot for a moment be compared to the mechanical resistance in a system of lifeless tubes.

The rapid variations in blood volume from diminution or increase in the vasoconstrictor (pressor) influence of the vasomotor center is perhaps shown most strikingly by the effects on the blood of section of the spinal cord below the vasomotor center in the medulla. Cohnstein and Zuntz found that very quickly after section and consequent fall of blood pressure the proportion of red corpuscles fell to about half, while the proportion rose rapidly again on stimulation of the cord just below the section, with consequent rise of blood pressure.[38] The blood appears to take up or lose plasma rapidly when the capacity of the blood vessels is diminished or increased.

It was discovered by Lorrain Smith with the help of the carbon monoxide method that in chlorosis and in secondary "anaemias" the blood volume is increased without any diminution, or with only a very slight one, in the total haemoglobin in the blood. The anaemia is thus in reality a hydraemia or dilution of the haemoglobin.[39] Boycott and I found the same condition in the "anaemia" of ankylostomiasis.[40] Miss FitzGerald found later that in chlorosis the alveolar CO_2 pressure is not diminished but normal, so that in this form of anaemia there appears to be no anoxaemia during rest.[41] These facts suggest that the apparent anaemia is due to some cause leading to abnormal dilation and consequent increased capacity of the blood vessels, with the natural sequence of hydraemia, but so that the oxygen pressure in the tissues is not diminished. Possibly, therefore, the anaemia is produced through the vasomotor nervous system, or through substances, or the deficiency of substances, which act primarily on the blood vessels. The facts that salts of iron have a striking curative action in chlorosis, and that iron is a constituent of haemoglobin, have led to the idea that the anaemia is caused by the absence of sufficient iron for a normal formation of haemoglobin; but in the cure of chlorosis by iron Lorrain Smith could find no appreciable increase in the total

[38] Cohnstein and Zuntz, *Pflüger's Archiv.*, 88, p. 310, 1888.
[39] Lorrain Smith, *Trans. Pathol. Soc. of London*, LI, p. 311, 1900.
[40] Boycott and Haldane, *Journ. of Hygiene*, III, p. 112, 1903.
[41] FitzGerald, *Journ. of Pathol and Bacteriol.*, XIV, p. 328, 1910.

amount of haemoglobin in the body. The characteristic dyspnoea and faintness on exertion in chlorosis, etc., are probably due to the impossibility of sufficiently increasing during exertion the already greatly increased circulation.

In pernicious anaemia and the anaemia of haemorrhage, Lorrain Smith found a very marked diminution of the total haemoglobin present; but often enough the blood volume was increased above normal.

Although the intimate connection between breathing and circulation is already very evident, many points in the connection are still uncertain or obscure. There is an abundant field for clinical and physiological investigation in elucidating this subject, though it must always be remembered that not only are breathing and circulation closely dependent on one another, but they are dependent also on other physiological activities.

Addendum. The experiments by Douglas and myself on the regulation of the circulation in man have now been completed, and are in course of publication. A very complete series, in which Douglas was himself the subject, shows that during complete rest the mixed venous blood had only utilized about 19 per cent of its available oxygen, and gained a corresponding charge of CO_2. During hard work, with the oxygen consumption increased about nine times, about 65 per cent of the arterial oxygen was utilized. The pulse rate was increased about 2.6 times, and as the utilization of the arterial oxygen was increased 3.4 times, the output of blood per heartbeat was practically the same during hard work as at complete rest, and the blood flow had simply increased in proportion to the increase of pulse rate.

Various other subjects, including myself, had a similar high rate of blood flow (about 8 liters per minute) during rest, but one or two had a markedly lower rate of flow, with the percentage utilization of oxygen as high, in one case, as 33 per cent. In this case the output per beat during rest, and the circulation rate (about 4.7 liters per minute) were a good deal lower than in the other subjects, but the output per beat increased to about double during hard work. There are thus considerable individual differences (quite apart from differences in weight) as regards the rate of general blood flow and the particular manner in which the circulation adapts itself to varying amounts of work.

As some doubt has arisen lately as to whether oxygenation of blood within the living body has the same influence on the CO_2

carrying power of blood as after the blood has been removed and defibrinated, we made careful observations on this point. The experiments showed clearly that oxygenation produces the same effect in the living body as outside it.

A full account of the method, and of the results reached by it, will be found in our paper.

CHAPTER XI

Air of Abnormal Composition.

In the present chapter I propose to describe the mode of occurrence and physiological effects of the more commonly occurring gaseous constituents of air. The number of noxious gases, vapors, and particulate impurities, which may, under particular circumstances, be present in air, is of course very large, and only the commoner additions to air can be dealt with here.

Outside Air. Pure country air, freed from moisture, contains 20.93 per cent by volume of oxygen, .03 per cent of carbon dioxide, and 79.04 per cent of a residue usually designated as "nitrogen," although of this 79.04 per cent about .94 per cent consists of argon. Very minute traces are also present of hydrogen and various rare gases. Ordinary atmospheric air contains, however, aqueous vapor in varying proportions; and about 1 per cent is on an average present in a climate such as that of Great Britain. The composition of dry country air is the same to the second decimal point all over the world. In summer weather the percentage of CO_2 near the ground may be as low as .025 during the day, and as high as .035 during the night, owing to the influence of vegetation, etc.; and doubtless the oxygen percentage rises or falls correspondingly, though this has not yet been shown directly.

In towns the composition of the outside air varies surprisingly little from that in the country. The percentage of CO_2 seldom rises above .05, nor does that of oxygen fall below 20.9, even in a large town, like London; and in summer weather there is hardly any difference between the oxygen and CO_2 percentages of town and country air. In a London park on a summer day the percentage of CO_2 may fall quite as low as in the country. Considering the great area of a town like London, and the enormous quantity of coal and gas burnt, this fact is very striking, and shows clearly that apart from horizontally-flowing wind there are very active up-and-down movements of the air, and these keep the air of a town pure. It is only in foggy weather that these up-and-down movements cease more or less; and then the impurities in the air of a large and smoky town may become very

appreciable. Russell found, for example, that in London the percentage of CO_2 might rise to 0.14 during a dense fog.

Along with CO_2 there are present in the air of towns a number of other impurities. From fires a good deal of unburnt CO passes off. In the air of the underground railways when steam locomotives were still used, I found that about 1 volume of CO was present for every 12 volumes of CO_2. If we assume the same proportion for the air of a town, there would be about .01 per cent of CO present in the air of a bad London fog. This would be sufficient in time to saturate the haemoglobin with CO to the extent of about 17 per cent, and might thus produce appreciable effects on persons already in bad health, though healthy persons would not notice any effect.

Much more appreciable, however, are the effects of the particulate impurities. Ordinary coal contains a good deal of sulphur; and the sulphur, in the process of combustion, is mainly oxidized to sulphuric acid, which condenses along with water in the form of minute droplets and thus helps to form fog. Of the unpleasant irritant effects of this sulphuric acid one can form a good idea in passing through a railway tunnel, particularly if the train is moving slowly up an incline and the coal burnt contains much sulphur. Those familiar with sulphuric acid fumes in chemical laboratories or factories will at once recognize them in the tunnel air. When badly purified lighting gas is burnt in a room, the same irritant effect is also noticeable to a less degree. In a bad fog in a large town the choking effects of sulphuric acid contribute largely to the unpleasant effect of the fog and the manner in which the fogginess of the air persists even when the air is warmed in the interior of a house. There is no escape from this effect unless the air is scrubbed or filtered. The sulphuric acid is also destructive to metal and other materials.

Besides sulphuric acid the smoky air contains particles of black carbonaceous matter which greatly help absorb the light, and also contains substances which have an unpleasant odor and more or less irritant effect on the air passages. As will be shown below, there is no reason to believe that the continued inhalation of these particles has any deleterious effect on the lungs, and in ordinary town air they are not present in sufficient concentration to be of any direct consequence in other ways to health. Their greatest importance arises from the inconvenience and expense caused by their obstruction of light and the manner in which they dirty clothes, walls, ceilings, and everything else in a house. By the

substitution of well-purified gas for coal in fires, or by smokeless combustion of coal, the trouble might be avoided, and indeed has been much diminished within recent years.

Lower organisms, and particularly plants, are on the whole far more sensitive to impurities in air and other changes in environment than higher animals, and particularly man. The real reason for this is that between the living tissue elements and the outside environment higher organisms possess an internal environment which is not only highly developed, but is maintained with an efficiency which increases with the scale in development. Plants are extremely sensitive to the particulate and other impurities in air and the obstruction of light by smoke and opaque fogs. But few trees and plants can flourish in the air of a town or industrial area. The traces of acid and other impurities present in the air can act more or less directly on their tissue elements, which have very little between them and the external environment.

Air of Occupied Rooms. In rooms of all kinds where men are present the composition of the air becomes altered, owing to respiration and evaporation and to any gas or oil lamps which may be burning. Both respiration and lamps consume oxygen and produce CO_2 and moisture. The combustion in the lamps is perfect, so that no CO passes into the air; and unless the gas is badly purified from sulphur the products of combustion have very little unpleasant effect apart from what may be due to heat. It was formerly supposed that some volatile toxic substance is given off in the breath; but the experimental evidence in support of this belief was found to be fallacious, and all attempts to demonstrate the existence of such a substance have failed. Some of the most striking evidence on the subject is afforded by experience in submarines, in which a limited volume of air is quite commonly rebreathed until after a few hours a light will not burn and 3 per cent or more of CO_2 may be present. Provided the air remains cool, as it does in a temperate climate owing to the cooling influence of the water, the only effects observed are those due to CO_2.

Even in the most crowded and ill-ventilated rooms the proportion of CO_2 seldom rises above 0.5 per cent, with, of course, a corresponding drop in the oxygen percentage. From the account already given of the physiology of breathing it is evident that a difference of this order in the composition of the air is in itself of no appreciable importance. The breathing simply becomes very slightly deeper and the composition of the alveolar air and arterial blood remains practically unaffected as regards either CO_2 or oxygen.

Although apart from CO_2 no appreciable amount of any poisonous substance is given off to the air by the body, various substances which affect the olfactory nerves are given off in minute amounts from persons or furniture in a room. As a rule these substances are only perceived on entering a room, and are not noticed after a short time by those who remain in it. In sensitive persons, however, they may produce an unpleasant reflex effect; and for this reason apart from any other a good ventilation is desirable. When, however, there is no musty furniture, and the bodies and clothing of those present are fairly clean, there is little or no inconvenience from this cause.

A far more important factor in connection with the physiological effects of the air in rooms is temperature, and along with it moisture. The maintenance of a constant internal body temperature depends on constant physiological adjustment between actual heat loss from the body and variations in environmental conditions which tend to make the heat loss greater or less than the heat production. The variations in environmental conditions consist in variations in temperature, moisture content, and movement of the air, and also variations in the radiant heat gained or lost by the body, apart from the actual temperature of the air. The actual heat loss is regulated physiologically, apart from conscious regulation by variation of clothing, etc., partly by varying the rate of blood circulation through the skin, and partly by varying the amount of water evaporated by the skin. The latter means of regulation does not come into play unless the air is warm, or heat production in the body is greatly increased by muscular exertion.

When the air of a room is so cold, or the movement of the air is so great, that the skin, or parts of it, become uncomfortably cold, we are always clearly aware of the cause of discomfort. But when the air is so warm as to lead to the skin being uncomfortably warm we are apt to attribute the discomfort to some other cause than the heat. The matter is also complicated by the fact that in different persons the air temperature at which discomfort is felt varies considerably. Thus persons who have been undergoing "open-air" treatment and are accustomed to rooms with open windows feel much discomfort in rooms with closed windows where other persons are just comfortable. Similarly Americans accustomed to the warm air associated with central heating find British houses with fires very uncomfortably cold in winter, while British visitors to America find the warm air of American houses very trying.

The discomforts of warm or cold air are not usually associated with rise or fall of internal body temperature. When suffering great discomfort from sitting in a very cold room, I have found the rectal temperature slightly raised rather than lowered, and on going to an uncomfortably warm room there was a slight fall in rectal temperature. Persons going unaccustomed into very warm air may become faint or suffer from nausea or headache without any appreciable rise of body temperature. There appears to be a fall of arterial pressure owing to failure on the part of the vasomotor center to compensate for the increased flow of blood through the skin in a warm atmosphere, and this probably accounts for the more striking symptoms. In any case persons soon become more or less acclimatized within limits to the effects of warm air. One can observe this in miners who become accustomed to warm places in mines, or in people who become accustomed to Turkish baths.

It is somewhat noteworthy that men accustomed to hard outdoor work seem to be much less sensitive to heat or cold indoors than other persons. This is probably due to the fact that though they are not accustomed to external heat they are accustomed to what in this reference comes to much the same thing, namely, greatly varied internal heat production, which involves the same capacity for vasomotor adaptation as exposure to external heat or cold. Those who are most affected by external heat or cold indoors are persons who are not only unaccustomed to external heat, but are also unaccustomed to hard muscular exertion.

Part of the discomfort of warm air in rooms is due to its drying effect on the skin and particularly the upper air passage. Winter air warmed to a temperature of about 70°F. is very dry; and if the skin and upper air passages are kept warm by the air they lose far more moisture than usual and become uncomfortable. With cold air the inside of the nose is kept cool, and during expiration moisture condenses in it, so that it is kept moist in spite of the fact that the cold air contains very little moisture. With warm dry air, on the other hand, there is much evaporation during inspiration and little or no condensation during expiration, so that the nose is apt to become very dry; and this appears to lead to swelling of the mucous membrane.

The combination of physiological disturbances produced by warm air in a room is apt to be attributed to chemical impurities in the air. Owing to this fact, and general ignorance as to the physiology, as distinguished from the chemistry, of respiration,

too much stress was formerly laid on the chemical purity of the air in rooms. The chemical purity is nevertheless a very important index of the chances of infection through the air from person to person in a room. The more air is passing through the room the less the chances of infection become; and for this reason as high as possible a standard of chemical purity is desirable where a number of persons, some of whom may be carriers of infection, are present. A reasonable standard to aim at under these circumstances is that the excess of CO_2 in the air of the room should not be over .02 per cent unless lights are burning, or that about 50 cubic feet of air per person and per minute should be supplied. This standard can easily be maintained in ordinary houses with natural ventilation; and even in the case of crowded buildings a similar standard can be attained by the right application of modern engineering methods.

When air becomes very warm the regulation of body temperature becomes dependent on increased evaporation from the skin and not merely on variation in the blood flow through it. If muscular work is being done this point is soon reached if the air is fairly still. The amount of moisture in the air then becomes very important, as the rate of evaporation from the skin depends on the amount of moisture already present in the air. In still air, or in air moving at any given rate, a temperature is finally reached at which in spite of profuse sweating the skin cannot evaporate water quickly enough to prevent the body temperature from rising. As I showed experimentally in 1905, this temperature is reached when the wet-bulb temperature reaches a certain point.[1] Thus in still air and with hardly any clothing, the body temperature begins to rise when the wet-bulb temperature exceeds 88°F (31°C). It does not matter what the actual air temperature is, or the actual percentage of moisture in the air, provided that the wet-bulb temperature reaches 88°. Thus it was indifferent whether the air temperature was 88° with the air saturated, or 133° with the air very dry, provided that the wet-bulb temperature was 88°. When the wet-bulb temperature was far above 88° the rate of rise of body temperature was proportional to the rise of wet-bulb temperature.[2]

When even moderate muscular work was being done the critical wet-bulb temperature was, even with almost no clothing, at

[1] Haldane, *Journ. of Hygiene*, V, p. 494, 1905.
[2] Haldane, *Trans. Inst. of Mining Engineers*, XLVIII, p. 553, 1914.

least 10° below 88° in still air. With the ordinary clothing of temperate climates the critical wet-bulb temperature is much lower than without clothing, especially during muscular work. On the other hand, with the air in motion, the critical wet-bulb temperature is higher. The beneficial effects of fans, punkahs, etc., during heat is well known. With the wet-bulb temperature above the body temperature, however, the rise of body temperature is the more rapid the more the air is in motion.

In the climate of Great Britain the wet-bulb shade temperature very seldom rises above 70°, even on very warm summer afternoons; but during heat waves in America a wet-bulb temperature of 75° is not infrequently reached, and cases of hyperpyrexia from the heat then become common. Wet-bulb temperatures of over 80° are of course common in tropical countries, and are met by proper adaptation of clothing and mode of life; but the amount of muscular exertion which is possible with a wet-bulb temperature over 80°, except in a good breeze, is limited. In ordinary rooms in a temperate climate, and when ordinary clothing is worn, a wet-bulb temperature of even 65° becomes oppressive and likely to cause fainting and headaches in persons not accustomed to heat or heavy muscular exertion.

In order to obtain a simultaneous measure of the cooling action on the body of air temperature, movement of air, and maximum evaporation from the skin, Dr. Leonard Hill has devised an instrument known as the katathermometer. This consists of an alcohol thermometer with a very large bulb, which, when an observation has to be made, is heated to about 100°F. The flask is jacketed with an absorbent jacket which can be moistened with water. By the rate at which the water cools, a comparative estimate can be obtained of the maximum possible combined cooling action on the human body of movement of air, temperature, and evaporation. The actual cooling effect of the air depends, of course, on the physiological responses of the body, but cannot exceed the maximum shown by the wet katathermometer.

The physiology of temperature regulation lies outside the scope of this book; but temperature effects are so liable to be confused with effects due to chemical impurities in air that it seemed necessary to refer briefly to the physiological disturbances due to warm air.

The air of occupied rooms is liable to be contaminated by escapes of lighting gas; and under certain circumstances fatal or very serious accidents from this cause may occur and lighting

gas may be used very easily for purposes of suicide or even murder. The great majority of accidental deaths from poisoning by lighting gas have been in bedrooms, owing to the gas being in some way left turned on after being extinguished. In 1899 a Departmental Committee of which I was a member reported on the influence of the use of water gas in connection with poisoning by lighting gas, and I investigated the conditions under which poisoning may occur in bedrooms.[3]

It might be supposed that the sense of smell would always give warning of an escape of lighting gas in a room. On going into a room in which gas is escaping one notices the smell at once, and long before sufficient gas is present to cause any symptoms of poisoning; but a person inside the room when the escape begins may quite probably never notice it. The reason for this is that the sense of smell for any particular substance becomes fatigued very rapidly, and if the proportion of the odoriferous substance in the air is only very gradually increased the smell is never noticed. In this way an escape of gas in a bedroom is often unnoticed.

When a continuous escape of gas occurs in a room, the percentage of gas in the air goes on increasing until the rate of escape through walls, roof, etc., balances the rate of inflow of gas. In any ordinary room the walls, roof, and floor are permeable to air, and, if any cause such as pressure of wind or difference of temperature between inside and outside tends to produce air currents in and out of the room, the flow of air is surprisingly free. If, for instance, the door and windows are closed and all visible chinks pasted up, it will be noticed that when a fire is lit the chimney draws just as well as before. Large volumes of air are passing up the chimney, and this air comes in through the walls, roofs, etc. Brick and stonework, for instance, are fairly permeable to air, as can easily be shown by suitable means. Small rooms in a dwelling house do not require artificial ventilation, provided the passages, etc., are well ventilated, since the ratio of surface to cubic capacity is high, so that ventilation through the surfaces of the room counts for more in relation to the cubic space per person in the room.

It will thus be readily seen that what happens in a room when gas escapes continuously will depend on various circumstances, such as the difference in temperature between inside and outside, the presence of a fire or of central heating by warm air, the

[3] Report of the Water-gas Committee, *Parl. Paper*, 1899. Appendix 1.

amount of wind, etc. But even if there is little or no cause of exchange of air before the gas escape begins, the escape itself will furnish a cause, since the gas is much lighter than air, so that air to which gas has been added will tend to pass out by the roof. Hence even under conditions least favorable to ventilation, the gas can never accumulate to more than a very limited concentration in the air of a room.

Another complication in connection with gas escapes is that the gas may or may not mix evenly with the air of a room. Gas escaping from a burner passes straight upwards to the roof and there spreads. I found that unless the temperature of the windows and walls was below the air temperature of the room the gas never came down again to any very great extent. With a very rapid escape of gas, as when a burner was completely removed or a pipe cut, this was very marked. It was impossible to obtain a poisonous atmosphere at the ordinary breathing level, but there was a heavy concentration of gas near the roof. The danger of poisoning was to persons in the floor above, and not to those in the room where the escape was occurring. Near the floor level, however, a curious phenomenon was observed. The gas actually present in the air was found to be nearly pure hydrogen. This showed that it was only by diffusion, and not by convection currents, that gas had penetrated downwards. Hydrogen, being much more diffusable than any of the other constituents of lighting gas, had diffused downwards much more rapidly; and in general it was found that the hydrogen in lighting gas separates off by diffusion very readily, leaving a mixture containing more of CO and the other heavier constituents of the gas. At night, when the windows were cold, and the tendency to convection currents down them was consequently strong, mixture of the gas by convection was much more apt to occur, especially if the escape was at a moderate rate. There was consequently more danger at night to persons sleeping in the room.

When the percentage of gas was determined at intervals in the air of a room with gas continuously escaping from a burner and mixing by convection currents down the windows, I found that, if the conditions of wind, etc., remained constant, the percentage became constant after a certain time which depended on the size of the room among other conditions, and might vary from about one to three hours according to the size of the room, rate of gas escape, amount of wind, etc. The maximum percentage obtained was 2.7 per cent at the breathing level. With larger escapes of

gas this percentage could hardly be increased, as most of the gas remained at the roof. The air at all parts of the rooms tested was examined with a miner's safety lamp to see if the air ever became explosive; but with such escapes as could be produced when burners were not taken off, I never succeeded in obtaining an explosive atmosphere even at the roof. It requires about 8 per cent of lighting gas to render air explosive.

These experiments had a very definite practical significance in connection with the composition of lighting gas used for domestic purposes: for it is evident that whether or not a dangerous result will ensue from an escape of gas in a room will depend on how poisonous the gas is, and not simply on the time during which the escape continues. The poisonous action of lighting gas largely diluted with air depends exclusively on the CO contained in it. In every case of persons found dead in air containing lighting gas the post mortem appearances are those of CO poisoning, and the percentage saturation of blood as determined by the method described in the appendix has turned out to be round 80, just as in the case, referred to below, of miners poisoned by CO. Thus, broadly speaking, the danger of poisoning from escape of lighting gas depends on whether the air will be poisonous from CO when less than 2 or 2.5 per cent of gas is present.

Lighting gas as originally introduced is made by the distillation of bituminous coal, and usually contains about 7 or 8 per cent of CO. With 2 per cent of this lighting gas in the air there would only be about 0.14 per cent of CO; and this, though a formidable percentage, would not, so far as known, produce fatal effects in a healthy person, as the haemoglobin would, in all probability, not become much more than about half-saturated. To judge from all our present knowledge, and from the results of experiments on animals, about 0.3 per cent would usually be needed to produce death within a few hours.

Excellent lighting gas can also be made by blowing steam through incandescent coke or coal. The product is what is called "blue" water gas consisting roughly of equal parts of hydrogen and CO. This gives a very hot, though small, flame, and although the flame by itself is "blue" and practically nonluminous, an excellent light is given when a properly adjusted mantle is used. On the other hand the calorific value of a given volume of this gas is very low as compared with ordinary coal gas; and as the value of gas depends mainly on the heating power of a given volume of it, as well as, to a certain extent, on the luminosity of its flame when

no mantle is used, water gas is usually "carbureted" by the addition of cheap oil in a chamber where the oil is "cracked" by means of heat. The product is known as carbureted water gas, and is very largely used as a substitute for ordinary coal gas. It has a luminous flame and more or less satisfactory calorific value, but contains about 30 per cent of CO.

It is evident that with gas containing 30 per cent of CO, poisoning will occur very readily with an escape of gas during the night in a house. On inquiring into the deaths from gas poisoning in American towns supplied with carbureted water gas, the committee referred to above found that about 100 to 200 times as many deaths occurred from gas poisoning with a given distribution of gas as in English towns supplied with coal gas only. The gas was also used very extensively for purposes of suicide, and sometimes also as a means of murder. Apart from actual danger from poisoning, there was also the constant anxiety as to danger from gas poisoning. An American mother, for instance, told me that she regularly got up every night to make sure that gas was not escaping where her children were sleeping. The result of the committee's inquiries was to show that if gas is to be used for domestic purposes the percentage of CO in it should be reasonably low; and in consequence of this finding the use of undiluted carbureted water gas was discontinued in Great Britain, where, indeed, it had only been introduced in one or two places, though with unfortunate results which led to the inquiry. It should, however, be mentioned that with the general introduction of mantles the danger of poisoning from accidental escapes from burners is considerably diminished, as less gas escapes, and if there is a pilot flame the risk is further greatly diminished.

Gas poisoning in houses may not only occur from escapes within the house, but also from escapes from street gas mains; and many serious accidents from this cause have occurred, particularly with carbureted water gas. The danger is much increased from the fact that in passing through earth the odoriferous constituents (benzene, etc.) of the gas are apt to be more or less absorbed, so that the gas entering the basements of houses is more or less odorless. Probably, also, it may have lost a good deal of its hydrogen by diffusion, and this will make it more poisonous. A large number of persons in several houses and many different rooms may be poisoned by one serious breakage of a main. Pettenkofer recorded an interesting case where, in the times before clinical thermometers, illness through gas poisoning from a broken

main was mistaken for a peculiar and rapidly infectious form of typhus. No smell of gas was noticed at first, and the percentage of CO must have been so low, and perhaps inconstant, that it took some hours before any distinct symptoms of illness were produced. At last the smell became noticeable, probably because the earth through which the gas was escaping had become saturated with the odoriferous constituents, and so ceased to absorb them completely.

Air of Mines. The air of mines is liable to be contaminated by various gases known to British miners as black damp, fire damp, afterdamp, white damp, and smoke. Of these, black damp is the commonest and most universally present; fire damp is hardly found except in connection with coal or oil; afterdamp occurs only after explosions; white damp in connection with spontaneous heating of coal; and smoke in connection with fires or blasting.

Black damp is distinguished by miners through its characteristic properties of extinguishing lamps without exploding and not causing danger to life provided a lamp will still burn. As ordinary black damp is heavier than air, it was formerly identified with CO_2. Its true composition was first ascertained in 1895 by Sir William Atkinson and myself.[4] It is the residual gas of an oxidation process, and thus consists of nitrogen with anything up to about 21 per cent of carbon dioxide. It is now evident that black damp may be formed by several different oxidation processes, among which oxidation of timber, of coal, and of iron pyrites (FeS_2) are the most important.

When timber oxidizes in the process of decay, it gives off nearly as much CO_2 as it consumes oxygen. Hence the black damp formed consists of about 80 parts of nitrogen and 20 of CO_2. Freshly broken coal also oxidizes slowly for some time at ordinary temperatures, but to a very limited extent. The oxidation process is a simple chemical one and not dependent on microörganisms; and extremely little CO_2 is formed. In the oxidation of pyrites, which is also a simple chemical process, no CO_2 is directly formed; the sulphur is oxidized to sulphuric acid, which partly combines with the iron to form ferrous and ferric sulphates, but may react with calcium carbonate to form calcium sulphate, CO_2 being of course liberated.

Black damp of one sort or another is found in practically all mines, though in coal mines where there is much fire damp its

[4] Haldane and Atkinson, *Trans. Instit. of Mining Engineers,* 1895.

presence can often be detected only by analysis, on account of the predominance of fire damp. Occasionally there is so little CO_2 present in black damp that it is lighter than air; or it may be lighter than air owing to admixed fire damp. I found that the black damp formed simply in the oxidation of coal at ordinary temperatures contains small percentages of CO,[5] but black damp as ordinarily found in considerable concentrations in mines is practically free from CO.

The action of black damp on lamps and candles is of much practical importance, particularly as a miner trusts to his lamp to warn him of the presence of black damp or fire damp. A flame is extremely sensitive to any variation in the oxygen percentage in air. If the oxygen percentage is increased the flame becomes brighter and hotter, and substances which are not inflammable in ordinary air may then become readily inflammable. If the oxygen percentage is diminished the flame becomes dimmer and less hot, unless the diminution is due to the addition of an inflammable gas to the air. When the oxygen percentage is diminished by the addition of nitrogen or black damp to the air, the light given by a candle or lamp diminishes by about 3.5 per cent for a fall of 0.1 per cent in the oxygen percentage.[6] With a fall of about 3 to 3.5 per cent in the oxygen an oil or candle flame is extinguished. Aqueous vapor is even more effective than nitrogen in causing extinction of flame. It should be noted that it is to the *percentage,* and not the partial pressure, of oxygen that the flame is so sensitive, whereas it is the partial pressure that is of physiological importance. A fall in the oxygen percentage of 3 per cent is of very little importance to a man, though it extinguishes a flame. On the other hand a flame still burns well when the atmospheric pressure is diminished to a third, while a man is soon asphyxiated. Gas flames may be much less readily extinguished by fall in oxygen percentage than oil or candle flames. Thus a hydrogen flame may not be extinguished till the oxygen percentage falls to half or even less, the extinction point depending to a considerable extent on the velocity with which the gas is issuing from the burner. An acetylene lamp will burn till the oxygen percentage falls to about 12.

The physiological action of black damp added to air depends within wide limits on the percentage of CO_2 in the black damp,

[5] Haldane and Meachem, *Trans. Inst. of Mining Engineers,* 1899.

[6] Haldane and Llewellyn, *Trans. Inst. of Mining Engineers,* XLIV, p. 267 1902.

and can be deduced from the data already given as to the physiological actions of CO_2 and oxygen. It should be noted that the CO_2 diminishes greatly the risk that would otherwise exist from diminution of the oxygen percentage. This risk is greatly diminished, owing to the fact that the CO_2 firstly increases the oxygen percentage in the alveolar air by stimulating the breathing, and secondly raises the hydrogen ion concentration of the blood, thus increasing the circulation rate and assisting the dissociation of oxyhaemoglobin in the tissue capillaries. There is therefore little or no danger from lack of oxygen till the oxygen percentage in the air falls to 6 or 7 per cent; but if the oxygen falls much lower death occurs from want of oxygen. The very evident effect of the CO_2 on the breathing gives good warning of the danger, so that apart from the ample warning given by a lamp a man is not likely to go into a dangerous percentage of black damp unless he does so suddenly, as in descending a shaft or steep incline.

In former times miners often worked in air containing so much black damp as to put a great strain on their breathing while they were at work. Air containing, say, 3 per cent of CO_2 doubles the breathing during rest; but this effect is scarcely noticeable subjectively. During work, however, the breathing is also about double what it would otherwise be, and the lungs are thus strained to the utmost. Probably a great deal of the emphysema from which old miners used to suffer was due to this cause.[7]

The ordinary fire damp of coal mines is, practically speaking, pure methane (CH_4). In a very "fiery" seam as much as 1,500 cubic feet of methane may be given off per ton of coal extracted. The methane is adsorbed in the coal,[8] and may come off under a pressure of 30 atmospheres or more. Of other higher hydrocarbons a small amount is also adsorbed in the coal, but held more firmly, so that only in the last fractions of gas coming off from coal can their presence be clearly demonstrated by analysis. No carbon monoxide comes off with the methane, but appreciable quantities of CO_2 and nitrogen are often given off. It occasionally happens, however, that enormous quantities of CO_2 are adsorbed in coal and may come off in very dangerous outbursts. This is unknown in British and American coal fields, but has been met with in France. Sudden outbursts of adsorbed gas, whether methane or CO_2, can only occur, however, where coal has been locally disintegrated, as is apt to be the case near a fault. Ordinary solid coal

[7] Haldane, *Trans. Inst. of Mining Engineers*, LI, p. 469, 1916.
[8] Graham, *Trans. Inst. of Mining Engineers*, LII, p. 338, 1916.

is so impermeable to gas that it only adsorbs or gives off gas very slowly. In the inflammable gas associated with oil fields higher hydrocarbons are present in considerable amount, so that the gas may burn with a luminous flame and has toxic properties. Methane may of course also be produced by the action of bacteria on old timber or other organic matter in the absence of oxygen; and accidents from the explosion of gas from this source have occasionally occurred in British ironstone mines.

When about 6 per cent of methane is present in air, the mixture becomes inflammable with an ordinary light, and explodes violently with a somewhat higher percentage. Curiously enough, however, an excess of methane prevents explosion, although plenty of oxygen is still present; and with more than about 12 per cent

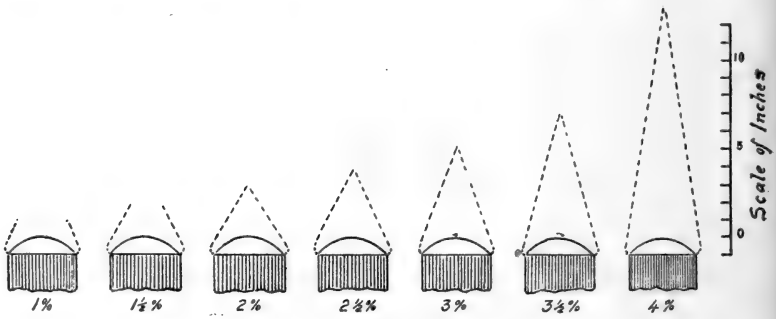

Figure 74.

Diagram showing outlines of caps visible on an oil flame with different percentage of methane.

of methane the mixture ceases to be inflammable. This fact limits considerably the direct dangers from explosions of fire damp.

The presence of nonexplosive proportions of fire damp in air can easily be detected by the appearance of a "cap" on the flame of a lamp. The cap is a pale, nonluminous flame which appears on the top of the ordinary flame. In order to see it properly the ordinary flame must be either effectively shaded or lowered till little else than a blue flame is present, as otherwise the light from the ordinary flame produces a dazzling effect which renders the cap invisible, though it can be photographed without difficulty. The length of the cap depends on the temperature and size of the flame, and with the very hot hydrogen flame the test becomes far more delicate, so that as little as 0.2 per cent of methane can be detected easily. Figure 74 shows the outlines of the cap visible

with different percentages of methane when an ordinary oil flame is lowered to the extent required in testing.

To obviate the danger arising from ignition of fire damp mixtures by lamps, some sort of safety lamp is now always used in fiery mines. A safety lamp may be either an oil lamp constructed on the general principle introduced by Davy, or an electric lamp; but the latter has of course the disadvantage that it does not indicate the presence of fire damp and black damp.

As regards its physiological properties, fire damp behaves as an indifferent gas like nitrogen or hydrogen. A mixture of 79 per cent of methane and 21 of oxygen has the same physiological properties as air, except that the voice is altered; and the physiological action of methane is simply due to the reduction which it causes in the oxygen percentage. Its action can thus be deduced from the data in Chapters VI and VII. In actual practice the danger from asphyxiation by fire damp is considerably greater than from black damp, since a man going with an electric lamp or no lamp into air progressively vitiated by fire damp has little physiological warning of impending danger. He is in a similar position to an airman at a very high altitude, and if he suddenly falls from want of oxygen he is very likely to die from failure of the respiratory center.

Afterdamp. Afterdamp is the gas produced as the result of an explosion, and has been known for long to be specially dangerous. In 1895 I made an inquiry into the causes of death in colliery explosions,[9] and found that nearly all (about 95 per cent) of the men who died underground were killed by CO, although a considerable number had received such serious skin burns that they could hardly have survived in any case. Death was never due to deficiency in the oxygen percentage of the air, nor to excess of CO_2, nor, apart from exceptional cases, to more than 2 per cent of carbon monoxide. It was clear that the men had died in air containing plenty of oxygen, and not much carbon monoxide. That carbon monoxide was the actual cause of death was clear from the fact that the venous blood was usually about 80 per cent saturated with CO; and that death was slow, and therefore due to a low percentage of CO, follows from the fact that about the same saturation was found all over the body. With more than about 2 per cent of CO the venous blood has not time to become evenly saturated and the saturation is usually a good deal lower.

[9] Haldane, *Report on the Causes of Death in Colliery Explosions and Fires*, Parl. Paper C, 8112, 1896.

Colliery explosions were formerly attributed simply to explosions of fire damp. About 40 years ago it was first clearly pointed out by Mr. Galloway that this explanation is unsatisfactory, and that the spread of an explosion must be due to coal dust. Further evidence of the predominant part played by coal dust in all great colliery explosions was soon brought forward; and it became clear that many explosions occur in the complete absence of fire damp, the coal dust being originally stirred up and lighted by the blowing out of flame in blasting, and the explosion carried on indefinitely by further stirring up and ignition. In other cases the starting point is some, perhaps quite small, explosion of fire damp, caused by a defective lamp, a spontaneous fire in the coal, or perhaps even by a spark from falling stone. The ease with which coal dust explosions may be produced by blasting when even a very little coal dust is lying on a road, and the astounding violence which they may develop after the flame has traveled about a hundred yards, were strikingly shown in experiments made with pure coal dust at Altofts Colliery under Sir William Garforth's direction.[10] On account of their danger in a populous neighborhood these experiments were transferred to Eskmeals on the Cumberland coast; and finally showed that when an equal weight of shale dust or other similar material was present along with the stone dust the mixture could not be ignited by blasting or gas explosions.[11]

Sir William Garforth's plan of stone-dusting all the roads in collieries with shale dust, so that at no point is there more than half as much coal dust as shale dust, has now been adopted very generally in Great Britain; and the only serious recent explosions have been in mines where this precaution was not adopted. Stone-dusting is far more efficacious and cheaper than watering the dust; and indeed efficient watering is impossible in many cases, owing to the effect of water on the roof and sides of a colliery road.

In the Altofts experiments, samples of afterdamp were analyzed by Dr. Wheeler. The following is a typical example.

Carbon dioxide	11.9
Carbon monoxide	8.6
Hydrogen	2.9
Methane	3.1
Nitrogen	73.5

[10] *Record of British Coal-dust Experiments*, 1910.
[11] *Reports of the Explosions in Mines Committee*, Parl. Papers, 1912–1914.

It will thus be seen that pure afterdamp, free from air, may contain as much as 8.6 per cent of CO. Fresh afterdamp also contains an appreciable percentage of H_2S (not shown in the analysis). This is a very poisonous gas, and 0.1 per cent will knock a man over unconscious in a very short time. The most immediate effect of fresh afterdamp may be due to H_2S; but on this point there is no definite knowledge as yet.

Considering the deadly composition of pure afterdamp it is at first sight somewhat surprising that in actual colliery explosions the men are not killed at once by the afterdamp, and that the CO is so dilute in the atmosphere that kills them. It must, however, be borne in mind that along the roads of collieries the coal dust is never pure, and often contains so much shale dust that an explosion is not possible. The combustion is probably, therefore, far from complete, so that much air is left, apart from what is drawn in as soon as the air cools. Possibly, also, the percentage of CO in the pure afterdamp is lower.

Afterdamp is, of course, extremely dangerous to rescuers, and many lives of rescuers have been lost owing to poisoning by CO. They have gone too far into the poisonous air before becoming aware of any danger, and the first symptom noticed is usually faintness and failure of the legs, so that return is impossible. Moreover the mental condition of men beginning to be affected by CO is usually such, as already explained in Chapter VI, that they will not turn back, and are reckless of danger. A lamp is of course useless for indicating the danger.

In order to give miners a practical means of detecting dangerous percentages of CO, I introduced the plan of making use of a small warm-blooded animal such as a mouse or small bird.[12] Owing to their very rapid general metabolism and respiration and circulation small animals absorb CO far more rapidly than men. Hence they show the effects of CO far more quickly, and can thus be used as indicators of danger, although in the long run they are possibly rather less sensitive to CO than men are. Thus a dangerous percentage which would require nearly an hour to affect a man at rest will affect the bird or mouse within about five minutes. This test has now come into very general use, and was, for instance, largely used during the war by the tunneling companies. It is easier to see the signs of CO poisoning in a bird in a small cage, as it becomes unsteady on its perch, and finally drops, while

[12] Haldane, *Journ. of Physiol.*, XVIII, p. 448, 1895.

a mouse only becomes more and more sluggish; but the mouse is easier to handle, and less apt to die suddenly and thus leave the miner without any test. The animals recover very quickly as soon as purer air is reached and this greatly increases their value as a test.

After an explosion it is very necessary to have some test for CO. The ventilation system is thrown out of action owing to doors and air crossings being blown in. On the other hand it is very important to get in as soon as possible in case men are still alive, and in order to deal with any smoldering fires left by the explosion.

When air in a mine is for any reason not safe to breathe, self-contained breathing apparatus are now frequently employed. It is beyond the scope of this book to describe these apparatus in detail;[13] but it may be mentioned that the usual principle employed is that the wearer breathes through a mouthpiece into and out of a bag, the nose being closed by a noseclip. Into the bag there is directed a stream of oxygen from a steel cylinder carried behind; and by means of a reducing valve and properly adjusted opening beyond it the stream is kept steady at not less than 2 liters per minute. This is as much as a man uses during pretty hard exertion. If he uses less, the excess is allowed to blow off. If he uses more, the oxygen percentage in the bag may fall rather low, or the bag may become flat before the end of a full inspiration. In the former case he will begin to pant more than usual, but will not fall over so long as the 2 liters are coming in. If less than about 2 liters are coming in he will be liable to fall over, owing to a rapid fall in the oxygen percentage. If the bag begins to go flat he will notice this, and either turn on more oxygen through a by-pass, or exert himself less. The carbon dioxide in the expired air is absorbed by a purifier containing caustic alkali.

In another form of apparatus the delivery of oxygen is governed by the state of fullness of the bag; but in applying this principle there is the difficulty that the oxygen may not be quite pure, and the contained nitrogen may thus accumulate in the bag, or a little nitrogen may leak in from the air at the mouthpiece.

In still another form use is made of liquid air, of which a large amount can be carried, so that most of the expired CO_2 can be allowed to pass out and only a small purifier is needed.

[13] A thorough discussion of the apparatus in use in America and the principles and practice applicable to it is given in *U. S. Bureau of Mines Technical Paper*, No. 82, 1917, by Yandell Henderson and J. W. Paul. Numerous investigations, including two full reports by myself, have appeared in Great Britain.

Whichever form of apparatus is used it is very necessary that it should be extremely reliable in its action, and that the users should be thoroughly instructed and trained in its proper use and upkeep. A number of lives have been lost or endangered through defective supervision and mode of use, or defective design, of apparatus; and as a consequence of these defects men wearing the apparatus in quite breathable air have often had to be rescued by men without apparatus. With proper and scientific supervision these accidents do not occur, as has been shown again and again during extensive operations in irrespirable air.

By white damp miners understand a poisonous form of gas coming off from coal which has spontaneously heated. The term seems to have arisen from the fact that steam commonly comes off from the warm coal with this poisonous gas and causes a white mist. By experiments on animals and analyses I have frequently found that the poisonous constituent of the gas was CO.

Freshly broken coal is, as already mentioned, liable to a slow oxidation process. This of course produces heat, and if sufficient coal is present, so that the heat is not lost as quickly as it is produced, the coal will heat, and the heated coal will oxidize faster and faster until at last it is red hot or bursts into flame if sufficient oxygen is present. It is for this reason that coal may be a dangerous cargo on long voyages, and that coal cannot be stacked safely in very high heaps. In many seams there is great trouble and no little danger from spontaneous heating of broken coal underground; and the residual gas coming off from heated coal is often called white damp. The higher the temperature of coal which is slowly oxidizing, the greater the proportion of CO in the residual gas. The effects of white damp are thus much the same as those of afterdamp; and the same precautions are required.

Smoke in mines may come either from fires or from blasting. The smoke from a fire is usually, of course, visible and irritates the air passages and eyes owing to the irritant properties of the suspended particles. If, however, smoke has slowly traveled some distance in a mine, the particles have subsided and the smoke has become a more or less odorless and transparent gas. Many very serious accidents, involving sometimes the loss of 100 lives, have occurred through the poisonous action of smoke from fires in mines. In these cases the deaths have always, so far as hitherto ascertained, been due to CO poisoning. A large amount of unburnt CO is given off from smoky or smoldering fires, so that the gases from a fire are almost as dangerous as the afterdamp of an

explosion. Practically speaking, afterdamp and smoke from fires produce nearly the same effects, and require the same precautions. A fire in the main intake of a mine is a most dangerous occurrence, since the poisonous gas is apt to be carried all over the mine, and to kill all the men in it. To afford a means of dealing with this danger, the ventilating fans provided at British coal mines are now so constructed that the air current can be at once reversed, so as to drive back the smoke.

Smoke from blasting may contain various poisonous gases, along with CO_2, according to the nature of the explosive. Some explosives, such as guncotton, give much CO, and some very little; but all seem, in practice, to give some. Hence there is always risk of CO poisoning where explosives are used in mines, unless the proper precautions are taken. Black gunpowder, as used for blasting, produces both CO and H_2S; and in the cases of gassing it is often difficult to decide whether CO or H_2S has been mainly responsible for the effects. With explosives containing nitro-compounds another and very serious danger is met with. When these explosives detonate properly the nitrogen is given off as nitrogen gas; but when they burn instead of detonating, the nitrogen comes off as nitric oxide, along with CO instead of CO_2. In practice, owing to defective detonators or other causes, some of the explosive is apt to burn instead of detonating. The nitric oxide then passes into the air and combines with oxygen to form yellow nitrous fumes. These have a somewhat irritant effect at the time, but this is not sufficient to give proper warning of their dangerous properties. The immediate effects are very slight. If, however, enough of the mixture has been inhaled, the result is that after a few hours symptoms of very severe lung irritation appear, and finally oedema of the lungs and great danger to life. I have found that exposure to the fumes from as little as .05 per cent of nitric oxide in air may be fatal to an animal. This subject will be referred to more fully below in connection with poisonous gas used in war.

Poisoning with CO in mines is so apt to occur, that a few words may not be out of place as to the treatment of CO poisoning. The symptoms and their cause have already been dealt with. The first thing, is, of course, to get the patient out of the poisonous air. In doing so, however, it is important to keep him well covered and avoid in any possible way exposing him to cold. For some reason which is at present not clear, a man suffering from CO poisoning gets much worse on exposure to cooler and moving air, as in the

main intake of a mine. If the breathing has stopped artificial respiration should be applied promptly; and this can best be done by Schäfer's well-known method. If oxygen is available it should be given at once. It immediately increases greatly the amount of dissolved oxygen in the blood, and also expels far more rapidly the CO from the blood, as will be evident considering the properties of CO haemoglobin. The oxygen will do most good at first, and may be continued with advantage for at least twenty minutes. Suitable apparatus for giving oxygen can now be obtained easily. Henderson and Haggard have recently shown, however, that owing to the great washing out of CO_2 which occurs during the hyperpnoea produced in acute CO poisoning, or perhaps owing to temporary exhaustion of the respiratory center, the breathing is apt to remain for some time inadequate.[13A] They found by experiments on animals that under this condition the removal of CO from the blood is greatly accelerated by adding CO_2 to the air or oxygen inhaled. The desirability of having some safe and practicable means of adding CO_2 to oxygen used in reviving men poisoned by CO seems evident from these experiments.

A man who has been badly gassed by CO, and has been unconscious for some time, is sure to have very formidable symptoms, lasting long after all traces of CO have disappeared from the blood. He may never recover consciousness at all; but when he does his nervous system generally is likely to remain very seriously affected for days, weeks, or months, so that he requires to be carefully watched, nursed, and treated. Mental powers and memory may be much impaired, and the nervous system seems to be injured in many different directions. Thus the regulation of body temperature is apt to be imperfect, and symptoms resembling those of peripheral neuritis are common. A condition of neurasthenia, similar to that so often seen during the war, appears to result frequently, with the usual affections of the respiratory and cardiac nervous system. In some cases there seems to be acute dilatation of the heart; and probably almost every organ in the body has suffered from the effects of want of oxygen.

As mines grow deeper and warmer, the importance of the wet-bulb temperature in connection with mine ventilation becomes more and more prominent. The reasons for this will be evident from what has already been said on this subject; especially when the fact that a miner has to do hard physical work is also taken into

[13A] Yandell Henderson and Haggard, *Journ. of Pharmac. and Exper. Therap.*, XVI, p. 11, 1920.

consideration. To this subject I have given very close attention in recent years, and a full general discussion of it will be found in the recent Report of the Committee on Control of Temperature in Mines.[14]

Owing to the nature of their work and the dry conditions in deep and well-ventilated mines, miners are very much exposed to dust inhalation; and the prevalence of "miners' phthisis" among certain classes of miners led me to the investigation of the effects of dust inhalation. Both men and animals are in general more or less exposed to dust inhalation. The problem presented by dust inhalation in mining and other dusty occupations is thus only a part of a general physiological problem as to how the dust inhaled along with air is dealt with by the body. It is evident that if the insoluble dust which is constantly being inhaled by civilized men, particularly in towns and in dusty occupations, accumulated in the lung alveoli, the effects would in time be disastrous. There is, however, no evidence that such effects are ordinarily produced. The lungs of a town dweller, for instance, are more or less blackened by smoke particles, but remain perfectly healthy; and the same applies to the lungs of coal miners and of persons engaged in many other very dusty occupations. In other cases, however, such as certain kinds of metalliferous mining, steel grinding, pottery work, etc., the effects of continuous inhalation of the dust are disastrous. Why have certain kinds of insoluble dust no cumulative bad effect on the lungs? Why, on the other hand, have other kinds such disastrous cumulative effects? When the first question is answered the second becomes relatively easy.

It is in the production of phthisis (pulmonary tuberculosis) that the continued inhalation of a dangerous variety of dust shows its effects most clearly. The following table, which I compiled from the statistics of the Registrar General for England and Wales, shows the marked contrast between different occupations as regards the effects of dust inhalation in producing phthisis. Two dusty occupations are included—coal mining and tin mining. Of the two, coal mining is much the dustier occupation. It will be seen, however, that among coal miners there is not only very little phthisis, but even less than among farm workers, and much less than the average for all other occupations. Among tin miners, on the other hand, there is a great excess of phthisis; and detailed

[14] First Report of the Committee on Control of Underground Temperature, *Trans. Inst. of Mining Engineers*, 1920.

investigation has shown clearly that it is to dust inhalation that this excess is solely due.[15]

A very large proportion of the dust in inspired air is caught on the sides of the nasal and bronchial inspiratory passages, from which it is continuously removed by the action of the ciliated epithelium. It is only the very finest particles that penetrate to the lung alveoli. Nevertheless large amounts of dust do, as a matter

DEATH RATES FROM PHTHISIS PER 1000 LIVING AT EACH AGE PERIOD FOR ENGLAND AND WALES, 1900–1902

Age period	15-25	25-35	35-45	45-55	55-65
All occupied and retired males	1.1	2.1	2.9	3.2	2.6
" coal miners	0.7	1.0	1.1	1.5	2.0
" farm workers	0.6	1.15	1.3	1.4	2.6
" tin miners	0.4	7.0	11.7	16.1	16.2

of fact, reach the alveoli. Arnold showed that even what, in human experience, is relatively harmless dust, will produce, if inhaled in very large amount, foci of scattered broncho-pneumonia in the lungs, and that quartz dust is specially apt to produce inflammatory changes followed by development of connective tissue.[16] In connection with the use of shale dust for preventing colliery explosions Beattie showed that neither coal dust nor shale dust produce any harm in animals if the dust is inhaled in the moderate quantities comparable to what a miner inhales. On the other hand, the dust from grindstones produces signs of fibrosis.[17] The subject was followed further in my laboratory by Mavrogardato in an investigation undertaken for the Medical Research Committee.[18] This work showed that the very fine particles which reach the alveoli are rapidly taken up by special cells of the alveolar walls. When coal dust or shale dust was inhaled, these cells soon detached themselves and wandered away with their load of dust particles. Some pass directly into the open ends of the bronchial tubes, and are thence swept upwards by the cilia. Others pass into lymphatic vessels and are carried to the nodules of lym-

[15] Haldane, Martin, and Thomas, *Report on the Health of Cornish Miners*, Parl. Paper Cd, 2091, 1904.

[16] Arnold, *Untersuchungen über Staubinhalation und Staubmetastase*, 1885.

[17] Beattie, *First Report of Explosions in Mines Committee*, Parl. Paper, Cd, 6307, 1912.

[18] Mavrogardato, *Journ. of Hygiene*, XVII, p. 439, 1918.

phatic tissue surrounding bronchi and then pass right through the walls of the bronchi and are swept out. Others reach the lymphatic glands at the roots of the lungs, and finally seem to pass from there into the blood. In this way the dust is removed from the lungs, and if too much dust is not inhaled the process of removal will keep pace with the introduction of dust. The well-known "black spit" of a collier, which continues for long periods when he is not working underground, is apparently a healthy sign showing that dust particles are being removed from the lungs. It seems quite probable, also, that the efficiency of the physiological process for dealing with dust improves with use, like other physiological processes. Moreover the dust-collecting cells appear to be identical with cells which collect and deal with bacteria in the lungs. Possibly, therefore, the somewhat remarkable immunity of colliers from phthisis is connected with their capacity for dealing with inhaled dust particles.[19]

At the end of a few months the lungs of a guinea pig which have been heavily charged with coal dust or shale dust by experimental inhalations are again free from dust. On the other hand this was not the case when the dust inhaled was quartz. Most of the quartz remained *in situ,* though mainly within the dust-collecting cells. Part had, however, been carried onward to lymphatic glands. The quartz did not seem to excite the cells to wander in the same way as the coal dust or shale dust did; and it appeared as if this difference in the properties of different kinds of dust explained why some dusts are much more apt than others to produce cumulative ill effects in the lungs. Presumably the quartz particles are so inert physiologically that they do not excite the dust-collecting cells to wander away. Other kinds of dust particles may be equally insoluble, but may also be charged with adsorbed material which makes them physiologically active. Coal, for instance, though very insoluble in water, adsorbs substances of all kinds, and the importance of its power of adsorbing gases has already been pointed out.

Shale dust was found by Dr. Mellor to contain about 35 per cent of quartz. Nevertheless the quartz in shale dust does no harm to the lungs and is eliminated readily. There are many other kinds of stone which contain still more quartz, but also produce a harmless dust. In fact nearly all the dust ordinarily met with is of the harmless variety, and Mavrogardato's investigation indi-

[19] Haldane, *Trans. Inst. of Mining Engineers,* LV, p. 264, 1918.

cated that quartz dust becomes relatively harmless when it is mixed with other dust of the harmless variety. The lung cells appear to clear out the quartz when they are clearing out the other dust.

It is evident that much further investigation is needed in order to elucidate completely the physiology of dust excretion from the lungs. It is equally evident, however, that this process is under physiological control, just as much as other physiological activities are.

Air of Wells. The case of the air of wells and other unventilated underground spaces differs from that of mines owing to the fact that no artificial ventilation is provided for. It might be supposed that the air in a well, with only rock or brickwork round it, pure water at the bottom, and the top more or less open, would never be more than slightly contaminated. Experience shows, however, that this is not the case, and that the air in even a shallow well, only a few feet deep, is sometimes dangerously contaminated. In 1896 I investigated this subject, visiting various wells where men had been asphyxiated, in order to see what had happened.[20] I found plenty of foul air, and that its composition was similar to that of black damp, and not simply CO_2, as was then believed. The composition of the gas varied from about 80 per cent nitrogen and 20 per cent CO_2 to almost pure nitrogen; and it was quite evident that this black damp or choke damp was simply the residual gas from oxidation processes occurring in the strata round the well.

Another point which emerged quite clearly was that the state of the air in any well liable to foul air depended entirely on changes in barometric pressure. With a rising barometer the air was quite clear, and with a falling barometer it was foul. Thus any fall in barometric pressure might make a well very dangerous, though an hour before the air was quite pure. Moreover with a falling barometer the well might be brimfull and rapidly overflowing with dangerous gas. The danger to which well sinkers are exposed is thus evident. At one well an engine house which covered the top of the well had been built, and sometimes it was unsafe to enter this building owing to the gas, unless doors and windows were wide open. The engine man was much comforted when I lent him an aneroid barometer and thus convinced him that the outbursts of gas were due to natural and not supernatural

[20] Haldane, *Trans. Inst. of Mining Engineers,* 1896.

causes. By always carrying a lighted candle or lamp with him, a well sinker can guard most effectually against the danger from black damp; but it is quite unsafe to trust to previous tests.

It is thus evident that a well acts as a chimney communicating with a large air space in the substance of the surrounding rock, or in crevices within it. Air may either be going down this chimney or returning; and if the rock contains any oxidizable material such, for instance, as iron pyrites, the returning air or gas has lost more or less of its oxygen, and possibly also gained some CO_2. If, however, less than about 4 per cent of CO_2 were present in the black damp it would be lighter than air, and thus likely to escape unnoticed.

An interesting case which came under my notice later may be mentioned in this connection. While a tunnel was being driven with compressed air under the Thames it was found that in a large cold storage on the river bank lamps or candles were extinguished. The air was analyzed for CO_2, but no noticeable excess was found. On analysis I found the air very poor in oxygen. On further investigation it turned out that air very poor in oxygen, but with practically no excess of CO_2, was coming up the shaft of a well belonging to the building.[21] The flow did not depend on barometric pressure, and nothing of the sort had occurred before the construction of the tunnel began. It was evident, therefore, that the flow was due to compressed air escaping deep down through the London clay from the advancing end of the tunnel, and forcing a way to the well, but at the same time losing oxygen owing to the presence in the clay of oxidizable material such as iron pyrites. The pure black damp contained 99.6 per cent of nitrogen and 0.4 per cent of CO_2.

Air of Railway Tunnels. Although the great difficulties formerly experienced in the ventilation of long railway tunnels have been overcome by the substitution of electric traction for steam locomotives, it may be worth while to record here some of these difficulties. Probably the worst cases were those of single-line tunnels on a stiff gradient in the Apennines. When the wind was blowing in the same direction as a train was traveling on an up-gradient the smoke from the engine or engines tended to travel with the train. Thus the air rapidly became poisonous from the presence of CO, and the oxygen percentage fell so low that sometimes lights were extinguished and steam began to fail, owing

[21] Blount, *Journ. of Hygiene*, VI, p. 175, 1906.

to the engine fires burning badly. The passengers could partly protect themselves by closing the windows; but the engine drivers were liable to become unconscious, and at least one very serious accident occurred, owing to a train running on with the men on the engine unconscious.

In the London Underground Railway there was also much trouble, owing to the great traffic, although there were numerous openings to the street along all parts of the system, and a colliery fan had also been installed at one point. The difficulties were referred to a Board of Trade Committee of which I was a member, and I made numerous analyses of the air.[22] It was never so bad as appeared to have been sometimes the case in the Apennine tunnels, and the trouble from sulphuric acid and smoke was largely mitigated by the use of Welsh steam coal containing very little sulphur. The air was often, however, very unpleasant, and many persons were unable to use the railway. At busy times the percentage of CO_2 might rise as high as 0.8, and of CO to .06; but of course passengers and railwaymen were not long enough exposed to this air to suffer from the effects of CO, and repairing work on the line was not carried out except at night. At the end of the inquiry it was agreed to introduce electric traction, and since this was done there has been no further difficulty. The tunnels are close to the surface, and the trains push abundance of air out and in through openings to the outside air.

In the (London) tubes, which lie much deeper, the ventilating action of the trains proved insufficient by itself to prevent the air from becoming rather unpleasant; and systematic ventilation by fans was therefore adopted. In various other railway tunnels simple shafts are provided; and in the Severn Tunnel there is a nearly central shaft provided with a powerful fan. By these means the air is kept fairly pure.

Air of Sewers. The air of sewers is perhaps mainly of interest in connection with the time-honored belief that "sewer gas" spreads infection. Some of my earliest scientific work was concerned with the air commonly present in sewers, and was started by the late Professor Carnelley and myself[23] at the request of a House of Commons' Committee appointed in consequence of alarm as to the sewers of the House of Commons.

The air of a sewer has, of course, an unpleasant smell, which, however, is hardly noticed except at the manhole by which access

[22] *Report of the Committee on Tunnel Ventilation*, Parl. Paper, 1897, Appendix 1.
[23] Carnelley and Haldane, *Proc. Roy. Soc.*, 42, p. 501, 1887.

is gained to the sewer. The air is saturated with moisture, and may be somewhat warm if much warm water flows into the sewer. Chemically speaking, however, the air is very little contaminated. Even in the sewers of Bristol, where ventilating shafts were reduced to a minimum, I found only about 0.2 per cent of CO_2. On determining the number of bacteria in the air we found that fewer were present in the sewer air than outside, but of much the same kinds. In sewers which were well ventilated there were far more than in badly ventilated sewers; and it was evident that nearly all the bacteria came from the outside through the ventilators. Where there was much splashing, however, a few were thrown into the air. These results, which have been confirmed by other investigators, are just what might be expected. Particulate matter is not given off from moist surfaces apart from mechanically acting causes, and any bacteria or other particles driven into suspension in the air of a sewer will tend to fall back again. It is conceivable that infection might be carried by sewer air; but innumerable other paths of infection are much more probable.

Although ordinary sewer air is chemically very pure, and not even a trace of H_2S can be found, accidents to sewermen from foul air are not very uncommon; and there is no doubt that most of these accidents are due to H_2S. I investigated one case of this kind where five men had lost their lives at a manhole—the last four in attempts at rescue.[24] All the symptoms described, including irritation of the eyes, were those of H_2S poisoning; and though the air was not poisonous when I descended, a little H_2S was present. When some of the sewage was put into a large bottle and shaken up, H_2S was found to be present, and a mouse lowered into the bottle showed severe symptoms of H_2S poisoning. These symptoms were absent when lead acetate was added before shaking, or when caustic soda was added.

It is only when sewage stagnates or deposits solid matter that H_2S is formed. Any cause that stirs this sewage, or liberates H_2S from it, may make the air dangerous. About 0.2 per cent will kill an animal within a minute or two; and 0.1 per cent will rapidly disable it. H_2S is thus a good deal more poisonous than CO, and far quicker in its action.

Another source of danger is lighting gas from leaky street mains. Lighting gas is frequently met with in sewers, and I have several times smelt it in sewers. In one recent case which I investigated two men were killed by CO poisoning from lighting

[24] *Lancet*, Jan. 25, 1896.

gas. There seems to be no evidence of accidents in sewers from any other gas than H_2S or CO; but many strange smells are encountered, and we were once much alarmed by chlorine coming from a bleaching factory.

Air of Ships. In the compartments of a ship air is specially liable to become foul owing to the air-tight conditions which often exist. In a double bottom compartment, for instance, the whole of the oxygen may disappear, owing to rusting or to absorption of oxygen by drying paint. In an ordinary compartment battened down the same thing may also occur owing to slow absorption of oxygen by articles of cargo, such as grain, wool, etc. Accidents from this cause are not infrequent if men descend without first testing the air with a lamp or giving time for ventilation to occur. In coal bunkers fire damp may accumulate in the absence of proper ventilation, or else the oxygen may fall very low. Coal trimmers are occasionally also affected by what appears to be CO poisoning due to small quantities of CO formed at ordinary temperatures in the slow oxidation of coal, as described above.

The ventilation of passenger and crew spaces on ships was very defective, particularly in rough weather, until fan ventilation was generally introduced. It was forgotten that the rooms in a ship do not ventilate themselves naturally through walls and roof, as a house ashore does. Owing to the close quarters, it is often difficult to ventilate the spaces in a ship properly without causing intolerable draughts. In the mess decks of warships this is specially difficult, as there are hammocks everywhere at night. The matter was investigated recently by an Admiralty Committee of which I was a member and a system introduced by which equal amounts of air can be made to issue from a large number of louvres on the sides of ventilating ducts. In this way the men are supplied with an average of 50 cubic feet of air each per minute, without any unpleasant draught impinging on any one. The temperature, and particularly the wet-bulb temperature in warm weather, can also be controlled very efficiently by this plan. With men perspiring more or less from heat, and giving off perhaps fifty times as great a volume of aqueous vapor as of CO_2, very ample artificial ventilation is needed when no other means of ventilation is available.

Gas Warfare. It would be out of place to attempt to discuss the nature and mode of action of the various substances used in gas warfare; but a certain number of facts of physiological interest in connection with respiration may be fitly referred to here.

The first serious gas attacks were made, as is well known, with

chlorine, discharged into the air in a good breeze as "drift gas" from cylinders of liquefied gas. The liquefied gas quickly evaporated, thus cooling a large body of air which rolled along the ground, producing at the same time a mist if the air was nearly saturated, and passing downwards into every trench. From accounts given by officers and men at the time, I estimated that along the lines attacked there was usually about .01 per cent of chlorine in the air; but of course the percentage would vary. At about this and higher concentrations, chlorine has an immediate and severe irritant effect on the air passages, and a less severe action on the eyes. Bronchitis follows if the exposure lasts for more than a very short time, and some time later symptoms of oedema of the lungs appear, owing to the action of the gas on the alveolar walls. The symptoms are then similar to those which follow exposure to nitrous fumes. The men suffering from this condition were deeply cyanosed, with superficial veins about the neck prominent, greatly increased depth and rate of breathing, and a frequent, but usually fairly strong pulse. Intelligence was clouded, but the distress seemed very great.

On testing a drop of blood by diluting it to a yellow color, saturating with coal gas and comparing the pink tint thus produced with the tint of normal blood similarly diluted, it was evident that there was no decomposition of the haemoglobin. The cyanosis was therefore due to imperfect saturation of the blood with oxygen. That the imperfect saturation was due, not to slowing of the circulation, but to imperfect saturation in the lungs, was shown at once by the effect of giving oxygen. This abolished the cyanosis, cleared up the clouded intelligence, but had no great effect on the breathing. On post mortem examination of fatal cases it was found that the lungs were voluminous and greatly congested. Large quantities of albuminous liquid could be squeezed out through the cut bronchi, and there was much emphysema.

The interpretation of the more dangerous symptoms seems fairly clear. The cyanosis was due to the fact that the blood in passing through the lungs was imperfectly oxygenated, owing mainly to swelling and exudation, which hindered the diffusion of oxygen inwards to the blood. On raising the alveolar oxygen pressure when oxygen was given, the diffusion became much faster and the blood was properly oxygenated. The hyperpnoea remained, however, and was probably attributable to the fact that though much air was entering the lungs, a great deal of it

only went into the emphysematous spaces where there was little or no circulation, leaving the rest of the lung imperfectly ventilated, with an abnormal excess of CO_2 in the alveoli which were permeable to blood, and consequently an abnormal excess of breathing.

Considering the depth of the cyanosis it was somewhat remarkable that consciousness was not more impaired; but the excess of CO_2 which accompanied the cyanosis would of course facilitate the dissociation of oxyhaemoglobin in the tissue capillaries, and thus diminish the real anoxaemia. The distention of superficial veins was an indication of the veno-pressor effect of excess of CO_2 combined with failure on the part of the heart to respond normally to the large amount of blood returning to it from the tissues. This failure was evidently due to the anoxaemic condition of the blood supplied to the heart. The failure was presumably most marked in the left ventricle, which has far the most work to do, and the consequence would be a rise of blood pressure, not only in the veins, but also in the right side of the heart and the whole pulmonary circulation. The rise in pulmonary blood pressure would of course tend to aggravate greatly the oedema of the lungs, and would thus in itself be a very serious source of danger. The ease with which oedema of the lungs follows on increased venous blood pressure, even when there is no injury to the lungs, has been shown experimentally by Knowlton and Starling.[25]

The cause of the greatly increased flow of blood was simply the fact that the arterial blood was in a venous condition, with both a lowered oxygen pressure and raised CO_2 pressure. The perfectly normal effect of this, as pointed out in Chapter X, is to cause dilation of capillaries and increased blood flow through the tissues. Owing, however, to the pressor reaction of the vasomotor center, the arterioles and probably also the venules in most parts of the body except the central nervous system were contracted, and in this way the blood pressure was maintained, so that the pulse was of good strength.

It was first observed by Macaulay and Irvine of Johannesburg that in the treatment of cases of oedema of the lungs from poisoning by nitrous fumes in mines, great benefit is often obtained by free bleeding to the extent of about half a liter. From the foregoing account it is clear that bleeding will reduce the venous and pulmonary blood pressure, and thus also reduce the

[25] Knowlton and Starling, *Journ. of Physiol.*, XLIV, p. 206.

tendency to oedema of the lungs. The indication for bleeding is evidently the distention of superficial veins. Bleeding was frequently employed in the treatment of the chlorine cases, and with great success. It is evident, however, that if there is no venous distention, bleeding could not be expected to do anything but harm.

A more radical treatment is the continuous administration of air enriched with oxygen. Unfortunately the problem of continuous administration of oxygen had never been attacked before the war, and no suitable apparatus was available for the early chlorine cases. But in the later stages of the war many cases of lung oedema were successfully treated continuously with oxygen by means of a nasal tube or the apparatus described in Chapter VII.

The next lung irritant gas used was phosgene ($COCl_2$). This produces dangerous effects in considerably lower concentration than chlorine, and its action is distinguished by the fact that it has relatively less effect on the air passages and eyes and in the end more on the alveolar walls. Thus a man exposed to a dangerous concentration of phosgene may notice but little irritant effect at the time, or this effect may pass off rapidly, while the dangerous effects on the alveoli only show themselves some hours later. Phosgene was at first used as drift gas; but when drift gas was abandoned as more or less ineffective against the protective measures adopted, and also unmanageable owing to uncertainties of wind, etc., phosgene was largely used in shells or bombs. Various other substances with similar toxic properties were also employed.

A change in the type of the symptoms accompanying lung oedema was now noticed. The deep plum-colored cyanosis and venous distention were usually absent, and bleeding was useless. The cyanosis was still very marked, but was of a pale or "gray" type. The breathing was also shallower, and the pulse feeble and rapid. Many slighter cases were also observed in which no definite lung symptoms were observed, but only general malaise with cyanosis and fainting on any muscular exertion.

In all these cases it seems evident that the rate of diffusion of oxygen through the alveolar walls was diminished, but without any marked interference with diffusion of CO_2 outwards, so that owing to the hyperpnoea from want of oxygen there would be a deficiency of CO_2 in the arterial blood. This is very intelligible in view of the fact that on account of its greater solubility CO_2

diffuses outwards from the blood much more readily than oxygen diffuses inwards (see Chapter VIII). The deficiency of CO_2 in the arterial blood would prevent or minimize the true hyperpnoea, and lessen the increase of circulation through the tissue capillaries and the pressor excitation of the vasomotor center. But it would increase the true tissue anoxaemia with a given degree of cyanosis. Anoxaemia in the coronary circulation would also lead to the enfeebled action of the heart, as shown by the very weak and feeble pulse. The symptoms generally were those of a pure anoxaemia with urgent danger of failure of the respiratory center in the manner already referred to in Chapter VI.

In these cases bleeding was of course useless. On the other hand injection into the blood of saline solution or, still better, gum-saline, seemed likely to be of some use in view of the failing blood pressure. By far the most effective treatment, however, was the continuous administration of air enriched with oxygen, particularly if this was begun early and before there was time for the dangerous effects which continued severe anoxaemia causes. By this means the oxygen pressure in the alveolar air was sufficiently raised to permit of a nearly normal aëration of the arterial blood; and the administration could be continued till the lung inflammation subsided.

The chronic after effects on the respiratory center of irritant gases have already been referred to in former chapters.

CHAPTER XII

Effects of High Atmospheric Pressures.

THE foundations of our scientific knowledge of the physiological effects of high and low atmospheric pressures were laid broad and firm by the investigations of Paul Bert, collected together in his book, already so often referred to, "La Pression Barométrique," published in 1878. It will be convenient to consider first the effects of high atmospheric pressures.

Very high atmospheric pressures are met with in deep diving and in engineering work under water or in water-logged strata.

Apart from laboratory experiments on animals, the highest atmospheric pressures (up to ten atmospheres) have been met with in deep diving. To understand the conditions under which a diver is placed, it is necessary to understand the design of the ordinary diving dress, which was introduced early last century by Siebe, the founder of the well-known London firm of manufacturers of diving apparatus. The dress consists of a copper helmet which screws on to a metal corselet, the latter being clamped water-tight to a stout waterproof dress covering the whole body except the hands, which project through elastic cuffs (Figures 75 and 76). Air is supplied to the diver through a non-return valve at the back of the helmet from a stout flexible pipe strengthened with steel wire and connected with an air pump at the surface. The air escapes through an adjustable spring valve at the side of the helmet (Figure 77). The arrangement is thus such that the pressure of air in the helmet is at least equal to, and can, by varying the resistance of the valve, be made greater than, the water pressure at the outlet valve. For every 34 feet of fresh water (or 33 feet or 10 meters of sea water) the pressure increases by one atmosphere, or nearly 15 pounds per square inch. At a depth of 33 feet of sea water the diver is therefore breathing air at an excess pressure of one atmosphere, or a total pressure of two atmospheres. It is absolutely necessary that he should breathe compressed air, otherwise his breathing would be stopped instantly by the pressure of the water upon the abdomen; and at a greater depth blood would probably pour from his nose and mouth on account of the squeezing to which all parts of his body, except his head in the helmet, would be subjected.

Figure 75.
Diving dress, front view, with air pipe and life line, which are connected with the helmet behind.

Figure 76.

Diving dress, back view, showing attachment of air pipe and life line with telephonic connection; new pattern, with legs laced up to prevent diver from being capsized and accidentally blown up to surface, or hung in a helpless position.

In order to enable the diver to sink and stand firmly on the bottom, the dress is weighted with 40-pound leaden weights, back and forward, as shown, with 16 pounds of lead on each boot—about 112 pounds of lead in all. Besides the air pipe, the diver is connected with the surface by a so-called life line, which usually contains a telephone wire. He goes down by a rope at-

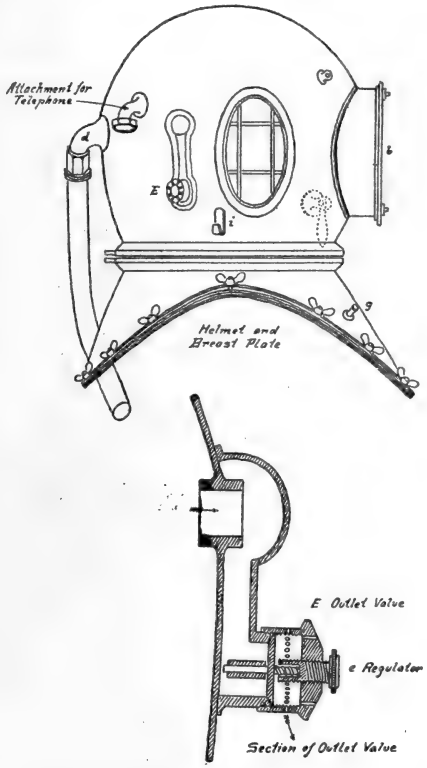

Figure 77.
Helmet and section of outlet valve.

tached to a heavy weight which has been lowered to the bottom previously, and on reaching the bottom he takes with him a line attached to this weight, so that he can always find the rope again.

As a diver enters the water, the superfluous air in his dress is driven out through the outlet valve by the pressure of the water round his legs and body. The water seems to grip him all round. If the valve is freely open he feels his breathing somewhat

labored by the time he gets first under water. The reason of this is that the pressure in his lungs is that of the water at the valve outlet, whereas the pressure on his chest and abdomen is greater by something like a foot of water. He is thus inspiring against pressure, and if he has to breathe deeply, as during exertion, the breathing is apt to become fatigued in the manner described in Chapter III. With another foot of adverse pressure the fatigue is very rapid. One of the first things which a diver has to learn is to avoid the adverse pressure by regulating the spring on the outlet valve, so that the breathing is always easy. The spring regulates at the same time the amount of air in the dress, and therefore the buoyancy of the diver. A practiced diver can thus slip easily, and without exertion, up or down the rope. A pressure gauge attached to the air pipe where it leaves the pump indicates the depth of the diver at any moment.

The breathing is of course easiest when the dress is full of air down to the level of the diaphragm, but when this is so the diver is in danger of being "blown up"; for if he is crawling on the ground, it may easily happen that the air gets into the legs of his dress. His head goes down so that the excess of air cannot escape readily. He is then blown helplessly to the surface, while his arms are fixed in an outstretched position (see Figure 78). His air pipe may be caught by a rope or other obstruction, so that he is hung up in a helpless position with his legs upwards, the excess of air being unable to escape at the valve since it is downwards. In very deep diving there is considerable risk of being blown up; and to avoid this risk the arrangement for lacing up the legs, shown in Figure 76, was introduced (see also Figure 79).

In the Denayrouze apparatus, extensively used on the Continent, the air is pumped into a steel reservoir on the diver's back. By means of a reducing valve his air is supplied from the reservoir according to his requirements. The arrangement is a beautiful piece of mechanism, but an encumbrance which gives rise to various inconveniences and dangers, one being that the depth of the diver cannot be read off at the surface, and another that he cannot regulate the pressure in his helmet.

For engineering work in preparing foundations, etc., on the sea bottom, a diving bell is sometimes employed. This is a heavy metal box, open below, and supplied with compressed air by a pipe (Figure 80). It is lowered to the bottom with the workmen sitting in it, and they can work dry on the bottom. The diving

Figure 78.
Diver in ordinary dress blown up. His head is down and his arms outstreched.

Figure 79.
Diver in laced-up dress purposely blown up. His head is up and his arms free.

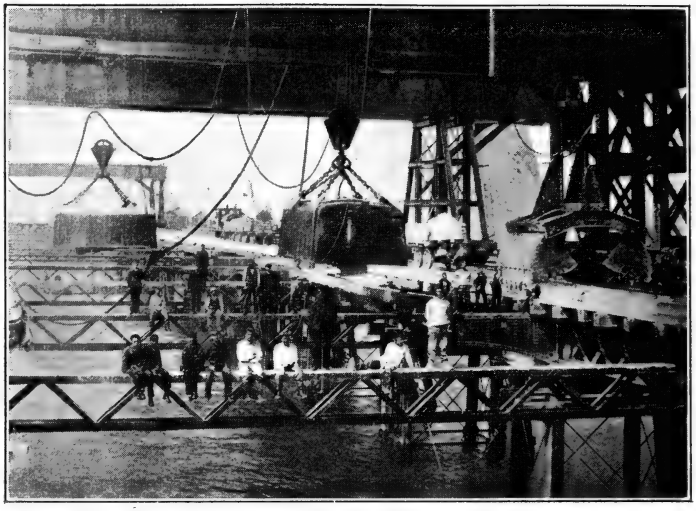

Figure 80.
Diving bell in use at National Harbour Works, Dover. Each bell measures 17 x 10 feet by 6½ feet high, and weighs about 35 tons.

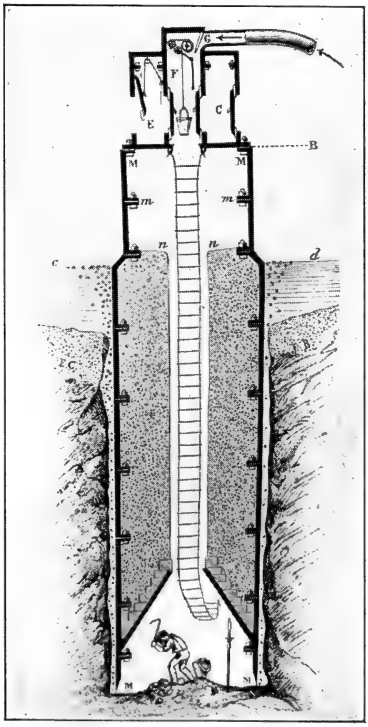

Figure 81.
Diagram showing use of caisson in making the foundations of a bridge. (After Foley.)

bell in its crude original form was invented by Sturmius in the sixteenth century, and further developed by Halley two centuries later.

The caisson introduced about 1840 by the French engineer Triger, for sinking colliery shafts through water-logged strata near the surface, is a further development of the diving bell. It is now largely used for carrying the foundations of the piers of bridges, etc., through soft ground on the bottom of a river or the sea. The caisson (see Figure 81) is the bottom section of the steel pier, and resembles a diving bell except for the fact that it communicates with surface through a tube occupying the center of the future pier and kept full of compressed air. This tube serves for access and for removal of excavated material. The men excavate the soft bottom so as to allow the caisson to sink down to a secure foundation, and the sections of the pier are added from above and filled with concrete as the caisson sinks. Access to the central tube is through an air lock on surface. The men enter the air lock, close the door, and then let the air pressure rise till they can open the door into the central tube; and in coming out the reverse process is used.

In tunneling operations in soft strata under water, the advancing tunnel is kept full of compressed air, so as to hinder the penetration of water into the advancing end, as the steel rings forming the permanent walls of the tunnel are successively put in. The men thus work in an atmosphere of compressed air, to which access is gained through one or more air locks. The tubes and large tunnels under the Thames or deep in the water-logged London clay, and under the Hudson and East Rivers at New York, have been, or are being, constructed by this means. In the sinking of colliery shafts through water-logged strata the freezing or cementation processes are now generally used, as, except in strata fairly near the surface, the water pressures are too high for the compressed-air process.

Various physiological disturbances are associated with exposure to compressed air, and these must now be considered one by one. As the pressure rises when a man goes below water, in a diver's suit, or as compressed air enters an air lock through which he is passing to a caisson or tunnel, the first trouble usually noticed is a sense of pressure and pain in the ears. This is due to unbalanced pressure on the *membrana tympani,* owing to the fact that the Eustachian duct does not open freely so as to equalize the air pressure in the middle ear with the atmospheric pressure

outside. The passage is specially liable to be blocked if any catarrh of the air passages is present; and if the warning pain is disregarded the membrane may burst, though this is not a very serious accident. In men accustomed to compressed air the Eustachian tubes open easily, so that no inconvenience is felt, and a diver goes quite easily within two minutes to a pressure of seven atmospheres or more, while one who is not accustomed to compressed air may have a long struggle with his Eustachian tubes before he can reach an extra pressure of half an atmosphere. It also happens occasionally that there is trouble with the frontal sinuses. The same difficulties with the middle ear may, of course, be met with by airmen during rapid descents, or even, to a minor extent, in descending a deep mine shaft.

A man who has reached a pressure of six or seven atmospheres, and is breathing pure air, is perfectly comfortable if he has escaped ear trouble. His voice is, however, altered by the compressed air, and this is so marked that it is often difficult to make out through the telephone what he is saying. At first sight it might seem that an increased mechanical pressure of several atmospheres would in itself be expected to have an appreciable effect on a man or animal. It was commonly supposed, for example, that the increased pressure on the skin must at first tend to drive blood into the internal organs, producing congestion of the brain, etc., with a converse effect on diminishing the atmospheric pressure. The pressure is, however, transmitted instantly throughout all the liquid and solid tissues of the body, so that this idea was totally fallacious, and indeed ridiculous. As will be seen below, many divers have lost their lives owing to well-meant injunctions to descend and ascend slowly. As regards other possible effects of a few atmospheres of mechanical pressure, it should be remembered that the intrinsic pressure of water is calculated to be over 10,000 atmospheres. As the tissues are largely composed of water, the addition to this of a few atmospheres of mechanical pressure in the liquid or semi-liquid parts of the body cannot be of much account.

As Paul Bert showed experimentally, the serious inconveniences and dangers to which workers in compressed air are exposed are due (apart from easily avoidable effects on the ears) not to the mechanical pressure, but to the increased partial pressures of the gases in the air breathed. If the air breathed is pure, the only gases which come into consideration in this connection are nitrogen and oxygen; but if the air is rendered impure by

respiration, as is commonly the case in diving, carbon dioxide also comes into consideration. The case of this gas may be considered first, though Paul Bert did not himself allude to it in connection with work in compressed air, as he was not practically familiar with diving.

Owing to the difficulties frequently experienced by divers in attempts to work at depths over about 12 fathoms a Committee, including myself as the physiological member, was appointed by the British Admiralty to investigate the whole subject of the difficulties and dangers associated with deep diving.[1] It appeared that men who attempted to make any serious exertion when at depths of over about 12 fathoms often became unconscious or greatly exhausted. The symptoms pointed to excess of CO_2, and, on taking samples from the divers' helmets at about this depth, we frequently found 2 or 3 per cent of CO_2. This occurred in spite of an apparently abundant supply of air from the pumps, which were working at a much faster rate than was sufficient to keep the diver comfortable at a lesser depth. As explained in Chapter II, the physiological effects or 3 per cent of CO_2 at 11 fathoms, or a total pressure of three atmospheres, is equal to that of $3 \times 3 = 9$ per cent at normal atmospheric pressure; so no wonder the divers became unconscious. The pumps were often found to be leaking badly through the piston rings, as many of them were old, and no tests were then employed to detect this leakage. Apart from this cause, however, the air supply was often insufficient.

It is evident that in order to keep down the pressure of CO_2 in the air of the helmet to a proper limit, the amount of air as measured at surface by the strokes of the pump must be increased in proportion to the increase in the total atmospheric pressure in the helmet. The diver at 3 atmospheres pressure, requires, therefore, three times as much air, and so on in proportion to the pressure. When this was attended to, and the piston rings kept tight, no discomfort whatsoever was experienced at a depth of even 35 fathoms. With a full air supply, hard exertion is actually easier to a diver at some depth than near surface, on account of the higher oxygen pressure, as explained in Chapter IX.

By far the most serious danger to divers and other workers in compressed air is of a quite different character. From the earliest days of diving and work in compressed air it had been observed that soon after returning to atmospheric pressure the men fre-

[1] *Report of the Admiralty Committee on Deep Water Diving*, Parl. Paper, C. N., 1549, 1907.

quently became ill, and sometimes died or became paralyzed. The risk of these attacks increased with the pressure and the duration of exposure to it, but they never occurred except on return to atmospheric pressure. Divers are exposed to the highest pressures, and in divers the attacks were of the most dangerous character. In the worst cases the diver began to feel faint a few minutes after return to surface; soon he became unconscious and his pulse disappeared; and in a few minutes he was dead. In other cases his legs became paralyzed, and cases of "diver's paralysis" used to be not uncommon in British hospitals. In the slighter cases, very common among workers in caissons and tunnels under construction, there is severe pain, known to the workmen as "bends," in one or other of the limbs, or in the body. Another of the common slight symptoms is itching of the skin. Various other nervous symptoms are also met with, the whole complex being designated as "caisson disease"— a somewhat misleading name.

Paul Bert investigated on animals the nature of compressed air illness or "caisson disease," and found that it is due to liberation in the blood and tissues of bubbles of gas consisting almost entirely of nitrogen. In the rapidly fatal cases the heart becomes filled with a mass of bubbles which stop the whole circulation. In the cases of paralysis bubbles have obstructed the circulation and so caused necrosis of parts of the spinal cord; and it is evident that the bubbles may produce the most varied symptoms according to the positions in which they are formed.

The cause of the bubble formation was evident. At the high pressure the blood in the lungs is exposed to greatly increased partial pressures of nitrogen and oxygen, although, as shown in Chapter II, there is no increased pressure of CO_2. As, in accordance with Henry's law, liquids take up in simple solution a mass of any gas proportional to its partial pressure, the blood in the lungs takes up in the compressed air an extra amount of nitrogen and oxygen proportional to the increased pressure. The extra oxygen disappears at once when the blood reaches the tissues, but the extra nitrogen does not disappear, and gradually saturates the whole of the tissues till they are charged with nitrogen at the partial pressure existing in the air breathed. When the external atmosphere is reduced to normal, the internal partial pressure of nitrogen is of course far above the atmospheric pressure. The blood and tissues are therefore supersaturated with nitrogen and bubbles begin to form. These bubbles consist primarily of nitro-

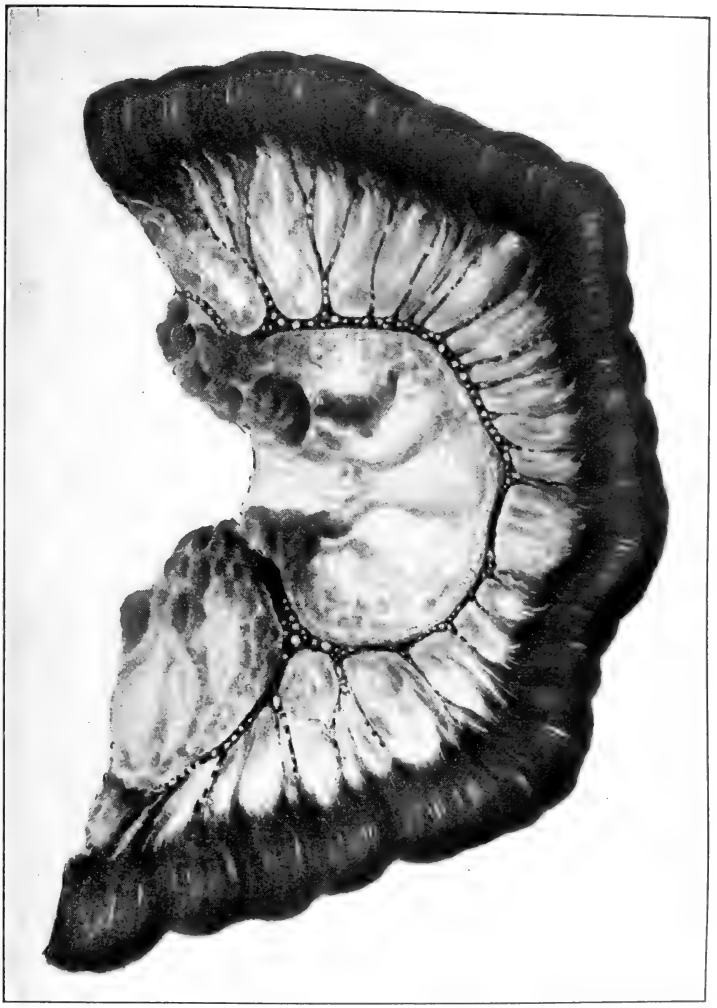

Figure 82.

Portion of goat's mesentery showing bubbles in blood vessels caused by rapid decompression in 1½ minutes from 100 lbs. pressure, after 1½ hours exposure at this pressure.

gen, but of course take up a little oxygen and CO_2 from the surrounding blood and tissue liquids. If they are formed in the blood they tend to block the circulation on account of the great resistance which they cause. Figure 82 is from a photograph of blood vessels in the mesentery of a goat killed by rapid decompression, and shows abundant bubbles in the veins.

The bubbles are formed, not merely in the blood, but also in the tissues outside it. We found that fat in particular is apt to be very full of bubbles and thus become spongy. It had been found by Vernon in connection with another investigation that gases are much more soluble in oils than in water. In connection with our investigations he determined the solubility of nitrogen in body fats at blood temperature, and found that it is about six times as great as in water.[2] The tendency of fatty substances to act as a special reservoir of dissolved nitrogen is thus intelligible; and Boycott and Damant[3] afterwards showed that fat animals, other conditions being the same, are considerably more liable to symptoms of caisson disease than spare animals. Not only ordinary fat, but the myelin sheaths of nerve fibers, will form reservoirs of dissolved nitrogen; and for this reason bubbles will tend to be liberated in the white matter of the brain and spinal cord, and inside the sheaths of large nerves. The "bends" and certain other associated symptoms from which workers in compressed air so frequently suffer are probably due to liberation of bubbles from the gas dissolved in the myelin sheaths. It is difficult to understand otherwise the severe pain of "bends." Figure 83 shows the positions of a large number of bubbles found in the white matter at different parts of the spinal cord.

The increased amount of nitrogen dissolved in the blood at high atmospheric pressures was demonstrated by Paul Bert by blood-gas analyses; and Hill and Greenwood[4] not only confirmed this, but showed that there is the same excess in the urine. Hill and Macleod also observed directly the sudden appearance of gas bubbles in the capillaries of the frog's web when the animal was decompressed from a high atmospheric pressure.[5]

As a preventive of the occurrence of caisson disease Paul Bert recommended slow and gradual decompression; but his experiments in this direction were not very successful, as he had not

[2] Vernon, *Proc. Roy. Soc.*, LXXIX, B, p. 366, 1907.
[3] Boycott and Damant, *Journ. of Hygiene*, VIII, p. 445, 1908.
[4] Hill and Greenwood, *Proc. Roy. Soc.*, LXXIX, B, p. 21, 1907.
[5] Hill and Macleod, *Journ. of Hygiene*, III, p. 436, 1903.

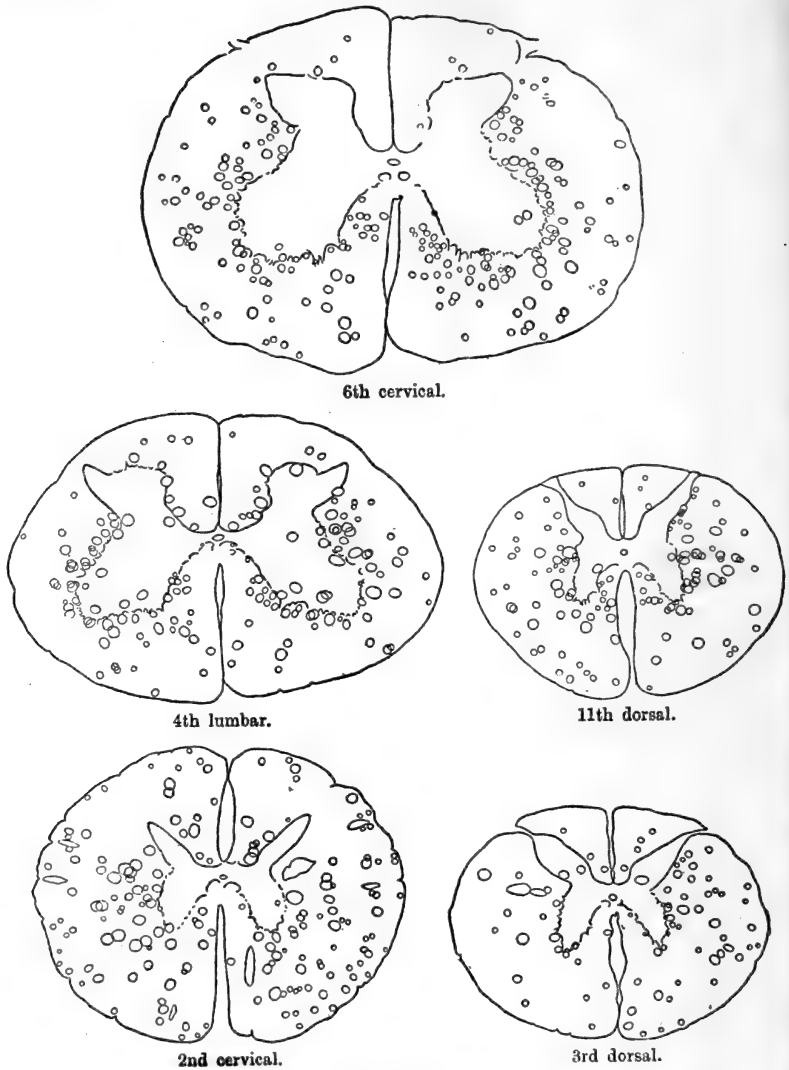

Figure 83.

Shows the distribution of extravascular bubbles in five regions of the spinal cord of goat 3 (series IV). The animal died of oxygen poisoning during decompression after 3 hours' exposure at 81 lbs. in an atmosphere containing 36 per cent oxygen. The bubbles are practically confined to the white matter and are there especially concentrated in the boundary zone where the circulation is least good. Each diagram is a composite drawing showing all the bubbles in 0.4 mm. length of cord. (After Boycott, Damant, and Haldane.)

completely realized the conditions. Slow and uniform decompression was, and still is, also enjoined by various government regulations, etc., in different countries, but with only very moderate success; and deaths or paralyses from caisson disease remained common if the extra pressure used was above about 1.5 atmospheres. Workers in compressed air had soon discovered that the pain of "bends" can be relieved at once by returning into the compressed air; and this became quite intelligible from Paul Bert's experiment. He made some experiments on the curative effects of recompression, but here again he was not very successful, as he applied the remedy only in extreme cases. Medical recompression chambers for the treatment of compressed air illness were first introduced by Sir Ernest Moir in connection with the construction of the first East River tunnel at New York, and the Blackwall Tunnel under the Thames, about 1890. They proved strikingly successful when applied to the cases which occurred with the comparatively slow decompression in the air lock. Paralyses and "bends" were relieved at once, even when they had occurred a considerable time after leaving the tunnel. The provision of medical recompression chambers has now become a necessary adjunct of all considerable engineering undertakings at pressures of over about 1.5 atmospheres, and in extensive deep diving operations. Figures 84 and 85 show one of the recompression chambers used in the British Navy. The trouble, however, about the use of recompression chambers is that it is often very difficult to get the patient out without the symptoms recurring. The decompression may require many hours, or even days in bad cases.

Paul Bert also tried another method of treatment—that of administering pure oxygen to his animals. This must hasten the diffusion outwards of nitrogen, while the oxygen itself is absorbed by the tissues. At first sight it might seem as if this plan ought to be very successful, either in treatment or in the prevention of bubble formation during decompression. The results, however, were disappointing and from causes which will be made evident below. There seems, however, to be some scope for oxygen administration where there is great difficulty in getting a patient out of a medical air lock, and where there is no fear of oxygen poisoning—a condition which will be discussed presently.

When the Admiralty Committee had dealt with the troubles traced to CO_2, it was faced by the dangers of caisson disease, which of course became much more important after it had been

rendered possible for divers to work at great depths without inconvenience. The existing precautions against "caisson disease" were evidently quite insufficient. The divers were officially enjoined to descend and come up at a slow and even rate of about 5 feet per minute, but many serious or fatal cases were occurring in spite of this. The problem was to find a safe and reasonably short method. Very slow methods are impractible on account of changes of tides and weather. The whole physiological side of compressed-air illness had therefore to be reconsidered.

The formation of bubbles depends, evidently, on the existence of a state of supersaturation of the body fluids with nitrogen. Nevertheless there was abundant evidence that when the excess of atmospheric pressure does not exceed about 1¼ atmospheres there is complete immunity from symptoms due to bubbles, however long the exposure to the compressed air may have been, and however rapid the decompression. Thus bubbles of nitrogen are not liberated within the body unless the supersaturation corresponds to more than a decompression from a total pressure of 2¼ atmospheres. Now the volume of nitrogen which would tend to be liberated is the same when the total pressure is halved, whether that pressure be high or low. Hence it seemed to me probable that it would be just as safe to diminish the pressure rapidly from 4 atmospheres to 2, or 6 atmospheres to 3, as from 2 atmospheres to 1. If this were the case, a system of stage decompression would be possible, and would enable the diver to get rid of the excess of nitrogen through his lungs far more rapidly than if he came up at an even rate. The duration of exposure to a high pressure could also be shortened very considerably, without shortening the period available for work on the bottom.

The whole matter was put to the test in a long series of experiments carried out on goats by Professor Boycott, Commander Damant, and myself[6] at the Lister Institute, London, in a large steel chamber which was given for the purpose by the late Dr. Ludwig Mond (see Figures 86 and 87). We found that after very long exposure of a number of the animals at a total pressure of 6 atmospheres sudden decompression to 2.6 atmospheres produced not the slightest ill effect. This decompression is in the proportion of 2.3 to 1, and the drop of pressure was 3.4 atmospheres. In a corresponding series where the drop of pressure was

[6] Boycott, Damant, and Haldane, *Journ. of Hygiene*, VIII, p. 242, 1908. The Report of the Admiralty Committee contains a short abstract of the work.

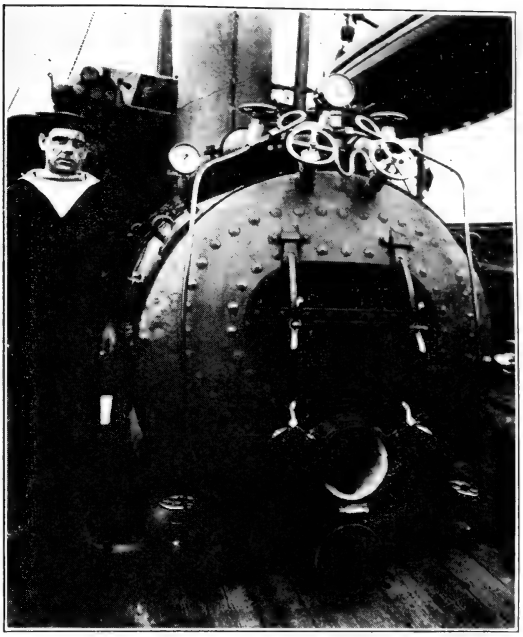

Figure 84.
Outside of naval recompression chamber, showing manhole for access, and air lock for food.

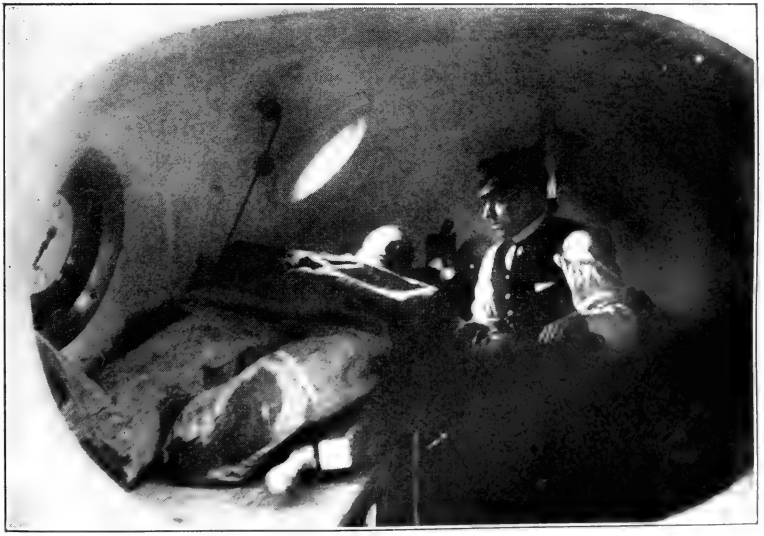

Figure 85.
Inside of recompression chamber, showing bed for patient.

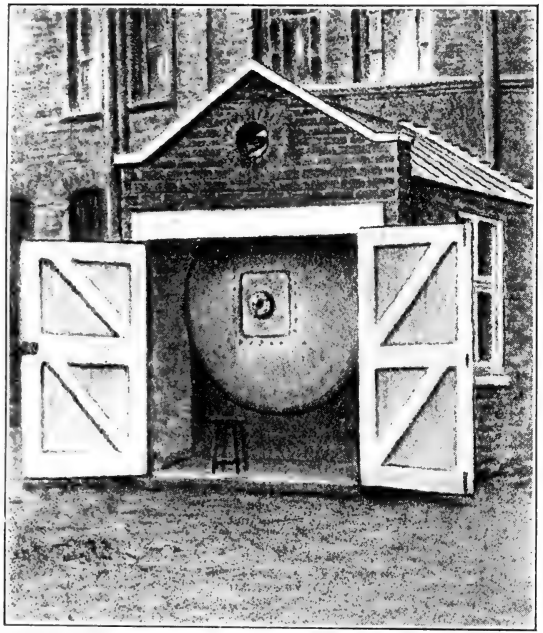

Figure 86.
The steel chamber at the Lister Institute. View from outside, showing the back end of the chamber, with the large door and one inspection window.

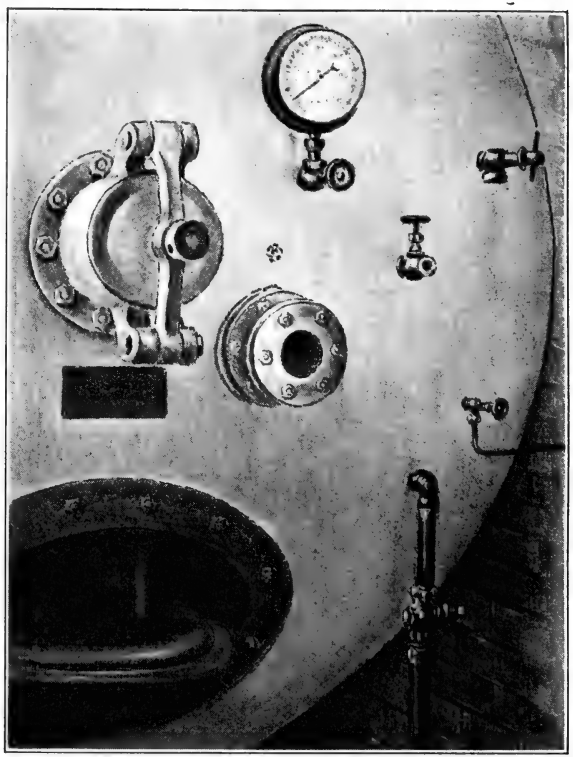

Figure 87.
The steel chamber at the Lister Institute. Front end, showing the manhole for entering, the small air lock for passing food, etc., into the chamber, an inspection window, a pressure guage, and several valves, etc.

the same, but from 4.4 to 1 atmosphere, or in the proportion of 4.4 to 1, only 20 per cent of the animals escaped symptoms, while 20 per cent died, 30 per cent had severe symptoms, and 30 per cent had "bends," quite easily recognized in the animals by their behavior and the manner in which they held the affected limb (Figure 88). It seemed evident, therefore, that it is quite safe to halve the absolute pressure rapidly. Before venturing on such extensive rapid decompressions of divers under water we repeated the goat experiments on men in the steel chamber, Commander Damant and Lieutenant Catto being the subjects. There were no ill effects in a number of experiments, nor in subsequent trials by them under water at sea; and rapid decompression to half the absolute pressure is now the routine practice of divers, and is not known to have ever resulted in harm.

We were still, however, only at the beginning of the inquiry. It was evident that the whole danger lay in the last stages of the decompression. "On ne paie qu'en sortant," as was remarked by Pol and Watelle, who were the first to give a medical account of the symptoms of caisson disease.[7] The problem was to get divers completely clear of the compressed air without paying. This problem had resolved itself into that of avoiding the critical supersaturation with nitrogen in any part of the body at or before the last stage of decompression.

Let us consider the process of saturation and desaturation more closely. The blood passing through the lungs of a man breathing compressed air will, in accordance with what has been explained in Chapter IX as to the permeability of the lung epithelium to gas, become instantly saturated to the full extent with nitrogen at the existing partial pressure in the air. When this blood reaches the systemic capillaries, most of the excess of nitrogen will diffuse out and the blood will return for a fresh charge, this process being repeated until at length the tissues are fully charged with nitrogen at the same partial pressure as in the air. But the blood supply to different parts of the body varies greatly, as we have seen. The capacity of different parts of the body for dissolving nitrogen varies also. Thus the white matter of the central nervous system has but a small blood supply and at the same time a high capacity for storing nitrogen; and the same remark applies to fat. The gray matter, on the other hand, has an enormous blood supply and no extra capacity for storing nitrogen. Other tissues,

[7] Pol et Watelle, *Ann. d'hygiene publique*, (2), p. 241, 1854.

such as muscles, may or may not have a great blood supply, according to the amount of work a man is doing. We can easily see, therefore, that the time taken for different parts of the body to become saturated with nitrogen will vary greatly.

Taking into consideration the amount of fatty material in the body, we estimated that the whole body of a man weighing 70 kilos will take up about 1 liter of nitrogen for each atmosphere of excess pressure—about 70 per cent more nitrogen than an equal weight of blood would take up. Now the weight of blood in a man is about 6.5 per cent of the body weight; hence the amount of nitrogen held in solution in the body, when it is completely saturated with nitrogen, will be about $\frac{170}{6.5}$ or 26 times as great as the amount held in the blood alone. If, therefore, the composition of the body were the same at all parts, and the blood distributed itself evenly to all parts, the body would have received at one complete round of the blood after sudden exposure to a high pressure of air one twenty-sixth of the excess of nitrogen corresponding to complete saturation. The second round would add one twenty-sixth of the remaining deficit in circulation, i.e., $1/26 \times 25/26$ of the total excess. The third round would add $1/26 \times (25/26 \times 25/26)$, and so on. On following out this calculation, it will be seen that the body would be half saturated in less than 20 rounds of the circulation, or about ten minutes, and that saturation would be practically complete in an hour. The progress of the saturation would follow the logarithmic curve shown in Figure 89. Actually the rate of saturation will vary widely in different parts of the body; but for any particular part the rate of saturation will follow a curve of this form, assuming that the circulation rate is constant.

There is abundant evidence, both from human experience and from experiments on animals, that liability to compressed-air illness increases with duration of exposure. We found that in goats the liability increased up to about 3 hours' exposure, but did not increase further even with far longer exposure. In man, on the other hand, limitation of exposure to 3 hours has been found to diminish the liability distinctly, and we calculated from the goat experiments, taking into account the greater rate of circulation in the goat on account of its much smaller weight (see Chapter X), that in man the liability would increase up to about 5 hours' exposure. We had therefore to allow for parts of the body which would only become half saturated in about 1¼ hours, but for nothing slower than this.

Figure 88.
"Bends" of foreleg in a goat.

The longer any part of the body takes to saturate, the longer will it also take to desaturate to the point at which it is safe to reduce the pressure to normal. But if we know the pressure and duration of exposure, we can now calculate a safe rate of further decompression after the initial reduction of total pressure to half

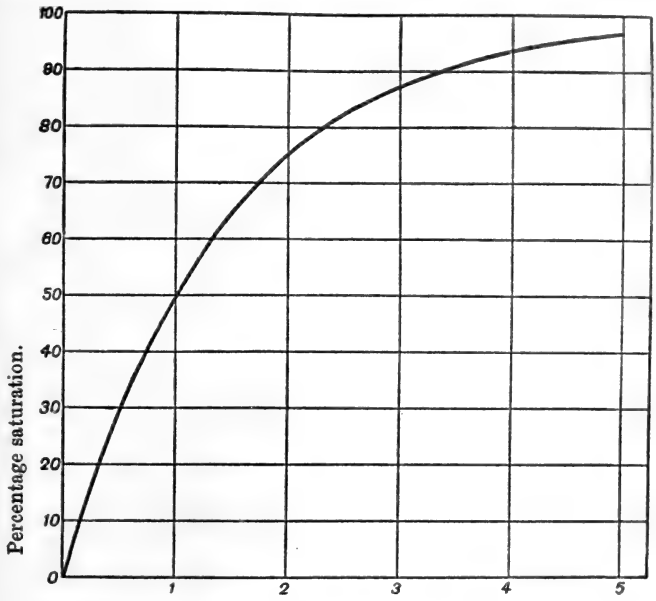

Figure 89.

Curve showing the progress of saturation of any part of the body with nitrogen after any given rise of pressure. The percentage saturation can be read off on the curve, provided the duration of exposure to the pressure, and the time required to produce half saturation of the part in question, are both known. Thus a part which half saturates in one hour would, as shown on the curve, be 30 per cent saturated in half an hour, or 94 per cent saturated in 4 hours.

has been carried out: for we can calculate the rate at which nitrogen is being carried away from parts which saturate and desaturate quickly, or from those which do so slowly. We can thus regulate the rate of decompression so that no part of the body is at any time supersaturated to such an extent as to cause risk of bubble formation. In this way tables were calculated for regulating the rate of decompression of divers and other workers in compressed air. For the sake of convenience the decompression

rate was calculated in stages, each of which represents a reduction in depth of 10 feet, so that a diver is stopped by signal at every ten feet of ascent.

Figure 90 represents what is happening during a dive to 28 fathoms, with the stay on the bottom limited to 14 minutes, and

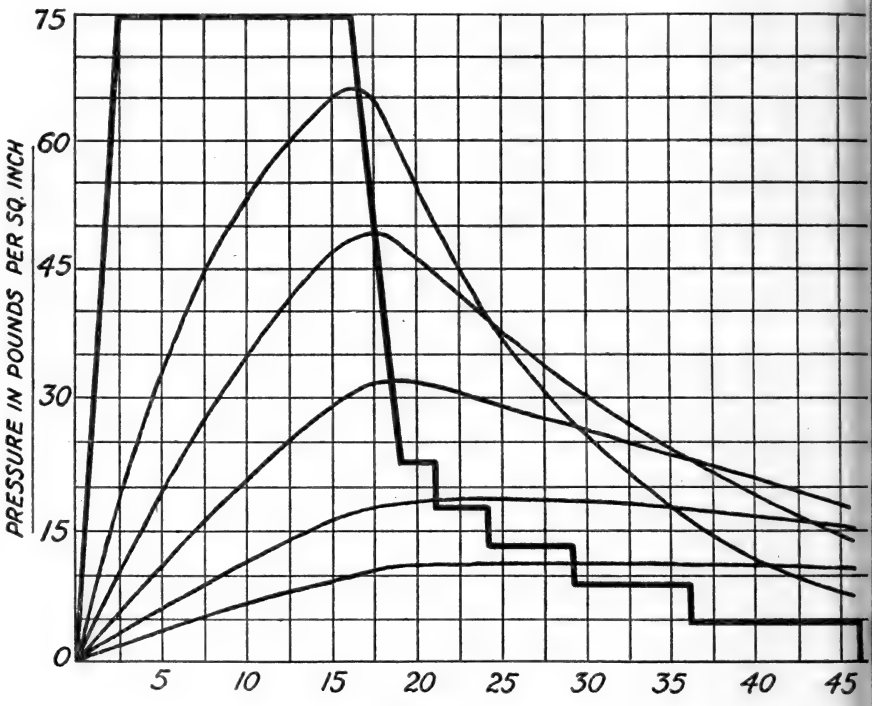

Figure 90.

Diving to 168 feet by new method: Diver 14 minutes on the bottom and 46 minutes under water. The curves from above downward represent, respectively, the variations in saturation of parts of the body which half saturate in 5, 10, 20, 40, and 75 minutes; the thick line representing the air pressure.

the new method carried out of rapid descent and ascent by stages. It will be seen that when the diver reaches surface, the maximum condition of supersaturation with nitrogen in any part of the body corresponds to only 17½ pounds per square inch (or 1.17 atmospheres) of air pressure. This leaves a margin of safety. Figure 91 shows what happened by the old method, with the same time on

the bottom. It will be seen (1) that the dive took twice as long a time, and (2) that when he reached surface the maximum supersaturation was 36 lbs. (2.4 atmospheres), so that he would run a

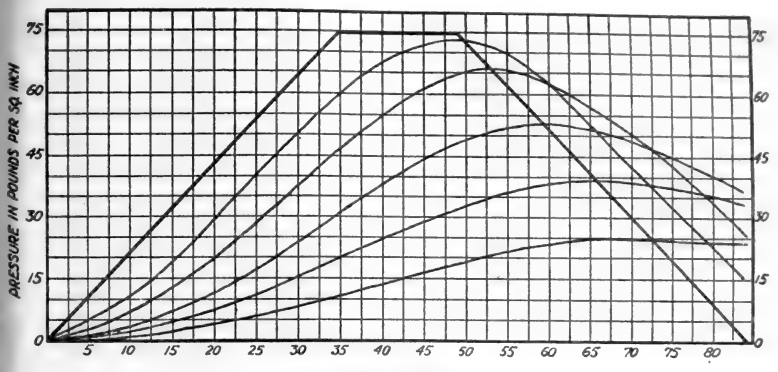

Figure 91.

Diving to 168 feet by old method: Diver 14 minutes on the bottom and 84 minutes under water. The curves from above downward represent, respectively, the variations in saturation of parts of the body which half saturate in 5, 10, 20, 40, and 75 minutes; the thick line representing the air pressure.

most dangerous risk. It is evident from the figure that the slow descent and most of the slow ascent were simply adding to the

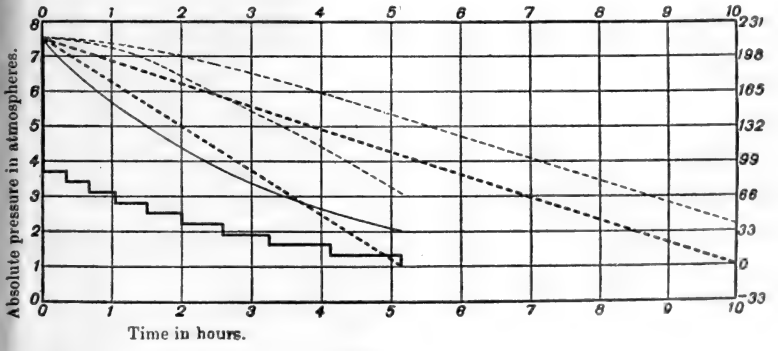

Figure 92.

Theoretical ascents of a diver after a prolonged stay at 213 feet of sea water. Stage decompression in 309 minutes compared with uniform decompressions in 309 minutes and in 10 hours. Continuous lines = stage decompression: interrupted lines = uniform decompression. Thick lines = air pressure: thin lines = saturation with atmospheric nitrogen in parts of the body which half saturate in 75 minutes.

danger. These figures show also in a clear way, the advantages of cutting down the duration of stay on the bottom. It appears from Figure 90 that with the short stay on the bottom the more slowly saturating parts of the body have not time to reach a dangerous degree of saturation, though they might do so if similar dives were repeated after short intervals on one day.

With a long exposure to a high air pressure the time required for safe decompression, even by the stage method, becomes much too long for ordinary diving work. Figure 92 shows, for instance, that it would take nearly five hours by the stage method, and ten hours with uniform decompression, for completely safe decompression after a stay of some hours under a pressure of 35½ fathoms of water, or an excess pressure of 6½ atmospheres. In the ordinary diving table, therefore, the stay on the bottom is so limited that the diver can be decompressed safely in half an hour. Nevertheless, it may happen that it is justifiable to stay longer, or that a diver's air pipe is fouled by something on a wreck and even that he cannot be liberated till the tide slackens or turns. To meet such cases a supplementary table was drawn up. These two tables are reproduced below.

Since the introduction into the British Navy twelve years ago of the method of decompression embodied in the tables, with the corresponding regulations as to air supply and testing of the pumps, deep diving has been conducted with comfort and safety to the divers, so that compressed-air illness has now practically disappeared except in isolated cases where from one cause or another the regulations have not been carried out. When a medical compressed-air chamber is available, it is justifiable to cut down the time for the last wearisome stages of the decompression, and so extend the time on the bottom. This has been cautiously tried under Commander Damant's supervision, but the result was that the divers began to suffer from "bends." These could easily be relieved in the chamber, but much loss of time and inconvenience resulted, and the "bends" were apt to recur. It seemed better to keep the chamber as a precaution against emergencies or unforeseen accidents. I calculated the tables with great care on the theoretical lines borne out by the experiments and in the light of all the available evidence from human experience; and it appears that the times cannot be cut down without risk of trouble, unless the divers are placed in the chamber as a matter of routine after each dive.

If a diver develops serious symptoms of compressed-air illness,

and no compressed-air chamber is available, the best plan is to screw on his helmet and drop him down under water till his symptoms disappear. An unconscious man (who had developed bad symptoms as a result of disregarding orders to stop at the proper stages) soon answered the telephone when he was dropped down in this way. The trouble, however, is to get the man up again safely. A very cautious ascent is needed. When once bubbles of any considerable size have formed it takes a considerable time to get them redissolved.

The reason why a bubble in the blood or elsewhere in the body tends to disappear, is that the partial pressure of nitrogen in the bubble is greater than in the blood. The blood is saturated in the lungs with nitrogen at a pressure of about 75 per cent of the existing atmospheric pressure. In the venous blood, and therefore in the tissues, the pressure of oxygen, as shown in Chapter X, is only about 6 per cent and of CO_2 about 6.5 per cent of an atmosphere. There is also a pressure of about 6 per cent of aqueous vapor. As the bubble is at atmospheric pressure and the total gas pressure in the surrounding tissues is only about $75 + 18.5 = 93.5$ per cent of an atmosphere, its nitrogen pressure is above that of the tissues by 6.5 per cent. It must therefore gradually go into solution, and at high atmospheric pressures it will do so all the sooner since the pressures of oxygen and CO_2 do not increase proportionally to the atmospheric pressure. If the bubbles are only very small they will probably dissolve very rapidly on recompression; but if they are large, and particularly if they have been formed at places where there is but little circulation, they will take a long time to disappear. Great patience may therefore be needed in treatment by recompression.

In the experiments made at sea under the direction of the Admiralty Committee, the greatest depth at which trials were made was 35 fathoms. At this depth Commander Damant and Lieutenant Catto were perfectly comfortable, and in all the numerous experimental dives which they made up to this depth with stage decompression, no symptoms whatever of compressed-air illness were observed. This depth was, however, greatly exceeded in the course of operations for the recovery of a United States submarine at Honolulu in 1915. A diving crew had been trained in the new methods at New York, and proceeded to Honolulu to assist in getting hawsers in position round the submarine, which was lying at a depth of 50 fathoms (corresponding to an excess pressure of over 9 atmospheres or 135 pounds per square

inch). The operations were successful, and these remarkable dives are described in a paper by Assistant Surgeon French, U. S. N., who was one of the medical officers in immediate charge.[8]

Eleven dives were made to depths of from 306 to 270 feet, the time on the bottom being usually about 20 minutes. The stage decompression, which was shortened as a recompression chamber was always ready, occupied about 110 minutes. When everything went according to plan, as turned out in eight of the dives, there were no symptoms except in one case. One of the divers, however, got foul at a depth of 250 feet and was delayed there about three hours before he could be liberated. When he was freed he came up beyond the proper stopping places, disregarding the telephoned orders. Possibly he was partly stupified by the prolonged action of the high pressure of oxygen. At forty feet from surface he collapsed. This was about 40 minutes after starting the ascent. He was then pulled up to surface, where he was still able to say a few words before becoming unconscious. His dress was quickly ripped off and he was hurried into the recompression chamber along with the two doctors and the other diver who had rescued him. By this time he was black in the face, his breathing had ceased, and no pulse could be felt at the wrist. Artificial respiration was at once applied, and at the same time the pressure was run up to 75 lbs. in 3½ minutes, which ruptured both the eardrums of one of the doctors. As 75 lbs. pressure was reached the patient suddenly recovered and sat up, feeling all right again. He was then gradually decompressed to 20 lbs. in about 1½ hours, but at this point severe pain developed, so that the pressure had to be raised again. For the next five hours many attempts at decompression below 20 pounds had to be given up. At last he was very gradually decompressed in about 3 hours in spite of the pain. Soon after being taken from the chamber he was in a very precarious condition, with the pulse no longer palpable. In spite of haematuria, almost complete suppression of urine, extreme pain, and other threatening symptoms, he recovered gradually; and when it was possible to examine his lungs he was found to have double broncho-pneumonia, the result, presumably, of the very high oxygen pressure, as will be explained below. In a few weeks he had completely recovered.

This case shows clearly the efficacy of recompression even under

[8] French, U. S. Naval Medical Bulletin, p. 74, January, 1916.

conditions of apparently the most desperate character. It would have taken over four hours to bring him up at all safely by stage decompression, and his blood was certainly full of bubbles before he was got into the chamber.

The difficulty of safe decompression in the chamber is one that has often been met with before in bad cases. It may be necessary to keep a patient in the chamber for 24 hours or more.

In work in tunnels or caissons the pressures encountered are not nearly so high as in diving work; but the durations of exposure are usually a good deal longer. Hitherto the time given to decompression in the air lock has hardly ever been sufficient to prevent symptoms, though in recent years it has often been sufficient to prevent almost entirely the very dangerous symptoms produced by rapid decompression, which leaves most of the body in a condition of supersaturation with nitrogen. On this account most of the symptoms in tunnel workers, etc., consist of the "bends," itching of the skin, etc., due to bubbles in the tissues which saturate and desaturate very slowly. In divers, on the contrary, the symptoms met with before stage decompression was introduced were mostly of a far more serious character, and due to wholesale formation of bubbles in the blood and in tissues which saturate and desaturate fairly quickly. Death or more or less permanent paralysis were therefore common. With shortened stage decompression it is usually the less serious symptoms which appear among divers, and if the stage decompression is shortened these symptoms must be expected. It is unfortunate that stage decompression cannot be introduced in some countries on account of antiquated state regulations enjoining decompression at a constant rate, or even decompression starting very slowly and increasing in rate as atmospheric pressure is approached.

During decompression, or immediately after it, it is very desirable that as much muscular work as possible should be carried out, so as to increase the circulation, and therefore the rate of desaturation, over all parts of the body, and particularly those parts which, owing to muscular exertion during exposure to the high pressure, may have become saturated to a greater extent than would otherwise be the case. For this reason the naval divers were enjoined to keep their arms and legs moving as much as possible during the stoppages at each stage. Bornstein has more recently brought forward evidence collected at the Elbe tunnel works that muscular exertion just after decompression diminishes greatly the liability to "bends."

It is probable that the bubbles first formed in supersaturated blood and tissues are extremely small and comparatively harmless. One can observe the formation of these minute bubbles in water which has stood in a pipe under pressure in contact with air. When the tap is opened the water comes out milky with minute bubbles, but no large bubbles are present. The smallness of the bubbles leaves time to deal with cases of sudden decompression. Thus a diver who is blown up accidentally from a great depth comes to no harm if he is sent down again at once or very quickly got under high pressure in a recompression chamber. The small bubbles already formed seem to go into resolution at once. With any delay, however, the bubbles become larger and more difficult to redissolve. In the diver referred to above bubbles had evidently formed long before he reached surface and was recompressed.

In the case of workers in tunnels and caissons it is practically very difficult, and undesirable in various ways, to keep the men very long in an air lock during decompression. Another plan seems much better, and has been partially carried out in recent years in tunnels under construction at New York.[9] The very high pressures needed to keep the advancing face secure are only employed in a section close to the face, this section being separated from the rest of the tunnel by a steel air dam. If the total air pressure in the advanced section is not more than 1¼ times that in the rest of the tunnel, the men can come through the air lock without any delay. Let us suppose that the excess pressure is 35 lbs. at the face and 7.5 lbs. in the rest of the tunnel. The total atmospheric pressure is thus 50 lbs. at the face and 22.5 lbs. in the rest of the tunnel. It is evident, therefore, that the men who have been working at the face can come straight through either air lock, even after very long shifts, provided that they are kept for a sufficient time (fully an hour) in the low-pressure part of the tunnel before coming through the second lock. If there were arrangements for washing, changing, and meals in the low-pressure section, this hour could be profitably employed. A six-hour shift could be worked at the face, with an interval for a meal in the low-pressure section, and there would be no blocking of the air locks. The men could also go home at once, without the risk of symptoms developing later. A plan of this kind, modified to suit the varying conditions at different undertakings, seems to afford the best means of solving the difficulties with air locks; but exist-

[9] Japp, *Trans. Intern. Congress on Hygiene,* Section IV, Washington, 1912.

ing state regulations might need modification to enable the improvement to be introduced. In any case there is now no justification for imperiling men's lives by methods of decompression which are known to give imperfect protection.

At present the tendency of the supervising medical officers is to shorten the periods of work at the face under high pressure; and of course the period of decompression may then be shortened also. While this may cover the physiological aspects of the problem, it is evidently very uneconomical as compared with the method above suggested.

Not only may increased partial pressures of nitrogen and CO_2 cause trouble, but also increased pressure of oxygen. The poisonous action of oxygen at high partial pressure was discovered by Paul Bert; and his numerous and very thorough experiments on the subject are described in his famous book. There is a popular belief, based on the supposed similarity between life and combustion, that the breathing of oxygen at a high partial pressure must quicken the processes of life, and Paul Bert's experiments on the effects of a high partial pressure seem to have been begun with the view of testing this belief. He found that when the partial pressure of oxygen exceeds three or four atmospheres, very remarkable tonic convulsions are produced in warm-blooded animals, and they soon die. More remarkable still, perhaps, their body temperature falls in the compressed oxygen, and the consumption of oxygen and production of CO_2 are markedly diminished. The oxygen acts as a poison.

He then extended his observations to other forms of life besides warm-blooded animals, and proved conclusively that for life in every form, including the very lowest, oxygen at high pressure is a poison. Plants, infusoria, and bacteria are killed just as certainly as the higher animals. His experiments left no doubt that it is the partial pressure of oxygen, and not mere mechanical pressure, that matters. When air was used instead of pure oxygen, the pressure required to produce fatal effects was nearly five times as great as when pure oxygen was used, but the pressure of oxygen was the same. He also found that oxygen pressures of less than one atmosphere would kill or retard the growth of various small organisms of different classes in the animal kingdom, and of plants; and he came to the conclusion that any increase over the normal oxygen pressure of ordinary air is more or less detrimental to living organisms directly exposed to it. He had discovered a biological fact of the most far-reaching significance.

It is usually not till the oxygen pressure in the air reaches more than three atmospheres that warm-blooded animals show marked immediate symptoms of oxygen poisoning. This we can understand. The extra oxygen taken up in the arterial blood is nearly all in simple physical solution, as Paul Bert showed by blood-gas analyses of the arterial blood. At three atmospheres of oxygen the blood will only take up about seven volumes of oxygen in solution. On the other hand, the blood commonly loses about as much oxygen in its passage through the capillaries. It is also indicated by the results of experiments described in Chapter X, that the effect of the increased oxygen is to slow the circulation, so that more oxygen than usual is lost. Hence the oxygen pressure will probably be very little above normal in the tissues or venous blood until the oxygen pressure in the arterial blood is over three atmospheres. As was shown in Chapter VII, animals in which the haemoglobin has been thrown out of action by CO or nitrite poisoning are still a little short of oxygen when they are breathing oxygen at two atmospheres pressures. We can therefore easily understand why so high an oxygen pressure as three or four atmospheres is needed before the nervous system and other tissues are markedly affected by the oxygen.

In his experiments on warm-blooded animals Paul Bert had, however, overlooked one thing which his other experiments might have led him to look for. Although the tissues generally in a higher animal are protected from the high pressure of oxygen, since they have round them that wonderfully constant internal environment which protects them from so many variations in the external environment, yet the cells lining the air passages and lungs are exposed to the high oxygen. It was discovered by Lorrain Smith in 1899[10] that oxygen at a pressure quite insufficient to affect the nervous system appreciably will, if time is given, produce fatal inflammation of the lungs. The higher the pressure of the oxygen, the sooner this appears. The lungs are filled with exudation, so that they sink in the fixing fluid, a general oedema similar to that in phosgene poisoning being produced. Probably the animals only survive as long as they do in the compressed oxygen because they get sufficient oxygen in spite of the oedema. As Lorrain Smith showed, the oedema protects them against the effects of very high oxygen pressure on the nervous system. At an oxygen pressure of 180 per cent of an atmosphere (that to which

[10] Lorrain Smith, *Journ. of Physiol.*, XXIV, p. 19, 1899.

the American diver referred to above was exposed for three hours) one of the animals died from lung inflammation in 7 hours.

The higher the oxygen pressure the more rapidly was the fatal inflammation produced. The lowest oxygen pressure at which fatal pneumonia was observed was 73 per cent of an atmosphere, after 4 days' exposure. At 40 per cent no ill effects were observed. It is evident from these observations that when oxygen is used continuously for therapeutic purposes the percentage ought not to be increased more than is really necessary. A lung that is already inflamed may be extra sensitive to an unusually high oxygen pressure. At an oxygen pressure corresponding to 57 fathoms of water we found that out of seven goats one died in three hours from pneumonia, while the others were also affected, but recovered on decompression. At an oxygen pressure corresponding to 40 fathoms we could not detect in ourselves any subjective symptoms during short exposures; but quite probably such symptoms might appear after longer exposure, and the behavior, described above, of the experienced American diver seems suggestive of this.

Although oxygen at high pressure acts generally as a poison, yet as shown in Chapter IX, the living swim bladder may contain oxygen at a pressure of 100 atmospheres without harm to the cells lining its walls. These cells are apparently "acclimatized" to the oxygen, just as the cells lining the stomach wall are acclimatized to hydrochloric acid. It is not improbable that the lungs are capable of acquiring some degree of acclimatization or immunity to the effects of a high pressure of oxygen; but on this point there are as yet no observations.

CHAPTER XIII

Effects of Low Atmospheric Pressures.

VERY low atmospheric pressures are met with on mountains or high plateaus and in ascents by balloons or aëroplanes to great altitudes. Mountain sickness, one of the characteristic effects of low atmospheric pressures, was known long before atmospheric pressure and the composition of the atmosphere were understood. It was commonly attributed to poisonous emanations. A good account of earlier records of it is given by Paul Bert. His experiments on animals and men showed clearly that the physiological effects produced by low atmospheric pressure are simply the result of the diminished partial pressure of oxygen. The nature of these effects and the manner in which they are produced have been described generally in Chapters VI and VII in connection with the symptoms and causes of anoxaemia. It remains, however, to discuss the subject in detail.

Although Paul Bert's very important conclusion that the physiological actions of oxygen and other gases depend on their partial pressures has often been referred to in preceding chapters, no very definite account has been given of his experiments. It will be convenient to summarize them here, and at the same time refer to certain points on which later investigation has thrown new light.

By studying the conditions producing death in animals (chiefly sparrows) confined in a closed vessel at varying atmospheric pressures and with varying compositions of the initial air breathed, Paul Bert proved that if the pressure of oxygen was not sufficiently high to produce oxygen poisoning, death was due either to increased pressure of CO_2 or to diminished pressure of oxygen. At ordinary barometric pressure, and with ordinary air inclosed in the vessel, death occurred when the oxygen percentage fell to about 3.5. At half the ordinary pressure 7.0 was the fatal oxygen percentage, so that the partial pressure of oxygen was the same; and so on down to pressures of a third or even a fourth of an atmosphere. If the vessel was filled with air highly enriched with oxygen and the pressure was reduced to a fourth, or even a tenth, the result was the same as regards the fatal partial pressure of

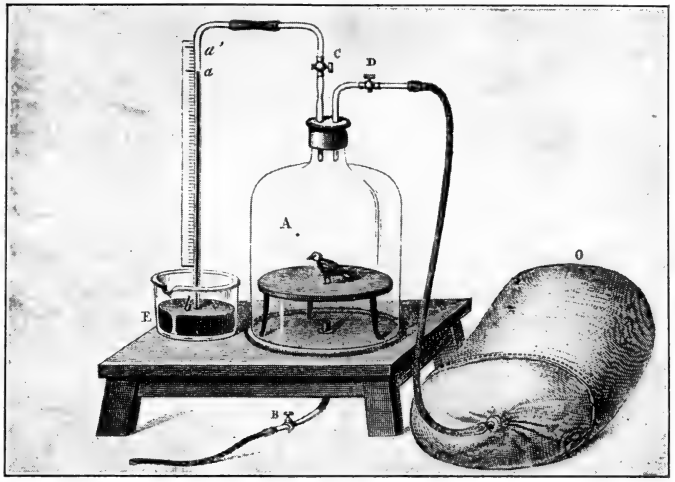

Figure 93.

Paul Bert's apparatus for showing the effects of varying low pressures of oxygen and CO_2. The tap B is connected with an air pump, and D with a bag of oxygen or nitrogen, while C connects with a mercury manometer.

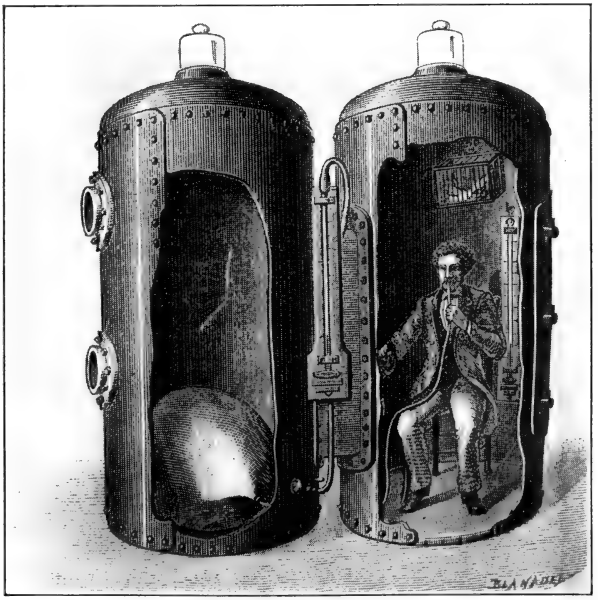

Figure 94.

Paul Bert's twin steel chamber for studying in man the effects of very low atmospheric pressures with respiration of oxygen.

oxygen. On the other hand if the vessel was filled with the enriched air and left at ordinary barometric pressure, death occurred when the percentage of CO_2 reached about 26, although the oxygen pressure was far above the danger point; and similarly if the vessel was filled with compressed air at a pressure not sufficient to cause oxygen poisoning. The cause of death depended simply on whether the partial pressure of 3.5 per cent of an atmosphere of oxygen or 26 per cent of an atmosphere of CO_2 was reached first. The mere mechanical pressure had no influence. When, however, the partial pressure of oxygen was raised to the dangerous limits referred to in Chapter XII, death was due to oxygen poisoning, or hastened by it; and the results suggest that increase of the circulation rate, owing to the presence of CO_2, with consequent increase of the partial pressure of oxygen in the tissues, increased the poisonous action of the oxygen, though Paul Bert was unaware of the action of CO_2 on the circulation.

Figure 93 shows an apparatus used by Paul Bert for showing that it is the diminished pressure of oxygen, and not simply the diminished barometric pressure, that affects an animal. The following are the notes of an experiment on a sparrow.

"At 3.20 pressure reduced to 250 mm. in a few minutes. On further reduction to 210 mm. the animal turned round and round, fell down, and was at the point of death. I restored the normal pressure by letting in air enriched with oxygen; the animal recovered immediately and appeared lively and well. The air in the bell jar now contained 35 per cent of oxygen. At 3.30 pressure reduced to 180 mm. when the animal again became very ill. Pressure again restored to normal by letting in oxygen, when the animal recovered at once. The air now contained 77.2 per cent of oxygen. On again reducing the pressure the animal did not fall over till 100 mm. pressure was reached. Immediate recovery on restoring the pressure by letting in oxygen. The air now contained 87.2 per cent of oxygen. On reducing the pressure to 100 mm. at 3.50 the animal did not seem at all in danger; but at 80 mm. it fell over in a dying condition. It recovered at once on letting in oxygen. The air now contained 91.8 per cent of oxygen, and at 4.05 the pressure was reduced to 75 mm., when the animal again became very ill, so that there was only just time to open the taps and let it recover." This experiment shows very clearly that in air greatly enriched with oxygen the barometric pressure could be reduced to about a third of what was possible in ordinary air.

It was evident that oxygen could be used to avert the very

dangerous effects of the rarefied air in balloon ascents; and Paul Bert proceeded to test this on himself in a steel chamber which he had procured. The arrangement is shown in Figure 94. In this chamber he not only studied in himself and others the subjective and other effects of low barometric pressure when ordinary air was breathed, but also showed that by breathing oxygen all these effects could be prevented in man, down to very low pressures. Figure 95 is a diagram showing the variations of pressure in one

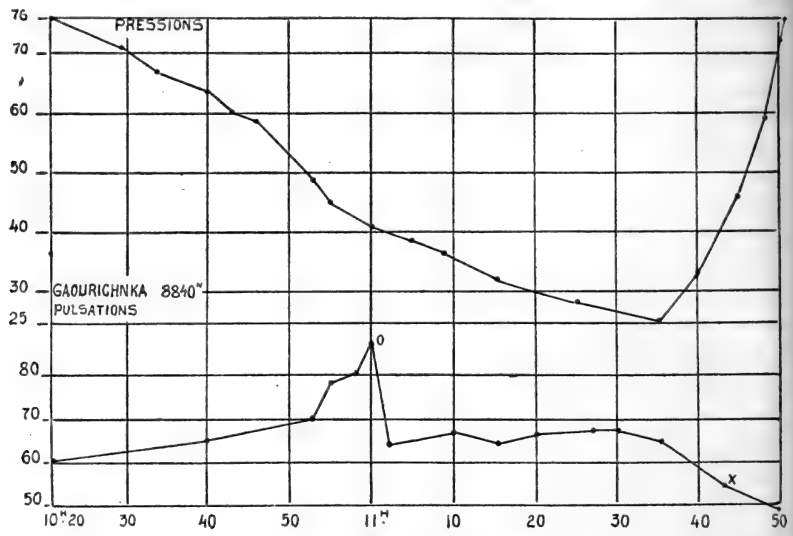

Figure 95.

Tracing showing Paul Bert's pulse rate during a decompression experiment in his steel chamber. Upper line = barometric pressure in centimeters. Lower line = pulse rate. At o the breathing of oxygen was begun and continued till the end of the experiment.

of his experiments, and the striking effect on his pulse when he began the continuous breathing of oxygen. The oxygen abolished at once the various symptoms, of which an account was given in Chapter VI.

I have frequently verified in steel chambers, and also when air very poor in oxygen was being breathed, Paul Bert's statements as to the effects of oxygen. He noted the sudden increase in apparent brightness of light and loudness of sounds, the return of powers of memory and of intellectual powers, etc. As illustrating how even one who is perfectly familiar with the effects on vision of rapid relief of anoxaemia may be deceived by the subjective

effect, I may mention a recent personal experience. Dr. Priestley and I had gone to a barometric pressure of about 360 mm. in a steel chamber to test a piece of apparatus; and, being anxious to test our Eustachian tubes, we opened the inlet tap full, so as to raise the pressure to nearly normal within about a minute, as in a nose dive of about 18,000 feet. Our ears were all right, but I was alarmed to see the filament of the electric lamp suddenly become intensely bright, as if it were about to fuse; and on hastily pushing the door open at the end of the decompression I inquired what had gone wrong with the voltage. The appearance was of course only subjective. I had forgotten the increase of oxygen pressure, and had only been thinking of the mechanical effect on the eardrums.

Nothing in subsequent investigation has shaken Paul Bert's conclusions as to the effects of gases being dependent on their partial pressures, though the scientific world has taken a long time to assimilate his reasoning, so that much of what has been subsequently written on the subject of high and low atmospheric pressures has been simply out of date. On a number of points, however, later investigations have thrown new light. To take one quite minor point first, the action of CO in air does not depend upon its partial pressure, since the higher the pressure of an atmosphere containing CO is raised the more innocuous does the CO become, from the causes already discussed in Chapters IV and VII. But at a constant partial pressure of oxygen the physiological action of CO depends upon its partial pressure. There may be other apparent exceptions to Paul Bert's rule, but we may be confident that they will also turn out to be only apparent.

In his experiments Paul Bert took into direct account only the pressure of oxygen and other gases in the inspired air. But we have already seen that what directly matters is the gas pressures in the alveolar air. When the barometric pressure is lowered the alveolar oxygen pressure falls at a greater proportional rate than the oxygen pressure of the inspired air. This is because, even though the breathing is increased, which would in itself tend to keep up the alveolar oxygen pressure, and may nearly prevent the alveolar CO_2 percentage from rising, the percentage of aqueous vapor is constantly rising. At a barometric pressure of 47 mm. no air at all would enter the lungs, since the pressure of aqueous vapor would be 47 mm., and the liquids of the body would from this cause alone be just about their boiling point; as a matter of fact they would boil at a higher pressure, as they contain much free CO_2. At a pressure of 100 mm. in an atmosphere of pure

oxygen, the alveolar air *in situ* would contain 47 per cent of H_2O; probably about 20 per cent of CO_2; and 33 per cent of oxygen, with a partial pressure of about 4.3 per cent of an atmosphere or 33 mm. of mercury. This pressure of oxygen is only one twenty-third of that in dry oxygen at atmospheric pressure, though the oxygen pressure in the inspired oxygen is only reduced to a little over a seventh.

It is thus somewhat remarkable that until extremely low barometric pressures, such as under 100 mm., were reached, the deaths of the animals from want of oxygen should have coincided so closely with a threshold oxygen pressure in the inspired air. The probable explanation of this has already been referred to in Chapter VI. With fall of barometric pressure the rate of diffusion in a gas increases rapidly, since the mean free path of each molecule before it strikes another molecule is increased. As a consequence, the oxygen molecules in the neighborhood of the alveolar epithelium reach it more rapidly, so that when there is scarcity of oxygen the blood can be more readily saturated to the existing mean oxygen pressure in the alveoli, or to whatever higher oxygen pressure can be produced by active secretion. The excessive fall in alveolar oxygen pressure at low barometric pressures is thus partially compensated.

An experiment which Paul Bert describes (p. 749 of his book) would seem to confirm this explanation. A bird was placed in the apparatus (Figure 93) and the pressure reduced to 220 mm., at which the animal had severe symptoms of anoxaemia. The pressure was then raised to normal, not with air, but with nitrogen. The animal died almost at once, though the partial pressure of oxygen was 6 per cent, and the alveolar oxygen pressure must have been raised, owing to the greatly diminished proportion of aqueous vapor in the alveolar air at normal barometric pressure.

The importance of the CO_2 present in the air was not noticed by Paul Bert. In all his experiments where the oxygen pressure of the inspired air fell to about 3.5 per cent before death there was also a considerable proportion of CO_2 in the inspired air. This CO_2 must have stimulated the respiration greatly, in the manner already explained so fully, thus diminishing the fall in alveolar oxygen pressure. The presence of CO_2 tends to diminish the percentage saturation of the haemoglobin in the arterial blood, owing to the Bohr effect already referred to at length in Chapters IV and VII, but there is the counterbalancing advantage that the haemoglobin holds on less tightly to oxygen in the systemic

capillaries. The excess of CO_2 has, however, another quite distinct effect in counterbalancing the effects of the low alveolar oxygen pressure: for the circulation can increase, owing to the stimulus of anoxaemia, without the counteracting effect due to the production of alkalosis through deficiency of CO_2. In this way the oxygen pressure in the systemic capillaries is kept considerably higher than if there were no excess of CO_2 in the inspired air.

Other things being equal, the presence in the inspired air of a moderate proportion of CO_2 diminishes the effects of oxygen deficiency, as can easily be shown experimentally. The CO_2, by increasing the breathing, raises the percentage of oxygen in the alveolar air; and a very small excess in the alveolar CO_2 pressure is sufficient to produce a large effect on the breathing. There is consequently a considerable increase in the alveolar oxygen pressure. That, however, the effects of CO_2 in relieving anoxaemia are not simply due to the increased oxygenation of the blood can be shown most strikingly in CO poisoning. A given percentage of CO is less poisonous when administered to an animal breathing human expired air. As this does not raise the alveolar oxygen pressure, the effect cannot be due to increased oxygenation of the arterial blood, and must be put down to increase in the circulation rate, and consequent better supply of oxygen to the tissues. Lorrain Smith and I found that excess of CO_2 has no effect in stimulating oxygen secretion by the lungs.

Although Paul Bert had in reality proved quite conclusively that the physiological effects of low atmospheric pressures depend on the lowering of the oxygen pressure, the theory was prominently brought forward by Mosso twenty years later that these effects are due *primarily* to excessive loss of CO_2 from the body, or "acapnia." Mosso imagined that as a physical consequence of the low atmospheric pressure more CO_2 than usual is washed out of the blood in the lungs, and that this is the cause of mountain sickness.[1] His physical chemistry was completely at fault. If the volume of air breathed did not alter, the partial pressure of CO_2 in the alveolar air would remain the same, and no more CO_2 would be given off at low than at ordinary atmospheric pressure. Actually, however, there is an excessive loss of CO_2 at low atmospheric pressure, and this is due to the increased breathing caused by the anoxaemia. Moreover we can, for the reasons already explained, mitigate the anoxaemia by adding a suitable proportion of CO_2

[1] Mosso, *Life of Man on the High Alps* (translation), London, 1898.

to the inspired air. Acapnia may thus be looked on as a contributary cause of the symptoms, so that at first sight there seems to be some experimental support for Mosso's theory. The acapnia, although most important, is, however, only a secondary result of the lowered oxygen pressure. This aspect of the matter has become clear only recently through the work of Kellas, Kennaway, and myself (see Chapter VI), and independently along closely similar lines by that of Yandell Henderson and Haggard.[2]

Mosso held to his acapnia theory till the time of his death, and it was quite in vain that I myself endeavored to persuade him that Paul Bert was right. "Acapnia" became for a time to many physiologists the same sort of *ignis fatuus* as "reduced alkaline reserve" has been in recent years. In 1906, however, Zuntz and his colleagues placed the main facts in true perspective in an account of investigations carried out at high altitudes in the Alps.[3]

We must now consider acclimatization to high altitudes and anoxaemia caused in other ways. Paul Bert in his book (pp. 336, 1105) describes and discusses acclimatization, though he had not himself studied it experimentally. The evidence pointing to the fact of acclimatization was clear. He suggested that the tissues become gradually accustomed to a smaller supply of oxygen in the blood, and perhaps become more economical in their use of oxygen. He also, however, suggests that the oxygen capacity of the blood may become increased at high altitudes; and this he afterwards verified by actual examination of blood taken from animals living at high altitudes.[4]

In 1892 Viault showed that the number of red corpscles per unit volume of blood is increased at high altitudes, and Müntz that the percentage of iron is increased. Various subsequent observers established clearly the fact that in animals and persons living at high altitudes there is an increase in both the percentage of haemoglobin and the number of blood corpuscles in the blood. By far the most complete and accurate series of observations on the increase in haemoglobin was that carried out in connection with the Pike's Peak Expedition by Miss FitzGerald on persons living permanently at different altitudes in the Rocky Mountains and elsewhere in America. Figure 96. shows graphically the average results obtained at different altitudes.

It will be seen from this figure that on an average the per-

[2] Haggard and Henderson, *Journ. Biol. Chem.*, XLIII, p. 15, 1920.
[3] Zuntz, Loewy, Müller, and Caspari, *Höhenklima und Bergwanderungen*, 1906.
[4] Paul Bert, *Comptes rendus*, XCIV, p. 805, 1882.

centage of haemoglobin varies inversely with the barometric pressure, and that even quite small diminutions in barometric pressure are effective in causing a rise in the haemoglobin percentage. In different individuals, however, the effects on the haemoglobin percentage of a given diminution in barometric pressure vary

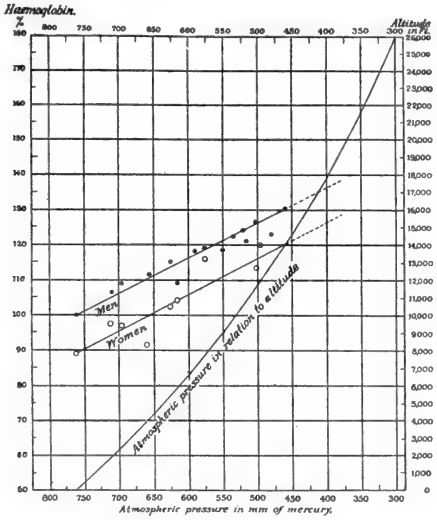

Figure 96.
Average haemoglobin percentages in persons living permanently at different altitudes (FitzGerald).

considerably. Thus among the persons acclimatized on the summit of Pike's Peak (barom. 453 mm.) the rise in haemoglobin percentage varied from 13 to 53 per cent of the normal. The rate at which the haemoglobin percentage rises when a person goes to a high altitude varies also. In some persons the rise is very slow; and in consequence of this some observers have failed to detect any rise on going for a short time to a high altitude.

As the average rise in haemoglobin percentage is appreciable with only small increases of altitude, one would expect to find that with increase of atmospheric pressure above normal the haemoglobin percentage would fall below the normal value at sea level. That this is actually the case was shown for dogs and a monkey by A. Bornstein, who kept the animals under atmospheric pressure of about three atmospheres or 2,280 mm. in the Elbe tunnel at Hamburg during its construction.[5] She found that the

[5] Adèle Bornstein, *Pflüger's Archiv.*, 138, p. 609, 1911.

haemoglobin percentage and number of red corpuscles fell about 20 per cent, and that there was no fall in the case of animals kept in the tunnel at a place where the atmospheric pressure was not increased. It appears, therefore, that the haemoglobin percentage is regulated generally in relation to the oxygen pressure in the arterial blood, and rises or falls according as this pressure is diminished or increased.

It is easy to see what the physiological advantage will be, other things being equal, of a rise in the haemoglobin percentage. As the blood passes through the systemic capillaries, its oxygen pressure will fall more slowly than usual. Hence although the arterial oxygen pressure is considerably below normal, the venous oxygen pressure will be much more nearly normal, so that the lowering of the oxygen pressure in the tissues is diminshed. There may be much more of available oxygen in the arterial blood at a high altitude than at sea level, but this in itself avails nothing, since it is the pressure, and not the quantity, of oxygen in the blood that counts. To explain the beneficial effects of increased haemoglobin percentage at high altitudes and in other conditions where chronic arterial anoxaemia exists we must consider the effects of the increased haemoglobin on the oxygen pressure in the tissues. At the same time we must bear in mind the influence of increased haemoglobin percentage in diminishing the CO_2 pressure, and therefore the hydrogen ion concentration, in the tissues; and this brings us to a second factor in acclimatization.

In recent years it has gradually been shown more and more clearly that at high altitudes the volume of air breathed is increased and remains so after acclimatization. This was already more or less evident from the measurements by Zuntz and his colleagues of the volume of air breathed and respiratory exchange at high altitudes, and, as mentioned in Chapter VI, was rendered quite clear by the experiments of Boycott, Ogier Ward, and myself on the alveolar air at low atmospheric pressures. We drew the conclusion that the blood, apart from the CO_2 contained in it, becomes less alkaline at low atmospheric pressures, so that less CO_2 is needed to excite the respiratory center. This diminution in the "fixed" alkalinity of the blood was already known through titrations. Barcroft then found on the Peak of Teneriffe that in spite of the lowered pressure of CO_2 in the arterial blood, the dissociation curve of the oxyhaemoglobin of the blood in presence of the alveolar CO_2 pressure remains sensibly normal. This also pointed in the same direction. The phenomena did not, however,

correspond with those accompanying excess of lactic acid in the blood, and Ryffel was unable to find any such excess in the blood or urine. Accordingly the conclusion was drawn by my colleagues and myself after careful observations during the Pike's Peak Expedition, that the diminution in available alkali in the blood must be due to a lowering in the level of concentration to which the kidneys regulate the fixed alkali in the blood. We thought that the anoxaemia must influence the kidneys specifically in this direction.

The Anglo-American Pike's Peak Expedition[6] was planned with the special object of studying acclimatization to the oxygen deficiency of the air at high altitudes. We selected Pike's Peak (14,100 feet) because it was possible, not only to get apparatus and supplies to the summit easily by the cogwheel railway, but also to live there without the disturbing effects of cold and hardship. We were thus enabled to watch in ourselves the progress, which was very striking, of acclimatization, and to observe the effects of the rarefied air on the numerous unacclimatized persons who came up.

It is evident that a simple increase in the breathing must greatly diminish the *arterial* anoxaemia at high altitudes: for not only will the alveolar oxygen pressure be increased, but in consequence of excessive removal of CO_2, the haemoglobin passing through the lungs will combine more readily with oxygen, in accordance with the discovery, already often alluded to, of Bohr and his pupils. It might thus appear as if a simple increase in breathing were the natural adaptive response to the anoxaemia of high altitudes and other conditions. But, as already pointed out, such a response is, except for a very short period, or to a very limited extent, prevented, owing to the effect of the lowered CO_2 pressure in diminishing the breathing; and an increased circulation rate (which would also tend to diminish the fall of oxygen pressure in the tissues) is also prevented in the same way. Moreover the increase in percentage saturation of the haemoglobin in the tissues is in any case of only limited advantage, since, owing to the lowered CO_2 pressure, the haemoglobin holds on more tightly to the oxygen. Nevertheless there will be some increase in breathing and circulation rate; and this will represent a compromise between the effects of want of oxygen and of deficiency

[6] Douglas, Haldane, Henderson, and Schneider, *Phil. Trans. Roy. Soc.*, B, 203, 1913.

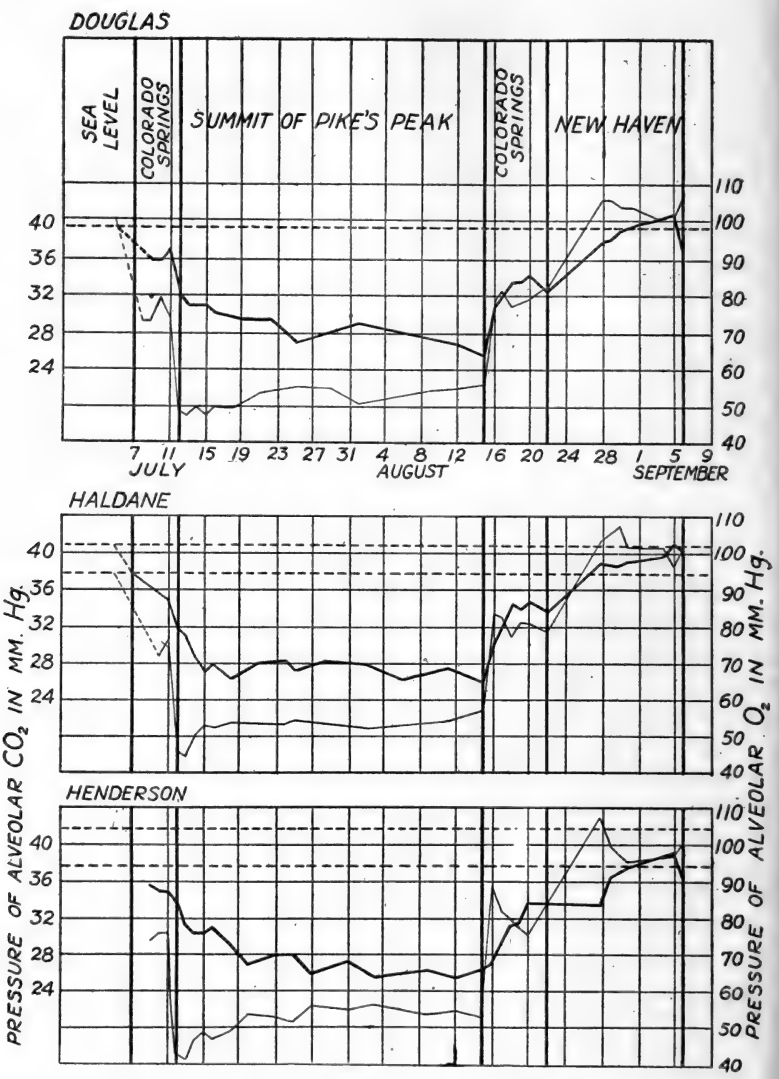

Figure 97.

Pressure of CO_2 and oxygen in alveolar air of three members of the Pike's Peak Expedition at about sea level (Oxford and New Haven), at Colorado Springs (6,000 feet), and on Pike's Peak (14,100 feet). Thick line = alveolar CO_2 pressure, and thin line = alveolar oxygen pressure. Interrupted lines = normal alveolar CO_2 and oxygen pressures at sea level.

of CO_2. It is during this condition that mountain sickness is produced.

In the course of a day or two, or of several days, the mountain sickness passes off if the altitude is not too great; but the breathing is only slightly increased further, as we found on Pike's Peak (Figure 97) by analyses of the alveolar air. Further light on acclimatization was afterwards thrown by Hasselbalch and Lindhard[7] in a series of observations during which they remained for a number of days in a steel chamber at reduced pressure. They found by direct measurement that after acclimatization the hydrogen ion concentration of the blood is approximately normal, thus confirming Barcroft's conclusions from observations of the dissociation curve of the oxyhaemoglobin of the blood. They also found that the excretion of ammonia in the urine is distinctly diminished; and this led them to the conclusion that the very slight acidosis which presumably causes the increased breathing is due to diminished formation of ammonia in the body.

In a still more recent investigation[8] by Kellas, Kennaway, and myself, we found that on exposure to a considerable diminution of atmospheric pressure there is at once a very marked decrease in the excretion of both acid and ammonia by the kidneys. The urine may become actually alkaline to litmus. These observations threw a new and quite clear light on the increased breathing at high altitudes. It became evident that the increased breathing is primarily due simply to the stimulus of anoxaemia. This increased breathing not only raises the alveolar oxygen pressure, but also washes out an abnormal proportion of CO_2 and thus produces a condition of slight alkalosis, to which the perfectly normal response is a diminution of ammonia formation and in the acidity of the urine, as explained in Chapter VIII. This response tends to continue until the normal reaction of the blood is restored, owing to reduction in the "available alkali" in the body. There is no acidosis at any stage of the process; the supposed acidosis is only the compensation of an alkalosis. Nevertheless the process of compensation is never quite complete. If it were so the excretion of ammonia would return to its normal value on acclimatization, whereas actually there is still, as shown by Hasselbalch and Lindhard's observations, a slight but distinct diminution in ammonia excretion. Moreover if the compensation were complete

[7] Hasselbalch and Lindhard, *Biochem. Zeitschr.*, 68, pp. 265 and 295, 1915; and 74, pp. 1 and 48, 1916.

[8] Haldane, Kellas, and Kennaway, *Journ. of Physiol.*, LIII, p. 181, 1919.

there would be no extra breathing caused by the immediate effect of the anoxaemia. Actually there is still a slight amount of extra breathing from this cause, since on raising the alveolar oxygen pressure there is an immediate, though comparatively slight, rise in the alveolar CO_2 pressure, as we found on Pike's Peak when a mixture rich in oxygen was breathed in place of ordinary air. The evident reason why the compensation does not become more complete is that if it were made more complete the normal composition of the blood would be very seriously altered; and such alterations tend to be resisted. The compensation thus represents a compromise.

A similar interpretation of the apparent slight acidosis of high altitudes was reached on independent grounds by Yandell Henderson, and published shortly before our paper appeared.[9] As already mentioned in Chapter VIII, he and Haggard made the very important discovery that with prolonged and very excessive ventilation of the lungs (thus producing great alkalosis) the available alkali or "alkaline reserve" of the blood diminishes greatly. A similar diminution occurs at high altitudes, and Henderson attributed it to the increased breathing produced by the anoxaemia, and was thus the first to identify its true nature as a compensatory response to the alkalosis produced by the increased breathing.

It is evident that the compensatory change in the available alkali of the blood and whole body tends to make increased breathing possible with a minimum stimulus from actual anoxaemia. The anoxaemia tends, therefore, to be relieved. In other words a process tending to acclimatization has occurred. It will be noted that the phenomena have been interpreted on what is usually called a teleological basis, though no conscious adaptation of means to end is implied, but only a tendency of the living body to maintain its normal standards. The justification for this mode of interpretation, and the demonstration that it constitutes the necessary scientific basis of physiology, will be postponed to the next chapter.

In connection with the Pike's Peak expedition Miss FitzGerald carried out a large series of investigations of the alveolar air of persons living permanently, and therefore fully acclimatized, in towns and villages at different altitudes in or near the Rocky Mountains. At a later date further observations were made at

[9] Yandell Henderson, *Science*, May 8, 1919; and Haggard and Henderson, *Journ. Biol. Chem.*, XLIII, p. 15, 1920.

lower altitudes in South Carolina.[10] The average results are shown in Figure 98. The results for men and women are given separately, as men have a higher average alveolar CO_2 pressure than women, as mentioned in Chapter II. It will be seen that within the limits of atmospheric pressure investigated, the aver-

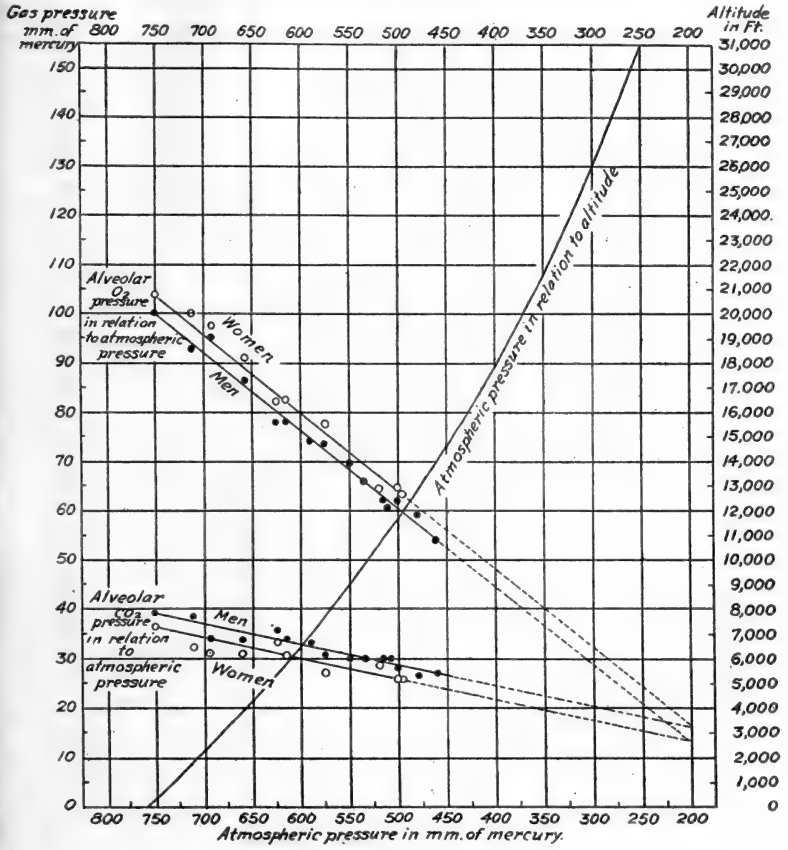

Figure 98.
Alveolar gas pressures in relation to barometric pressure or altitude.

age alveolar CO_2 and oxygen pressures fall proportionally to the atmospheric pressure. To judge from these results the alveolar oxygen pressure at the height of 24,600 feet reached by the

[10] FitzGerald, *Phil. Trans. Roy. Soc.*, B, 203, p. 351; and *Proc. Roy. Soc.*, B, 88, p. 248.

Duke of Abbruzzi's expedition would only be about 31 mm., and the CO_2 pressure about 21 mm. The figures, according to a formula of Henderson,[11] would be oxygen 38 mm., and CO_2 15 mm.

Acclimatization would be a very incomplete process if it depended solely on the increased breathing observed at high altitudes. In spite of increased breathing and coincident increased saturation of the arterial blood owing to the alkalosis produced, there is at first very distinct cyanosis when persons first go to a high altitude. On Pike's Peak this was very striking, though in different persons the degree of cyanosis varied greatly. The fact that there was so much cyanosis although the mean alveolar oxygen pressure was about 50 mm.—sufficient in presence of the lowered alveolar CO_2 pressure to saturate the haemoglobin of average human blood to 85 per cent or more—is now explicable by the fact that, as explained in Chapter VII, the oxygen pressure of the mixed arterial blood is very appreciably below that of the mixed alveolar air, and particularly at lowered atmospheric pressure. The cyanosis disappears, however, after a day or two, or sometimes longer, of mountain sickness; and in persons who have reached the high altitude by gradual stages, as in the Himalayas, there may, apparently, be little or no cyanosis, and certainly no mountain sickness. Among the party of four Europeans with the Duke of the Abbruzzi, who gradually reached a height of 24,600 feet in the Himalayas, there were no signs of mountain sickness or undue exhaustion at any stage. In the account of the expedition the conclusion was even drawn that "rarefaction of the air, under ordinary conditions of high mountains, to the limits reached by man at the present day (a barometric pressure of 12.28 inches or 312 mm.) does not produce mountain sickness."[12] Mountain sickness, and its accompaniments were considered to be "in reality phenomena of fatigue." The writer of this account was not aware of the fact that mountain sickness is easily produced in unacclimatized persons without any fatigue, and occurs quite readily in persons sitting in a steel chamber or going by train to a high altitude.

We may contrast the experience of the Duke of Abbruzzi's party with that of Hasselbalch and Lindhard in their steel chamber.[13] They started altogether unacclimatized, from the sea-level air pressure of Copenhagen, and only reduced the pressure

[11] Y. Henderson, *Journ. Biol. Chem.*, XLIII, p. 29, 1920.
[12] Filipo de Filippi, *Karakouram and Western Himalaya*, London, 1912.
[13] Hasselbalch and Lindhard, *Biochem. Zeitschr.*, 8, p. 295, 1915.

to 520 mm., corresponding to a height of 11,000 feet; but after a few hours they became so seriously affected by mountain sickness, with alarming cyanosis, intolerable headache, and feelings of asphyxia during the night, that they had to raise the pressure to 584 mm. (about 7,000 feet). Those ascending Pike's Peak started from a height of about 6,000 feet and were thus partially acclimatized; otherwise their symptoms would doubtless have been more marked than they actually were.

In Chapter IX the quantitative evidence has already been given that at high altitudes after acclimatization the lungs actively secrete oxygen inwards even during rest, and that were it not so the immunity from symptoms of mountain sickness among acclimatized persons would be totally unintelligible. It only remains to discuss here some special points with regard to oxygen secretion.

The fact that some time is needed before oxygen secretion is effectively established at a high altitude, accords exactly with the fact that it takes a man some time to get his lungs and other parts of his body into good physiological training for heavy muscular exertion. As was pointed out in Chapter IX there is now very clear evidence that in persons who are in good training oxygen secretion by the lungs plays a very important part, whereas in persons not in training any secretion evoked by muscular work is so feeble as to be quite ineffective. Both at high altitudes and in training for muscular exertion the power of secretion develops with use; and development occurs in exactly the same manner with the exercise of all other physiological functions. At high altitudes the stimulus to secretion originates in consequence of the imperfectly saturated condition of the arterial blood; and although after acclimatization is established the saturation of the arterial blood with oxygen becomes less incomplete, yet part of the incompleteness must remain; otherwise there would be no stimulus to oxygen secretion. In this connection it should be noted that the arterial oxygen pressure given by the carbon monoxide method is the average oxygen pressure of the blood leaving the alveoli, and not the oxygen pressure of the mixed arterial blood. The latter value is undoubtedly a good deal lower for the reason already explained.

It has for long been well known to mountaineers that persons who are in good physical training for hard work are far less susceptible to mountain sickness and the other characteristic effects of high altitudes than those who are not in training. This fact is

the origin of the common and quite erroneous opinion that mountain sickness is due simply to exhaustion and has nothing to do with barometric pressure. It now seems probable that in so far as acclimatization is due simply to increased power of oxygen secretion good physical training in heavy exertion will do as much as continued exposure to the high altitude. As we have already seen, however, acclimatization consists not merely in increased power of oxygen secretion, but also in increased haemoglobin percentage and diminution in the available alkali in the blood and tissues so as to permit of increased breathing without the development of alkalosis. It takes time to bring about these changes, and they are not brought about by training for muscular work. The increased haemoglobin, though it was the first acclimatization change to be discovered, is probably of relatively minor importance, inasmuch as recovery from mountain sickness and related conditions commonly occur before there is any noticeable change in the haemoglobin percentage. The diminution in available alkali seems to be much more important, but the process is evidently a rather slow one. This is readily intelligible when one considers the amount of alkali that has, apparently, to be got rid of, partly by excretion through the kidneys, and partly through suspension of formation of ammonia inside the body. Possibly this part of acclimatization might be greatly hastened by the administration of ammonium chloride, the striking effects of which on the blood reaction were described in Chapter VIII.

The question of acclimatization has assumed new interest, owing to the recent great extension of the use of aëroplanes at high altitudes. The great advantage of good physical training seems evident in this connection. At the same time it also seems evident that only a limited amount of acclimatization can be produced either by physical training or by intermittent exposures in aëroplanes to low atmospheric pressure. The limitation was distinctly evident in the experiments, mentioned in Chapter IX, on the degree of acclimatization produced by intermittent exposures at low pressures.

We must now discuss the symptoms of balloonists and other airmen at very great altitudes, and the means of averting these symptoms. Enormous heights can easily be reached by balloons; and quite recently, in consequence of the great improvements during the war in the construction of aëroplanes and their engines, a height nearly as great as those reached in balloons has been reached in aëroplanes. The limitation in the heights to which men

have hitherto been able to go is due entirely to the physiological effects of the reduced oxygen pressure and the quite evident imperfections of the apparatus used for overcoming these effects.

Hot-air balloons were devised by the brothers Montgolfier, and first used at Paris in 1783. Shortly afterwards the well-known French physicist Charles invented the hydrogen balloon and made the first ascent in 1785, reaching a height of 13,000 feet. Higher ascents were soon after made, and in 1804 another Frenchman, Robertson, reached about 26,000 feet and was greatly affected. In the same year Gay-Lussac went to about 23,000 feet, but only noticed slight effects. It seemed pretty evident that the limit of safety was about 25,000 feet, but until 1875 no balloonist seems to have been actually killed by asphyxiation due to the rarefied air.

In 1862 the well-known meteorologist Glaisher and the balloonist Coxwell made a famous very high ascent from Wolverhampton; and Glaisher's account of the symptoms observed was very full and valuable.[14] In 48 minutes they had reached a height at which the barometer stood at 10.8 inches (274 mm.). Glaisher found that after this he could no longer read his thermometer or even his watch. His last reading of the barometer was 9.75 inches (248 mm.), which he estimated as corresponding to 29,000 feet.[15] He then found that his arms and legs were paralyzed, and then his neck also, so that he could not hold up his head. He could still vaguely see Coxwell, who had climbed up to free the rope of the valve, this having got tangled, owing to rotation of the balloon. He tried to speak, but could not, and then suddenly he became blind. He says, "I was still completely conscious, and my brain was as active as in writing these lines." Then suddenly he lost all consciousness and appears to have been unconscious for about seven minutes, during which Coxwell had fortunately succeeded in stopping the ascent of the balloon and bringing it down again for a considerable distance. During Glaisher's return to consciousness he first heard the words "temperature" and "observation," but without seeing anything. Then he began to see his instruments vaguely, and then other objects, and finally was able to take up his pencil and continue his observations. The barometer was then 11½ inches (292 mm.). Coxwell had never lost consciousness. He climbed down with great difficulty. Seeing Glaisher's condition he tried to pull the valve rope, but found that his own arms were now paralyzed. He then, with great presence of mind, got hold

[14] Glaisher, *Travels in the Air*, London, 1871.

[15] It is somewhat doubtful whether the aneroid barometer was correct.

of the rope with his teeth, and so succeeded in opening the valve and turning the balloon downwards. By his presence of mind and determination he saved both Glaisher's life and his own.

The next very high ascent was made by the three French scientists Crocé-Spinelli, Sivel, and Tissandier in 1875, and resulted in the death of the two former. This tragic occurrence revealed in a very clear manner the insidiousness of the onset of dangerous anoxaemia, and the absolute necessity for taking the most efficient means of guarding against it at very high altitudes. Crocé-Spinelli and Sivel had tried the effects of oxygen in Paul Bert's steel chamber, as well as during a previous ascent to about 25,000 feet. They were thus familiar with its effects. The balloon was therefore provided with bags of oxygen. Paul Bert, who was away from Paris at the time, had, however, written to them that the bags provided were too small to last for more than a short period. There was not time, however, to get larger ones, and for this reason they decided not to begin using the oxygen till they felt themselves really in need of it. They reached a height of about 24,600 feet with the barometer at 300 mm. and the balloon no longer rising. At this point Sivel asked both his companions whether they would go higher, and on receiving their assent cut the strings of three bags of sand used as ballast. Figure 99 represents the appearance of the car of the balloon at this point. In Tissandier's notebook there was the entry "1.25, T = —10°, B = 300. Sivel throws ballast. Sivel throws ballast." The writing was scarcely legible, and the repetition of the words was characteristic of the symptoms of anoxaemia. The balloon then rose rapidly. Tissandier relates that he tried to take up the mouthpiece of the oxygen tube, but his arms would not move. Nevertheless he had no sense of the danger, but felt happy that they were rising. He saw the barometer passing 290 and then 280 and wished to call out that they were at 8,000 meters, but his voice was paralyzed, and immediately afterwards he lost consciousness and did not wake up till about forty minutes later.

The balloon was then descending rapidly and he noted that the barometer was at 315. His companions were still unconscious. He let go some ballast, and shortly afterwards Crocé-Spinelli woke up and let go more, including the aspirator. He then became unconscious again. The balloon must have gone up, and he did not wake up again till an hour and a quarter later. The balloon was then at about 20,000 feet and falling very rapidly. Both Sivel and Crocé-Spinelli were dead. Tissandier had great difficulty in

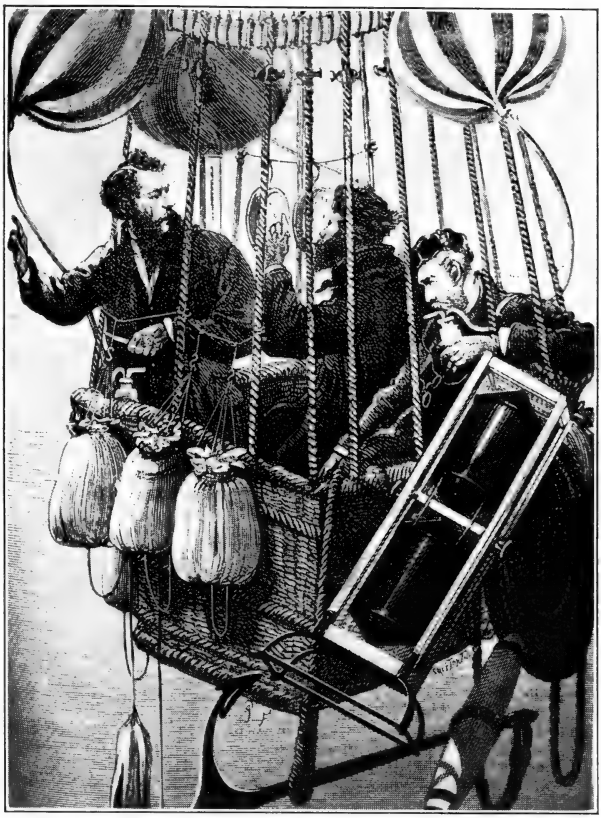

Figure 99.

Sivel, Tissandier, and Crocé-Spinelli in the car of the Zenith. Sivel preparing to cut the strings of the ballast bags at 300 mm. barometric pressure. Crocé-Spinelli with the bubbling arrangement for breathing oxygen in his hand. Tissandier reading the barometer. The oxygen bags are seen above the car, and the reversible aspirator fixed to the basket work.

letting go the anchor and landing safely, but succeeded. Figure 100 indicates diagrammatically the course of the balloon. The maximum height was given by an automatic recorder.

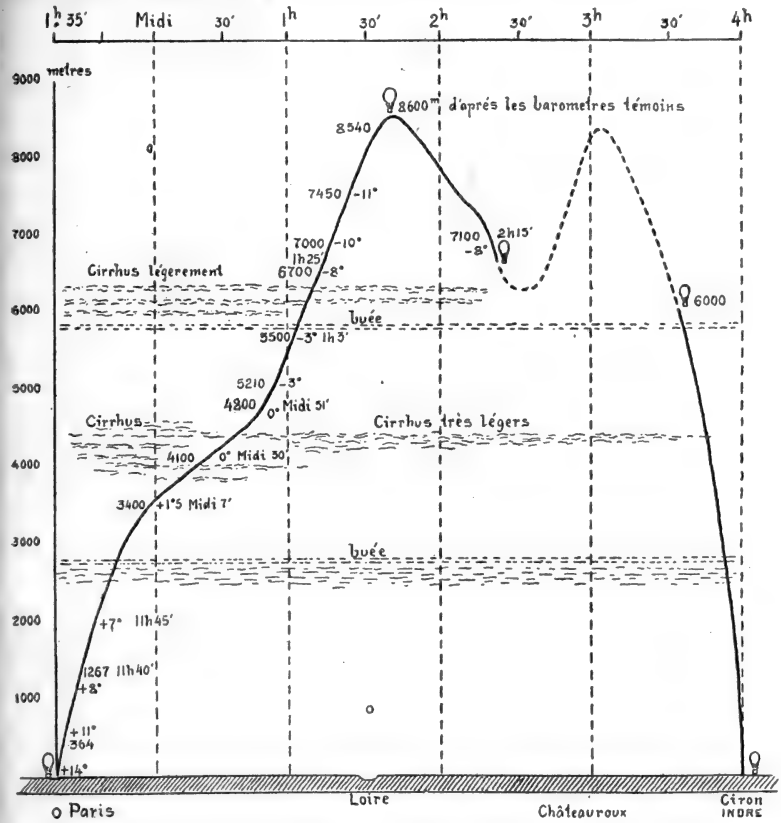

Figure 100.
Diagram of the voyage of the Zenith, April 15, 1875.

It was clear that all three had been paralyzed before they tried to breathe the oxygen. Doubtless they were all convinced that they felt all right and in full possession of all their faculties. The feeling of self-confidence seems always to be present in conditions of gradually advancing anoxaemia. I have experienced it myself, not only in steel chambers, but also in experimental CO poisoning; and the conviction that one is fully competent is still present in spite of the knowledge that this conviction may be a gross illusion. A man who is grossly intoxicated by alcohol has just the same

insane confidence that he is all right. At very high altitudes in balloons or aëroplanes it is imperative that oxygen should be breathed continuously.

For about twenty years after the accident just described no further very high ascents in balloons seem to have been attempted. The next high ascents were made in Germany, starting with an ascent by Berson and Gross to 26,000 feet in 1894. Berson alone then reached a height of 30,000 feet; and finally in 1901 Berson and Süring reached about 36,000 feet (11,000 meters), with a barometric pressure of 180 mm. In all these ascents oxygen was used, without which they would have been quite impossible; but at the end of the last ascent both Berson and Süring became unconscious, though fortunately not before the former had pulled the valve rope and thus turned the balloon downwards. Berson had the coöperation of the Austrian physiologist, von Schrötter, and the latter in his book describes not only the ascents, but various preliminary experiments in a steel chamber and experimental ascents in which he made physiological observations. Von Schrötter had thoroughly grasped Paul Bert's work and was not misled by the mistaken opposition of some physiologists to the oxygen theory.[16]

Berson and Süring used steel oxygen cylinders from which a constant stream of oxygen came to them through a tube which they could hold in the mouth. The cylinders were a great improvement on the bags used by Crocé-Spinelli and his companions, but in other respects the arrangement was very imperfect, as von Schrötter pointed out. With any increase of breathing the volume of oxygen supplied became insufficient, so that only a mixture of air and oxygen was breathed, the air being taken in through the nose or by opening the mouth. Moreover it required constant attention to inspire through the mouth, even if the supply of oxygen was adequate. It was no wonder, therefore, that first Süring and then Berson was overcome.

In one of the ascents by Berson and von Schrötter liquid air was tried for the first time. It failed, partly because there was no proper means of gasifying as much of the liquid as they required, and partly because the oxygen percentage in the gasified liquid air was not high enough. Cailletet had, however, already indicated a method of controlling the gasification, and this method in an improved form was extensively used by the Germans during

[16] Von Schrötter, *Der Sauerstoff in der Prophylaxie und Therapie der Luftdruckerkrankungen*, 1906.

the war—for instance in the very high flights needed for bombing London. It is of course necessary to use liquid oxygen. Simple liquid air would evidently be quite useless; but if ordinary liquid air is allowed to evaporate for a sufficient time the nitrogen distills off, leaving a residue very rich in oxygen. It was this residue that was employed by von Schrötter and Berson.

To improve upon the simple tube hitherto used, von Schrötter strongly recommended the use of a face piece, and figures the first form used. The face piece covers both mouth and nose, and the oxygen passes into it through a tube in a constant stream. This arrangement was introduced for aëroplanes before the war, and is now extensively used. The airman can inspire or expire air freely, but always receives a certain amount of oxygen, and has not to think of his breathing. The amount of oxygen, whether from a steel cylinder or from a Dewar flask of liquid oxygen, can be adjusted according to the height, but it is simpler to arrange for a constant supply which is sufficient, or more than sufficient, up to a certain height. About half the oxygen is wasted, as it reaches the face piece during expiration. This waste can be prevented by an arrangement similar to that already described (Figure 49) in connection with the administration of oxygen to patients. Priestley and I found in steel-chamber experiments that with this arrangement about 1 liter a minute (measured at sea-level pressure) was sufficient up to a height of 28,000 feet during rest; but at least 2 liters were needed for such exertions as an aëroplane observer or pilot has to make. With the light steel cylinders or large Dewar flasks now in use the waste of oxygen with the ordinary arrangement of mask does not greatly matter, however.

A height as great as Berson and Süring reached in a balloon has quite recently (March, 1920) been reported as reached in an aëroplane by Major Schroeder of the American Army Air Service, who, however, also became unconscious, and had a very narrow escape. How it was that the oxygen supply became insufficient in this remarkable ascent has not yet been reported.

The heights hitherto attained represent by no means the limit which Paul Bert's experiments on animals indicated when pure oxygen is breathed. All that is shown by them is that the oxygen supply was insufficient. At 36,000 feet a man breathing pure oxygen would be quite unaffected by the altitude. The barometric pressure is about 180 mm. In the alveolar air there would be a pressure of 47 mm. of aqueous vapor and 40 mm. of CO_2. Hence (by difference) there would be 93 mm. of oxygen pressure; and in

the rarefied air this would certainly suffice to saturate the arterial blood to the same extent as at sea level. At 140 mm. of barometric pressure there would still be at least 53 mm. of alveolar oxygen pressure; and it is probable that marked symptoms of oxygen shortage would only begin to appear at pressures below this. At 100 mm. they would become urgent in unacclimatized persons. At 80 mm. Paul Bert's animals were at the point of death.

It is difficult to see how the addition of CO_2 to the inspired oxygen could be of any service, although at moderate diminutions of pressure CO_2 is of considerable service, as already pointed out. When pure oxygen is breathed it is impossible to raise the alveolar CO_2 pressure without lowering the alveolar oxygen pressure; and at very low barometric pressures every millimeter of alveolar oxygen pressure counts. Moreover rise of alveolar CO_2 pressure would, on account of the Bohr effect, tend of itself to diminish the percentage saturation of the arterial blood with oxygen and thus counteract any advantage gained by increased rate of circulation. Aggazotti has shown[17] that when animals are placed in oxygen containing a considerable percentage of CO_2 they are capable of withstanding extremely low pressures; but the same was found by Paul Bert when the atmosphere was one of pure oxygen. Aggazotti himself reached the very low pressure of 120 mm. in a steel chamber while breathing oxygen with CO_2 added.

To make it safe to go much above 30,000 feet it would be necessary to have an apparatus which made it certain that the wearer always breathed pure oxygen, or at any rate oxygen not mixed with any other gas than CO_2. An ordinary mine-rescue apparatus with the usual constant oxygen supply of about 2 liters per minute (measured at ordinary atmospheric pressure) would secure this result with a very moderate expenditure of oxygen. Care would, however, be necessary to insure that both the purifier and the oxygen supply worked properly at the low temperature and pressure met with at very high altitudes. With a larger consumption of oxygen an apparatus could be made to work safely without a purifier. If it were required to go much above 40,000 feet, and to a barometric pressure below 130 mm., it would be necessary to inclose the airman in an air-tight dress, somewhat similar to a diving dress, but capable of resisting an internal pressure of say 130 mm. of mercury. This dress would be so arranged

[17] Aggazotti, *Arch. ital. de Biologie*, XLVI, 1905.

that even in a complete vacuum the contained oxygen would still have a pressure of 130 mm. There would then be no physiological limit to the height attainable.

The problem of going to very high altitudes with an oxygen apparatus is similar to that of using a self-contained breathing apparatus in mine air which is either intensely poisonous from the presence of CO or H_2S, or contains little or no oxygen. This problem has been solved successfully, so that teams of miners have worked daily for weeks or months at places a long distance from where there was any oxygen in the air. The same care as is needed and actually taken in the case of the mining apparatus is even more necessary in the case of airmen at great altitudes, but, owing to prevailing ignorance, has not yet been applied. At 36,000 feet, for instance, with the barometric pressure at a quarter the normal, an airman breathing pure oxygen would be much nearer danger if, owing to some accident, he took several breaths of the surrounding air, than a miner using a self-contained breathing apparatus would be if he took several breaths of an atmosphere of fire damp. The miner would have in his lungs to start with a pressure of 700 mm. of oxygen, whereas the airman would have only about 90 mm. To the airman at very high altitudes it is therefore specially necessary to have an apparatus which is perfect in its action and is used with all the precautions which our existing physiological knowledge shows to be necessary.

CHAPTER XIV

General Conclusions.

On looking back at the results reached in successive chapters of this book certain points of general physiological significance emerge. The present chapter will be devoted to their discussion.

It is evident that within the limits of health the breathing represents the lung ventilation required to keep the reaction and the pressure of oxygen in the blood supplying the respiratory center constant within certain narrow limits, and that the breathing increases or diminishes in accordance with the quantity of air needed to produce this effect. The "chemical" and "nervous" stimuli acting on the respiratory center coöperate in bringing about the constancy. The circulation is, in the main, similarly regulated so as to maintain a normal reaction and oxygen pressure in each of the various organs, although other factors may also determine the local circulation rate to some extent.

The quantity of respired air required to keep the arterial blood normal varies with the very variable consumption of oxygen and output of carbonic acid by the whole of the living tissues. In different individual parts of the body the variations in consumption of oxygen and output of carbonic acid are still more striking; and meeting these variations there are equally striking variations in the local circulation rates.

What is regulated by the breathing and circulation is not primarily the consumption of oxygen and formation of carbonic acid, but the partial pressures, or diffusion pressures, of these substances. If their diffusion pressures become more than slightly abnormal the result is, not a mere slowing or quickening of physiological activity, but totally abnormal activity and abnormal change in structure. What is immediately effected is the maintenance of these pressures. The supply of oxygen and removal of carbonic acid are such as to keep them approximately steady. We have also seen that it is simply as an acid that carbonic acid is of physiological importance, so that in reality a normal reaction, or normal diffusion pressure of hydrogen and hydroxyl ions, and not merely a normal diffusion pressure of carbonic acid, is maintained.

After Harvey's discovery of the circulation and Lavoisier's discoveries with regard to respiratory exchange and animal heat, many physiologists looked upon circulation and breathing as processes which primarily determine and regulate tissue activity. We can trace this, for instance, in the physiological ideas of Descartes and Liebig, and in ideas still to some extent prevalent as to the causes of respiratory exchange, secretion, and growth. Closer examination has shown that breathing and circulation are responses to tissue activity, and do not primarily determine it.

Another tendency has been to regard the nervous system as the primary autonomous regulator of breathing and circulation. The evidence brought forward above has shown, however, that the regulative influence of the nervous system is not autonomous, but dependent on conditions of environment determined mainly by varying tissue activity.

In his "Leçons sur les phénomènes de la vie" (p. 121) Claude Bernard drew the conclusion that "all the vital mechanisms, varied as they are, have only one object, that of preserving constant the conditions of life in the internal environment" (the blood). No more pregnant sentence was ever framed by a physiologist, and the long series of investigations described in the present book may be regarded as an attempt to follow out in regard to blood reaction and oxygen supply the line which Bernard indicated. Physiological activities can in one sense be summed up in the "preservation of the conditions of life in the internal environment," with consequent maintenance of normal structure. In another sense, however, physiological activity is constantly disturbing the internal environment. What is actually maintained is a dynamic balance between the disturbing and restorative activities. The order displayed in this dynamic balance is the order of biology.

In view more particularly of Paul Bert's experimental demonstration that the physiological action of gases dissolved in the blood depends on the pressures which they exert in the surrounding atmosphere—that is to say on their vapor pressures—we may conclude that it is the diffusion pressures of substances dissolved in the blood that correspond to Bernard's "conditions of life." This definition includes temperature: for diffusion pressure, other things being equal, varies as the absolute temperature and indeed gives us our measure of temperature, since the expansion of gases or liquids, by which we measure temperature, depends on increase of diffusion pressure.

It is a familiar fact that, apart from the contained gases, the composition of blood plasma is extremely constant. The varied experiments initiated by Ringer and carried forward by many other observers indicate directly the physiological importance of the various salts or their ions which are present in blood plasma, and render intelligible the exactitude with which their concentrations are regulated by the kidneys. The facts collected in the present book show that also as regards hydrogen and hydroxyl ions and free oxygen the composition of the blood plasma in contact with any particular part of the tissues is, and must be, very constant, and is kept so by regulation of breathing, circulation, kidney excretion, and other physiological activities. Thus oxygen and hydrogen and hydroxyl ions take their place in a strict quantitative sense beside the salts, proteins, sugar, etc., which help to make up Bernard's "conditions of life."

We also now know that what is called the osmotic pressure of blood plasma is so constant that the existing methods of measuring it by depression of freezing point or vapor pressure are too coarse for the detection of such differences as are constantly occurring during life and evoking the ordinary physiological responses of the kidneys and other organs. Osmotic pressure depends, however, as already mentioned (Chapter VIII) on the difference between the diffusion pressure of a solvent in a solution and in the pure solvent. It is thus in reality the diffusion pressure of water in the blood that is maintained so constant. The diffusion pressure of water can thus be placed in the same category as that of other substances among Bernard's "conditions of life." The experiments of Priestley and myself[1] on the excretion of water by the kidneys show that the regulation by the kidneys of the diffusion pressure of water in the blood is comparable in its extreme delicacy to the regulation of blood reaction.

As a general rule salts, water, and various other substances present in blood plasma are to only a very small extent used up by or given off from the tissues. Hence in the case of most tissues it would require only a very slow circulation to keep the concentrations of these substances constant in the blood, provided that the temperature was constant. If, however, the circulation were much slower than it is, and if this were rendered possible by the provision in the blood of much greater capacity for carrying oxygen and CO_2 as easily dissociable compounds,

[1] Haldane and Priestley, *Journ. of Physiol.*, L, p. 296, 1916; Priestley, *Ibid.*, L, p. 304, 1916.

the even regulation of temperature in the body would apparently become impossible, and in other ways the physiological interconnection between different parts of the body would be less close and rapid.

Although water and salts are by ordinary measurements neither absorbed by nor given off from most living tissues, it is evident that this only means that passage of them into the tissues is balanced by passage outwards. A liquid, like a gas, consists of molecules in rapid movement and diffusing in all directions. We cannot follow the movements of individual molecules, and can only detect gain or loss when either the relative proportions of different kinds of molecules alter, or the total number increases or diminishes. When as many molecules or ions of any one substance are passing in as are passing out there appears to be neither absorption nor giving off of the substance. Nevertheless there is continuous molecular or ionic exchange, and the blood is in constant and active physiological connection with the surrounding tissues. As is shown by the immediate effects of altering the diffusion pressure of salts, water, or other blood constituents, the exchange of molecules continues during life, whether a tissue is "active" or "resting." In reality there is constant physiological activity, and the conventional sharp distinction between conditions of rest and activity is extremely misleading.

From the standpoint of physical chemistry life depends upon the maintenance of a balance of molecular exchanges between the tissue elements and their environments. If the balance is disturbed, so that, for instance, too many or too few water molecules or potassium, calcium, or sodium ions are passing from the blood to the tissues or vice versa, life is imperiled. The case is exactly similar with oxygen molecules, or with hydrogen and hydroxyl ions. If the oxygen diffusion pressure in the plasma falls so low that the proportion of oxygen molecules passing in is abnormally low as compared with that passing out there is physiological disturbance; and similarly, as shown in Chapter XII, when too much oxygen is passing inwards.

Hitherto the supply of oxygen has not been regarded from this standpoint. It has been generally assumed that the oxygen molecules are all passing in one direction and that an irreversible reaction occurs in the living tissues by which oxygen is fixed so that no free oxygen molecules are returned to the environment. The facts indicating the great importance of a certain definite diffusion pressure of oxygen in the immediate environment of the

tissue elements are inconsistent with this view. The experimental evidence shows that we must place the diffusion pressures of oxygen and carbonic acid in exactly the same category as the diffusion pressures of water, salts, and other dissolved constituents of blood plasma. This means that oxygen molecules are constantly passing both outwards and inwards, although in ordinary tissues more are passing inwards. It is only in oxygen-secreting tissues that we find that on one side of the secreting membrane oxygen molecules are passing more readily outwards, and only, so far as yet known, in the green parts of plants and in the presence of light that free oxygen is on all sides passing more readily outwards from living tissue elements than inwards. But even in green plants, as Paul Bert showed, a considerable diffusion pressure of oxygen is necessary for life.

We can thus compare living structures to dissociable chemical molecules and particularly molecules which, like haemoglobin, form molecular compounds only capable of existing in so far as rate of loss is balanced by rate of gain. We must, however, assume that the dissociation and association are taking place simultaneously in many different directions, corresponding to the many different substances present in the blood plasma and necessary for life. We have also to remember that although the individual tissue elements are all in connection, direct or indirect, with the blood plasma, they are also in connection with one another, and that this implies additional conditions of stability in connection with which molecular or ionic gains and losses are balanced against one another.

It is clear that the stability in respect of one kind of molecular gain or loss determines the stability in respect of others. Thus a small deficiency of oxygen molecules, or a small excess of hydrogen ions, in the blood plasma, disturbs the equilibrium of the receptor elements in the respiratory center and leads to the extra molecular discharges which show themselves in increased activity of the center. Disturbances in other directions of the composition of the blood plasma have similar results, though the receptors are specially sensitive to changes in reaction or deficiency in oxygen pressure. We can interpret similarly the mode of action of various stimuli acting on living tissues, including what, for want of more intimate knowledge, we call mechanical stimuli. Hence we are led to the conception of a living organism as the seat of a vast system of mutually dependent reversible chemical reactions. For irreversible chemical reactions physiology has but little use.

The mechanistic interpretation of life fails to take account of the mutual dependence throughout a living organism of these reactions. When we remove any part of the organism from its physiological connection with its environment including the other parts, we at the same time necessarily alter its reactions and the stability of its living structure. Hence we cannot investigate an organism as we investigate the parts of a machine by taking them apart and ascertaining the properties and structure of each separate part. The same criticism applies to what may be called the "hormone" theory of the interconnection between the parts of an organism. On this theory the interconnection is brought about through the existence of special chemical messengers, or "hormones," produced in minute quantities by each organ, and bringing about specific excitatory effects, resulting in coördinated action. The hormone theory, like the mechanistic theory, tacitly assumes that, apart from the influence of hormones, and of the central nervous system, each part of an organism leads an independent existence. The truth is that every substance which enters into the life processes of any part of an organism is as much a hormone as any other such substance. Water, for instance, is the most abundant constituent of the body, and a very minute excess in the diffusion pressure of water in the blood excites very striking reaction in the kidneys. This minute excess seems, therefore, to act as a hormone, just as a minute deficiency in alkalinity or in oxygen pressure acts as a hormone to the respiratory center. Since, however, water, hydrogen and hydroxyl ions, and oxygen are influencing the body continuously, the conception of them as hormones, acting only occasionally, is quite misleading. The physiological interconnection between different parts of the body is continuously in existence and far more intimate than is assumed by either the ordinary mechanistic theory or the hormone theory.

In the case of chemical compounds which we ordinarily regard as being stable in their existing environment, and not in a constant state of association and dissociation, it is well known that the particular nature of one of the atomic linkings may make a great difference to the others. Thus the general properties of an organic compound may be greatly changed when a hydrogen atom is replaced by a chlorine atom or a methyl radicle. We have also seen in Chapter IV how in oxyhaemoglobin the affinity of the haemochromogen part of the molecule for oxygen is affected by changes in environment affecting primarily another part of the molecule. From the point of view of our present chemical knowl-

edge there is thus nothing new in principle in the fact, characteristic of physiological reactions, that any particular reaction is dependent upon the whole life of an organism. Nevertheless it is just here that we strike the dividing line between the physical sciences and biology.

A physiological reaction, when we examine it closely, is always found to depend on a vast number of conditions of structure and environment. It is true that under "normal conditions" the same stimulus will produce the same reaction again and again; but when we inquire what normal conditions represent we find something which is indefinitely complex from the physical and chemical standpoint. We have only to alter slightly the diffusion pressure of one or other of the many substances, only partially known, in the blood plasma, in order to obtain a quite different reaction. For instance a given fall in the diffusion pressure of oxygen fails to excite the respiratory center if the hydrogen ion concentration of the blood is very slightly below normal; and if the calcium ion concentration were a little above or below normal there would doubtless also be an abnormal result. The presence of a trace of ether or morphia, or probably of numerous other substances, affects the center in a similar manner. The excitability of a tissue to any given physical or chemical stimulus may thus vary indefinitely under slightly different conditions.

If we attempt to investigate physiological phenomena from the standpoint merely of physics or chemistry, we are thus at once landed in confusion. In investigating ordinary physical or chemical phenomena, we can examine one by one the parts or units we are dealing with and ascertain their properties, so that from the empirical knowledge thus gained we can predict what will result when they act on one another. In other words we can give physical and chemical explanations of their mutual action. But when we attempt to do this as regards the actions on one another of the parts of an organism, or of the organism and its environment, we are met by the difficulty that we cannot ascertain the structures and properties of any of the separate parts, since their structures and properties actually depend on the existing physiological relations of the parts and environment to one another. The relativity of the phenomena confronts us at every turn in the attempt to reach physical and chemical explanations of physiological reactions.

Up to a certain point we can, it is true, understand living organisms mechanically. We can, for instance, weigh and measure them

and their parts, and investigate their mechanical and chemical properties. This enables us to predict certain points in their behavior, as shown, for instance, in Chapters IV and V. But when we look more closely it becomes quite evident that the knowledge we gain from mere physical and chemical examination hardly touches any fundamental physiological problem. We cannot escape from the relativity of the phenomena we are dealing with.

The only way of real advance in biology lies in taking as our starting point, not the separated parts of an organism and its environment, but the whole organism in its actual relation to environment, and defining the parts and activities in this whole in terms implying their existing relationships to the other parts and activities. We can do this in virtue of the fundamental fact, which is the foundation of biological science, that the structural details, activities, and environment of organisms tend to be maintained. This maintenance is perfectly evident amid all the vicissitudes of a living organism and the constant apparent exchange of material between organism and environment. It is as if an organism always remembered its proper structure and activities; and in reproduction organic "memory," as Hering figuratively called it,[2] is transmitted from generation to generation in a manner for which facts hitherto observed in the inorganic world seem to present no analogy. We can discover and define more and more clearly by investigation these abiding details of structure and activity, distinguishing accidental appearances from what is really maintained; and this process of progressive definition is the work of the biological sciences.

If we look back on the general outcome of the investigations summarized in this book, it is evident that the progress made has consisted in distinguishing underlying identity of activity amid superficial appearances which at first sight present confusion. In the second and third chapters it was shown that behind the irregularities of ordinary breathing the mean pressure of CO_2 in the alveolar air is maintained steady within narrow limits for each individual; and in a later chapter it was more definitely shown that this implies a similar steadiness in the CO_2 pressure of the respiratory center. In Chapter VIII this conclusion is widened by the evidence that CO_2 pressure is only important as an index of blood reaction, and that it is blood reaction, and not mere pressure of CO_2, that is kept so constant by the breathing. In Chap-

[2] E. Hering, *Memory as a Generalized Function of Organized Matter* (1870). English Translation, Chicago, 1913.

ters VI, VII, and IX it is shown that there is similar maintenance of the pressure of oxygen in the blood, and in Chapter X evidence is collected that the circulation is so regulated as to keep both the oxygen pressure and the reaction very nearly steady in each part of the body. Chapter XIII deals with the manner in which the body adapts itself to an abnormal atmosphere in accordance with the principles laid down in preceding chapters.

It is thus with the dominant fact that in various definite respects the internal environment of the living body tends to be maintained very steady that the investigations brought together in the preceding chapters have mainly dealt. This dominant fact is what makes a scientific treatment possible in actual practice, and furnishes us with principles by means of which we can predict physiological responses and at the same time gain a practical control of the living body, such as is required in medicine and surgery.

When we find that a certain characteristic structure and internal environment exists within a living organism, we have discovered what at first sight appears to be a fact capable of definition, though not of explanation, in physical and chemical terms. Thus the "normal" diffusion pressures of substances present in the blood are simply diffusion pressures which we can measure and define, one by one, in ordinary physical and chemical terms. But when something occurs which tends to alter one of the diffusion pressures, or to disturb the structure, we realize more fully the real nature of what is maintained in a living organism: for the alteration is not entirely prevented, but met by active readjustment of such a character that what we easily recognize as organic identity is maintained. If, for instance, the oxygen pressure in the air inspired is lowered, a quantitatively corresponding lowering in the oxygen pressure of the blood passing through the tissues is prevented by increased breathing, oxygen secretion by the alveolar epithelium, and rise in the haemoglobin percentage. At the same time other disturbances which would naturally result from these changes are met by diminution in the "available" alkali in the blood, increase in blood volume, and so on. A widespread readjustment of physiological activities and of blood composition has thus occurred, but with the result that the more fundamental diffusion pressures of oxygen, hydrogen and hydroxyl ions, etc., have altered only very little, and in this slight alteration they have held together as a whole. The oxygen pressure, for instance, is not restored at the expense of hydrogen-ion pressure or excessive

work of the heart or lungs. What is maintained in the tissue environment is oxygen pressure in its organic relations. The relativity to one another of the phenomena of life stands out clear in this maintenance of organic identity.

In the course of biological investigation we meet on all hands with similar examples of maintenance and reëstablishment of organic identity; and the existence of this actively-maintained identity is the scientific basis of practical medicine and surgery. But for the fact that functional as well as structural compensation is constantly occurring, not only under ordinary physiological conditions, but also in cases of injury by disease or accident, and that by observation and experiment we can learn to understand, predict, and aid it, physicians and surgeons would be absolutely helpless. Neither scientific biology nor scientific medicine could be based on the ordinary working hypotheses of physics and chemistry, since these hypotheses furnish no sufficient means of understanding and predicting biological phenomena. Biologists, physicians, and surgeons are not, and never will be, simply chemists and physicists.

In physiology we are always dealing with responses to immediate stimuli; but the responses are evidently determined in relation to the maintenance of organic identity. They are organic responses, and are simply rendered unintelligible when by the common confusion in thought running through so much of the present teaching of physiology they are represented as examples of mechanical determination. Such expressions as the "mechanism" of respiration, or secretion, or of maintenance of the internal environment generally, are examples of this confusion. On closer examination all the assumed mechanical reactions turn out to be expressions of the organic maintenance which is the subject matter of the biological sciences.

Biology must take as its fundamental working hypothesis the assumption that the organic identity of a living organism actively maintains itself in the midst of changing external appearances. This identity is not physical identity nor identity of form or chemical composition, but something which we can perceive and trace by exact quantitative investigation just as readily and exactly as we perceive and trace physical identity in what we interpret as the inorganic world. The science which traces this organic identity is biology. Anatomy or morphology traces it as regards structure, and physiology as regards activity. But since organic structure is only the outcome or expression of ordered activity,

and organic activity only the activity which expresses itself in organic structure, the two branches of biology are in reality one, and we may look forward to a time when the present wholly artificial and sterilizing separation of them will disappear along with the disappearance of the mechanistic theory to which the separation is due.

The true scientific procedure of biology is different from that of the physical sciences. In physics and chemistry the procedure employed is to ascertain the properties of the separate units of matter and energy with which it is assumed that these sciences deal. Thus from the properties and movements of the parts of a material system such as a machine we can predict its behavior and can design and control machinery. From the properties and movements of the molecules in a given quantity of gas we can predict its behavior. From the properties of the atoms of carbon and other elements we can predict the existence and many of the properties of carbonaceous and other compounds. But we cannot predict in this way the behavior of a living organism. The relationships, for instance, into which the carbon atoms as interpreted by chemistry enter within living organisms show themselves to be too complex and changeable, so that, apart from the biological method of treatment, we should be totally at a loss. In the physical sciences we are looking at collections of units, each of which is looked at from the outside. In biology we are looking at each unit from the inside, and biological results afford abundant justification for this method of looking at them.

It may appear at first sight as if the biological method were unscientific, and the claim may be made that it ought to be, and ultimately must be, possible to advance in biology by the method of the physical sciences. This claim must now be examined carefully.

The reason why the physical or chemical method of treatment is so unsatisfactory in biology is that in connection with living organisms the properties of the parts show peculiarities which we do not meet with in what we distinguish as the inorganic world. Let us take the case of nitrogen atoms. When nitrogen is present as a gas at an ordinary temperature the properties of its molecules seem to be very simple for all practical purposes. The molecules simply repel one another when they meet, or when they encounter molecules of other gases; and the kinetic theory of gases, based on this simple assumption, enables us to predict with the greatest accuracy the behavior at ordinary temperatures and

pressures of a mass of gaseous nitrogen or of a mixture of nitrogen with another gas. But if we raise the temperature sufficiently, and hydrogen or oxygen is present, the nitrogen combines with it, forming ammonia or oxides of nitrogen. The properties of nitrogen have thus shown themselves to be more complex than the simple kinetic theory of gases assumed. But from the atomic theory as applied in chemistry, and the theory of valencies, we can still predict more or less successfully the composition of the compounds formed by the nitrogen. Most of their special properties have to be ascertained by experiment; but once ascertained they can be used for the purpose of predicting how these compounds will behave under quite new conditions. It is exactly the same when we come to the complex proteins and other organic nitrogenous compounds which can be separated from the bodies of organisms. So long as they are separated from living organisms we can investigate them just as we investigate other chemical compounds, and they present no real obstacle to such investigation.

The obstacle appears whenever the assumed chemical molecules are participating in the life of an organism. Their properties seem then to become fluid and dependent from moment to moment on the position of each molecule relatively to multitudes of other molecules of the most diverse kinds. We consequently cannot trace the individual molecules, and cannot tell whether or how they are in combination with other molecules. They seem to develop a quite indefinite potentiality of exhibiting unsuspected properties.

Now this fact shows us clearly that the simple atoms and molecules of physics and chemistry are only a sensuous illusion: for, behind the supposed simplicity, indefinite potentialities are hidden and actually show themselves in connection with the phenomena of life. The properties and activities of what we call atoms or molecules are in reality a function of their relations to other atoms and molecules; and this fact, which is not at once evident in what we call the inorganic world, becomes perfectly evident in biological phenomena. Organic individuality is something very evident to our perception, and has thus the same claim to reality as inorganic structure; but, from a purely physical and chemical point of view, living structure and activity constitute not merely a molecular flux like that of a river or a flame, but an altogether undefinable flux—undefinable because we cannot define the molecular changes. It is *biological* and not physical or chemical structure and activity which biological investigation enables

us to define more and more accurately and fully. Only when an organism is dead do we seem to have before us a physical and chemical complex.

Those who insist that physiological activity must in reality be physical and chemical change have to answer a previous question as to the justification for the assumption of physical and chemical reality. The molecules, atoms, and electrons of the physical sciences seem real enough so long as we confine ourselves to the superficial aspect of reality which is dealt with by the physical sciences; but it is the same reality that is dealt with by biology, and we reach a different interpretation of it through the study of biological phenomena. In this interpretation the self-existent individuality of atoms and molecules fades away in relativity.

The modern world has become so accustomed to the materialistic assumption which identifies the mechanical interpretation of reality with actual reality that in spite of the existence of biology, psychology, ethics, religion, and philosophy it is difficult at present to obtain even a hearing for the view that physical reality represents no more than superficial sensuous appearance. By the help of various makeshift hypotheses such as those of vitalism or animism, the real philosophical problem as to the ultimate validity of the physical interpretation of reality has been evaded for the time. But these evasions cannot satisfy us, and the problem comes up in a clear-cut and definite form in connection with the relation of biology to physics and chemistry. The facts dealt with in the latter sciences present us with one interpretation of "reality," or "nature," and those dealt with by the former present us with a different one.

Which of the two interpretations corresponds more closely to actual reality? There appears to me to be no doubt that the biological interpretation does. The progress of the physical sciences has taught us that the gases, liquids, and solids which to superficial examination appeared to be continuous and inert substances are not only discrete but made up of molecules in continuous relative movement, and, in the case at least of solids and liquids, continuously affecting one another's movements and properties. We now know also that atoms themselves are systems of still more elementary units moving relatively to one another at enormous velocities, and that in chemical combination, and even in solution or what we call simple mechanical interaction, these systems are modified, as shown, by electrical phenomena. The chemist can

determine with great apparent accuracy the proportions of hydrochloric acid and water in an aqueous solution. In actual fact there may be practically no hydrochloric acid molecules present and far fewer simple molecules of water than would appear from the analysis, since the molecules are partly ionized and partly combined with one another in various forms. Consequently the results of the analysis represent only a "practical" convention, however useful this convention may be. In reality the properties of both the conventional hydrochloric acid and the conventional water depend on the particular conditions existing in the solution. But the inquiry can be, and has been, pushed still further. At first sight it seems as if, in whatever way the molecules of water and hydrochloric acid may be split up or combined, the mass present is something independent of changeable relations. But here, again, the progress of physical science has indicated that even the mass of what is present depends upon relative movement, and finally that absolute movement in empty space is a conception to which no experimentally verifiable meaning can be attached.

We only deceive ourselves when we imagine that in physical and chemical investigation we are free of relativity. Behind all the superficial appearances of a "real" physical world, relativity finally appears; but in biological phenomena the relativity is always evident and prominent, and precludes the possibility of even a conventional physical and chemical interpretation of the observed facts. In frankly accepting relativity, and framing her interpretations on a principle based upon it, biology comes a step nearer to actual reality than the physical sciences.

It has come to be popularly believed that if we knew enough of the physics and chemistry of what occurs in a living organism biological interpretation could be reduced to physical and chemical interpretation. Though the attempts to give physical and chemical interpretations of biological phenomena have never been successful, and their failure in detail is becoming more and more evident with the progress of both physiological and physical investigation, labored endeavors are still made to teach physiology and represent the growing body of physiological knowledge in physical and chemical terms. The investigations described in the present book illustrate the fruitlessness of these attempts. In the phenomena connected with breathing we are everywhere dealing with organic regulation—in other words with the manifestations amid superficial changes which at first sight puzzle and confuse

us, of organic identity. It is the same in connection with the phenomena of circulation, excretion, absorption, and other physiological activities. I wish to claim very definitely that in dealing with biological phenomena and putting her questions to Nature, biology must use her own working hypothesis, and not those of the physical sciences.

The organic regulation which we find everywhere in a living organism does not represent something imposed from without on the processes occurring in the organism, but is simply a natural expression of the reality which is present. It is Nature we are studying in biology, not a special "vital force" or other supernatural influence. But the biologist must be free to interpret Nature in his own way; and it is Nature as Hippocrates saw her, and not as Democritus saw her, that he sees and cannot help seeing. Organic regulation, maintenance, and reproduction are nothing but the expression of this biological Nature.

The universal acceptance among biologists of the doctrine of evolution has often been assumed to carry with it the corollary that life has arisen out of inorganic conditions; and in this way a short cut has been made to the conclusion that biology must in ultimate analysis be nothing but physics and chemistry. This reasoning cannot be justified. Even in the simplest forms of life it is still unmistakably life that we are dealing with; and if we succeed in tracing life to yet simpler forms we shall still find life, so that the "inorganic conditions" into which we have traced life will appear to be something very different from inorganic conditions as we now represent them to ourselves.

We can see, and particularly clearly in the case of higher organisms, that the life of each organism is an association of the lives of more elementary organisms, each of which shows its full being only in the life of the whole, but is also more or less capable of independent existence. It is by the separation and subsequent full development of these more elementary organisms that reproduction is brought about. The life of a higher organism has been said to be the "sum" of the lives of its constituent cells. Such an expression is, however, misleading: for a cell apart from its particular place in the living body, or the particular environment which exists there, behaves very differently from the same cell in its proper place. It thus cannot be physiologically defined apart from its place in the whole organism. The organism as a whole is no less real because it includes in its life the lives of individual cells, and each cell, as shown very clearly in connection with the

facts first discovered by Mendel with regard to reproduction, includes the lives of still more elementary centers of life. The same reasoning applies, of course, to communities of what appear at first to be quite separate organisms. An organism separated from its kind is an artificial abstraction, just as is an organism separated in other ways from its environment.

Although such processes as respiration, circulation, secretion, absorption, and various forms of nervous activity, occur independently of consciousness, many bodily activities are accompanied by consciousness. Muscular exertion, for instance, is for the most part consciously determined, and as muscular activity determines breathing, and in other ways the breathing is determined by conscious activity and under direct conscious control, it is necessary to refer to the relation of conscious to unconscious bodily activity.

We can interpret unconscious physiological activity from the biological standpoint which has hitherto served us in the interpretation of breathing, circulation, etc.; but it is different with conscious activity. In perception we are aware of what we interpret as "objective reality," and voluntary actions are quite evidently determined by this awareness. The awareness signifies that in perception, as distinguished from a simple physiological reaction, the reaction is not simply definable as occurring at a certain moment or within a certain definite time, but involves also past and future times, as well as surrounding space. When I see my pen now, I see it as a material structure which has existed and will continue to exist. I also see it as being in relation to many other things not at the moment visible in the physiological sense. The light in which I see it is not merely that of an electric lamp but of all my other experience. When I write with the pen the movements of my muscles are determined by the actual presence to me of innumerable past, present, and anticipated future events in both my own individual history and that of mankind. The past events are not simply past and done with, like events interpreted physically or biologically, but they, and not their mere effects, are still present and active. What I have experienced before, what, for instance, I have read of Hippocrates, or Johannes Müller, or Claude Bernard, or Paul Bert, is still taking on fresh meanings in my mind and directly determining my action now. The same is true of all I have absorbed of the common spiritual heritage and anticipations for the future of my country or of mankind. Actual memory is no mere organic memory. I am living and acting in a

spiritual world for which separation, not merely in space, but also in time, has none of the meaning which it possesses for the world interpreted physically or biologically. Along the years and across the oceans action and reaction are direct in this spiritual world.

It is evident that in conscious activity we are face to face with facts that neither physical nor biological hypotheses are capable of interpreting. Yet conscious activity manifests itself in connection with the same beings that seem also to live and breathe as mere organisms, or to consist of nitrogen, hydrogen, oxygen, carbon, and other atoms leading a wild and undefinable dance. In presence of the evidence of life we cannot rest satisfied with the physical and chemical interpretation of these beings; but similarly in the presence of conscious activity we cannot rest satisfied with the biological interpretation. Biological phenomena show us that the physical interpretation of the universe is only an imperfect preliminary interpretation for which all that can be said is that it is of essential practical use in the absence of fuller knowledge. But the facts relating to perception and volition show us that the biological interpretation is also no more than a practical makeshift. As mathematicians, physicists, chemists, biologists, we are only "practical" men, though we often take our practical working hypotheses for representations of actual reality. We do so by unconsciously neglecting for the time a great part of the facts to be explained—in particular the facts that our world not only includes living organisms, but is a *known* world and a world of spiritual values. In reality our sciences are only making use of abstractions of a limited practical value.[3]

In conscious activity the self-conserving and species-conserving organic activities of living organisms take on a new and far wider interpretation. Mere organic self-conservation appears now as conservation of a system of consciously realized interests; and social interests assume a commanding position as compared with individual interests. In so far as bodily interests are carried out consciously, therefore, the physiological interpretation of them recedes into the background; and this is still more true of the physical and chemical interpretation.

In the preceding chapters, I have attempted to justify the physiological interpretation of unconscious bodily activities by pointing out how breathing, circulation, etc., are manifestations

[3] A fuller discussion of this point of view will be found in my book "Mechanism, Life and Personality," New Edition, 1921.

of the maintenance of organic identity. Up to a certain point one can apply the same reasoning to conscious activities by showing how exquisitely dependent they are from moment to moment on the integrity of normal "conditions of life" in the internal environment, and how they play their part in maintaining this integrity in accordance with Claude Bernard's conception. But such treatment of them is wholly insufficient, since they evidently participate in that spiritual world to which reference has already been made. Hence they cannot be described in terms of the working hypotheses of biology, and attempts to describe them adequately in such terms are merely childish. *A fortiori* they cannot be described in physical terms.

Perception and volition are often referred to as processes occurring in the cerebral hemispheres as a result of physical impulses communicated along sensory nerves from outside. For certain limited practical purposes this is a useful view to take of them. But, as already pointed out, perception and volition as such are not capable of description as events occurring at a certain time and place, since from their very nature they include other times and places, and may be said to be creative of time and space. The working conception under which we attempt to describe them as events occurring here and now is totally inadequate; and in so far as we express them in terms of this conception we reduce them to mere abstractions. By a process of abstraction we can observe in ourselves and interpret as mere physiological or even physical events our perceptions and voluntary actions. These observations constitute an important part of our existing practical knowledge, but they belong to physics or physiology, and not to psychology, since in making them we deliberately leave out of account all that is characteristic of conscious activity.

To those who argue that all our conscious activities are dependent on physical conditions, the reply is that "physical conditions" are in ultimate analysis only imperfect abstractions. If once we regard them as anything more, we are plunged into all the difficulties which modern philosophy since Descartes has been continuously and successfully grappling with. The universe is a spiritual universe, and not a dualistic universe of matter and mind.

This book is concerned with physiology and not psychology. I have claimed for physiology its rightful practical sphere in distinction from that of physics and chemistry. But we have reached a limit to the sphere of physiology when we come to deal with conscious activity.

APPENDIX

THIS appendix contains a description and discussion of several special methods of blood examination associated with my name, together with modifications introduced by myself and others since the methods were originally described. Methods of gas analysis are not included, since these are collected in my book "Methods of Air Analysis."

Until a few years ago the gases present in the easily dissociable and free state in blood were universally determined by means of the mercurial vacuum pump, which had been gradually perfected by Lothar Meyer, Ludwig, Pflüger, and others, while Leonard Hill had considerably simplified it for ordinary uses. It required, however, an inconveniently large amount of blood and was also not very accurate, since even when large volumes of blood were used errors due to gas adhering to the glass could not be avoided. The presence of these errors was clearly shown by the fact that the amount of nitrogen apparently obtained from the blood was not only variable, but much greater than the amount which the blood was capable of dissolving. The excess of nitrogen could be calculated as due to contamination with air from the pump; but this correction was not very satisfactory, since gas must also be left in the pump at the end of the operation of pumping. The discovery which I made in 1897, that oxygen or CO can be liberated quantitatively from oxyhaemoglobin or CO haemoglobin by ferricyanide,[1] made it possible to dispense with the blood pump and greatly simplify blood-gas determination and increase its accuracy. With the new method Lorrain Smith and I found also that the oxygen capacity of blood varies exactly as its coloring power, so that the oxygen capacity can be determined colorimetrically. The methods now to be described are based partly on the ferricyanide reaction and partly on the colorimetry of blood.

A. Determination of Oxygen Capacity of Blood Haemoglobin by Ferricyanide

The following method of determining very accurately the oxygen capacity of the haemoglobin in blood or a solution of haemoglobin was first fully described in 1900.[2] Although the oxygen capacity can be determined with much smaller quantities of blood by the apparatus described below, it seems useful to describe also the earlier method, as it

[1] Haldane, *Journ. of Physiol.*, XXII, p. 298, 1898.
[2] Haldane, *Journ. of Physiol.*, XXV, p. 295, 1900.

can be carried out with very simple apparatus, easily put together in any laboratory, and suitable not only for exact research, but for use by students. The chemical facts on which the method is based have already been referred to in Chapter IV.

The apparatus is shown in Figure 101 and the process is as follows. Twenty cc. of the oxalated or defibrinated blood thoroughly saturated with air by rotating it in a large flask, are measured out from a pipette into the bottle A, which has a capacity of about 120 cc.

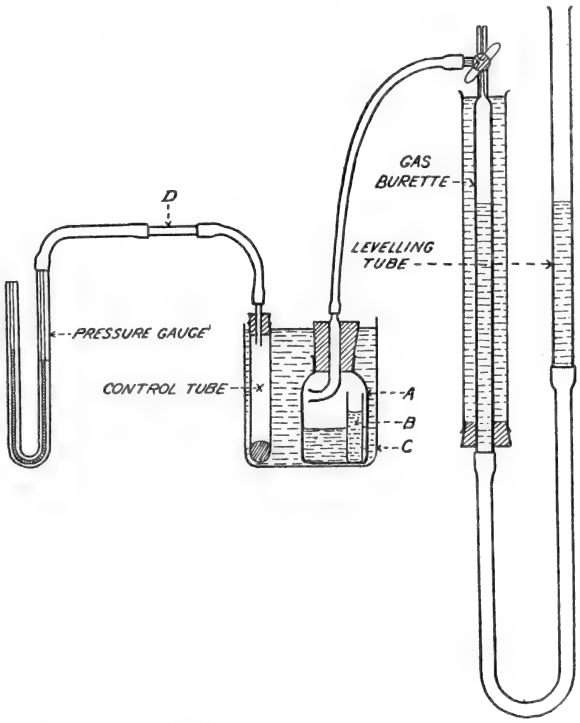

Figure 101.
Apparatus for determining the oxygen capacity of haemoglobin in blood.

As it is important to avoid blowing expired air into the bottle, the last drops of blood are expelled from the pipette by closing the top and warming the bulb with the hand. In filling the pipette, care must also be taken that the corpuscles have not had time to begin to subside in the vessel from which the pipette is filled. Thirty cc. are then added of a solution prepared by diluting ordinary strong ammonia solution. (sp.

gr. 0.88) with distilled water to 1/250th, and the mixture shaken. The ammonia solution prevents CO_2 from coming off and also lakes the blood. Unless the blood is laked, the ferricyanide cannot act on the haemoglobin, since the corpuscle walls are impermeable to ferricyanide. About 4 cc. of a saturated solution of potassium ferricyanide are then poured into the small tube B (the length of which should slightly exceed the size of the bottle) and placed upright in A. The rubber stopper, which is provided, as shown, with a bent glass tube connected with the burette by stout rubber tubing of about 1 mm. bore, is then firmly inserted, and the bottle placed in the vessel of water C, the temperature of which should be as nearly as possible that of the room and of the liquid in the bottle. If the stopper is not heavy enough to sink the bottle, the latter should be weighted. By opening to the outside the three-way tap (or a T tube and clip) on the burette, and raising the leveling tube, which is held by a spring clamp, the water in the burette is brought to a level close to the top. The tap or T tube is then closed to the outside, and the reading of the burette (which should be graduated to .05 cc., and read to .01 cc.) taken after careful leveling, as soon as the temperature has become constant, as shown by the constancy of the reading. Meanwhile the water gauge (which has a bore of about 2 mm.) attached to the temperature and pressure-control tube is accurately adjusted to a definite mark. This is easily accomplished by sliding the rubber backwards or forwards on the narrow glass tube D. The control tube is an ordinary test tube containing some mercury to sink it.

As soon as the reading of the burette is constant, the bottle is tilted so as to upset B, and is shaken as long as the gas is evolved. During this operation B should be repeatedly emptied, as otherwise the oxygen dissolved in its liquid might not be completely given off. When the evolution of gas has ceased, the bottle is replaced in the water. If, as is probable, the very sensitive pressure gauge indicates an alteration in the temperature of the water, cold water from a tap, or else warmed water, is added till the original temperature has been reëstablished, and the reading of the burette noted as soon as it is constant. The bottle is again shaken, etc., to make sure that the result is constant; and usually about fifteen minutes will be needed to complete the operations. The temperature of the water in the jacket of the burette[3] and the reading of the barometer are now taken, and the oxygen evolved is reduced to its dry volume at 0° and 760 mm. A table can be used for the reduction, and one is given in *Methods of Air Analysis*.

[3] The jacketing of the burette may be omitted, in which case the thermometer should be suspended with its bulb close to the upper part of the burette.

To calculate the oxygen evolved from 100 cc. of blood, allowance must be made for the fact that a 20 cc. pipette does not deliver 20 cc. of blood, but only about 19.6 cc. The actual amount of shortage can easily be determined by weighing. A further slight correction is needed on account of the fact that the air in the bottle at the end of the operation is richer in oxygen than at the beginning, so that, as oxygen is about a third more soluble than air, slightly more gas will be in solution. With a bottle of 120 cc. capacity and 20 per cent of oxygen in the blood, the air in the bottle will evidently contain about 26 per cent of oxygen, so that, assuming that the coefficients of absorption of oxygen and nitrogen in the 54 cc. of liquid in the bottle are nearly the same as in water, the correction will amount at 15° to .03 cc. in the reading of the burette, if the oxygen capacity is normal, or 0.75 per cent of the oxygen given off.

In order to make quite sure that no oxyhaemoglobin remains in the solution owing to a reshrinkage of corpuscles on adding the ferricyanide, and consequent escape of some of the oxyhaemoglobin from the action of the ferricyanide, the liquid in the bottle can afterwards be examined as follows. Part of it is diluted with 0.8 per cent salt solution, shaken up in a test tube with expired air so as to render the solution just acid, and examined spectroscopically. Any trace of oxyhaemoglobin left in incompletely laked corpuscles is shown by the presence of the characteristic absorption bands. These are completely absent if only methaemoglobin is present, as ought to be the case. If they are present the result will be too low, and the experiment must be repeated with saponin added.

If the blood is saturated with CO instead of oxygen the reaction is slower, but gives precisely the same result. The correction for physically dissolved gas is, however, scarcely appreciable, as CO is very little more soluble than air. If the blood has begun to decompose, owing to bacterial action, the result will of course be too low, and this can easily be detected, because of the fact that each successive reading of the burette will be lower, owing to the disappearance of oxygen.[4] There is no appreciable error, owing to the tension of ammonia vapor in the air; and the method is one of extreme accuracy and certainty. Different determinations ought not to differ by more than 1/200th of the quantity measured. On comparing the results with those from the pump, after allowance in the case of the pump for oxygen in simple solution in the blood, or adhering to

[4] Under certain abnormal conditions even fresh mammalian blood, as Douglas (*Journ. of Physiol.*, p. 453, 1910) has shown, may in presence of the ferricyanide absorb an appreciable amount of oxygen before a determination is complete: in which case the quicker method described below is greatly preferable. An appreciable absorption can also be detected in normal fresh human blood left for an hour or two in the apparatus.

the glass in the pump, I obtained the following results, using a large-sized Bohr pump with every precaution.

VOLUMES OF OXYGEN PER 100 VOLUMES OF BLOOD	*By blood pump*	*By ferricyanide method*
Defibrinated ox blood	24.38	24.43 24.35
Oxalated "	20.36	20.47 20.57
Oxalated "	22.40	22.20 22.33
Average	22.38	22.39

B. Determination of Oxygen Capacity of Blood Haemoglobin by Haemoglobinometer

Colorimetric methods of estimating the relative concentrations of haemoglobin in blood have been used for long; and in 1878 the late Sir William Gowers introduced his well-known and extremely convenient "haemoglobinometer" for clinical purposes.[5] In this apparatus there are two tubes A and B (Figure 102) of equal diameter; A is sealed and contains picrocarmine jelly of such strength and composition that when 20 cubic millimeters of normal human blood are diluted with water in the tube B to the mark 100, the tints of the liquid in the two tubes are the same. If the blood contains abnormally little or much haemoglobin, the quantity of water required to produce the tint of the standard picrocarmine solution will be correspondingly less or more, so that the percentage of the normal proportion of haemoglobin can be read off on the tube. The diameter of the tubes and strength of the picrocarmine or haemoglobin solution are so chosen that any variation from the normal strength can be perceived with the maximum of readiness. A solution much stronger or weaker would not be suitable. The design is thus not only extremely convenient, but also thoroughly correct in principle.

When it was discovered that the coloring power and oxygen capacity of haemoglobin are strictly proportional to one another it became evident

[5] Gowers, *Trans. Clinical Soc.*, XII, p. 64, 1878.

that the Gowers haemoglobinometer could be made a very exact instrument for determining the oxygen capacity of blood, and could also be improved in other respects. I introduced the necessary improvements in 1901.[6] For the picrocarmine solution there is substituted a 1 per cent solution of blood with an oxygen capacity of 18.5 cc. per 100 cc. of blood, since the average of a number of normal men showed that this is the average oxygen capacity for men. To make this solution keep its coloring

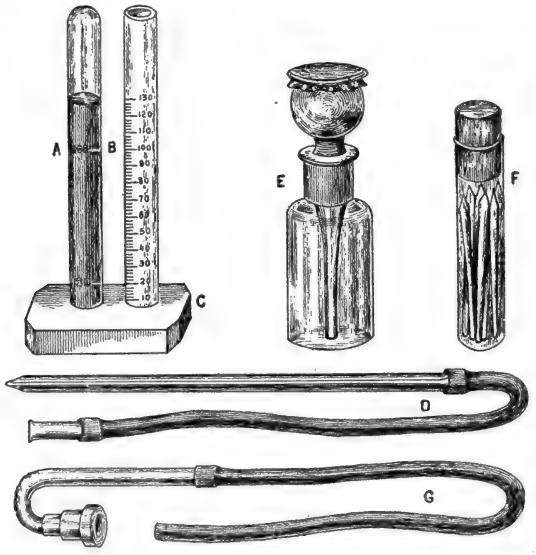

Figure 102.
Gowers-Haldane Haemoglobinometer
A—Glass tube containing blood solution of standard tint.
B—Graduated tube.
C—Rubber stand for tubes A and B.
D—Capillary pipette and suction tube; wires for cleaning the pipette are supplied.
E—Bottle with pipette stopper.
F—Glass tube holding 6 lancets.
G—Tube and cap for fixing over ordinary gas burners.

power it is saturated with CO, and sealed up with only CO, and no oxygen, in the empty space above the blood solution. Hoppe Seyler had already found that a strong solution of CO haemoglobin retains its coloring power. This is also true for a dilute solution; and the standard haemoglobinometer tubes filled and sealed twenty years ago have remained absolutely unaltered in color.

[6] Haldane, *Journ. of Physiol.*, XXVI, p. 497, 1901. The instrument is made by Hawksley, Wigmore Street, London, W.

One defect of the picrocarmine tubes arose from the fact that the picrocarmine is not completely stable, so that after a time its color alters. But even the original standard was somewhat indefinite, depending as it did on the particular percentage of haemoglobin in the sample of normal blood with which it was standardized. Another defect depended on the fact that the colors of the blood and picrocarmine solution are not the same spectrally. In consequence of this a color match with one quality of light is no longer a match with a different quality of light. Thus in ordinary artificial light the reading of the instrument is quite different from that in average daylight; and in different qualities of daylight, and with different observers, the match differs. The same defect exists in various later forms of haemoglobinometer, where colored glass or colored paper is used as a standard. By using CO haemoglobin as the standard solution, and saturating the blood under examination with CO or coal gas these defects are avoided.

To avoid errors due to inequality in the diameters of the tubes, each tube has first of all two marks placed on it—the first at the level when .2 cc. of water are introduced into a dry tube, and the second at the level given by 2 cc. The distance between these two marks must correspond exactly in the standard tube and measuring tube and this must be borne in mind if either tube gets broken and has to be replaced. The 20 cubic millimeter pipette is also standardized by weighing on a delicate balance.

To make a determination, some water is first introduced into the measuring tube. Twenty cmm. of blood from a prick in the finger or ear are then measured into this water from the dry pipette. The blood sinks, and the pipette is rinsed out with some of the water standing above the blood. Some coal gas or CO is then run into the upper part of the measuring tube through narrow rubber or glass tubing, and the top of the tube promptly closed with the finger. With the thumb of the same hand on the lower end of the tube the latter is then inverted several times so as to saturate the haemoglobin completely with CO, but without warming the contents of the tube. The finger can then be slid off the open end of the tube without the slightest loss of liquid. More water is now added by means of the dropping pipette until the tints appear equal. When this point is reached the level is read off after a short interval to allow liquid to run down. Another drop is introduced, and then another, until the tints appear unequal again; and the mean of the readings giving equality is taken as showing the required percentage. This indicates the oxygen capacity of the haemoglobin in percentages of 18.5 cc. of oxygen capacity per 100 cc. of blood.

In judging of equality in tint the tubes are held up before a window

or an opal shade covering a gas flame or electric lamp. At every observation the tubes are transposed. This is essential since it will be found that in all probability the tint of one tube will appear deeper when it is held on one side than when on the opposite side. If, for instance, the tubes are nearly equal in depth of color they will appear equal when one tube is on the right or left side, but not vice versa. A slight inequality of this kind is rather a help to accuracy, as probably only one reading will give equality on both sides. With careful work any error in a determination should not exceed 0.5 per cent. The method is thus one of great accuracy.

It is often loosely assumed that colorimetric estimations are uncertain. This is certainly not the case if they are properly carried out, with appreciation of the precautions needed to avoid the errors referred to above, of physiological origin. Another common misconception is that a uniform colored surface is necessary, and that, as a tube does not give this, a method such as that just described must be inaccurate. The surfaces need not be uniform, provided they are similar to one another, as in the case of two similar tubes.

The correctness of a Gowers-Haldane haemoglobinometer can be checked at any time by the ferricyanide method described under A or C. Another check on the correctness of the standard solution is that it must have practically the same pink tint as fresh blood saturated with CO. If there has been any defect in filling, the standard tube will appear yellower. With a proper standard tube one can tell at once by the absence or presence of yellow color whether a patient's blood is free from methaemoglobin or other abnormal blood pigments.

For ordinary clinical work it is convenient to work ordinarily with a picrocarmine standard tube, and only occasionally ascertain the correction necessary with this standard. The correction can easily be made by comparing the results for the same person and time with the two tubes.

C. Determination of Oxygen and Carbon Dioxide in Blood by Ferricyanide and Acid

As mentioned in Chapter IV, a method, based on the use of ferricyanide, was described in a paper by Mr. Barcroft and myself in 1902.[7] The principle of this method is that, without permitting any previous contact of the blood with air, the oxygen of a small measured volume of blood is liberated by ferricyanide in a closed vessel, and the pressure produced by the liberation measured without any alteration being allowed in the volume of gas in the vessel. The CO_2 is then similarly liberated by

[7] Barcroft and Haldane, *Journ. of Physiol.*, XXVIII, p. 232, 1902.

acid, and its pressure measured. When certain corrections are made, it is then possible to estimate either the total oxygen and total CO_2, or the combined oxygen and combined CO_2 in the blood. The gas is measured by the increase of pressure at constant volume, and not by the increase of volume at constant pressure. Theoretically, either method is correct, in accordance with Boyle's Law; but as Barcroft required a method for dealing with very small quantities of blood, and a very delicate pressure-gauge was needed in any case, it seemed simpler to graduate the pressure gauge in millimeters, and keep the gas at constant volume, retaining, however, the control vessel, as in the original form of apparatus. I therefore designed the apparatus as it was originally figured in our paper, and the tests we made gave very satisfactory results so far as they went.

One defect of the apparatus described in the previous section is that a considerable time is needed to reach temperature equilibrium and to shake out all the extra free oxygen from the blood solution. The latter defect would apply still more to an apparatus in which CO_2 had to be shaken out. In the new apparatus the volume of liquid was therefore greatly diminished, and the relative volume of air to blood solution greatly increased; and this was also rendered advisable owing to the fact that nearly as much CO_2 remains in solution in the liquid as is present in an equal volume of air. The increased volume of air had, however, the disadvantages, first that the pressure of ammonia in the air introduced an appreciable source of error, and secondly that much more care was needed as to temperature equilibrium in the blood vessel and control vessel. A further source of error was slight variation in capillarity at different levels in the gauges of the blood vessel and control vessel. In spite of all improvements in this apparatus and the methods of using it, there appears to be a range of error with it of at least 2 per cent of the quantity measured, even when the error due to ammonia vapor is completely eliminated.

The apparatus was rendered much more convenient, though also less easy to make or repair, by Brodie.[8] It was also simplified by Barcroft; who named his modification the "differential" apparatus.[9] Barcroft connects the gauges of the blood vessel and control vessel, so that there is only one manometer instead of two, and estimates the gas given off from the readings of this compound gauge. With this construction the apparatus works at neither constant volume nor constant pressure, so that the gas given off cannot be correctly deduced from the mere readings of the gauges. He therefore calibrates the apparatus empirically with the

[8] Brodie, *Journ. of Physiol.*, XXXIX, p. 391, 1910.
[9] Described fully in Barcroft's book, *The Respiratory Functions of the Blood.*

help of the oxygen liberated from a titrated solution of hydrogen peroxide. But this is a rather serious complication, and even if the calibration is correctly made it can only apply correctly at a certain barometric pressure and would not be quite valid over the variations of barometric pressure ordinarily met with. I cannot, therefore, regard this plan as satisfactory for some kinds of exact work. On the other hand this objection does not apply where the empirical calibration is not needed, as in determinations of the percentage saturation of haemoglobin with oxygen—for instance in investigating dissociation curves of oxyhaemoglobin. Barcroft has also devised a small model, for which only 0.1 cc. of blood is required.

A very different form of the ferricyanide method has recently been introduced by Yandell Henderson and Smith.[10] The blood (1 cc.) is introduced (under ammonia solution without contact with air, just as in the Barcroft-Haldane method) into the bottom of a diffusion tube of about 12 cc. capacity. This tube is provided with a 3-way tap at the bottom end and a thin rubber stopper at the top, and is graduated for a short distance from the top. A fine hypodermic needle is then thrust through the rubber to equalize the pressure inside and outside of the tube, the needle withdrawn, and the blood and ammonia solution mixed so as to lake the blood. Ferricyanide solution is then injected through the stopper, and the tube rotated for five minutes so that the whole excess of free oxygen diffuses out into the air of the tube. The tube is then inverted and the stopper removed under water so that the pressure inside and outside the tube is equalized. The volume of gas in the tube is read off; and finally nearly the whole of this gas is drawn into a Haldane gas-analysis apparatus, and the oxygen percentage determined. From the increased oxygen percentage of this gas as compared with air, and the volume of gas in the tube, the oxygen given off by the blood can easily be calculated. The CO_2 in the blood is estimated similarly; and both oxygen and CO_2 can be estimated in the same sample of blood. This method seems to be about as accurate as the Barcroft-Haldane method, and to be easier for those familiar with accurate gas analysis. It appears to be specially suitable for comparisons of the arterial and venous blood in animals; and evidently any CO in blood can be estimated conveniently by this method, which also has the advantage that corrections for physical solution of gases are greatly reduced.

Still another method is to use the Van Slyke vacuum apparatus in connection with ferricyanide.[11] This, however, involves the various

[10] Yandell Henderson and Smith, *Journ. of Biol. Chem.*, XXXIII, p. 39, 1918.
[11] Van Slyke, *Journ. of Biol. Chem.*, XXX, p. 347, 1917; and XXXIII, p. 127, 1918.

sources of error connected with the use of a vacuum pump, or necessitates analysis of the gas obtained from the blood.

Until recently we have used at Oxford the Brodie modification of the Barcroft-Haldane apparatus. As, however, the range of error with this apparatus has been about 2 per cent, I have quite recently devised a new apparatus, with a view especially to more accurate determinations of the oxygen in human arterial blood, and of dissociation curves.[12] With this apparatus it is possible to reach an accuracy as great as with the original ferricyanide apparatus—i.e., to within 0.5 per cent of the oxygen capacity of the blood. This new apparatus will therefore be described in full. On account of the present difficulty and expense in getting glass apparatus made, it was designed so that it could if necessary be put together in a laboratory from easily obtainable parts, just as in the case of the original apparatus.

When blood from a blood vessel is used, a glass syringe with solid glass piston is employed for obtaining the sample. This method was first applied to human arteries by Hürter, and developed by Stadie and others. Professor Meakins, with whom I have been associated in work on human blood gases, employs the following procedure. A very small quantity of finely powdered potassium oxalate is introduced into the bottom of the syringe. The piston is then introduced and a little liquid paraffin drawn in, and as much as possible expelled again with the syringe pointing upwards so as not to expel the oxalate. After disinfection of the skin the needle (previously sterilized) is introduced into the radial artery or other vessel, and about 5 cc. or more of blood withdrawn, a compress and bandage being afterwards applied over the place for an hour if the vessel was an artery. The needle is then removed and washed, and the blood transferred (with the syringe pointing upwards) through a rubber connection into a graduated pipette holding more than 2 cc. From this pipette an exactly measured quantity of about 2 cc. is introduced beneath the sodium carbonate or ammonia solution in the blood-gas flask. At the end of the operation about 0.5 cc. remains in the pipette, so that none of the blood has come in contact with air.

The apparatus is shown in Figure 103. In principle it is similar to that shown in Figure 101, but designed for small quantities of blood and for determining CO_2. The blood is received in one of the small flasks shown, while the other is for temperature control. Each has a capacity of about 20 cc. The procedure differs according as it is desired to determine the oxygen or the CO_2 of the blood. In the former case the first step is to measure 2 cc. of a 1 per cent solution of dried sodium carbonate into one of the two small flasks (about 20 cc. capacity) shown and add a

[12] Haldane, *Journ. of Pathol. and Bacteriol.*, XXIII, p. 443, 1920.

small quantity of saponin on the point of a penknife. Exactly 2 cc., or at any rate an exactly determined volume, of the blood is then measured out from the pipette into the flask beneath the sodium carbonate solution. The flask is then firmly corked and completely immersed beyond the cork in the bath alongside the other (control) flask until the temperature

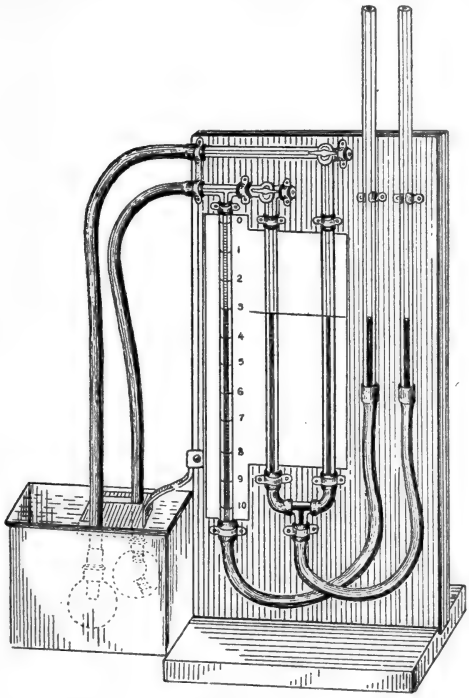

Figure 103.
Apparatus for blood-gas analysis.

of the air in the flask becomes completely steady. The flasks are connected, as shown, by means of thick-walled rubber tubing of about 2 mm. bore with the two gauges and gas burette fixed on the wooden stand. The glass connections, taps, and gauges are also of 2 mm. bore, and so arranged that the connections of the two flasks are of equal volume. The burette itself consists of an ordinary 1 cc. dropping pipette divided to .01 cc., and therefore capable of being read to .002 cc. The correctness of the graduation can easily be tested by weighing the water delivered by it. The taps are at first left open to air, but are turned after a few minutes so that the flasks communicate only with the gauges and burette; and the leveling tubes are previously adjusted so that the gauge levels

are at the zero marks and the burette level is at a convenient distance below zero. The gauges are then carefully observed, and the water in the bath is occasionally stirred by blowing air through it. It will be found that when both the gauges are exactly adjusted they do not keep even when left to themselves until at least ten minutes after the blood flask has been placed in the bath. The alterations are compensated by means of the leveling tubes; and when the gauges have come steady, or only move together, the burette is read off exactly. The confining liquid is distilled water containing a small quantity of bile-salts which make the readings more certain and sensitive.

The blood flask is now agitated for two or three minutes in order that the blood may take up all the gas it is capable of taking. At the same time it is laked by the saponin. In the process of agitation the flask is never removed from the bath. It is held by the neck with forceps or something else interposed to shield it from the warmth of the fingers. The gauges are now again adjusted, and, after they are quite steady, which should be the case almost at once, the burette is again read off. The difference between the two readings gives the gas absorbed by the blood from the air. From this we can calculate the volume of oxygen absorbed by the haemoglobin.

The first step in the calculation is to reduce the gas absorbed to its dry volume at 0° and 760 mm. and calculate its volume per 100 cc. of blood. For this purpose the barometer is read and the temperature given by a thermometer (not shown in the figure) fixed on the front of the stand, with the bulb close to the upper part of the burette. It is evident that what is required is not the temperature of the bath or connections, but that of the burette. The reduction is easily made with the help of a table with factors for correction, such as that at page 60 (second edition) of my book on Methods of Air Analysis.

We have now to calculate how much of the gas absorbed has simply gone into physical solution. Blood in the living body is saturated with nitrogen at the partial pressure of the nitrogen in the alveolar air. Allowing for the aqueous vapor present, this partial pressure is about 75 per cent of the existing atmospheric pressure. The coefficient of absorption of nitrogen in blood at 38°C is .011, according to Bohr's determination. Hence at ordinary atmospheric pressure there will be .83 cc. of nitrogen (at 0° and 760 mm.) in solution in 100 cc. of blood. The blood in the flask will become saturated at about 15° with nitrogen at a partial pressure of about 78 per cent of an atmosphere; and, as the coefficient of absorption is .016, about 1.25 cc. of nitrogen will be in solution per 100 cc. of blood saturated with air at 15°. Thus 100 cc. of blood will take up .42 cc. of extra nitrogen on saturation.

To calculate how much extra oxygen the blood will take up in simple solution, we must know the partial pressure of oxygen at which the blood taken from the living body is saturated, and this can be deduced pretty accurately from the percentage saturation of the haemoglobin and the dissociation curve of oxyhaemoglobin in human blood. Now it was found by Meakins and Davies[13] that the haemoglobin of normal human arterial blood is about 95 per cent saturated, which corresponds to an oxygen pressure of 11 per cent of an atmosphere, or 84 mm. The coefficient of absorption of oxygen in blood at 38° is .022. Hence there will be .24 cc. of oxygen in simple solution in 100 cc. of arterial blood. At 15° the coefficient of absorption is .031 and at ordinary atmospheric pressures the partial pressure of oxygen in the bottle will be 20.5 per cent of an atmosphere. Hence .63 cc. of oxygen will be in solution in 100 cc. of blood saturated with air at 15°, and the extra oxygen taken up in solution will be .39 cc. Thus the total extra gas taken up in solution will be $.42 + .39 = .81$ cc. in 100 cc. of blood, and only the balance of the proportion actually taken up in the blood flask will go to saturate the haemoglobin. Hence if the temperature of the water bath is 15° the allowance for gas in simple solution will be .81 cc.

If the bath is above or below 15° this allowance will be a little less or greater, and a calculation shows that for each degree above or below 15°, between the temperatures of 20° and 10°, the allowance will have to be diminished or increased by .038 cc.

An example will make the calculation of the percentage saturation of the haemoglobin clear. Let us suppose that 2.15 cc. of arterial blood have been delivered into the flask and the constant reading of the burette after temperature equilibrium had been obtained was .072 cc., and after agitating the blood .030. Thus 0.042 cc. of gas had been absorbed from 2.15 cc. of blood, or 1.95 cc. from 100 cc. The temperature was 14° and the barometer 755 mm. Hence the factor for reduction to dry gas at 0° and 760 mm. was 0.930. Therefore the dry gas at standard pressure and temperature was 1.81 cc. The temperature of the bath was 13°. Hence $.81 + .08 = .89$ cc. went into physical solution, so that 0.92 cc. of oxygen was absorbed by the haemoglobin.

To determine the percentage saturation of the haemoglobin it is necessary to know the total oxygen capacity of the haemoglobin; and this can now be determined directly. To the tube passing through the stopper of the blood flask there is attached a loop of wire into which a small tube of thin glass can be inserted. In the tube is placed .25 cc. of saturated ferricyanide solution and the flask closed and reinserted in the water bath till temperature equilibrium is reached. The burette is again

[13] Meakins and Davies, *Journ. of Pathol. and Bacter.*, XXIII, p. 451, 1920.

read off, and the flask turned up so as to let the ferricyanide flow into the blood solution. Before doing this, however, the blood solution should be observed to make sure that it is perfectly laked and transparent; otherwise more saponin must be added. The flask is now agitated as long as gas continues to come off as shown by the movements of the gauge. This will take three or four minutes. The burette is again read off, which gives the volume of oxygen given off. This is reduced to dry volume at 0° and 760 mm. and per 100 cc. of blood.

Let us suppose that the oxygen capacity of the haemoglobin in the above example was 17.4 cc. per 100 cc. of blood. The percentage saturation of the haemoglobin in the arterial blood was therefore

$$100 \times \frac{17.40 - .92}{17.40} = 94.7.$$

It is easier to determine the oxygen capacity by means of a Gowers-Haldane haemoglobinometer, in which 100 per cent corresponds to an oxygen capacity of 18.5. For this purpose a sample of the blood drawn from the artery is used for the determination. In the above example the oxygen capacity of 17.4 corresponds to 94 per cent on the haemoglobinometer scale, and the range of error in carefully made haemoglobinometer determinations is only about 0.5 per cent. The accuracy of both methods is strikingly shown by the fact that in 36 determinations by Meakins and Davies of the oxygen capacity of blood from patients and healthy persons the maximum difference between the results by the haemoglobinometer and by the new method was under 1 per cent of the oxygen capacity.[14]

A haemoglobinometer can, of course, be exactly standardized by the method just described. If the haemoglobinometer is used, it is unnecessary to use saponin or ferricyanide in determining the percentage saturation of the haemoglobin in the sample of blood. The total available oxygen in the sample of arterial blood is the oxygen combined with haemoglobin plus the dissolved oxygen. This was, in the above example, $16.48 + .24 = 16.72$ cc. per 100 cc. of blood.

If, instead of being normal arterial blood, the sample was venous blood, or arterial blood of abnormally low saturation with oxygen, the calculation must be slightly modified, since less oxygen in simple solution is present in the sample. Thus if the blood turned out to be only half saturated with oxygen the partial pressure of oxygen in the sample would only be about 4 per cent of an atmosphere. Hence there would only be .09 cc. of dissolved oxygen present, instead of .24 cc. This would increase the correction at 15° for dissolved gas from .81 to .96 cc.—a difference which, however, affects the result but little. Ordinary varia-

[14] Meakins and Davies, *Journ. of Pathol. and Bacter.*, XXIII, p. 454, 1920.

tions of barometric pressure do not sensibly affect the correction, but at high altitudes the correction must evidently be diminished in the proportion of about 0.1 cc. for every 100 mm. of diminution in atmospheric pressure.

If the blood is taken, not from the living body, but from a saturating vessel, the gases dissolved physically must be calculated on the same principle, allowing for their pressures in the vessel.[15]

The method just described has been tested for accuracy in several ways. In the first place it has been found that when blood fully saturated with air at room temperature is placed under the sodium carbonate solution in the ordinary way and then agitated after the gauges have become steady, there is no sensible variation in the reading of the burette afterwards. The constancy of the reading can be relied on to .002 cc. with careful work. Hence the percentage saturation can be relied on to 0.5 per cent, or the oxygen capacity per 100 cc. of blood to 0.1 cc., if the measuring pipettes are properly calibrated. This is as good a result as could be obtained with 20 cc. of blood by means of the original ferricyanide apparatus. The present method is therefore as exact as the original one for determining the oxygen capacity of blood, but is quicker and more convenient. By using sodium carbonate instead of ammonia solution the errors due to diminution of the vapor pressures of ammonia and water on mixing the blood with the solution are eliminated, while the use of saponin, first introduced by C. G. Douglas, produces the laking of the blood which is necessary in order to allow the ferricyanide to act on the oxyhaemoglobin. The fact that, as has been found by Meakins and Davies, haemoglobinometer estimations coincide within 1 per cent with the results by this method furnishes further confirmatory evidence.

The new apparatus gives sharper results than the constant volume method which Barcroft and I described in 1902. This is, I think, partly due to the larger volume (2 cc.) of blood employed; partly to the fact that the disturbance due to the use of ammonia solution is avoided and a sharper index of temperature equilibrium is given by the two gauges of the present apparatus; and partly because the gauge levels are always at the same place, whereas in the constant-volume apparatus the gauge levels shift to places wide apart, so that small errors due to varying capillarity of the gauge tubes are apt to tell. It is thus difficult, with the constant-volume apparatus, to avoid errors within 2 per cent on either side of the actual percentage saturation.

[15] In the paper by Barcroft and myself where we first described the constant volume blood-gas apparatus, the correction for gas in simple solution was unfortunately given incorrectly; and this doubtless accounts for the somewhat distorted forms of the dissociation curves of oxyhaemoglobin in Barcroft's earlier experiments on this subject.

When it is desired to determine the CO_2 content of the blood the procedure must be modified, as sodium carbonate cannot be used, and 2 cc. of blood would give too much CO_2 for the capacity of the burette, apart from other causes of error. Therefore only about 1 cc. of blood should be taken. This is delivered under 1.5 cc. of a solution of 4 parts of ordinary strong ammonia solution (sp. gr. .88) to a liter of boiled distilled water, and a trace of saponin added. To avoid the presence of any carbonate in the ammonia the strong solution is first shaken up with some unslaked lime and allowed to settle. The stock of dilute solution is kept tightly corked. As soon as the ammonia solution is placed in the flask, the latter is kept tightly corked until the blood is added, otherwise a considerable amount of CO_2 may diffuse in and cause error. The blood is shaken up to lake it, and .25 cc. of ferricyanide afterwards added to liberate the oxygen, since if this were not done some oxygen might be liberated by the acid. After all the liberated oxygen has been shaken off, the small glass tube containing .25 cc. of 20 per cent solution of tartaric acid is inserted and the burette read off after the gauges are steady. The tartaric acid solution is then spilt into the blood solution and the flask agitated under water till the CO_2 has completely ceased to come off, as shown by the gauge. The burette is then adjusted and read off and the volume of gas given off reduced to its dry volume at 0° and 760 mm. and calculated per 100 cc. of blood. Part of the CO_2 however, remains dissolved in the liquid in the flask, and must be allowed for. This liquid is exactly the same as in the case of determination of CO_2 by means of the constant-volume apparatus described by Barcroft and myself, so the correction is made in a similar manner. At a temperature of 13° the coefficient of absorption of CO_2 in this liquid was found to be 1.00. Hence if we know the total volume of the flask as compared with the volume of gas in it when the liquid is also present, and the temperature of the bath is 13°, the total CO_2 liberated from the blood will be to the amount shown by the burette as the total capacity of the flask to the volume of gas in it when the liquid is also present. The capacity of the flask to the cork is about 20 cc. Let us suppose that as determined by weighing with the cork in place it is 20.5 cc., including the capacity of a piece of glass tubing of about 4 mm. bore and two inches long which passes through the cork. The volume of liquid in the flask is 3.0 cc. Hence if the temperature of the bath is 13° the total volume of CO_2 liberated is obtained by multiplying the corrected volume actually read off by $\frac{20.5}{17.5}$ or adding 17 per cent. If the temperature is above or below 13° a fortieth must be subtracted from or added to this addition, since the solubility of CO_2 diminishes by about a fortieth for each degree above 13°, and increases

similarly for each degree below 13°. The glass tubing passing through the cork is 4 mm. in bore in order to give room for the CO_2 given off without its coming in contact appreciably with the rubber connecting tubing. For determining CO_2 in blood it is better to use an ordinary cork than a rubber stopper in the blood flask, as the rubber leads to a slow absorption of CO_2.

A further negative correction is required for any CO_2 present in the solutions used, or absorbed from the air in the flask; also for the small error in the opposite direction owing to disappearance of ammonia vapor from the air of the flask. The joint correction, which ought to be very small, and may be either positive or negative, can be ascertained by a blank experiment in which boiled distilled water in place of blood is used in the flask. Or if the capacities of the two bottles are nearly equal the blank experiment may be performed in one flask along with the blood experiment in the other. In this way the correction is eliminated.

As shown by this method by Meakins and Davies, arterial blood gives slightly more CO_2 than defibrinated blood at the same partial pressure of CO_2, as found in the experiments of Christiansen, Douglas, and myself.[16]

The following example illustrates the mode of calculation. The volume of CO_2 given off from 1.00 cc. of human arterial blood was 0.482 cc. as read from the burette. Reduced to dry gas at 0° and 760, and calculated per 100 cc. of blood, this was 45.9 cc. The correction at 13° for the CO_2 left in solution was 16.5 per cent, but as the temperature of the bath was 15° the proper correction was 15.3 per cent. Hence the CO_2 contained in 100 cc. of blood was 52.9 cc. A blank control experiment was made simultaneously in the other flask, so there was no further correction.

In any cases where both the oxygen and CO_2 in a sample of blood are required, it is better and quicker to make the determinations simultaneously in two different apparatus.

For the proper working of the apparatus it is essential that all the joints, including the cork, should be absolutely tight. There is no difficulty about this if the rubber tubing used is smooth and clean. To test for tightness the burette should be read after the gauges are steady. Positive or negative pressure is then produced for some time in the apparatus by raising or lowering the leveling tubes. On readjusting the gauges, the reading should be exactly the same as before, if the apparatus is tight. If a leak exists it can soon be localized by putting pressure on one part after another of the connections.

The apparatus can be put together without very much trouble, and if

[16] Christiansen, Douglas, and Haldane, *Journ. of Physiol.*, XLVIII, p. 272, 1914.

three-way taps are not available T tubes may be substituted. Messrs. Siebe Gorman & Co., 187 Westminster Bridge Road, London S. E., supply it.

D. Colorimetric Determination of Percentage Saturation of Haemoglobin with CO

This very convenient method is used in determining the oxygen pressure of arterial blood, the total haemoglobin in the body, or the blood volume, as well as for investigations as to the properties of CO haemoglobin and the phenomena of CO poisoning. It depends on the fact that a dilute solution of CO haemoglobin has a pink color, quite different from the yellow color of similarly diluted oxyhaemoglobin.

I originally used this color difference as an easy and delicate means of recognizing the presence of CO in blood and roughly estimating the saturation with CO; and I then thought that as it is impossible to recognize by the difference of tint a difference of less than about 5 per cent in the percentage saturation of haemoglobin with CO, the method was at best a rough one. Various recent writers have fallen into the same error. Further experience showed that with proper precautions the method gives results of great accuracy. The following description is taken almost verbatim from the account of the method given in 1912 by Douglas and myself in our paper on oxygen secretion.[17]

A solution of normal human blood (or blood from the animal experimented on) is prepared of such strength as to correspond to about 0.5 per cent of the proportion of haemoglobin in standard human blood of 100 per cent strength by the Gowers-Haldane haemoglobinometer scale. Two test tubes of equal bore of about 0.6 inch are selected, and into each of these 5 cc. of the blood solution are measured with a pipette. From a 0.1 per cent solution of carmine in ammoniacal distilled water (this solution being kept in the dark in a cupboard) a dilute solution of carmine in distilled water with a strength of tint about equal to or rather greater than that of the blood solution is then prepared in a measuring cylinder. The requisite amount of dilution (about one-twentieth of the 0.1 per cent solution if the latter has been recently prepared) can easily be estimated by the eye, and can be obtained at once, when experiments are made daily, by diluting to a definite extent. A burette is filled with the carmine solution, and another burette with water. The blood solution in one of the test tubes is then saturated with CO by allowing coal gas to run through the free part of the test tube, quickly closing the tube with the thumb, and shaking the blood solution with the gas for a few seconds.

[17] Douglas and Haldane, *Journ. of Physiol.*, XLIV, p. 305, 1912.

When looked at against the sky, the solution will now have a deep purplish-pink tint, as compared with the brownish yellow of the normal blood solution. The carmine is now added from the burette to the normal blood solution until its tint is about equal in quality to that of the saturated blood solution. It will then probably be found that the depth of tint is too great in the tube containing the carmine. Water is then added from the other burette until the depth of tint is equal, and if necessary more carmine, until complete equality of both tint and depth of color is obtained. In judging of this, the test tubes should be held up against the sky, and it is absolutely necessary to change them repeatedly from side to side; otherwise gross error is certain. It will nearly always be found that the right-hand tube appears a little yellower or pinker than the left-hand one; and a little deeper or less deep in color. This difference is in reality a great help to accuracy. A point is first reached when the tubes appear equal in tint or depth when held in one position, but unequal in the other, and the end point when the difference is the same on one side, whichever tube is on that side, can be estimated with great delicacy. The additions of carmine (or water) are continued until this point is passed; and if two successive additions both show equality, the mean of the two readings is taken as correct.

To the carmine solution in the measuring cylinder a proportion of water is now added equal to what had to be added from the water burette to the carmine required to reach the end point of the titration. The carmine solution is then ready for use. It will probably be found that about 6 cc. of carmine are needed to reach the end point. The amount required varies, however, according to the condition of the strong carmine solution and the quality of the daylight. The carmine solution is not stable, and it gradually becomes less deep in color, and redder in tint than when first prepared. Hence the quantity of carmine solution needed increases from month to month, and the extent to which it has to be diluted for use diminishes. If the dilute solution is left for a day or two exposed to light it becomes very markedly redder and more dilute.

The titration of a blood sample is carried out as follows. One or two drops of blood are needed, and are at once diluted with water. Half of the dilute solution is poured into one of the two test tubes (always the same one as that used for the saturated blood in standardizing the carmine), and 5 cc. of the normal blood solution are measured with a pipette into the other. Water is then allowed to drip from a tap into the solution of the blood under examination until its *depth* of tint is about equal to that of the normal solution. Carmine solution is now added to the normal blood solution from the burette until the tints are equal,

more water being also added to the other tube if necessary. The solution under examination is then saturated with coal gas and the addition to the normal blood solution of carmine is continued until the tints are again equal. To illustrate the method of calculating the result we may suppose that in the first result equality of tint was observed with 1.2 and 1.3 cc. of carmine, mean 1.25, and that in the second 6.4 and 6.8 cc. gave equality, mean 6.6; the percentage saturation X is then given by the result of the following proportion sum:

$$\frac{6.6}{5+6.6} : \frac{1.25}{5+1.25} :: 100 : X$$

or, more simply,

$$100 \times \frac{6.25}{1.25} \times \frac{6.6}{11.6} = 35.1 \text{ per cent.}$$

It is clear that the more carmine has already been added to the normal blood solution the less effect on its tint will any further addition have. Hence in approaching the point of equality only 0.1 cc. is added at a time if not more than 2 cc. have already been added, whereas after already adding 6 cc. it is useless to add less than about 0.4 cc. at a time.

The titration is repeated with the other half of the blood solution for further safety, and it will be found that apart from accidents the two results will nearly always agree within 1 per cent of the total saturation. This accuracy is very surprising at first sight, since colorimetric determinations have in general a rather bad reputation among chemists. The carmine titration is also no ordinary colorimetric titration, but one in which the quality, and not the density, of tint is estimated. We believe that the bad results commonly obtained with "colorimeters" are due to the two solutions being in some fixed position determined by the apparatus used. An error of 10 per cent or more may easily occur from this cause. Far more accurate results can be obtained with two ordinary test tubes repeatedly transposed, as above described, than with complicated and expensive colorimeters.

It will be found that the amount of carmine giving equality varies distinctly for different individuals. The proportional difference is, however, the same at the two stages of the titration, so that the percentage result obtained is the same. For the same individual the amount of carmine needed varies, also, with different qualities of daylight, and is usually less towards evening. This does not affect the percentage result, however, provided that the two stages of the titration are completed by the same light.

All these differences are due to the facts that the two solutions are not spectrally identical; nor is the daylight at different times of day; nor are the retinae of different persons equally sensitive to differences

in any particular part of the spectrum; nor, finally, is any part of the retina of one individual constant in its excitability for either white light or colored light; the excitability of any one part being dependent on side light falling on neighboring parts of the retina. The numerous colorimeters, haemoglobinometers, etc., in which these sources of error cannot be eliminated, are liable to very gross error, and appear to be responsible for the discredit under which colorimetric methods suffer.

With ordinary artificial light the differences in tint between the various solutions become almost invisible. The dimmest daylight is better than ordinary artificial light. With blue spectacles, however, the differences become very evident, and fairly good results can be obtained in the titration if the carmine is made of the proper strength (very much stronger) to suit the light. Daylight is, however, far better.

It is essential to accuracy with the carmine method that the carmine solution should accurately match the standard blood solution in *depth* of color. If the two do not correspond, it is easy enough to get a result: for when the solution in one test tube is too deep in color it is only necessary to incline the other in order to make its depth of tint appear equal. The calculation of the percentage saturation becomes fallacious, however, as is easily seen. One source of slight error in the titrations is that a carmine solution which, when made up, exactly matches the blood solution in depth, may, towards evening, be rather too strong, owing to change in the light. This change can, however, be detected and rectified very quickly, and attention would automatically be called to it by the fact that considerably less carmine than before would suffice to produce the tint of fully saturated blood solution.

A further source of possible fallacy depends on the liability of blood solution to decomposition. It is essential that the blood should be fresh, and diluted with clean water in a perfectly clean vessel. Solution which has been kept more than a few hours is useless. It may show no methaemoglobin band, and appear to be unaltered; but on saturating it with CO it will probably no longer give the full pink color of undecomposed haemoglobin, and its depth of color will also be found to be less than before. It is thus mixed with colored decomposition products which make it useless for titration. The tint on saturation with CO affords a far more delicate index than spectroscopic examination of the freedom of a blood solution from pigments other than haemoglobin.

When blood saturated, or partly saturated, with CO is diluted with water, a small part of the CO must necessarily go into solution in the water, as some dissociation of the CO haemoglobin occurs. To demonstrate this it is only necessary to saturate some blood with coal gas and dilute some of it to 0.5 per cent with water. It will be seen at once that

the diluted blood is distinctly less pink than some of the same solution re-saturated with coal gas; and on titration the blood which has been simply diluted will be found to be not more than 88 or 89 per cent saturated. The percentage dissociation can be calculated if we know the partial pressure of CO corresponding to various percentage saturations of the haemoglobin at room temperature, and also the coefficient of solubility of CO.

In the case of human blood, half-saturation occurs at room temperature in presence of air with about .05 per cent of CO. Hence with 50 per cent saturation of a blood solution saturated with air the partial pressure of CO will be .05 per cent of an atmosphere. Now 100 cc. of water (and presumably also of a very dilute blood solution) dissolves about 2.5 cc. of CO from an atmosphere of pure CO at room temperature (15°C.), so that at a partial pressure of .05 per cent it will dissolve $2.5 \times .0005 = .00125$ cc. of CO, whereas 100 cc. of 0.5 per cent blood solution can take up in chemical combination .0925 cc. of CO. Hence the proportion of the haemoglobin dissociated is .00125 in .0925, or 1.35 per cent, so that if 50 per cent saturation were found by titration to be present we should require to add 1.35 per cent to obtain the true result. By a similar calculation we find that if the blood were found by titration to be 89 per cent saturated, we should have to add on 11 per cent in order to obtain the true result, which would thus be 100 per cent. When human blood is fully saturated with coal gas, the result actually found by titration, after dilution of the blood to 0.5 per cent, is 89 per cent, provided the light is not bright. Hence the calculation agrees with the actual result. In the brighter light of the middle of the day the result is, however, 2 or 3 per cent lower, even with a north light; and on going outside so as to increase the light, and avoid the absorption of actinic rays by window glass, the result is still lower. This effect is due, as was pointed out by Haldane and Lorrain Smith, to the action of actinic rays in dissociating CO haemoglobin. The varying effect of light renders the carmine titration with very high saturations of the blood with CO somewhat uncertain. With low saturations, such as we have usually worked with, any error due to this cause is trifling. We have at all times avoided bright light as far as possible, and where it was necessary, as in the case of dissociation curves, to titrate with high saturations of the blood, up to 80 or even 85 per cent, we have done the titrations by evening light. As an alternative, we might have used narrower test tubes and a greater concentration of the blood solution, so as to diminish the correction for dissociation; but it is easier to judge the tints accurately when ordinary test tubes are employed, and comparatively few determinations were needed with very high saturations.

The following scalè of corrections was used for human blood.

Observed percentage saturation	*Correction added*
10 per cent	0.15
20 "	0.35
30 "	0.6
40 "	0.9
50 "	1.35
60 "	2.0
70 "	3.1
80 "	5.4
89 "	11.0

For mouse blood the corrections used were 50 per cent higher, since the partial pressure of CO required to produce a given saturation of the blood with CO is about 50 per cent higher for mice than for men.

As already mentioned, the results of duplicate or triplicate titrations of the same sample of blood agree very closely, the variation in the percentage saturation found hardly exceeding 1 per cent or 0.5 per cent from the mean. When, as in determinations of arterial oxygen pressure, two samples not differing much in percentage saturation are compared successively with the same standard blood solution, the difference in their percentage saturations with CO can be determined with corresponding accuracy; for any errors due to imperfect preparation of the standard solutions, or to the allowance for dissociation, will affect both results equally. To determine the absolute range of the latter errors we made a number of analyses of definite mixtures of normal blood with the same blood saturated with coal gas. The coal gas contained about 7 per cent of CO, and allowance was made for the small amount of CO present in simple solution in the saturated blood.

The ox blood used for these mixtures was measured out from a pipette, the blood being kept constantly stirred to prevent sedimentation of the corpuscles. This method, though fairly accurate, is liable to slight errors on account of variations in the quantity of blood which is left adhering to the pipette. The following percentage saturations were obtained on different occasions. The same carmine solution was used by both observers.

In series (2) and (3) the mixtures were made with blood laked by dilution to half, and were unknown to the observer. In (1) and (4) the mixtures were made with whole blood, and were known to one observer. In (4) each observer made up his own carmine solution.

It will be seen that the maximum error was 2.0 per cent, this including any error in making the blood mixtures and standardizing the carmine solutions. With double determinations the error was considerably less.

(1) *Calculated*	*Found*	(3) *Calculated*	*Found (C. G. D.)*
33.7	(33.9 (J. S. H.)	20.3	20.9
	(34.0 (C. G. D.)	33.9	32.1
		50.8	49.2
	(76.0 (J. S. H.)	67.7	68.1
75.8	(76.8 (C. G. D.)		
	(75.2 (J. S. H.)		

(2) *Calculated*	*Found (J. S. H.)*	(4) *Calculated*	*Found (C. G. D.)*	*Found (J. S. H.)*
25.4	26.8	11.2	10.3	11.4
33.9	33.8	25.2	26.0	27.1
50.8	52.3	50.5	51.9	52.5
67.7	68.3	80.8	79.9	81.4

E. Determination of Blood Volume in Man during Life by CO

Since CO is not oxidized or otherwise destroyed in the living body, and since it forms a relatively very stable molecular compound with haemoglobin, but with no other substance in the body, it is evident that if we administer to an animal a known amount of CO, and then determine the percentage saturation of the haemoglobin with CO and the total CO capacity of a given volume of blood, we can determine the CO capacity of the total blood in the body, and hence deduce also the blood volume. The blood volume during life was first determined in this way by Gréhant and Quinquaud,[18] who used dogs for the purpose and employed the blood pump for the blood-gas analyses. In 1900 Lorrain Smith and I introduced a much simpler method, easily applicable to man;[19] and this method has been extensively used for physiological, clinical, and pathological work, as mentioned in Chapter X.

The apparatus required for administering the CO to a man is shown diagramatically in Figure 104. The subject breathes through a glass mouthpiece A, the nose being clipped or held. The mouthpiece communicates by ½-inch rubber tubing with a bladder or india-rubber bag B of

[18] Gréhant and Quinquaud, *Journ. de l'anat. et de la physiol.*, p. 564, 1882.
[19] Haldane and Lorrain Smith, *Journ. of Physiol.*, XXV, p. 331, 1900.

at least 2 liters capacity. Between the bag and mouthpiece there is interposed a cylindrical metal vessel containing moist granulated soda lime or other suitable absorbent to absorb CO_2. The end of this vessel may be made to screw on and off, with an air-tight rubber washer; or may be made in two pieces, the outer of which slides over the inner, as shown in the figure, the junction being made air tight with plasticine. The soda

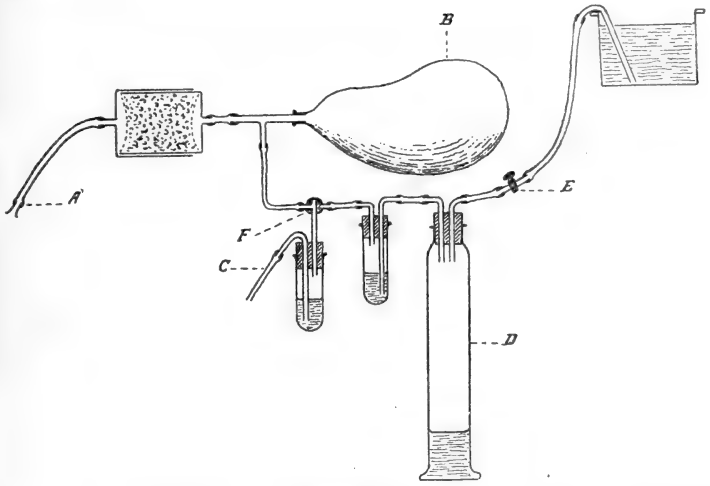

Figure 104.
Apparatus for determining blood volume in man.

lime is kept in position by two circular pieces of wire gauze, one of which is pushed into the end of the inner vessel, and the other into the end of the outer vessel. Good soda lime can be made by stirring fresh slaked lime in powder with a strong solution of caustic soda till the mixture granulates, and then sifting off the fine powder and coarse lumps by means of two sieves. Granulated caustic soda will also answer. There should be no appreciable resistance to breathing, and one tin of soda lime should last for several experiments. When the soda lime is spent it ceases to heat, and the breathing begins to become increased, owing to unabsorbed CO_2.

The narrow graduated cylinder D is filled under water with CO, of which a stock, prepared from formic and pure sulphuric acids, can be kept in a large bottle. Just before the experiment, some of the CO is, by turning the water tap E, driven out through the test tube and 3-way tap F to the outside. In this way all the air is expelled up to the 3-way tap. The water tap is then closed, and afterwards the 3-way tap. Oxygen from a steel cylinder is now turned on through the tube C to displace CO

from the tubing, which is then connected with the bag as shown in the figure, and the bag filled pretty full with oxygen. Meanwhile the height of the water in the cylinder is accurately read off, and the temperature of the cylinder and barometric pressure noted.

The subject of the experiment now begins to breathe from the bag, oxygen being supplied as required. The water tap is now slightly opened, and the tap F turned so as to let CO as well as oxygen pass. The required volume of CO is in this way very gradually driven in from the measuring cylinder, about 20 cc. being passed in per minute. After the CO has been passed in, the water tap is turned off, and the 3-way tap turned so as to shut off the CO. The CO is absorbed from the bag very rapidly and completely. The oxygen supply is continued for at least ten minutes, after which the subject is allowed to absorb most of the oxygen in the bag. About 15 minutes after the last of the CO has been given, a drop or two of blood is taken and diluted for analysis by the carmine method described above. At the same time the oxygen capacity of the blood is determined in the ordinary way by the Gowers-Haldane haemoglobinometer. For further certainty it is well to make both determinations in duplicate.

As a little air always gets mixed with the CO, a sample of the CO in the cylinder should be taken for analysis. It is usually sufficient to determine the CO_2 (of which none should be present) and oxygen. From the latter the proportion of air can be deduced.

Let us suppose that 150 cc. of CO were given, the temperature 12°, and the barometer 765 mm.; also that there was 0.82 per cent of oxygen in the CO, corresponding to 3.9 per cent of air. 150 cc. of gas saturated with moisture would correspond to 142.5 cc. of dry gas at 0° and 760 mm. But as 3.9 per cent of this was air, only 137 cc. of CO were administered. Let us also suppose that the percentage oxygen capacity of the subject's blood was 18.1 (98 per cent by the haemoglobinometer), and the percentage saturation with CO was 19.5. The total oxygen capacity or CO capacity must have been $137 \times \frac{100}{19.5} = 703$ cc.; the blood volume $703 \times \frac{100}{18.1} = 3880$ cc. If the subject's weight was 60 kilos this corresponds to 6.5 liters of blood to 100 kilos of body weight; and this result is usually expressed as a blood volume of 6.5 per cent of the body weight.

In the original description of our method, we directed that the blood sample should be taken within two or three minutes of the cessation of administration of CO, as we assumed that by that time the CO would be evenly distributed in the blood all over the body. The results from samples taken three minutes after the first sample confirmed this as-

sumption. When, however, Douglas and Boycott made a number of determinations with a much larger bag which necessitated continuation of the breathing for a considerable time after the CO had been given, they obtained higher average results for the blood volume in man than Lorrain Smith and I had got. Douglas and I therefore reinvestigated the question as to how long the CO requires to distribute itself equally, and found that when the samples were taken only two or three minutes after cessation of the administration of CO the percentage saturations of the blood were from 10 to 25 per cent higher than 15 minutes later. After 10 to 15 minutes, however, the saturation remained constant if the subject continued to breathe from the bag. Our original experiments gave, therefore, results for the blood volume which were too low—probably by about 25 per cent. The average blood volume in man by the CO method is about 6.5 to 7 per cent of the body weight, and the total oxygen capacity of the haemoglobin about 1.1 to 1.3 liters per 100 kilos of body weight.

It is probable that, as regards most of the circulating blood, mixture with any added substance such as CO takes place very rapidly. In some parts of the body, however, the circulation is so slow that a considerable time is required for mixture.

Douglas,[20] and also Boycott and Douglas[21] applied the above described CO method to animals, and took the opportunity of comparing the results with those obtained by the older colorimetric method of Welcker, which can only be applied after death. The series by Douglas showed an average difference of —3 per cent, and that of Boycott and Douglas of +5.5 per cent with the CO method as compared with the Welcker method. It is evident, therefore, that no substance except haemoglobin combines wth CO. It must be remembered, however, that many of the muscles contain some haemoglobin, and that by both methods this small fraction of the total haemoglobin is estimated as if it belonged to the blood.

In using the CO method for human experiments it is necessary to adjust the volume of CO administered to the patient's weight and probable oxygen capacity, so that the percentage saturation of his haemoglobin is not likely to rise above about 20; otherwise slight headache may result. For persons of ordinary weight about 150 cc. of CO would be suitable; but in cases of pernicious anaemia or anaemia from loss of blood, and in children or persons of low weight, far less CO should be given. On the other hand in cases of polycythaema it may be necessary to give 300 cc. or more in order to obtain a percentage saturation sufficient for a satisfactory titration of the blood. As CO only leaves the blood slowly when the percentage saturation is low, it is hardly necessary, except in very exact experiments, to keep the patient breathing from the bag after all the CO has been absorbed.

[20] C. G. Douglas, *Journ. Physiol.*, XXXIII, p. 493, 1906, and XL, p. 472, 1910.
[21] A. E. Boycott and C. G. Douglas, *Journ. Path. and Bact.*, XIII, p. 256, 1909, and A. E. Boycott, same Journal, XVI, p. 485, 1911.