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RESPIRATION

RESPIRATION

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BY

J. S. HALDANE

C.H., M.D., F.R.S.

FELLOW OF NEW COLLEGE, OXFORD
HONORARY PROFESSOR AT BIRMINGHAM UNIVERSITY;
HON. LL.D. BIRM. AND EDIN.; HON. D.SC. OXFORD, CAMB.,
DUBL., LEEDS, WITWATERSRAND

AND

J. G. PRIESTLEY

M.C., D.M., M.A.

READER IN CLINICAL PHYSIOLOGY IN THE
UNIVERSITY OF OXFORD

NEW EDITION

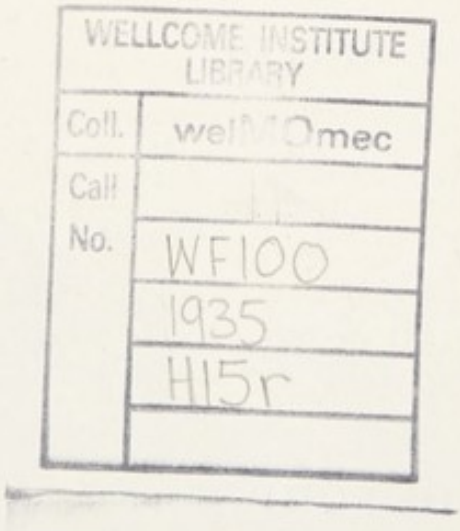
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PREFACE TO SECOND EDITION

SINCE the first edition of this book was published there have been many advances in our knowledge of the physiology of respiration. This has necessitated a thorough revision in the present edition. In carrying this out I have had the great advantage of the co-operation of Dr. J. G. Priestley, so that the new edition represents our joint work.

In rewriting it we have endeavoured not merely to bring it up to date, but to represent more clearly and sharply than before that the physiology of respiration deals with phenomena which are specifically those of life.

The headings of chapters are the same as in the first edition, but their order has been somewhat changed for the sake of greater continuity. The revision has entailed expansion in most of the chapters. On the other hand, space has been saved by the omission of the Appendix on special methods of investigation, since these are now well known. The last chapter, entitled 'General Conclusions', has also been omitted, since all that is immediately necessary could be said better in the present Preface. Wider philosophical discussion will be found in other books published by me since *Respiration* was first written, and more particularly in *The Philosophy of a Biologist*, now in course of publication by the Clarendon Press.

The physiology of respiration or breathing can be distinguished easily enough from other parts of physiology; but the manner in which the subject is treated will differ according to the way in which physiology or biology as a whole is regarded. Unless we are clear about this, confusion will inevitably arise; hence it seems desirable to discuss this point at the outset.

At present it is usual to treat the physiology of respiration as being nothing more than a description and analysis of all the physical and chemical processes by which oxygen is supplied to the living body and carbon dioxide removed from it. But when we survey such a description, it is quite evident that something essential is missing in it. Not only is oxygen supplied and carbon dioxide removed, but these processes, as will be made evident in the course of the book, are co-ordinated at every stage among themselves and with other physiological activities, in a manner which is characteristic for each organism. Moreover, the structures involved in the

process are maintained in a characteristic co-ordinated form during adult life, and have developed into this characteristic form from a germ in which no such form can be distinguished. A mere physical and chemical description furnishes no account of this co-ordination, maintenance, and development. We cannot disregard these features, since we find that they enter into all the facts which we are endeavouring to describe, and must be taken into account when we apply our knowledge for purposes of prediction, as in practical medicine.

One method of dealing with them is to describe the facts in so far as it seems possible to describe them in physical and chemical terms, and to leave on one side all that relates to co-ordination, maintenance, and development, as being at present too complex for scientific treatment. We can doubtless leave to embryologists the scientific treatment of development of the characteristic or normal structures and activities concerned in respiration; but the maintenance of what is normal in the bodily parts concerned in respiration is far too prominent a feature to be thrust on one side; and this is still more true of the co-ordination in a 'normal' manner of respiratory activity. Oxygen is absorbed, and carbon dioxide is given off, in such a manner as to co-operate in maintaining the characteristic structure and activities of an organism, while, on the other hand, structure is maintained in such a manner as to promote the maintenance of normal activity. Respiration is thus only an aspect of the co-ordinated and maintained phenomena which we call life. In calling it respiration we distinguish it as life from superficially corresponding processes which we interpret as being inorganic; and it is the same for other physiological activities called by their physiological names. The conception of life as an objective fact is thus essential in physiology. We can also see that in perceiving the fact of life we are perceiving more fully and deeply than is possible by an attempt at a mere physical interpretation of the same phenomena.

On the theory that life is no more than an example of an extremely complex physical and chemical mechanism—so complex that we do not yet understand it—the co-ordinated maintenance and reproduction depend on these unknown conditions, and physiology can do nothing more than regard the facts as at present unintelligible. But meanwhile, experimental investigation is continuously revealing new details of activity and structure to which the co-ordinated maintenance applies, so that the problem presented by it becomes con-

tinuously more extensive. By a strange failure to realize the significance of these new discoveries in physiology it is still often supposed that they can be looked on as helping towards a physical and chemical explanation of the co-ordinated maintenance—an interpretation, that is to say, which would enable us to dispense completely with the conception of life as an essential character of what we are describing.

In reality there is not the slightest scientific indication that we shall ever be able, in physiology, to dispense with the specific conception of life; and in this book the fact of life, with the co-ordinated maintenance which it implies, will be treated as an essential feature in the scientific description. In other words, the physiology of respiration will be treated as part of biology, in the sense that biology is a different branch of science from the physical sciences, since its fundamental axiom is that the life of an organism, including its relations to environment, implies the co-ordinated maintenance and reproduction which are everywhere in actual fact characteristic of life.

It is often argued that if we place biology on a different theoretical footing from physics and chemistry, we are thereby abandoning attempts to explain the phenomena of life, and that however unsatisfactory these attempts may have proved, we can do nothing better than continue them. The reply to this criticism is that an unjustifiable philosophical assumption is implied in the conception that we must be able to interpret in terms of physical science the universe which we perceive around us. The mere reflection that, in so far as it is anything at all to us, it is a perceived universe, involving all that is implied in perception, makes this conception impossible except as a provisional one. Existing physical science can give no account of the characteristic features of life and conscious experience, or their assumed origin in the course of evolution. If we seriously endeavoured to include the phenomena of life within the scope of physical science we should require to modify drastically the axioms on which existing physical science is based. They are sufficient for its own limited purposes, but physical science is certainly no more than a superficial aspect of ultimate philosophical truth.

In biology we are constantly making provisional use of physical and chemical interpretations, as will be abundantly illustrated in

this book; but it will also appear that this provisional interpretation, which by itself takes no account of the maintained co-ordination which lies behind it, is only superficial, and gives place to a fuller interpretation which takes into account the fact that the phenomena described are phenomena of life. As far as possible, this book has been written in the light of the fuller interpretation. Hence stress is everywhere laid on the part which each respiratory phenomenon plays in the maintenance of life, and on the importance from this standpoint of the co-ordination which is discovered in these phenomena. It is only when we realize how real the co-ordination and maintenance are that we can apply physiology effectively in the diagnosis, treatment, and prevention of disease. Hence this application occupies a prominent place in the book, but not as a mere accidental feature. The whole treatment of the subject takes as its working hypothesis that the phenomena of respiration are phenomena of life, and then proceeds, in the light of experimental investigation, to describe in detail the maintenance of physiological co-ordination during health. Disturbances during disease then stand out prominently. Physiological explanation is treated as being the experimental demonstration that physiological phenomena are an expression of the maintained co-ordination which we call life. In other words, physiology is regarded as part of biology and as treating our experience from a standpoint which is different from that of the physical sciences, and essential in the scientific description of the phenomena of life.

OXFORD J. S. HALDANE

November 1934

PREFACE TO FIRST EDITION

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 endeavour 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 endeavoured 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 honour 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. Mavrogordato, Dr. Priestley, Dr. Douglas, Professor Meakins, and my son. In connexion 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

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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 in some diseases. The discovery by Harvey of the circulation of the blood threw no positive light on the physiology of breathing, and belief in Aristotle's theory, that the main function of respiration is to cool the blood, was still general. Progress was impossible without corresponding progress in chemistry.

The first beginnings of a better knowledge date from the work at Oxford of Robert Boyle (1666), Lower (1669), and Mayow (1673). Boyle proved by means of the air-pump that air is necessary to life, and Mayow summarized their joint conclusions and compared together the influences of nitre in the combustion of gunpowder, and of air in respiration and ordinary combustion in air. They drew the conclusion that in all these processes a 'nitro-aerial spirit' combines with 'sulphur' (combustible matter). As regards respiration they concluded that the nitro-aerial spirit is present in limited proportion in air and that it is absorbed from the air in the lungs by the blood. Lower and Mayow supposed, in accordance with the theory of Descartes, which was generally accepted at that time, that the nitro-aerial spirit is carried by the blood to the brain, where it is separated off in the ventricles, and passed thence down the supposed nerve-tubules to the muscles. They thought that in the muscles it combines with 'saline-sulphureous' particles brought by the blood, and produces muscular contraction by the resulting effervescence. They explained the increased breathing which accompanies muscular exercise as a necessary accompaniment of the increased consumption of nitro-aerial spirit.

It thus appears that they had almost discovered oxygen, in so far as the rudimentary chemical ideas which they had formed permitted the discovery. They had also formed a sound physiological conception

of the relation between muscular work and increased breathing. The idea of 'animal spirits' passing down supposed nerve-tubules from the brain was apparently confirmed by the effects of cutting or ligaturing nerves; and Lower (1669) performed the remarkable experiment of completely disturbing the action of the heart by means of a ligature on the vagus nerve. He had stumbled on what afterwards was called inhibition and misinterpreted it in terms of their new theory.

About the same time another significant observation was made by Hooke[1] (1667), the Secretary of the Royal Society. He found that when the chest of an animal was opened so that the lungs collapsed, the animal could be revived and kept alive by artificial respiration, and, if holes were pricked in the lungs so that air could pass through them, it could still be kept alive if a stream of air was continuously blown through the lungs, although they did not move.

The foundations of our present knowledge of the physiology of breathing thus seemed to be laid; 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 almost allowed to die out for the succeeding two hundred years.

The next important advance in connexion with the study of 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 alkalis (carbonates), is given off by the lungs in respiration. Joseph Priestley discovered soon afterwards that what, in accordance with Stahl's phlogiston theory, he called 'dephlogisticated air' disappears both in ordinary combustion and in animal respiration, while it is produced by green plants. Lavoisier then followed up Black's and Priestley's work by showing that in combustion the gas which Priestley called dephlogisticated air, and which he was the first to name 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, as had been shown by Cavendish. He and Laplace (1780) also showed that the carbon dioxide produced by an animal is nearly equivalent to the oxygen consumed, and that the amount of heat formed by an animal is nearly equivalent to that formed in combustion of carbon

[1] Hooke had been assistant to Willis and Boyle at Oxford.

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 the output of carbon dioxide are increased. Curiously enough he expresses regret that this should be so, as the labouring classes, who have least money for buying food, consume more food than those who are better off (Lavoisier and Seguin, 1789). The essential connexion 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, a German country doctor, pointed out in connexion with his 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. The ultimate source of the energy of animal movements is thus oxidation. Every exact experiment made since then on this subject has confirmed Mayer's conclusion, and the increased consumption of oxygen during muscular work has become as intelligible as it was on the crude theory of the early Oxford physiologists, though how part of the kinetic energy liberated in a muscle is converted into mechanical energy remained, and still remains, obscure.

Every step made in connexion with the chemical and physical aspects of respiration was equally a step in the biological interpretation of the relations between living organisms and their environment. Not merely, for instance, was it discovered that living organisms are the seat of oxidation but also that consumption of oxygen is a main feature in the persistent co-ordinated activity which we call life. In virtue of its persistent co-ordination with the other phenomena of life we interpret the oxidation as being respiratory, and, if we neglect the co-ordination, we neglect an essential character in what we are studying.

These discoveries with regard to the chemical aspect of respiration raised further questions as to the exact nature of the oxidizable material, and where the oxidation 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 matter oxidized must correspond to the oxidizable constituents of the food. These were classified by Prout (1834) as belonging almost entirely to one or other of three groups of substances, known now as proteins, carbohydrates, and fats. Of these the former alone contain nitrogen, which is excreted in the urine mainly in the form of urea when proteins are oxidized in the body. Only water and carbon dioxide are formed by the complete oxidation of carbohydrates and fats. Hence, from the ratios and amounts in which nitrogen compounds and carbon dioxide are excreted, and oxygen is consumed, we can calculate how much protein, carbohydrate, and fat respectively is being oxidized in the body.

As regards the second question there was for a long time much doubt. It was, however, shown definitely by Magnus (1837, 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 established that the oxygen which disappears in the lungs is taken up by the blood almost entirely in the form of an easily dissociable chemical compound with haemoglobin, the characteristic chromoprotein of 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 in the lungs is due to the higher partial pressure of oxygen which prevails there, and the partial discharging in the systemic circulation is due to the lower partial pressure encountered there in consequence of consumption of oxygen by the tissues. The discharging is accompanied by a change of colour from scarlet to dark purple. Similarly carbon dioxide is taken up from the tissues, mainly in the form of a loose chemical compound with alkali, and is discharged in the lungs in consequence of the lower partial pressure of this gas in the air they contain. For a considerable time there was much doubt as to how far the actual oxidation occurs in the blood or in the tissues; but the investigations of Pflüger (1872) showed clearly that practically all the oxidation occurs in the tissues.

So far the main outlines of discovery relating to respiration have been discussed from an abstract physical and chemical standpoint.

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 (1851), 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 introduced into the lungs must increase the rate of oxidation and heat production. 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 scientific men.

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 (1883) 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. Thus 1 gramme of fat furnishes as much energy as $2\frac{1}{4}$ grammes of protein or carbohydrate, and 1 gramme of fat from the reserve in the body takes the place of $2\frac{1}{4}$ grammes 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 marvellous 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 oxidation, 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 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 very greatly reduced 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, Crawford (1788) and Pflüger (1876) 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 concerned in 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

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, but which really form a definite factor in the physiological regulations of the body. Hence, apart from seasonal variations, the daily nervous activities are usually pretty constant in total amount.

Although the internal body temperature is actually very constant, yet a very moderate actual rise or 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 indefinite number 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 with which we are so familiar 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 is 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. Examination of the fragments left has never thrown any light on why the association should have

existed at all, or endured so long, or finally come to an irreversible end. 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 one 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 that gives us that grasp of biological phenomena which enables us to predict them, and renders a scientific treatment of biology and medicine possible.

The remarkable discoveries and generalizations in physics made during the last few years have shown very clearly the inadequacy of the physical conceptions of the eighteenth and nineteenth centuries. They have indeed indicated that, so far from biological phenomena being wholly explicable by application of the theories of the older physics and chemistry, these theories are in themselves unintelligible without the conception of something resembling in at least some ways the old-fashioned φύσις, since matter is the seat of intense, co-ordinated, and persistent activities, in virtue of which it takes definite form as electrons, protons, atoms, molecules, or crystalline aggregates.

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 its co-ordination with other aspects of physiological activity must now be traced. Much difficulty arises, however, from the fact that the problem itself has only been realized with any

clearness within comparatively recent years. Previously respiration and circulation had been treated to a large extent 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. Heavy exertion, for instance, will increase tenfold or more the consumption of oxygen and output of carbon dioxide for the whole body, and increase in a still 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 co-ordinated with other activities. 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.

Legallois (1812) discovered that if a portion of tissue definitely localized in the medulla oblongata is destroyed respiration ceases and death ensues. This part of the medulla came to be known as the 'respiratory centre'; and round its responses to various nervous and other stimuli the physiological investigation of breathing was focused.

It was found by Legallois and subsequent investigators that the nervous connexions both above and below the respiratory centre can be successively severed without preventing the rhythmic discharges of inspiratory and expiratory impulses except in so far as efferent nerves connected with the centre are cut off from it. Thus the rhythmic discharges of the centre are not merely 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 centre is automatic. On the other hand, the mode of action of the centre is much affected by nervous stimuli.

In the first place its action is to a large extent under voluntary control. Thus, in the actions of speaking, singing, &c., the normal rhythm is interfered with greatly, and the breathing can easily be suspended voluntarily for about 40 seconds. 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.

Hering and Breuer (1868, *a b*) 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 centre 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 centre returns to its normal rhythmic activity. These effects are completely absent if the vagi have been divided. The slow rhythmic discharges of the centre go on quite independently of whether the inflation or deflation of the lungs is prevented or not.

It appeared to follow from these experiments, and from the marked slowing and deepening of the breathing after cutting both vagi, that distension of the lungs stimulates the pulmonary nerve-endings of the vagi in such a way as to terminate inspiration and initiate expiration, while deflation produces a corresponding stimulus acting so as to terminate expiration and initiate inspiration. Thus it seemed that inspiration was the cause of expiration and vice versa. Hering described this as the 'self-regulation' (*selbst-steuerung*) of the breathing, and for many years no one remarked that such a process of regulation is, by itself, completely out of relation with the physiological needs of the body.

Another series of observations related to chemical stimulation of the respiratory centre. 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 (1857) 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 centre 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. If in an animal artificial respiration is pushed so that the ventilation of the lungs is abnormally great, the activity of the respiratory centre 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 centre. If the degree of arterialization is diminished the breathing is increased, and vice versa, so that the respiratory centre 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 carbon dioxide. It might be one or the other, or else both, of these changes that determines the activity of the respiratory centre. The most immediately evident change in the blood during its passage through the lungs is its change in colour from a bluish to a bright scarlet colour, and this change, as already seen, is due solely to its oxygenation and not to loss of carbon dioxide. We thus naturally tend to think of blue blood as venous and scarlet as arterial; and with the blood-pump we can easily prove that the scarlet blood contains more dissociable oxygen than the blue.

Rosenthal (1882) came to the conclusion that it is solely, or almost solely, in virtue of its varying oxygen content that the blood does or does not stimulate the respiratory centre. 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 (Pflüger, 1868) 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 centre.

A further fact, discovered originally by L. Traube (1862, 1863), 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 centre. The inspiratory muscles, and especially 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 (1889 *a*, *b*), 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 was 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 by air very rich in CO_2 (Haldane and Lorrain Smith, 1893 *a*). It was also affirmed by Brown-Séquard (1871) 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 (1901) crossed the circulation of two animals by connecting the vessels in such a way that the respiratory centre 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 centre 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 persists after the distension ceases, and from this supposed fact the further inference was drawn that repeated distension of the lungs produces a summed vagus effect resulting in vagus apnoea after the distensions 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 distensions 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 centre, 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 centre. Miescher-Rüsch (1885) 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.

Geppert and Zuntz (1888) 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 centre, 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 (1877) had found that the breathing is much increased in poisoning by acids.

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. From consideration of the general characteristics which distinguish life from what we interpret as physico-chemical activity, it became clear that life cannot be correctly studied process by process separately, as the action of a machine can be studied, the working of the whole machine being deduced synthetically from the separate study of each of the parts. The life of an organism is constantly showing itself to be a co-ordinated self-maintaining whole, and each process must therefore always be behaving as an expression of such a self-maintaining whole. In the existing state of 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 the correctness of these theories seemed doubtful, and suspicion was raised that errors had arisen through the mistake of not studying the breathing as one of the co-ordinated activities of the whole body. The investigations detailed in succeeding chapters were largely inspired by these considerations; and, as will be seen in the sequel, the same considerations have led to a reinvestigation and reinterpretation of other physiological activities besides breathing.

II

CARBON DIOXIDE AND REGULATION OF BREATHING

OUR interest in the regulation of breathing arose out of a series of experiments carried out by Haldane and Lorrain Smith (1893 *a*, *b*) with reference to the question whether, as had been asserted shortly before by Brown-Séquard and d'Arsonval (1887; 1888 *a*, *b*, *c*, *d*, *e*, *f*) in view of an apparently convincing series of experiments, a poisonous organic substance is given off in expired air. The experiments of Haldane and Lorrain Smith, on the contrary, which were made partly on man and partly on animals, yielded results which were entirely negative. In the experiments on man an air-tight respiration chamber of about 70 cubic feet capacity was used, the air in which was allowed to become more and more vitiated by respiration. They seemed to leave no doubt that the apparent positive results described by Brown-Séquard and d'Arsonval were due partly to undetected air leaks which led to the animals being asphyxiated, and partly to other experimental errors.

The effects on the breathing of air so vitiated attracted attention particularly. It was found that when the proportion of CO_2 in the air rose to about 3 per cent. and the oxygen fell simultaneously to about 17 per cent. (there being 20·93 per cent. of oxygen and 0·03 per cent. of CO_2 in fresh 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 and caused 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 proportion of this gas present 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 to the limit of endurance it was found that the experiment had to stop at about 10 per cent. of CO_2, whether oxygen was added or not, and that the percentage of oxygen made no differ-

ence to the distress produced. In the experiments with air there was only about 8 to 9 per cent. of oxygen in the rebreathed air at the end of the experiment; but even this low proportion made no appreciable difference to the breathing. When, on the other hand, a mixture containing a very much reduced percentage of oxygen, but without any addition of CO_2, was breathed, the respiration was increased distinctly, as shown by graphic records taken with a stethograph, when the oxygen fell to about 12 per cent. The breathing was still more greatly increased by yet lower percentages of oxygen. If the proportion of oxygen were extremely low, e.g. about 2 per cent., consciousness was lost quite suddenly after about 50 seconds, and before there was time to notice any increase in the breathing.

It was quite 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-Rüsch (1885), 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 is very familiar in connexion with experiments with mine-rescue apparatus and diving apparatus, and there can be no doubt that the statement of Brown-Séquard and d'Arsonval (1889) that they were able to breathe air containing 20 per cent. of CO_2 for two hours without much distress must have been founded on some error. 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 result in animals led many previous observers to overlook almost entirely the ordinary effects of CO_2 in stimulating the breathing.

In 1903 the problem of the regulation of the respiration was again

taken up at Oxford, and a long series of experiments was carried out (Haldane and Priestley, 1905).

The main consideration on which this work was based was the fairly evident fact that in order to reach clear ideas on the regulation of breathing it was necessary to study very carefully the composition of the air in the alveoli of the lungs, which is in contact, through the alveolar epithelium, with the blood passing through the lungs. It also seemed clear that this could best be done on man. 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. The latter is presumably but little altered by diffusion through the walls of the trachea, bronchi, etc., and so far as the respiratory exchange is concerned the volume of the lumen of these tubes must constitute a 'dead space' in breathing. This dead space is filled with alveolar air at the end of expiration and by more or less unchanged atmospheric air at the end of inspiration. Zuntz (1882) had already introduced the conception of the dead space, and he and his pupils had calculated the composition of human alveolar air. Loewy (1894) carried the matter farther and tried to measure the dead space by taking a plaster cast of the respiratory passages in a dead body, and from the volume of this cast and the average volume and composition of a breath of expired air he calculated the composition of alveolar air. It is, however, impossible, as will be shown later, 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. In the bronchioles the muscle is arranged in a network of oblique bands, which extend as far as the openings of the ductuli alveolares into the atria (Miller, 1893, 1913). A considerable variation in the capacity of these terminal tubes and of the atria is thus made possible. 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, which varies greatly, as will appear below, with the depth of breathing.

It is evident, therefore, that a reliable knowledge of the composition of alveolar air can only be obtained by direct determinations. We introduced a simple method which makes it possible to obtain alveolar air for analysis. The procedure is simply to make a sharp and deep expiration through a piece of hose-pipe about 3 or 4 feet

long and 1 inch in diameter, and provided with a plain glass mouthpiece which is closed by the tongue at the end of the expiration (Fig. 1). By means of a narrow-bore glass tube filled with mercury and introduced air-tight through a hole in the side of 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 Fig. 1,[1] or else into a vacuous sampling tube.[2] When taking a sample of normal alveolar air it is important that the rate and depth of breathing should be quite normal until the moment when the deep expiration is made. Some care is needed to make sure of this because

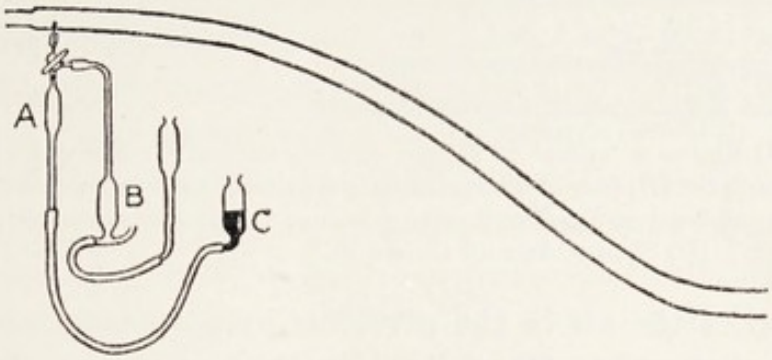


FIG. 1. Apparatus for obtaining and analysing alveolar air.

of the instinctive tendency to prepare for the deep expiration by taking a preliminary deep inspiration. 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 c.c. With less than this the sample is likely to be mixed with air of the apparent dead space; for, though with normal breathing the volume of the apparent dead space is far less than 800 c.c., at least three or four times its volume of alveolar air is needed in order to flush it and the breathing tube out thoroughly. It was shown by Yandell Henderson, Chillingworth, and Whitney (1915) 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

[1] For physiological work methods of air analysis which are both accurate and rapid are required. A description of the method introduced with this in view will be found in *Methods of Air Analysis*, I. Graham and J. S. Haldane, London, 1934.

[2] The sample must not be too large, to make sure that the alveolar air is not diluted with any pure air.

washed out by three or four times their volume of alveolar air. This is illustrated by Figs. 2 and 3, taken from their paper, and drawn from experiments made with smoke. If more than about 800 c.c. 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

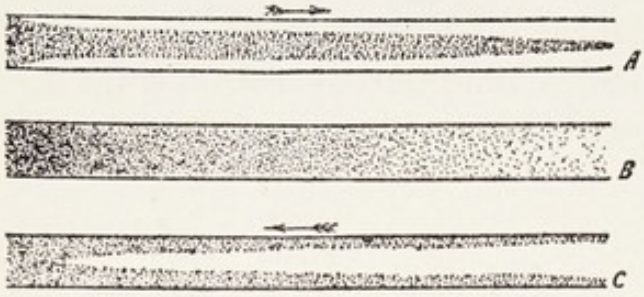


FIG. 2. (*A*) Shows a 'spike' of smoke moving through a glass tube. (*B*) Shows the condition when the current is suddenly stopped and mixing occurs instantaneously. (*C*) Shows clear air drawn in.

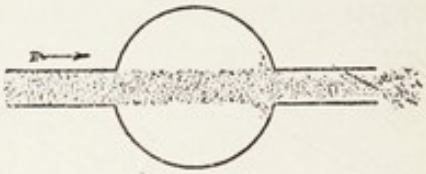


FIG. 3. Shows how a column of smoke crosses a bulb with little mixing or sweeping out of the air within it.

composition of the air in the alveoli is by no means such a simple matter as we thought. The following are the averages of the results obtained on this point when the samples were taken just at the end of expiration (Haldane, 1915):

Vol. of air expired through tube	*Per cent. of CO_2 in sample taken from tube*
190 c.c.	3·03
335	4·37
510	5·04
650	5·19
950	5·51
1,350	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-percentages during rest under normal conditions are surprisingly constant for each individual. As the depth of breathing is not normally 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—making the sudden deep expiration first just at the end of a normal inspiration and second just at the end of a normal expiration. It is obvious that if the deep expiration takes an appreciably longer time than a normal expiration, CO_2 will accumulate in the alveolar air to an abnormal extent. The deep forcible expira-

tions should therefore be performed as rapidly as possible. Pearce (1920) has drawn attention to the importance of this point. A useful modification of this procedure is to collect three samples taken at the end of inspiration, and three taken at the end of expiration, in two sampling tubes, the mercury level in which is lowered progressively one-third of the height of the tube for each sample. Yandell Henderson and Haggard (1925) endeavoured to devise a means of obtaining alveolar air without the need for voluntary assistance on the part of the subject. They collected a series of small fractions from the end of each expiration. Their method had the advantage of being automatic, but has been criticized on the ground that it is less accurate than the single deep expiration (Aitken and Clark-Kennedy, 1928).

The following tables give the CO_2-percentages in samples of our normal resting alveolar air, taken by the original method in a sitting position during rest at intervals over about twenty months in the years 1903 to 1905. Since then we have made many further determinations, but the percentages have remained nearly the same in J. S. H., though now they are distinctly lower in J. G .P. (p. 22). They are slightly lower or higher on some days than on others, and other observers have noticed this in themselves. The cause of this will be discussed below (p. 116).

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 variation 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

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
1914	..	..	5·7
1934 754	5·38	5·95	5·67
754	5·55	6·08	5·81

varied it became quite evident that the breathing is regulated 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 inspired 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	6·35	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 was subsequently obtained by Campbell, Douglas, and Hobson (1914), who found that for an increase of 10 litres 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 CO_2 of the alveolar air. 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 one and a half 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 centre 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 centre, 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 con-

taining an excess 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 (Campbell, Douglas, Haldane, and Hobson, 1913). 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 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 centre to CO_2 is thus clearly established in both an upward and a downward direction. A mean increase or diminution of 0·01 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 c.c. per minute in the lung ventilation.

It may be useful to review briefly the sources of error in the views held previously with regard to the causes of the apnoea produced by excessive ventilation of the lungs. One view (p. 11) 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 (1882) laid great 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 distension of the animal's lungs by the pressure, as in the experiments of Hering and Breuer (1868 *a*, *b*). 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 distension 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 second 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 aeration of the blood is impossible. Advocates of the vagus theory wrongly thought only of oxygen want in connexion with aeration 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 had 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

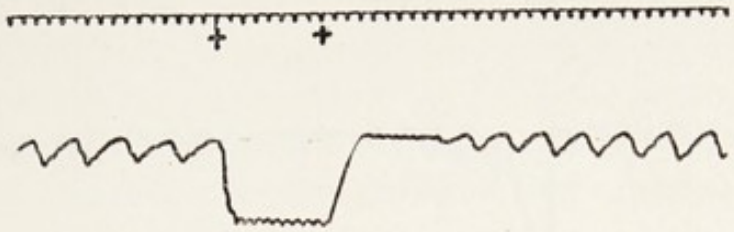


FIG. 4

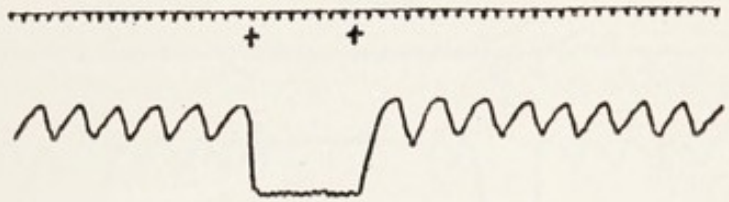


FIG. 5.

Effects of distension for 8 secs. Crosses show beginning and end of distension. To be read from left to right. In Fig. 4 pure air is used for distension; in Fig. 5 air containing 4·62 per cent. CO_2.

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 distension of the lungs was clearly shown by the observations of Christiansen and Haldane (1914), some of whose stethographic tracings are reproduced in Figs. 4–8. Fig. 4 shows apnoea as an after-effect of inflation of the lungs, while Fig. 5 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 Fig. 4 is therefore due to reduction of the alveolar CO_2 in consequence of the distension with pure air.

Figs. 6, 7, and 8 illustrate the same point. In Figs. 6 and 7 there is apnoea succeeding a short distension, but not immediately, since a few seconds were needed before the 'apnoeic' blood could affect the

respiratory centre. In Fig. 8 the distension was sufficiently prolonged for the 'apnoeic' blood to affect the centre before the end of distension. The effect is therefore similar to that in Fig. 4.

The regularity of ordinary breathing is constantly being interfered with in various ways, as, for instance, during talking or singing; and, after a preliminary deep inspiration, the breath can, if necessary, be held for about a minute by voluntary effort. The readiness with

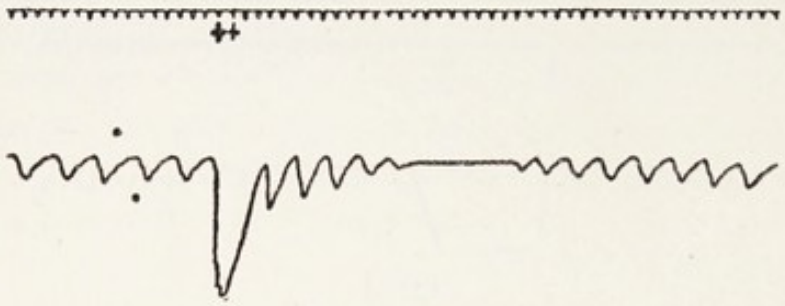


FIG. 6.

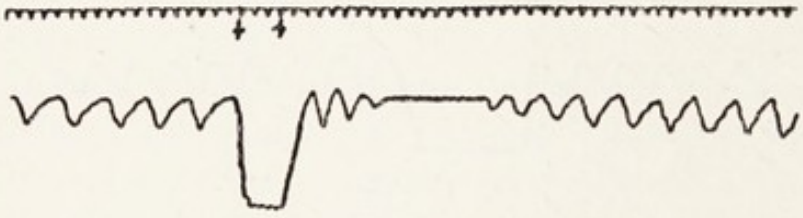


FIG. 7.

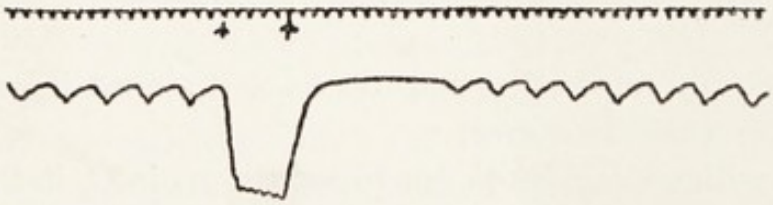


FIG. 8.

Effects of distension with pure air for increasing short periods. Crosses show beginning and end of distension. To be read from left to right. Fig. 6 distension for 1 sec.; Fig. 7 for 3 secs.; and Fig. 8 for 5 secs.

which these interruptions occur has given rise to the popular fallacy 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 we 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
,,	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 series of experiments ten years later (Haldane, 1915) 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 compensated for diminished or increased frequency. The manner in which this correspondence between depth and frequency is brought about will be discussed in chapter V.

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. We 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 endeavoured, mistakenly as afterwards appeared, to explain the lack of exact correspondence.

A more complete series was carried out later with much improved apparatus (Douglas and Haldane, 1912 *b*), Douglas being the subject. The table on page 31 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 they used the now well-known bag method of Douglas (1911) for determining the respiratory exchange.

It will be seen from this table that, with a CO_2 production increased from 264 c.c. per minute during rest standing to 1,398 c.c. per minute during walking at 4 miles an hour 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 or by 26·9 litres. This corresponds very closely to the estimate by Campbell, Douglas, and Hobson of an increase of 10 litres per minute in the breathing for every 0·26 per cent. of increased alveolar CO_2 at normal barometric pressure.

When, however, the CO_2 production was increased still farther, 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 (2,386 c.c.) and volume of air breathed (60·9 litres). 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

	O_2 consumption in c.c. per min. at 0° C. and 760 mm.	*CO_2 production in c.c. per min. at 0° C. and 760 mm.*	*Litres of air breathed per min. at 37° C. moist, and prevailing barometric pressure*	*Breaths per min.*	*Vol. of each breath in c.c. 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	1,296	4·25	6·04
2 miles an hour (grass)	780	662	18·6	14·7	1,271	4·39	6·04
3 miles an hour (laboratory)	907	737	20·9	14·9	1,433	4·38	6·14
3 miles an hour (grass)	1,065	922	24·8	16·2	1,535	4·62	6·10
4 miles an hour (laboratory)	1,182	1,057	29·0	14·4	2,010	4·55	6·23
4 miles an hour (grass)	1,595	1,398	37·3	18·2	2,064	4·67	6·36
4½ miles an hour (laboratory)	1,493	1,251	34·2	17·2	2,055	4·50	6·44
4½ miles an hour (grass)	2,005	1,788	46·5	18·5	2,524	4·72	6·20
5 miles an hour (laboratory)	2,125	2,000	51·3	18·3	2,810	4·80	6·28
5 miles an hour (grass)	2,543	2,386	60·9	19·5	3,145	4·79	6·10

be discussed later (p. 94); 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 (1878) that the physiological actions of CO_2, oxygen, and other gases present in the air breathed depend on their partial pressures. 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 vapour present in the

alveolar air, which in the living body must be saturated with aqueous vapour at the body temperature. The pressure exercised by this aqueous vapour is approximately 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

$$5{\cdot}6 \times \frac{760-47}{100} = 39{\cdot}9 \text{ mm.}$$

or 5·25 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 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.	1,261	3·64	5·83
,,	765	6·41	6·05
J. S. H.	1,258	3·42	5·46
,,	765	5·62	5·31
Means	1,260	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 (1905–6) and by Boycott and Haldane (1908) in steel chambers erected later for the investigation of the effects of high atmospheric pressures. Hill and Greenwood obtained the following results:

Atmospheric pressure 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
4,640	0·75	0·9	34·4	41·3
3,860	0·95	1·0	36·2	38·1
3,090	1·2	1·3	36·5	39·5
2,310	1·8	1·8	40·7	40·7
1,540	2·5	2·7	37·5	40·5
760	5·0	5·4	35·6	38·5

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.

The results of Boycott and Haldane, with Boycott as subject, are shown graphically in Fig. 9. 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 2,800 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; but there are other causes, discussed in chapter IV, which cause distinct variations in the alveolar CO_2-pressure. 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,

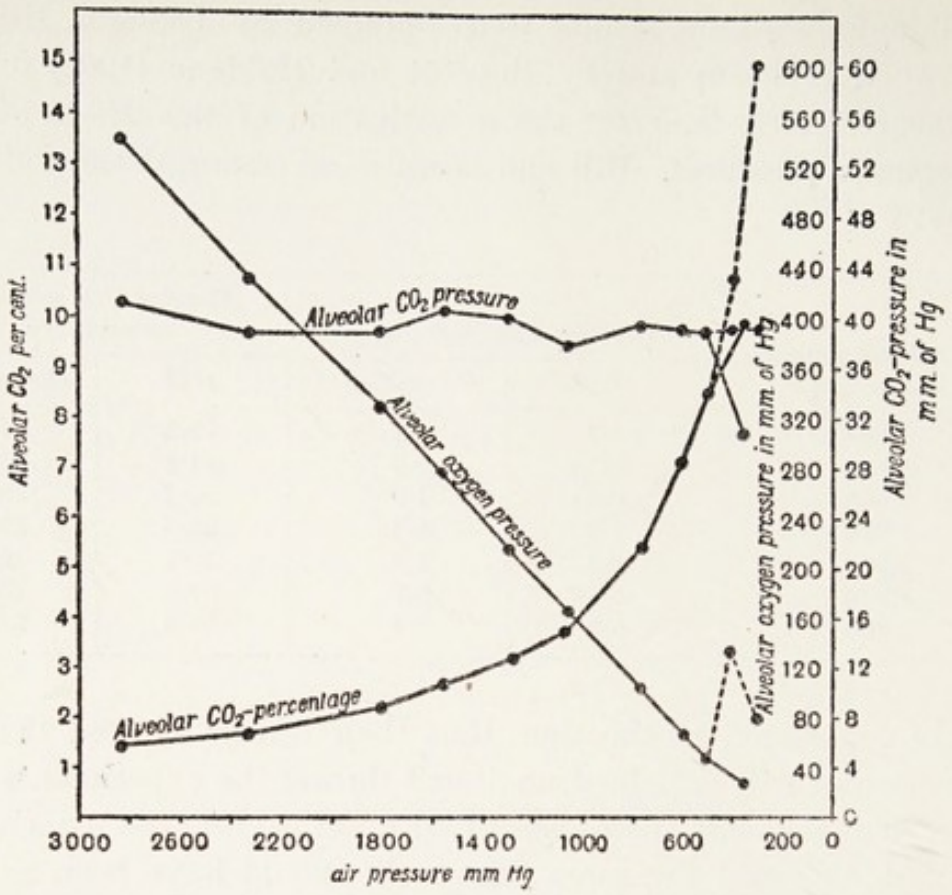


FIG. 9. Effects of variation in barometric pressure on alveolar gas pressures and percentage of CO_2 in A.E.B. The dotted lines show results when oxygen was added to the air.

and in different sexes and at different ages, were investigated by Haldane and Miss FitzGerald (1905). They obtained the following results from a number of different persons 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

The work of Haldane and Priestley 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 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

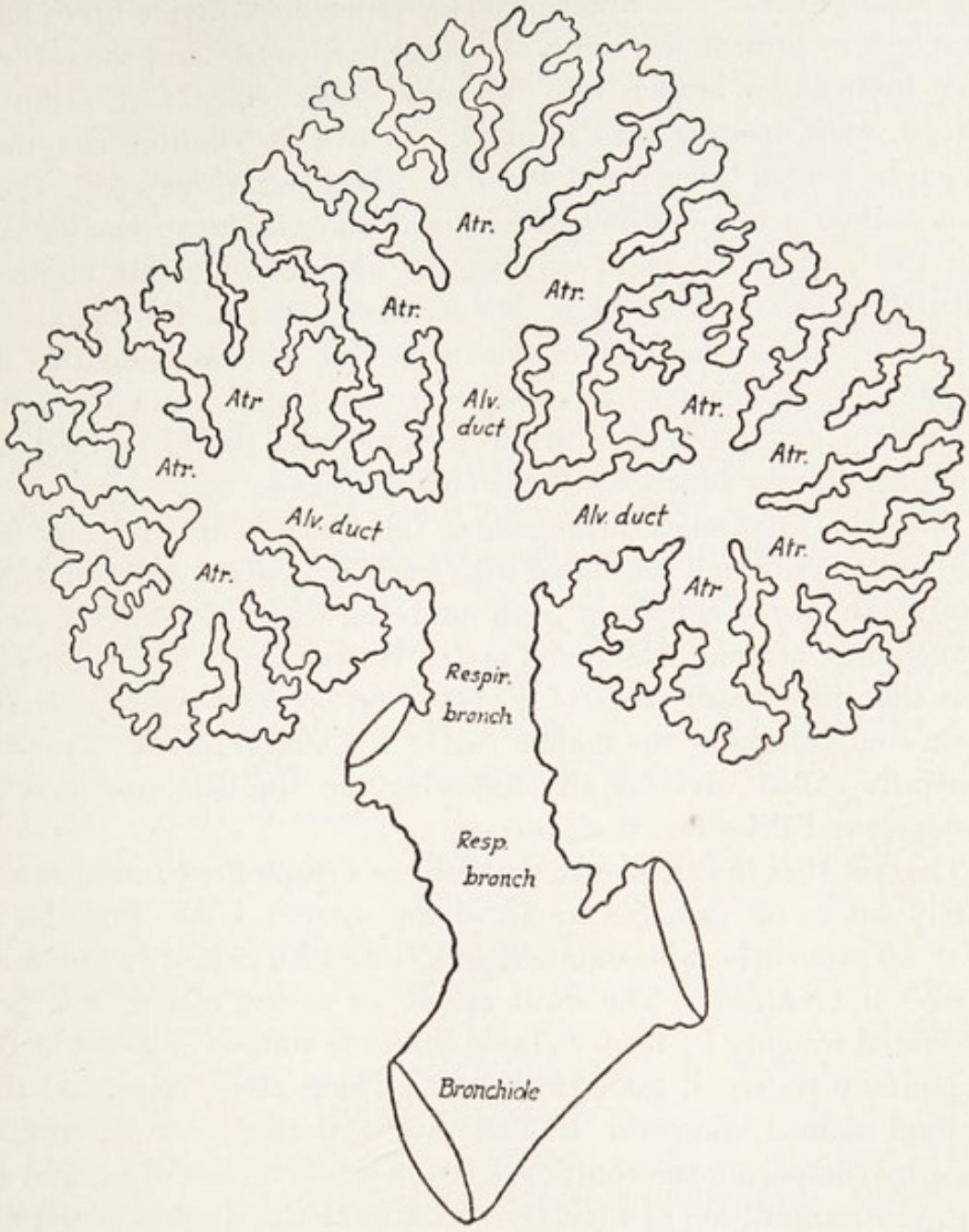


FIG. 10. Diagram showing arrangement of three lung lobules, with their bronchiole, respiratory bronchioles, alveolar ducts, atria, and air-sacs. (After coloured plate by Miller, *Journ. of Morphol.* **24**, p. 459, 1913.)

must get less fresh air than the alveoli near a bronchiole. It was somewhat of a puzzle that this was not the case. We were unaware of the anatomical investigations which had been carried out ten years earlier by a distinguished American investigator, W. S. Miller (1893, 1913, 1924), who by using the laborious 'reconstruction' method had discovered the true anatomical arrangement. Figure 10, modified from a coloured plate in Miller's second paper, shows diagrammatically

this arrangement. The finest ordinary bronchioles divide up to form 'respiratory bronchioles' with alveoli in their walls, and the respiratory bronchioles branch into 'alveolar ducts' lined with ordinary alveoli, 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, the walls of which 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 is generally called 'alveolar air', following the original term used by Haldane and Priestley, is air-sac air.

The fact that the atria, etc., partly have 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, as stated above, was first estimated roughly by Loewy (1894) from the volume of a cast of the respiratory passages, taken in a human lung after death. As this method seemed uncertain, Haldane and Priestley made determinations by comparing the composition of a whole breath of expired air with the composition of what they took to be the whole alveolar air. They calculated the expired air as a mixture of this alveolar air with fresh air occupying the dead space. In this way they 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 Haldane (1912 *b*) reinvestigated the question, collecting the whole of the expired air over a certain period, and making the same calculation from the average volume and composition of each breath, compared with the composition of the alveolar air. It was then found that the 'effective dead space' is far greater during the hyperpnoea of hard muscular work than during rest. As they were

then still unaware of Miller's work they interpreted their 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 folds would open out, and the lumen of the bronchi would greatly increase. They 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 (1913–14*a*) then redetermined the dead space, and concluded that it does not increase appreciably 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 (1915) at Yale, and Haldane (1915) at Oxford. They reached the same conclusion—namely, that the apparent effective dead space is enormously increased during hyperpnoea, as Douglas and Haldane had found, but that the increase is due simply to mechanical causes, and occurs whether or not the respiratory centre is excited by excess of CO_2 or other causes. Their papers appeared together in the *American Journal of Physiology*. 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 the experiments carried out at Yale and Oxford were made with the very deep breathing which is naturally associated with air hunger, and consequently the dead space was increased. Campbell, Douglas, and Hobson (1914) also found that the effective dead space is considerably increased during the hyperpnoea caused by breathing CO_2.

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 Haldane 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 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 relatively greater 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 up to the blood any appreciable extra amount of oxygen. During inspiration the air carried on to the air-sacs from the atria includes this extra CO_2, but during expiration the extra CO_2 passes into the expired air. Consequently the respiratory quotient of the 'alveolar air' (derived from the air-sacs) is lower than that of the expired air as a whole, since this is made up of a mixture of fresh air from the upper passages, air from the atria, with abnormally high R.Q., and air from the air-sacs with abnormally low R.Q. It follows 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 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 (1915) got similar results.

Frequency of respirations per min.	*Mean depth of expirations at 37 °C, saturated, in c.c.*	*Expired air*			*Alveolar CO_2-percentage*		
		CO_2 per cent.	*O_2 per cent.*	*Respiratory quotient*	*End of inspiration*	*End of expiration*	*Mean*
3	2,984	4·29	16·07	0·848	5·41	6·04	5·72
4	2,438	4·56	16·91	0·875	5·24	6·09	5·66
6	1,413	4·24	16·47	0·905	5·37	5·70	5·53
18·5	683	3·31	17·27	0·871	5·53	5·75	5·64
17·0	650	3·59	17·01	0·887	5·63	5·79	5·71
17·7	643	3·58	16·98	0·888	5·50	5·59	5·55
24	410	3·22	17·15	0·780	5·45	5·46	5·45
60	357	1·89	18·75	0·820	5·87	6·06	5·96

Alveolar O_2-percentage			*Alveolar respiratory quotient*	*Effective dead space minus that of mouthpiece, c.c.*	
End of inspiration	*End of expiration*	*Mean*		*Calculated from CO_2*	*Calculated from O_2*
14·56	12·84	13·70	0·745	683	920
14·98	13·07	14·02	0·814	467	619
14·51	14·25	14·38	0·803	272 224	392
13·95	13·74	13·84	0·762	171	223
13·44	13·99	13·72	0·721	161	231
13·88	13·42	13·65	0·692	111	136
13·15	12·85	13·00	0·703	185	199

It will be seen from this table how enormously the apparent dead space varies with the depth of breathing and how much greater is the dead space calculated from the oxygen 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 quotient had been noticed 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.

calculated even approximately, 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.

The conclusion reached by Haldane, Priestley, and Douglas 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 (1913–14*a*), 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 two 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 determining directly 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 the case of Haldane, the rise in alveolar CO_2-percentage was less than corresponded to the increase in breathing. This significant fact will be discussed later (p. 94).

Krogh and Lindhard (1917) maintained that the mean gas pres-

sures 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 Haldane and Priestley. 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 abandoned if Krogh and Lindhard are correct. Their reasoning was quite logical, but their premisses were unsound. They 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. In individual air-sacs, however, 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 may be said that it seems 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 in accordance with the alveolar CO_2-pressure; and a very slight increase or diminution in the alveolar CO_2-pressure implies a very great increase or diminution in the breathing. This conclusion, though subsequent observations, as will be seen later, have shown that it is not wholly correct and must be modified, has thrown a flood of clear light on the physiology of breathing. It has been the starting-point of a great number of researches the outcome of which has been to establish firmly the conclusion that the regulation of respiration is a physiological process adapted to maintain the internal conditions in an animal within narrow limits of variation despite what would otherwise be marked disturbing influences.

III

THE BLOOD AS A CARRIER OF CARBON DIOXIDE

THE gaseous exchanges which occur in the lungs between the blood and the external air are, of course, intimately connected with the gases of the blood. Clearly the physiology of respiration cannot be understood without some insight into the blood gases and their variations. Since, as we have seen, there is a close relation between the alveolar carbon dioxide pressure and the regulation of respiration it will be convenient to consider now the transport of CO_2 by the blood.

Observations on the CO_2-content of the blood became practicable when the mercurial blood-gas pump was perfected, and it was usually found that mammalian arterial blood contains roughly about 40 to 50 volumes of CO_2 per 100 volumes of blood, while venous blood from the right side of the heart contains about 5 volumes more. As an instance the results of Schoeffer (1860) may be quoted to illustrate the difference between venous and arterial dog's blood, though much doubt must exist whether the circulation and respiration were at normal resting values when the samples were taken.

	Oxygen	*CO_2*
Arterial blood	19·2	39·5
Venous blood from right heart . . .	11·9	45·3
Difference	7·3	5·8

Of recent years, however, it has become possible to obtain much more accurate figures for the CO_2-content of arterial blood. This increased precision has resulted firstly from the introduction of simple and rapid methods of blood-gas analysis (Haldane and Barcroft, 1902; Brodie, 1910; Haldane, 1919–20; Peters and Van Slyke, 1932), secondly from the development of a technique by which arteries may be punctured and blood withdrawn for analysis (Hürter, 1912; Stadie, 1919–20), and thirdly owing to recognition of the refinement of physiological control, and consequent attention to the precautions necessary to obtain samples of blood under standard conditions. Arterial puncture may be carried out easily in man, and apparently without ill effect despite repeated punctures of the same artery. The

determination of the CO_2-content of the venous blood is not so simple. It varies considerably in different veins, and consequently the only value which is of importance from the point of view of respiration is the CO_2-content of the mixed venous blood in the right side of the heart. Puncture of the heart has often been performed on animals and has also been carried out on human subjects (Lauter, 1930; Baumann and Grollman, 1931). Zuntz and Hagemann (1898) obtained blood from the right ventricle of a horse by means of a catheter passed down the jugular vein. Forsmann has obtained blood from the right auricle in human subjects by means of a catheter passed from the median basilic vein (Klein, 1930), but it may be doubted whether such methods are justifiable.

In man, as will be shown below, normal arterial blood contains during rest about 53 volumes per cent. of CO_2. Bohr (1905) calculated the absorption coefficients of carbon dioxide, oxygen and nitrogen in blood and obtained the following figures:

	Oxygen		*Nitrogen*		*Carbon Dioxide*	
	15°	38°	15°	38°	15°	38°
Blood-plasma .	0·033	0·023	0·017	0·012	0·994	0·541
Blood . .	0·031	0·022	0·016	0·011	0·937	0·511
Blood corpuscles .	0·025	0·019	0·014	0·010	0·825	0·450

Redeterminations of these solubility coefficients of CO_2 at 38° C. have been made by Van Slyke, Sendroy, Hastings, and Neill (1928). They found the following values: Water, 0·5455, normal serum, 0·510, and ox corpuscles, 0·44. They also found that the solubility of CO_2 in lipaemic sera may exceed its solubility in water. This is what might be expected in view of the fact that gases are much more soluble in oils than in water (p. 334).

Since 100 volumes of blood, according to the calculations of Bohr, take up in simple solution about 51 volumes of CO_2 in the presence of CO_2 at a pressure of one atmosphere and at body temperature, they can only take up $\frac{40}{760} \times 51 = 2{\cdot}7$ volumes in simple solution at the normal alveolar pressure of 40 mm. Hg or 5·3 per cent. of an atmosphere of CO_2. Hence only 2·7 volumes per cent. of CO_2 are in simple solution and the other 50·3 volumes must be present in some form of chemical combination. As will be shown below (p. 56), the difference between the partial pressures of CO_2 in human arterial

and venous blood during rest is only about 6 mm. Hg or 0·8 per cent. of an atmosphere. Hence the physically dissolved CO_2 given off by the lungs is only 0·4 volumes per cent., while actually about 4 volumes per cent. are given off. It is evident, therefore, that the removal of CO_2 from the blood in the lungs is almost entirely dependent on the dissociation of its chemical combinations.

In what form is the CO_2 chemically combined in the blood? This question cannot be answered in the same comparatively simple and definite manner as we shall see later it is possible to answer the same question in the case of the combination of oxygen in blood. CO_2 dissolved in water combines to form carbonic acid, and it seems probable therefore that it is as an acid that CO_2 enters into chemical combination in the blood. On analysis blood is found to contain radicles of strong inorganic acids (hydrochloric, phosphoric, and to a less extent sulphuric) and inorganic bases, of which, in the plasma, the greater part is sodium. Moreover, there is an excess of inorganic bases over inorganic acid radicles, and in fact the excess, as was first pointed out by Zuntz (1882), is sufficient to account for the whole of the CO_2 with which blood is capable of combining chemically. Since the blood always contains some free CO_2 in simple solution the particular form of carbonate present could only be bicarbonate.

At first sight therefore it would seem that in blood 2·7 volumes per cent. of CO_2 are present in simple physical solution and 50·3 volumes per cent. as bicarbonate combined with inorganic bases, chiefly sodium. Such a conclusion, however, by no means accounts for the properties of blood. A mere solution of sodium bicarbonate gives off CO_2, as Bohr (1909 *a*) showed, far less readily than does blood, and in presence of a vacuum leaves undissociated carbonate. A solution 0·02 molar, in distilled water in equilibrium with CO_2 at decreasing pressures, gives off CO_2 in accordance with the curve given in Fig. 11. Consideration of this curve shows that very little CO_2 is given off until the pressure has fallen to about 5 mm. Hg and that between this pressure and zero about half the chemically combined CO_2 is liberated. Blood, however, as shown in Fig. 13, gives off its CO_2 much more gradually and moreover yields the whole of it when the partial pressure of the gas is reduced to zero, as was shown originally by Pflüger (1864).

It is quite clear therefore that, if the CO_2 is to be supposed to be combined as an acid with inorganic bases in the blood, some additional

factor must be taken into account. This additional factor is not far to seek. If another, non-volatile, weak acid be added to a solution of bicarbonate, the dissociation curve at once becomes much more like that of blood, i.e. the CO_2 is given off more gradually and finally the whole of it is liberated if the second acid is present in sufficient

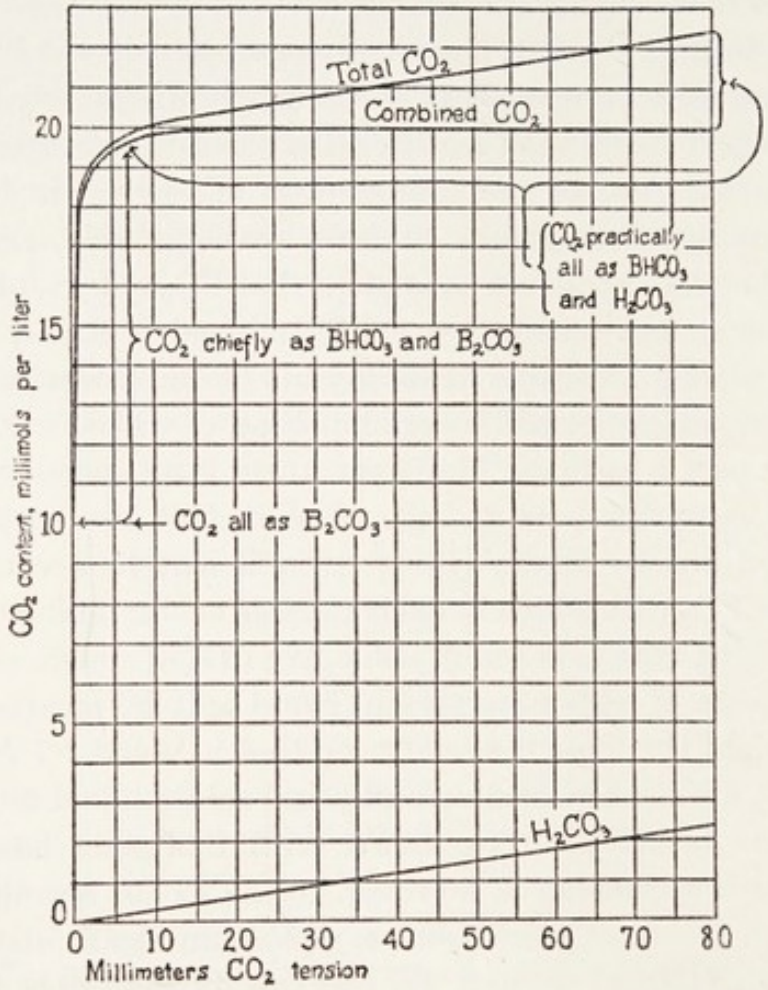


FIG. 11. Carbon dioxide dissociation curve of 0·02 molar sodium bicarbonate solution. (*Peters and Van Slyke*, vol. i, p. 899.)

amount. One is impelled therefore to seek for a second weak acid in blood. Now investigation of the physical chemistry of proteins has shown clearly that they are amphoteric electrolytes and are therefore capable of acting as weak acids or weak bases. In an acid solution they act as weak bases, in an alkaline solution as weak acids. It would be expected therefore that addition of protein to a solution of sodium carbonate would result in the CO_2 being given off gradually and completely on exposure to a vacuum, and, indeed, it was found by Sertoli (1868) that much of the CO_2 can be expelled in the pump from sodium carbonate solution if serum proteins are first added.

Joffe and Poulton (1920–1) investigated the dissociation curve of serum separated from the corpuscles (Fig. 12).

It will be seen from the figure that the dissociation curve of separated serum is intermediate between those of blood and of a bicarbonate solution, but that by no means the whole of the CO_2 can be pumped off from serum. It is found in fact that the serum proteins

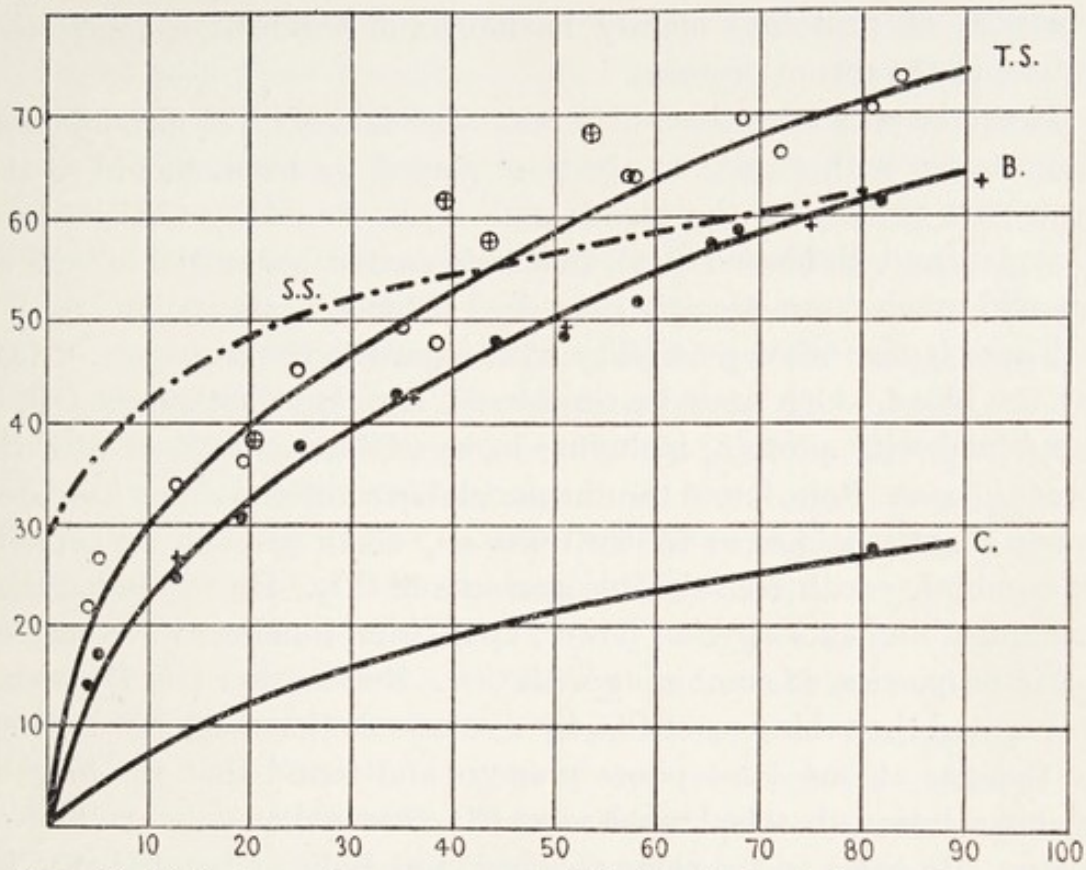


FIG. 12. Ordinates, volumes per cent. CO_2 absorbed; abscissae, CO_2-pressure, mm. Hg.

● Defibrinated blood. Corpuscles of 100 c.c. blood.
+ Oxalated blood.
○ True serum from defibrinated blood.
⊕ True plasma from oxalated blood.
S.S. Separated serum.

do promote the liberation of CO_2 but that they are not present in sufficient concentration to combine with the whole of the inorganic bases present in serum.

The serum proteins are not, however, the only protein present in blood. Haemoglobin is present in the corpuscles, and indeed normal human blood contains about three times as much haemoglobin as serum protein. Moreover, the capacity of haemoglobin to combine with alkali is two to three times as great as that of the serum proteins (Hastings, Van Slyke, Neill, Heidelberger, and Harington, 1924).

The presence of this substance in the blood accounts for the CO_2 dissociation curve in blood and the fact that the whole of the CO_2 can be pumped off from blood on exposure to a vacuum (Zuntz, 1882).

It would seem therefore that CO_2 is transported in the blood in combination with inorganic base, chiefly sodium, as bicarbonate, and that its liberation on reduction of the partial pressure is due to the presence of proteins—mainly haemoglobin—and to a much less extent to the serum proteins.

It will be seen later that there is another fact of great physiological importance with regard to the part played by haemoglobin in the transport of CO_2 by the blood; namely, as found by Christiansen, Douglas, and Haldane (1914), that oxygenated haemoglobin acts as an acid much more strongly than does reduced haemoglobin.

There is one other possibility with regard to the transport of CO_2 by the blood which must be considered, namely, whether the CO_2 is combined with protein, including haemoglobin, as well as with inorganic base. Bohr found that haemoglobin solutions which had been made slightly acid so as to neutralize any alkali present, are capable of combining with considerable amounts of CO_2. He concluded that haemoglobin has a specific power, apart from its alternative acid or basic properties, of combining with CO_2. Buckmaster (1917) also investigated the taking up of CO_2 by a solution of haemoglobin exposed to this gas at one atmosphere pressure and found that the haemoglobin solution absorbed much more CO_2 than did an equal volume of water. He came to the same conclusion as Bohr and stated that he obtained spectroscopic evidence of the existence of a compound of CO_2 and haemoglobin. This, however, has been shown to be an error due to the presence of dissolved air in liquid CO_2 (Priestley, 1920). The observation of Buckmaster that a solution of haemoglobin takes up much more CO_2 than an equal volume of water is no doubt accurate, but it has no bearing on the transport of CO_2 by the blood, since he saturated his haemoglobin solution with CO_2 at a pressure of one atmosphere. At this pressure the solution must have been acid and the haemoglobin therefore must have been basically dissociated and consequently capable of forming haemoglobin carbonate. In blood, however, in the body, since the reaction is weakly alkaline, this form of combination is impossible.

Bayliss (1919) supposed that CO_2 is adsorbed by the proteins of blood, but this theory 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 (1912). The apparent surplus is almost certainly due to what is rather a common source of slight error in gas analysis. When the gas pumped off from oxygenated blood is analysed, the first step is to bring the gas into contact with potash solution to absorb the CO_2. When this has been absorbed a gas mixture consisting almost wholly of oxygen is left in contact with the potash solution. But the latter is saturated with air, and consequently nitrogen diffuses from the potash solution into the gas mixture, while oxygen diffuses into the potash solution. The consequence is that the residue of the nitrogen found in the gas after the oxygen has been absorbed is greater than that which 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 was found in the case of reduced blood.

Bayliss maintained 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, in his view, it does not, under actual physiological conditions, compete as an acid with carbonic acid for the alkali available in the blood. The experiments, however, cited in support of this conclusion seem to be 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 to be quite impossible to reconcile Bayliss's theory with this fact; and it is difficult to see how any theory other than that given above is capable of interpreting the facts as a whole. It may be, as stated above, that a small amount of CO_2 is combined with free haemoglobin; but it seems to be 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 physiological carrier of CO_2. Campbell and Poulton (1920) who entirely disagree, on substantially the same grounds, with the conclusions of Buckmaster and Bayliss, have 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.

Henriques (1928 *a*, *b*, *c*, *d*, *e*) made a number of observations on the velocity with which the hydration of CO_2 and dehydration of carbonic acid occur. He came to the conclusion that, if haemoglobin is present, CO_2 is evolved much more rapidly when a bicarbonate solution is pumped out than Faurholt (1924) had found to be the case for a simple solution of bicarbonate. This observation has been confirmed by Van Slyke and Hawkins (1930).

Dirken and Mook (1930) also find that, while equilibrium is reached very rapidly on adding lactic acid to an alkaline phosphate solution, anhydrous CO_2 combines very slowly. On mixing CO_2-saturated water with haemoglobin solution they found, on the contrary, very rapid disappearance of CO_2. They therefore conclude that, either anhydrous CO_2 is bound as carbhaemoglobin, or that haemoglobin catalyses the reaction $CO_2 + H_2O \leftrightharpoons H_2CO_3$.

Henriques came to the conclusion that his results indicated that CO_2 does not exist in the cells as bicarbonate but in the form of anhydrous CO_2 loosely bound with haemoglobin as a compound which he terms carbhaemoglobin. This view, however, does not seem to be justified (Peters and Van Slyke, 1931). A more likely explanation is given by the work of Roughton and others (Meldrum and Roughton, 1932 *a*, *b*; 1933 *a*, *b*; Brinkman, Margaria, Meldrum and Roughton 1932; Ferguson and Roughton, 1934). This work has indicated that the blood contains an enzyme, carbonic anhydrase, which catalyses the reaction between CO_2 and water and that, while by far the greater part of the chemically combined CO_2 of the blood is present as bicarbonate, a small but appreciable amount—perhaps 5 per cent.—is present in some other form of combination, and Meldrum and Roughton give reasons for concluding that this compound is a haemoglobin carbamate and that, while it is probably of more importance in the transport of CO_2 in cold-blooded animals than in warm-blooded, it may well be of considerable physiological importance in relation to the difference in CO_2 capacity of arterial and venous blood

in mammals. Ferguson and Roughton, indeed, found that 50 per cent. or more of the extra total CO_2 taken up at a given pressure of CO_2 by reduced haemoglobin over that taken up in oxyhaemoglobin might be accounted for by the difference in the carbamino content of the two solutions.

Though there would seem to be little doubt as to the correctness of the main conclusion, namely, that CO_2 is transported in the blood in the form of sodium bicarbonate, it must not be forgotten that blood is not a homogeneous system like a simple solution of sodium bicarbonate. It is, on the contrary, a suspension of corpuscles in a liquid phase, and the bearing of this fact on CO_2 transport is important and will be considered later (p. 87).

We have seen already what predominant physiological importance is attached to the pressure of carbon dioxide in the arterial blood, and with what exactitude this pressure is regulated. It would therefore be expected 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 governing the dissociation of CO_2 from its combination in the blood, and this is a matter which must now be considered in more detail.

Until the second decade of this century the existing knowledge on this subject was very limited, although Bohr (1909 *a*) had constructed a tentative dissociation curve from observations made partly by Jacquet (1892) and partly by himself, on samples of blood from the ox and the dog. Christiansen, Douglas, and Haldane (1914) took up the matter, making use of the improved methods of blood-gas analysis mentioned at the beginning of this chapter. A most important point about their work was that, warned by previous failures of physiologists to recognize the extreme exactitude of normal physiological regulations, they used defibrinated human blood, fresh samples of which could be obtained at any time from the same individual under carefully controlled normal conditions. Even so they wasted much time at the outset through failure to realize that it was essential to have a fresh sample of blood for each experiment. It was found in fact that blood outside the body undergoes slow changes which diminish its capacity for carrying CO_2. This point was later investigated by Lovatt Evans (1922), who found that the change is due to the formation of lactic acid from glucose in shed blood.

Fig. 13 shows the results obtained with the blood of J. S. H. Attention may be directed first 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 over a period of about six months, they all lie on one smooth curve. The samples were taken at different times of the day during

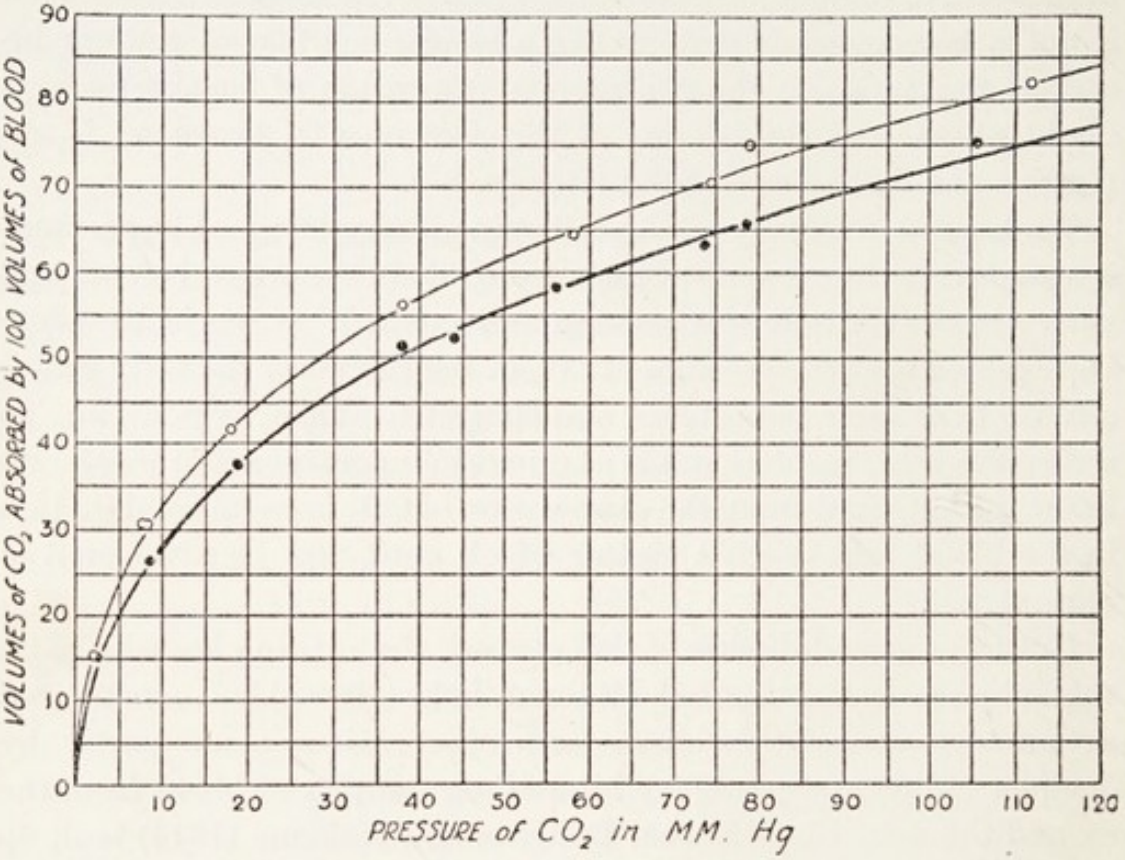


Fig. 13. Lower curve—absorption of CO_2 by blood of J. S. H. in presence of air and CO_2. Upper curve—absorption of CO_2 by blood of J. S. H. in presence of hydrogen and CO_2.

ordinary laboratory work. In regulating the temperature of the bath containing the saturator, analysing the samples of air from the saturator, observing the barometric pressure, measuring the sample of blood (of which about 1 c.c. was used for each analysis), and determining the CO_2 by means of the blood-gas apparatus (Brodie's modification of the original apparatus was used), it was impossible to avoid combined errors of about 1 to 2 per cent. of the quantities to be measured, so that no information could be obtained as to the actual exactness of Nature's regulation of the curve. At any rate it is so exact for the blood of J. S. H. that the most delicate chemical

methods then existing did not show any deviations from the curve, any more than, as we shall see later, they can show deviations from the oxyhaemoglobin or CO-haemoglobin dissociation curves. It was found, however, that marked temporary deviations could be produced by severe muscular exertion. With the blood of other persons the results were only slightly different. Thus the curves, so far as ascertained, for the bloods of Miss Christiansen and Dr. Douglas were slightly below, but otherwise parallel to the curve reproduced under normal conditions. The blood of most persons, in fact, seems to take up about 50 volumes of CO_2 per 100 volumes of blood at 40 mm. 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 unfavourable conditions which almost of necessity prevail in experiments on animals.

Let us now consider the two curves shown in Fig. 13. Many years ago it was suspected by Ludwig (1865) that oxygen may have some influence in turning out CO_2 from the venous blood which comes to the lungs. The experiments made, however, to ascertain definitely whether oxygen helps to turn out CO_2 from the blood gave only a negative result, and later work by Bohr, Hasselbalch, and Krogh (1904) led to similar negative conclusions. Christiansen, Douglas, and Haldane 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 again raised Ludwig's old question, which, with the new methods of blood-gas analysis available, could be investigated 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 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 Fig. 13 is the absorption curve for the blood of J. S. H. in the absence of oxygen, and shows that at the physiologically

important part of the curve blood takes up from 5 to 6 volumes per cent. more CO_2 if oxygen is absent. It was 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, or, in other words, to the saturation of the haemoglobin with oxygen. Saturation of the haemoglobin with CO had just the same effect on the curve as saturation with oxygen.

The effect is almost certainly due to saturated haemoglobin being a less alkaline substance than reduced haemoglobin, as appears, for

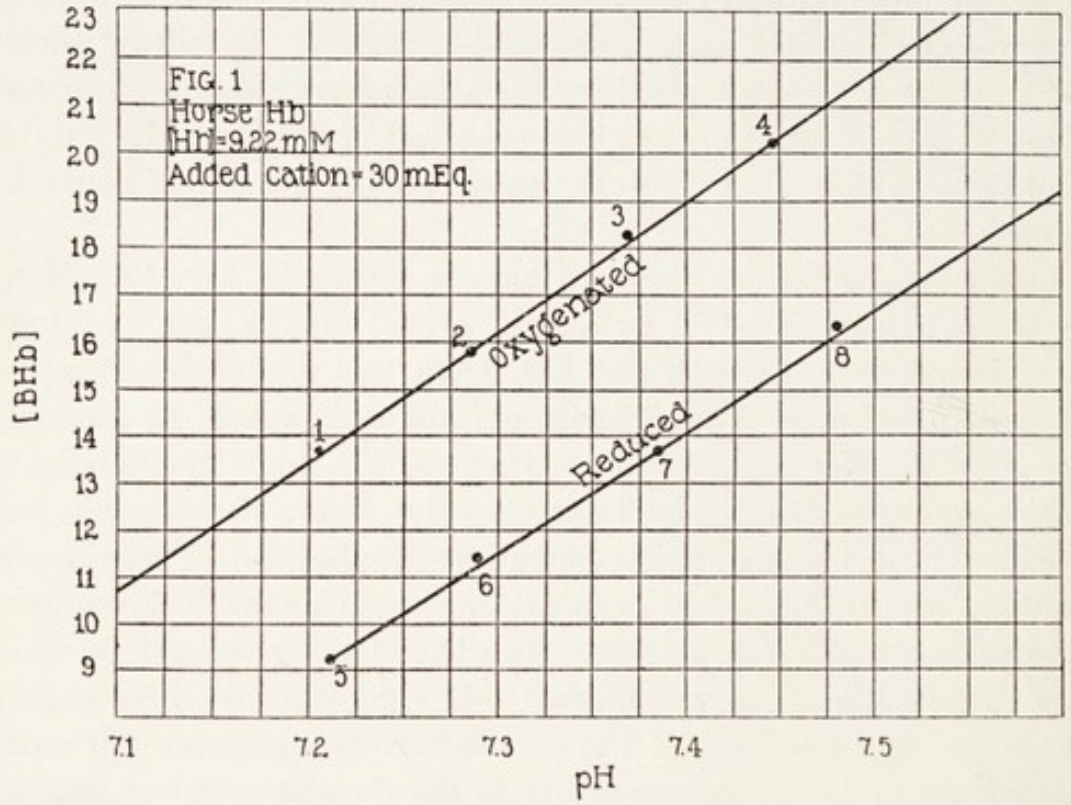


FIG. 14. Ordinates, equivalents of base bound by total haemoglobin; abscissae, pH.

instance, from the observations of Hastings, Van Slyke, Neill, Heidelberger and Harington (1924) on the amounts of alkali neutralized by reduced and oxygenated haemoglobin (Fig. 14).

The important physiological deductions which may be drawn from the CO_2-absorption curves of blood will become apparent on consideration of Fig. 15 (Douglas and Haldane, 1922). Human arterial blood is about 95 per cent. saturated and therefore contains about 17·6 volumes per cent. of oxygen in combination with haemoglobin as determined by the ferricyanide method. In addition there is about 0·3 volume in physical solution, so that 100 c.c. of arterial blood contain roughly 18 volumes in all.

The lower curve of Fig. 15 shows that such blood contains 51·8 volumes of CO_2 at a pressure of 40 mm. If we assume that all the oxygen is used up in the tissues and an equal volume of CO_2 is acquired, the completely deoxygenated venous blood would carry a charge of 69·8 volumes of CO_2 at a pressure of just over 70 mm. Hg as shown by the upper curve. Hence, owing to the deoxygenation, the CO_2-pressure only rises to 70 mm. instead of rising to 90 mm. as it would if the lower curve were followed. If the respiratory quotient

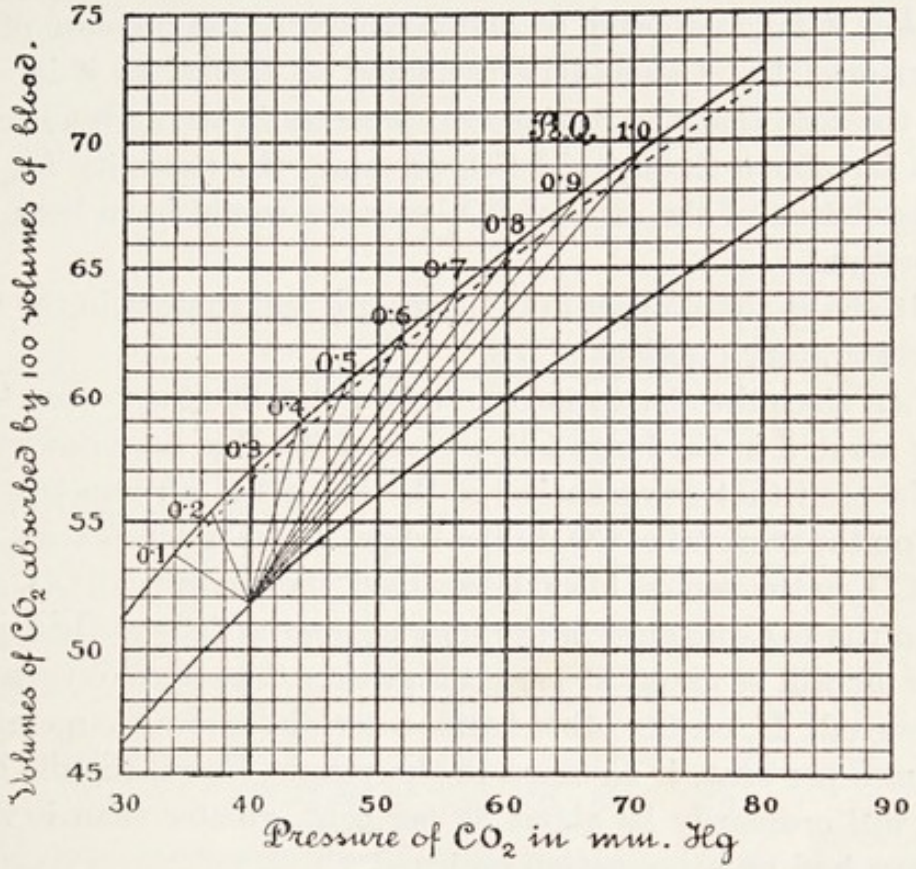


FIG. 15. Graphic representation o frelation between CO_2-pressure and CO_2-content of blood in the living body with varying respiratory quotients.

The upper curve shows the relation when the blood is completely deprived of oxygen; and the lower curve when the haemoglobin is 95 per cent. saturated with oxygen, as in average normal arterial blood. The thin lines joining the two curves represent the relations in the living body with varying respiratory quotients. It is assumed that the blood has the normal haemoglobin content, equivalent to 18·5 per cent. oxygen capacity. The dotted line shows how the upper curve is changed when the blood contains only 92 per cent. of the normal concentration of haemoglobin.

is less than 1, the volume of CO_2 added to the blood is less than the volume of O_2 removed, and the rise of CO_2-pressure is correspondingly less. The changes in CO_2-pressure corresponding to complete deoxygenation of the blood for different respiratory quotients are shown by the thin lines marked R.Q. 0·9, &c. It is clear from these

lines that for complete deoxygenation the CO_2-pressure would rise to 66, 60, 56, 52 mm., &c., for R.Q.s 0·9, 0·8, 0·7, &c. At any intermediate stage of deoxygenation and gain of CO_2 the point of intersection of the co-ordinates indicating CO_2-content and CO_2-pressure must fall on the thin line corresponding to the existing R.Q.

Actually, as will be shown later (p. 372), not more than about one-fifth of the arterial oxygen appears to be used up in man during rest. Consequently the pressure of CO_2 in the mixed venous blood rises only 5 to 6 mm. Hg above the CO_2-pressure in the arterial blood. This fact makes it far more easy to understand why the pressure of CO_2 in the arterial blood should be regulated so exactly as it is. Had it been the case that the resting CO_2-pressure in the systemic capillaries is 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.

Fig. 16 shows the changes in CO_2-pressure and content in the body witb a respiratory quotient of 0·8.

Further, since the absorption curve for CO_2 while the venous blood is being aerated in the lungs follows one of the thin lines downward, it will be seen that oxygenation of the blood has an important influence on the removal of CO_2 in the lungs. If the resting excess pressure of CO_2 in the venous blood is assumed, 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, a certain excess charge of CO_2 in volumes per cent. is assumed in the venous blood, the discharge of CO_2 will ordinarily be about 55 per cent. greater than it would have been had no oxygenation occurred.

It will also be evident that under certain 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 it is evident that the thin lines of

Fig. 15, which indicate the relation of CO_2-content to CO_2-pressure in the venous blood as it passes through the lungs in the living body, become vertical or even incline to the left instead of to the right. It is only necessary to suspend the breathing for a very short time in order to realize this condition. With the R.Q. 0·3 the CO_2-pressure of the venous blood does not rise till the blood is fully oxygenated.

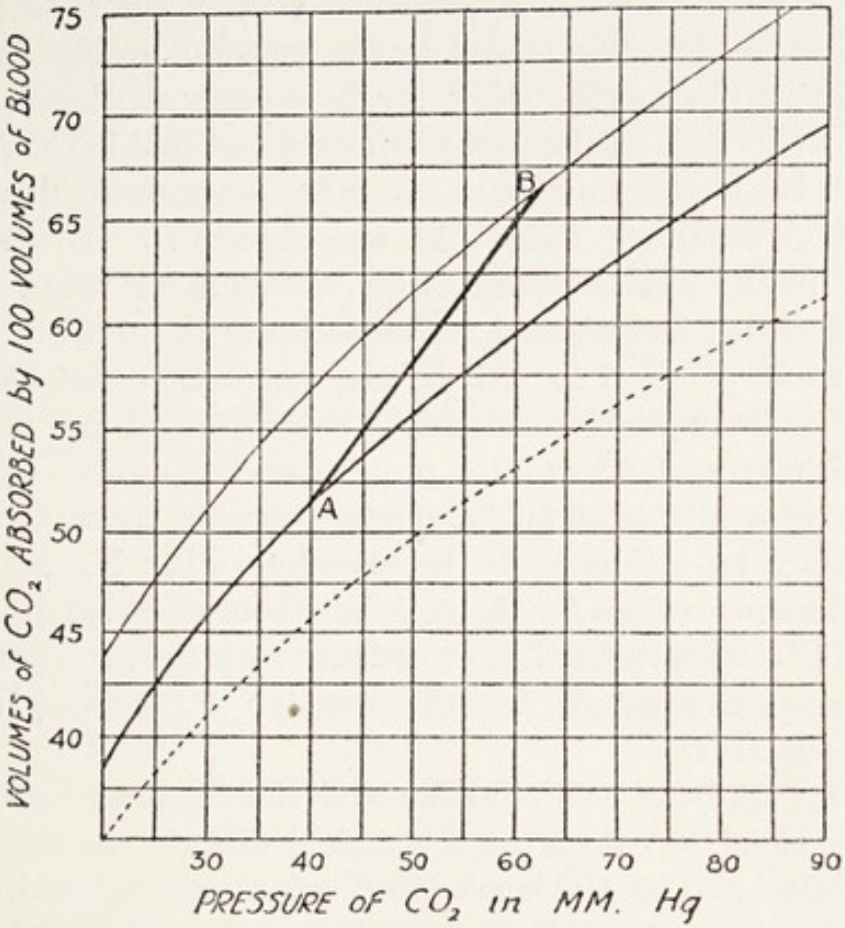


FIG. 16. Upper curve—absorption of CO_2 by blood of J. S. H. in presence of hydrogen and CO_2.

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

If air containing a large excess of CO_2 be breathed, CO_2 will be absorbed backwards from the alveolar air and the thin line will pass downward 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 Christiansen, Douglas, and Haldane

in human experiments, and earlier by Werigo (1892), and by Bohr and Halberstadt (Bohr, 1909 *b*), 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 the presence of air there is a large formation of CO_2 in the lungs, owing to a process of oxidation occurring there. As was shown by Lovatt Evans (1912–13) hardly any formation of CO_2 occurs in the lungs.

Parsons (1919) investigated mathematically the form of the absorption curve of blood for CO_2 on the assumption that blood is a physico-chemical system consisting of carbonic acid and one other weak acid (represented by all the proteins present) with a fixed concentration of available alkali distributed between them. This fixed concentration he estimated to be about $4{\cdot}5\times10^{-2}$ N. From this figure and known values for the molecular concentration of free and combined CO_2 he calculated in accordance with the mass action law the dissociation constant for the reaction $P.COONa+H_2CO_3 \rightleftharpoons P.COOH+NaHCO_3$.

Then, by applying this equation and the constant so found to Haldane's blood, he calculated a complete dissociation curve. The curve so calculated for Haldane's blood, completely reduced, is given in Fig. 17, which also indicates by +++ the points determined experimentally by Christiansen, Douglas, and Haldane. It will be seen that the agreement is remarkably close.

Fig. 18 shows the agreement between the curve calculated by Parsons for Haldane's blood fully oxygenated and the points determined by experiment.

It will be shown later 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 Fig. 19. In the living body the pressure of CO_2 is rising constantly as the blood becomes more and more venous during its passage through the systemic capillaries. The data embodied in Fig. 13 provide the means of calculating this rise, and it will be seen that it is much less than previously existing

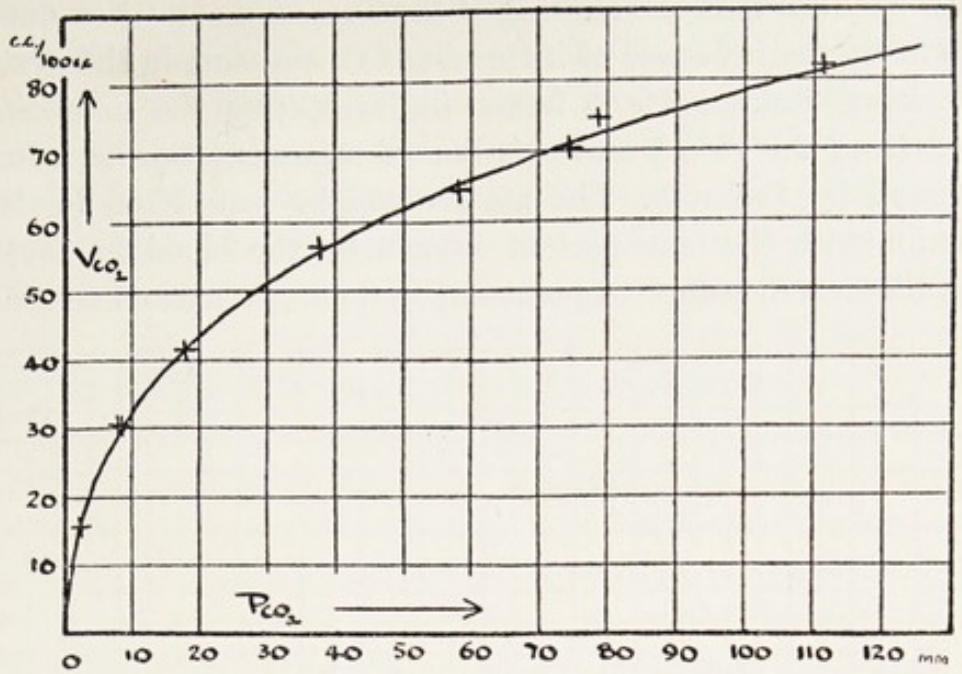


FIG. 17. Comparison between theoretical curve and experimental results for completely reduced blood of Haldane.

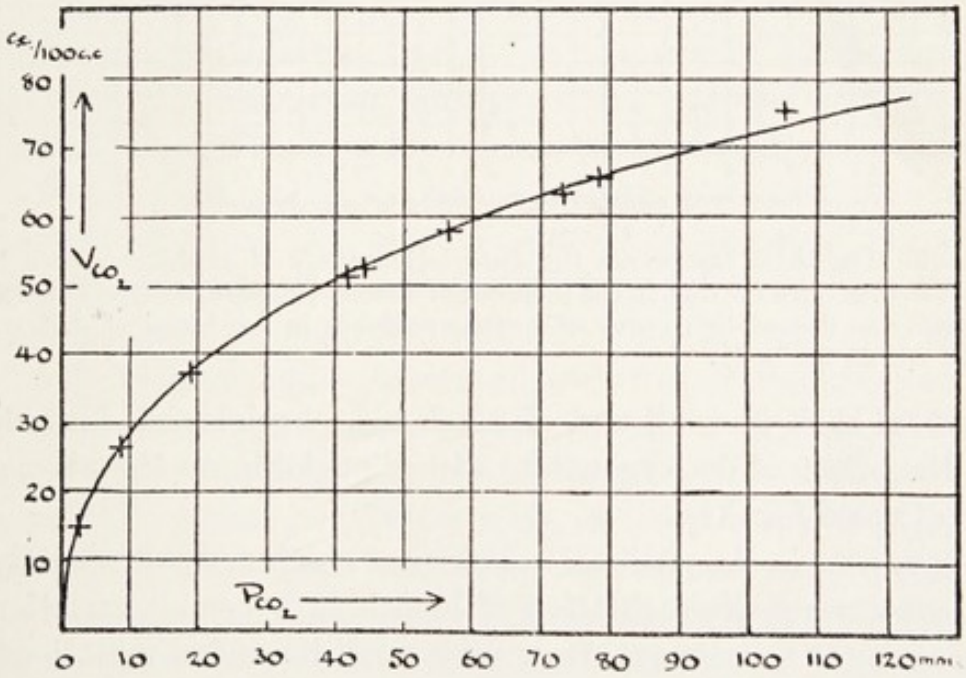


FIG. 18. Comparison between theoretical curve and experimental results for fully oxygenated blood of J. S. H.

knowledge would have indicated. The lower curve of Fig. 19 shows the oxygen dissociation of the blood of J. S. H. in the living body, calculated from Fig. 15 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 through the systemic capillaries.

Bohr believed that the shifting of the oxygen 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 matter will be considered further in connexion with the transport of oxygen by the blood (p. 159), and meanwhile it will suffice to point out that, under normal conditions,

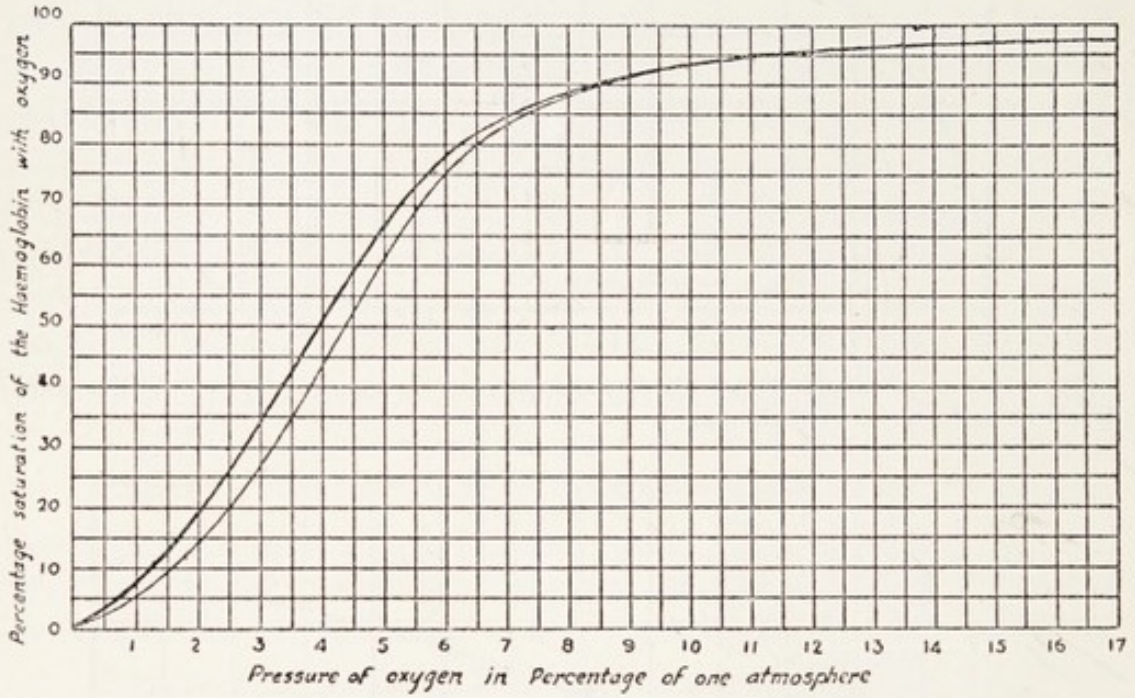


FIG. 19. The thick line shows the dissociation curve of oxyhaemoglobin in the blood of J. S. H. and C. G. D. in the presence of 40 mm. pressure of CO_2. The thin line represents the dissociation curve of oxyhaemoglobin in the blood of J. S. H. and C. G. D. within the body.

the actual shift is small and of much less physiological importance than the effect of deoxygenation of haemoglobin on the absorption curve of blood for CO_2.

We are now in the 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 seen already. On the other hand, the breathing is constantly being interrupted or interfered with in one way or another during ordinary occupation, 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 to be almost nil, and to popular ima-

gination it seems as if the breathing, instead of being regulated so rigorously as was shown to be the case in Chapter II, is hardly regulated at all. We are also familiar with instructions to increase the breathing so as to 'improve the oxygenation of the blood'. How does it come about that, although the regulation is so exact on the average, temporary deviations 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 sudden muscular exertion, yet the breathing responds gradually and easily to the new conditions?

The answer to these questions 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 centre, and that if it were not so the respiratory centre 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 the case of J. S. H. the mean volume of air in the lungs at the end of inspiration during rest is 3,650 c.c., measured dry at 0° C. and 760 mm. Hg, including about 3,000 c.c 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 c.c. of CO_2 would be normally given off per minute, or 20 c.c. 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, several hundred c.c. 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 into the blood. Fig. 13 shows that for every rise of 2·5 mm. or 0·36 per cent. in the alveolar CO_2-pressure the blood will take up, or hold back, one volume per cent. of CO_2. Hence the actual rise in the mean CO_2-pressure within the lungs cannot be as much as 0·6 per cent. in the 5 seconds during which the breath is held. The net result is that a certain part 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 the 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 centre itself. So far as we know, the reaction in all

parts of the body is slightly alkaline, just as in the blood; thus the tissues and lymph have, like the blood, a considerable 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 centre 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 Haldane (1909 *b*). The following table shows the results they obtained on determining the alveolar CO_2-pressure at various times after holding the breath. In order to exclude disturbing effects due to oxygen want on the respiratory centre, 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 seconds . .	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 breath for 40 seconds .	28·4	117
At eighth expiration following	29·4	..
At end of holding breath for 130 seconds 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

Fig. 20 is a stethographic tracing of the respirations during an experiment, and shows that the breathing returns gradually to normal after a hyperpnoea following 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 for the cumulative action of the stoppage of breathing. After the long stoppage of 130 seconds the breathing and alveolar CO_2-pressure had

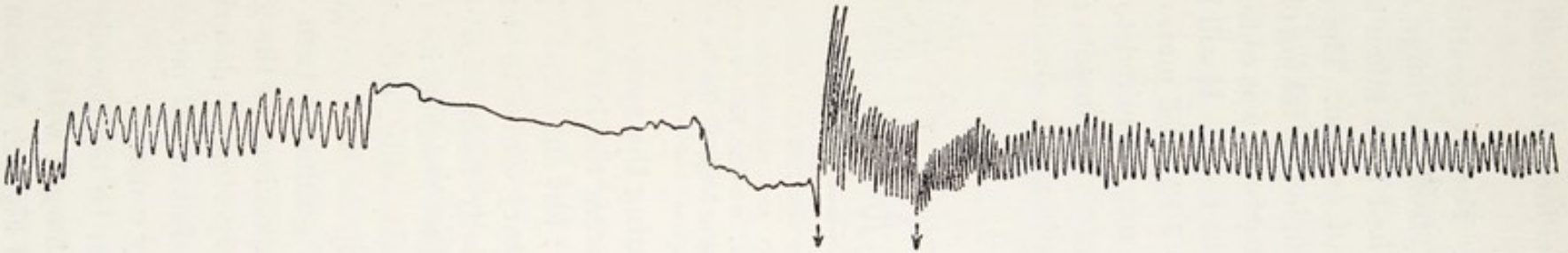


FIG. 20. Stethograph tracing. Breath held 130 seconds after six normal breaths of oxygen. At first arrow alveolar CO_2 = 8·66 per cent., O_2 = 38·22 per cent.; at second arrow CO_2 = 4·65 per cent. To be read from left to right.

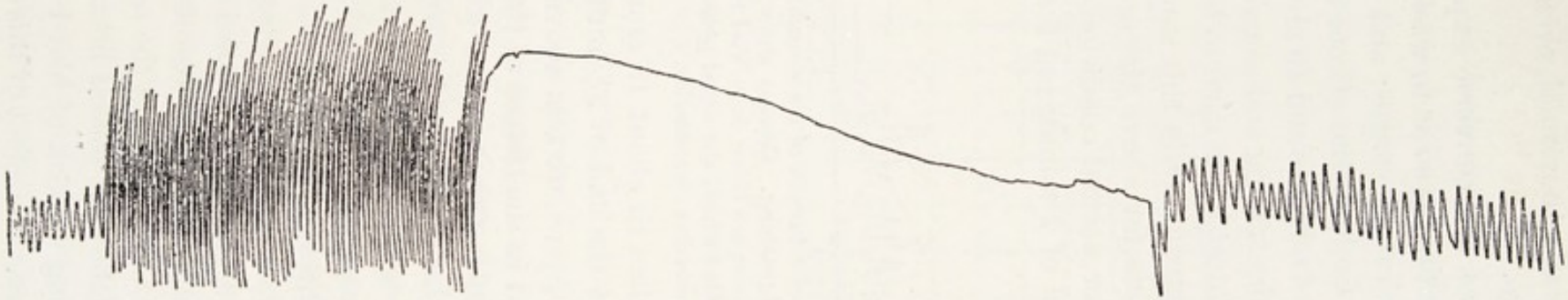


FIG. 21. Forced breathing for two minutes with six breaths of oxygen at the end. Apnoea 4′ 21″. At end of apnoea sample of alveolar air, O_2 = 56·22 per cent., CO_2 = 7·12 per cent. To be read from left to right.

not returned nearly to normal, even after the fortieth breath following the stoppage.

Fig. 21 shows the converse experiment. Forced breathing was continued two minutes so as to wash out CO_2 from the lungs, arterial blood, and respiratory centre; and oxygen had been taken into the lungs so as to exclude the effects of want of oxygen. The apnoea lasted just over 4 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 noted. It will be seen that the CO_2-percentage in this sample was 7·12 (51·5 mm. of CO_2-pressure), a value far above the normal 40 mm. required to excite the centre under normal conditions. Separate experiments showed that by the end of 2 minutes of forced breathing the alveolar CO_2-

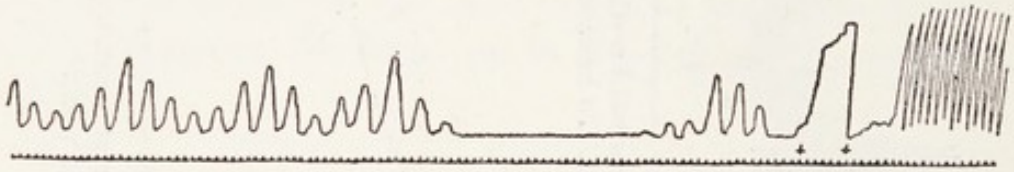


FIG. 22. Effect of a breath of air containing 9·0 per cent. of CO_2 during apnoea following forced breathing. Crosses show inspiration and expiration of breath. After an interval there are three deep, and two shallow, breaths, followed by a long apnoeic interval, after which the usual periodic breathing begins. To be read from right to left. Time-marker = seconds.

pressure had fallen to about 13 mm. and during the apnoea rose to normal again at the end of $2\frac{1}{3}$ 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 centre to stimulate it, till the alveolar CO_2-pressure had gradually risen to 51·5 mm. At this point the centre, 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 centre to normal, corresponding to the gradual return in Fig. 20, 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 centre.

The apnoea following forced breathing can be temporarily interrupted by sending a block of blood highly charged with CO_2 to the respiratory centre. The effect of this shown in Fig. 22. 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 10 or 20 minutes, were strikingly illustrated in some experiments carried out by Boothby (1912–13). Thus in an experiment on J. S. H. he found that during $1\frac{1}{2}$ minutes of forced breathing about 1,400 c.c. extra of CO_2

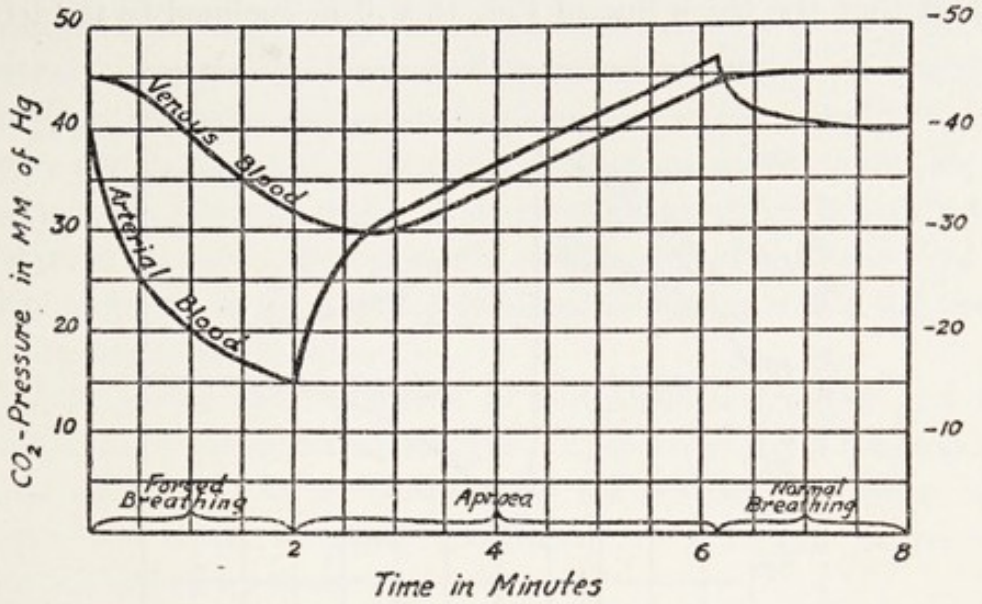


FIG. 23. Approximate variations in CO_2-pressure of arterial and venous blood during and after forced breathing of oxygen for 2 minutes.

had been removed from the body. During the subsequent apnoea of 2 minutes about 600 c.c. of CO_2 were regained, and about 200 c.c. more during 2 minutes of periodic breathing which followed. The remainder was regained during the following 6 or 8 minutes. In this latter period the alveolar CO_2-pressure 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 centre is represented in Figs. 23 and 24. The pressure of CO_2 in the respiratory centre is assumed to be about equal to that of the mixed venous blood, though it is probably lower.

The very powerful steadying influence of the capacity of the tissues for taking up CO_2 on the CO_2-pressure is evident from these figures. In consequence of this influence, and in a much less degree that of the reserve 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.

On examining Fig. 23 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 of the blood for CO_2 and thus raising its pressure. This effect is explained by the fact that the thick line of Fig. 16 will be inclined to the left, as

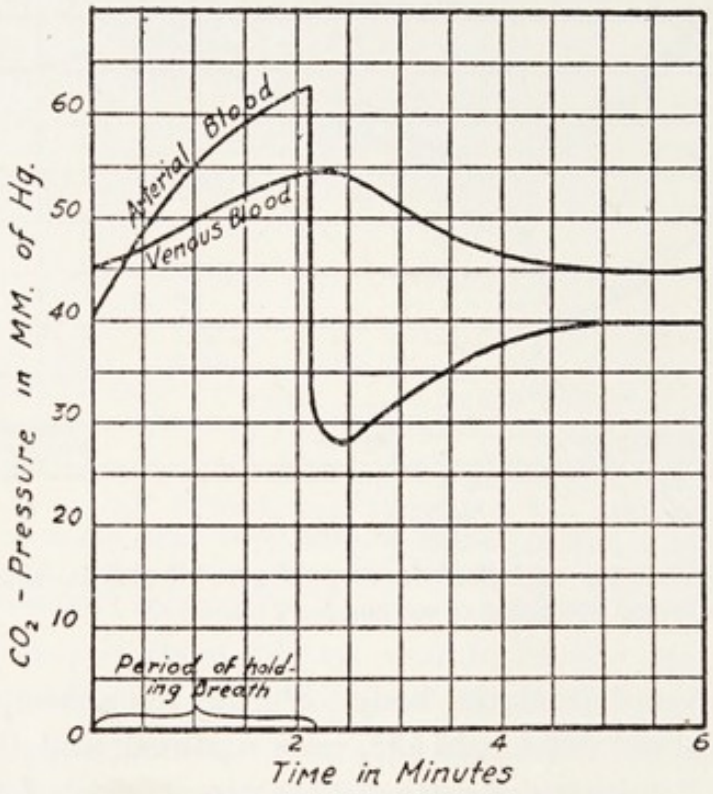


FIG. 24. Approximate variations in CO_2-pressure of arterial and venous blood during and after holding the breath for 130 seconds with oxygen.

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 the importance of the steadying influence just mentioned, we have only to turn to what happens when want of oxygen, instead of CO_2, is exciting the centre. Oxygen is no more soluble in the tissues and lymph than in water. They have thus practically no power of storing free oxygen. In the course of the investigations of Haldane and his colleagues on the effects of want of oxygen it became evident that the centre works very jerkily when excited by want of oxygen, and the subject was studied in further detail by Douglas and Haldane (1909 *a*). They found that the effects

of regulation of the centre 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 2 minutes, the oxygen percentage in the lungs runs down very low before the pressure of CO_2 in the respiratory centre has nearly risen to its normal value. In some subjects there is an alarming 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 centre down again, so that apnoea again follows, which is in turn followed by breathing and subsequent apnoea, this periodic rising and dying away of the breathing going on for about 5 minutes, as shown in Fig. 25, though not all subjects react alike.

Fig. 26 shows the variations of the alveolar oxygen and CO_2-pressure, as determined in samples of alveolar air. Reference to Fig. 22 shows that at no time during the periodic breathing is the CO_2-pressure in the respiratory centre more than just sufficient to excite the centre 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 centre; but this oxygen want is at once relieved by the breaths which follow, since the oxygen-pressure in the lungs is raised above the exciting point. The result is a prompt return of the apnoea, till the oxygen-pressure in the alveolar air again falls 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 fly-wheel or other steadying influence. The chief fly-wheel of the respiratory centre is the great storage capacity in the tissues for CO_2. There is no such storage capacity in connexion with oxygen, so the fly-wheel has disappeared.

When slight oxygen want, and not merely excess of CO_2, is exciting the centre, the breathing very readily becomes periodic. To realize this condition in a permanent manner we had only 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

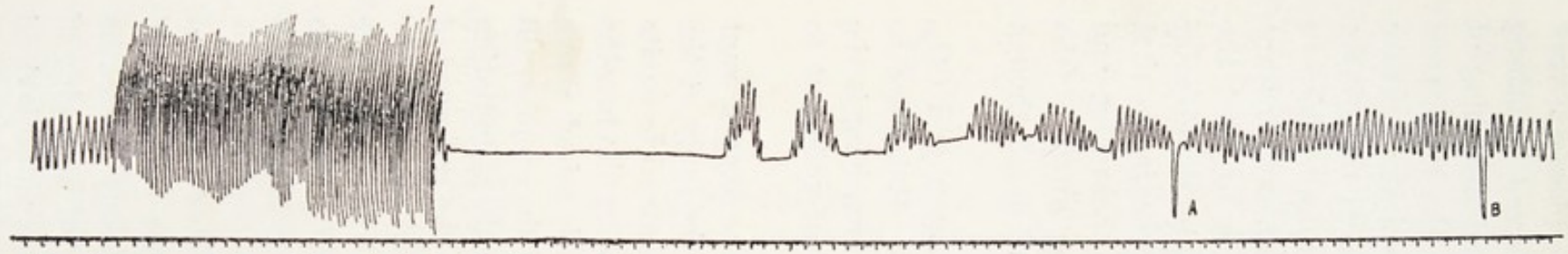


FIG. 25. Forced breathing of air for 2 minutes, followed by apnoea for 2 minutes and periodic breathing for about 5 minutes. At *A* sample of alveolar air, O_2 = 11·44 per cent., CO_2 = 5·58 per cent. Second sample at *B*, O_2 = 13·55 per cent., CO_2 = 5·57 per cent.

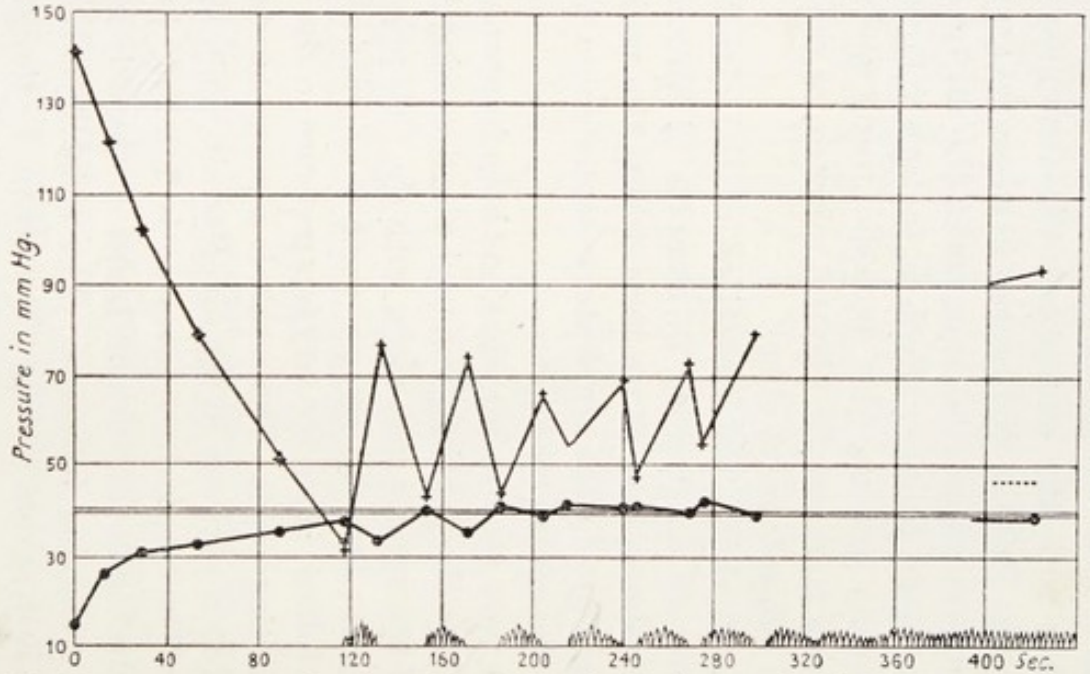


FIG. 26. Variations in alveolar gas pressures after forced breathing for 2 minutes. Thin line = oxygen-pressure, thick line = CO_2-pressure. Double line = normal alveolar CO_2-pressure. The actual breathing is indicated at the lower part of the figure.

any required extent. Fig. 27 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 (1905) and Pitt, Pembrey, and Allen (1907) 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

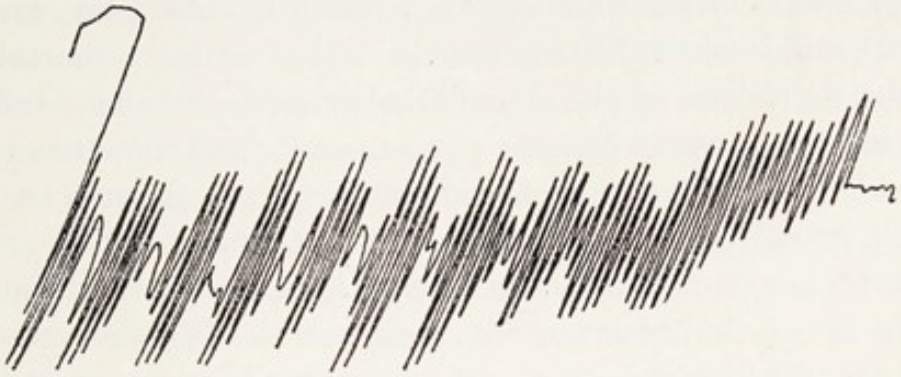


FIG. 27. Breathing through soda lime and long tube. Sample of alveolar air at the end of a dyspnoeic period, $O_2 = 8{\cdot}70$ per cent., $CO_2 = 5{\cdot}48$ per cent. Read from right to left.

Cheyne-Stokes breathing is caused by want of oxygen participating in the excitation of the centre. Pathological periodic breathing and that of hibernating animals will be discussed later (p. 217).

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 (Fig. 19) 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 centre, 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 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 persons who inhabit very high parts of the earth develop a greatly increased chest capacity (Barcroft, 1925).

The evidence discussed in this chapter leads to the conclusion that the close association between breathing and the CO_2-pressure of the arterial blood which was discussed in Chapter II gains an added importance from the physico-chemical equilibria which govern the taking up and giving off of CO_2 by the blood.

These, acting together with the other buffering agencies discussed, cause great variations in the breathing and removal of CO_2 to correspond to very small changes in the CO_2-pressure of the blood and tissues.

In other words, breathing is regulated physiologically so as to maintain a remarkable constancy of CO_2-pressure in the arterial blood and hence in the tissues. We shall have to consider in the next chapter how the hydrogen-ion concentration of the blood depends upon the CO_2-pressure thus regulated and the still more delicate relations between breathing and hydrogen-ion pressure.

IV

HYDROGEN-ION PRESSURE 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 become acid in dying. Knowledge as to the connexion between the blood reaction and normal breathing is, however, mostly of recent origin; and the same may be said of knowledge as to the extreme exactitude with which the reaction of the blood and tissues is regulated, and the physiological importance of the very slightest deviation from the normal reaction.

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 alkalis 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. These 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, &c., 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 is thus preserved.

More than sixty 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 (1877), 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 was shown in Chapter II. The 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, which ceased before the heart stopped beating.

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 gramme (sufficient, however, to neutralize about 2 grammes 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 and which has been extended and clarified by Krebs and Henseleit (1932), ammonia is converted into urea in the liver. It appears, therefore, that when acid is administered to carnivorous animals or men, some 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 shown definitely by perfusion, experiments (Löffler, 1918). 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 alkalis 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 of the most rapid method of all—varying excretion of carbon dioxide by the breathing—remained hidden till recent years, although Walter's experiments showed that, not only is there a great increase in the breathing, but also the amount of carbon dioxide present in the arterial blood is reduced in extreme cases to about a twelfth of the normal.

It was discovered by von Jaksch (1885) 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 (1884) 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 (1883) before him, to the search for organic acids. Thus the symptoms pointed to the presence of excess of acid. Shortly after Haldane and Priestley introduced their method of investigating alveolar air, Beddard, Pembrey, and Spriggs (1904, 1908) investigated at Guy's Hospital the alveolar air in cases of diabetic coma, 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 acidosis in diabetic coma and certain other conditions, 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. Some years ago, however, it became evident that the amount of acid required for neutralization is no reliable 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 are thus 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 may have to be added, when a weak acid is also present, before the weak alkalinity is neutralized. The same applies, *mutatis mutandis*, to weak alkalis.

Since, as we have seen, there is a close relation between the breathing and the arterial CO_2-pressure, it follows that there must also be a relation between the breathing and the reaction of the blood. Now the blood and tissues are full of buffer substances. In the first place, as already seen in Chapter III, 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 colour alters gradually in either direction as the neutral point for any particular indicator is approached. It was shown in Chapter III 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 was pointed out very clearly by L. J. Henderson (1909).

It may be desirable at this point to remind the reader of the conception of acidity and alkalinity to which chemical and physico-chemical investigation has led during recent years. The phenomena of electrolysis revealed to Faraday the fact that the constituents of any 'electrolyte' present in a solution are torn asunder into definite fragments, of which one kind travels, during electrolysis, towards

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 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. Arrhenius (1887) 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 (1877). 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, though Traube had not seen how to apply this membrane for measuring osmotic pressures. Some years later van't Hoff (1887) 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 exert if its molecules were present alone in the gaseous form at the same temperature. There must thus be a fundamental connexion between molecular concentration, osmotic pressure, and gas pressure; also between molecular concentration and the vapour 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 litre of solution; and this theory has served for the building up of the theory of solutions as it is still represented in current text-books of physical chemistry. In reality this theoretical interpretation was not even justified by Pfeffer's data if concentration *per litre* 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 some 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 attempts have been made to substitute for it some more intelligible conception.

It was shown quite clearly by Haldane (1918, 1928) that van't Hoff's conception of osmotic pressure was mistaken. It is neither the concentration per litre 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.

In a solution, just as in a gas mixture, the molecules are free to move about; and the mean free space round a molecule of either solvent or solute is the same, because the mean energy of translation per molecule is the same. Hence the free space in which water molecules are free to diffuse is in proportion to the total number of molecules present per litre. 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 pressures, vapour 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 (1916) are as follows:

OSMOTIC PRESSURE IN ATMOSPHERES

Grammes cane-sugar per 100 c.c.	*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 vapour 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 Haldane's book.

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 above discussion of osmotic pressure has been inserted because of the general confusion which prevails and because of the importance of its bearing on blood reaction.

The relative osmotic pressures observed by de Vries (1888, 1889) 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 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, in his view, were not merely due to the concentration 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 later became accepted universally. A dilute solution of sodium chloride, for instance, is not regarded as a solution of NaCl molecules, but, practically speaking, of sodium and chloride ions, and similarly a dilute solution of hydrochloric acid as a solution of hydrogen and chlorine ions. In such a solution the sodium ions carry a positive electrical charge (cations), the chlorine ions a negative charge (anions). Ions are not always simple atoms carrying an electrical charge, but may be groups of atoms. For instance, copper sulphate in aqueous solution dissociates into the ions $Cu^{\cdot}$, positively charged, and SO''_4, negatively charged. Sulphuric acid dissociates primarily into the ions $H^{\cdot}$, positively charged, and HSO'_4, negatively charged, and secondarily the HSO'_4 ions again dissociate into $H^{\cdot}$ and SO''_4. Thus a solution of sulphuric acid completely dissociated contains SO''_4 ions carrying a double negative charge and twice as many $H^{\cdot}$ ions each carrying a single positive charge. Again, potassium hydrate dissociates into the ions, $K^{\cdot}$ positive and OH' negative.

Pure water is an electrolyte, as is shown by the fact that it is a conductor of electricity, though a poor one. It is consequently dissociated, and the ions formed are $H^{\cdot}$ and OH'. There is no further stage of dissociation of the OH' ion. Since a molecule of water, when

it dissociates, splits into one H˙ ion and one OH′ ion it follows that the concentration of H˙ ions in pure water, i.e. the number per unit volume, must be exactly equal to the concentration of OH′ ions. Now acid properties in a solution are due to the presence of hydrogen (H˙) ions, alkaline properties to the presence of hydroxyl (OH′) ions, and the degree of acidity or alkalinity is proportional to the concentration of hydrogen and hydroxyl ions respectively. Hence pure water is a perfectly neutral liquid. Since, according to the mass action law of Guldberg and Waage (1867), the velocity with which a reaction proceeds is proportional to the active masses of the reactants, it follows that pure water dissociates into its ions with a velocity proportional to the active mass of the undissociated water molecules, and, equally the velocities with which the hydrogen ions and hydroxyl ions tend to recombine are proportional to their respective active masses. It has become customary to assume that the 'active masses' are proportional to the concentrations, i.e. the number of gramme-molecules or gramme-ions per litre. This convention, however, in the case of physiological fluids particularly, introduces error, though not in the case of watery solutions. The matter is discussed more fully below (p. 90).

The actual velocity with which undissociated water molecules are re-formed is proportional to the product of the active masses of the two ions. As dissociation of water proceeds the concentration of undissociated molecules tends to diminish, those of the ions to increase. Hence an equilibrium is attained when the respective concentrations are such that the velocity of dissociation is equal to the velocity of association. This is expressed, according to the mass action law by writing $[H].[OH] = K[H_2O]$,

where square brackets indicate concentrations as gramme-ions per litre, and K is a constant. Since the degree of dissociation of pure water is extremely small the concentration of undissociated molecules may be regarded as being sensibly constant. Hence the equation may be written

$$[H].[OH] = K_\omega$$

or

$$[H]^2 = [OH]^2 = K_\omega,$$

K_ω is known as the dissociation constant of water. It varies somewhat with changes of temperature. Careful determinations have shown that at 22° C. it is 10^{-14}, at 38° C. $3{\cdot}35 \times 10^{-14}$, hence $[H] = 10^{-7}$

and $1{\cdot}83 \times 10^{-7}$ respectively at these temperatures. At 22° C. therefore 10 million litres of water contain 1 gramme of hydrogen ion and 17 grammes of hydroxyl ion.

The relation $[H].[OH] = K_\omega$ always holds for watery solutions, hence as [H] is increased by adding an acid [OH] is decreased, and vice versa on addition of alkali.

All acids and bases combine with one another in chemically equivalent proportions, but different acids and alkalis vary greatly in the extent to which they are ionized. This is expressed quantitatively by their respective 'ionization constants' which are analogous to the dissociation constant of water. 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 rather molecular compounds of these with molecules of water. Further, the effectiveness with which water molecules will tear apart the solute molecules will depend on the relative concentration of water molecules. Hence dilute solutions are more fully ionized than concentrated solutions. And again molecules of different solutes offer differing resistance to the tearing apart by water molecules. Hence, at any given dilution, one electrolyte is more highly ionized than another as well as being itself more highly ionized in dilute solution than in concentrated solution.

An acid or a base which offers resistance and is but weakly ionized in relatively concentrated solution is known as a weak acid or base, e.g. acetic acid, carbonic acid, ammonium hydrate. An acid or base which is strongly ionized is known as a strong acid or base, e.g. hydrochloric acid, potassium hydroxide.

In the case of watery solutions of strong acids and bases the concentration of hydrogen and hydroxyl ions is practically determined by the concentration of the acid or base. In the case of weak acids and bases, however, the dissociation constant of the solute does not differ very widely from that of pure water. Hence 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:

$$KCN + H_2O \rightleftharpoons KOH + HCN$$

Now KOH is strongly ionized and the solution therefore contains a

high concentration of OH′ ions, and, since water is present, a correspondingly low concentration of H˙ ions. HCN, however, is very weakly ionized and thus contributes very few H˙ ions. The concentration of hydroxyl ions is therefore but little diminished by the simultaneous presence of H˙ ions derived from the HCN, and the solution is therefore alkaline. Carbonic acid is also a weak acid, though not so weak as hydrocyanic acid, and consequently the same relations hold, and both carbonates and bicarbonates yield solutions which are distinctly alkaline.

Salts of both weak acids and bases and strong acids and bases are very highly ionized. For instance, $NaHCO_3$ in 0·03N solution behaves as if it were present to the extent of about 80 per cent. as $Na^{\cdot}$ and HCO'_3 ions and of course there are also $H^{\cdot}$ and OH' ions derived from the water. The state of affairs in such a solution is indicated by the equation

$$NaHCO_3 + H_2O \rightleftharpoons \underbrace{Na^{\cdot} + HCO'_3}_{\text{high}} + \underbrace{H^{\cdot} + OH'}_{\text{low}}$$
concentration

On adding an acid to this solution the extra $H^{\cdot}$ ions derived from the added acid (e.g. HCl) at once tend to combine with the HCO'_3 ions to form H_2CO_3 owing to the low dissociation constant of carbonic acid. Hence the presence of the dissociated bicarbonate tends to prevent the rise of concentration of $H^{\cdot}$ ions which would occur on adding HCl to pure water, and no considerable change in $H^{\cdot}$-ion concentration will occur till the whole of the bicarbonate has reacted to form carbonic acid. This action of a salt of a weak acid in minimizing rise of $H^{\cdot}$-ion concentration on addition of another acid (Fernbach and Hubert, 1900) has already been mentioned and is now known generally as a 'buffering' action. Similarly, salts of weak bases tend to prevent rise of OH'-ion concentration when strong alkalis are added to their solutions. In blood these buffering actions are important since they minimize changes of $H^{\cdot}$-ion concentration when the CO_2-pressure varies.

The buffering effect of the bicarbonate of blood-plasma has been worked out by L. J. Henderson (1908, 1909), thus:

The hydrogen-ion concentration of carbonic acid in water is given by the equation

$$[H] = K\frac{[H_2CO_3]}{[HCO_3]}.$$

In the concentration in which it occurs in blood, sodium bicarbonate

is highly dissociated—about 80 per cent.[1] Calling the degree of dissociation of the bicarbonate δ, the concentration of HCO'_3 in such a bicarbonate solution is thus given by

$$[HCO_3] = \delta[NaHCO_3].$$

When both carbonic acid and bicarbonate are present this value may be inserted in the previous equation with the result that the H-ion concentration of the solution may be expressed in terms of concentrations of free carbonic acid and bicarbonate thus:

$$[H] = K\frac{[H_2CO_3]}{\delta[NaHCO_3]}.$$

It has been found (Hasselbalch, 1917) that δ does not vary much in blood and may therefore be combined with K to form a new constant giving

$$[H] = K_1\frac{[H_2CO_3]}{[NaHCO_3]}.$$

The hydrogen-ion concentration of blood may therefore be measured by the ratio of free carbonic acid to bicarbonate. This ratio is normally of the order of 1/20.

A notation for expressing hydrogen-ion concentrations was introduced by Sörensen (1909 *a*, *b*, *c*) on the score of convenience in plotting results on paper. In this notation only the negative logarithm of the concentration, expressed as pH, is written with changed sign.

Thus $cH = 10^{-7}$ is written $pH = 7$

$cH = 3{\cdot}5\times10^{-8}$ is written $pH = 7{\cdot}46$

The equation for hydrogen-ion concentration given above is readily changed to this notation by taking logarithms, thus:

$$[H] = K_1\frac{[H_2CO_3]}{[NaHCO_3]}$$

$$\log [H] = \log K_1 + \log [H_2CO_3] - \log [NaHCO_3]$$

$$-\log H = -\log K_1 - \log [H_2CO_3] + \log [NaHCO_3]$$

$$pH = pK_1 + \log\frac{[NaHCO_3]}{[H_2CO_3]} \text{ (Hasselbalch, 1917)}$$

[1] It should be stated, however, that investigation of the dissociation of strong electrolytes has given results which are difficult to explain by a theory of partial dissociation. Bjerrum (1909, 1919) has put forward the theory that strong electrolytes are completely dissociated, but that various complicating factors affect the 'activity' of the ions. According to this view δ expresses 'activity' not degree of dissociation, but the change is immaterial as regards the present argument.

The actual concentration of H_2CO_3 in solutions is unknown, but it is customary to take it as being a constant fraction of the concentration of dissolved CO_2. The values of K, and therefore of K_1, determined experimentally include this fraction, so that Hasselbalch's equation becomes

$$\mathrm{pH} = \mathrm{p}K_1 + \log \frac{[\mathrm{NaHCO_3}]}{[\mathrm{CO_2}]}.$$

Further both $[NaHCO_3]$ and $[CO_2]$ may be expressed as volumes per cent. CO_2 measured at 0°C. and 760 mm. Hg as is usual in blood-gas analysis.

Thus $[CO_2] = \frac{100pa}{760}$ c.c. CO_2 per 100 c.c. where a is the coefficient of solubility of CO_2 and p is the pressure of this gas.

$$[\mathrm{NaHCO_3}] = [\mathrm{NaHCO_3}] \times 2226 \text{ c.c. } CO_2 \text{ combined per 100 c.c.}$$
$$= \text{(say) B.}$$

Therefore the equation becomes, finally

$$\mathrm{pH} = \mathrm{p}K_1 + \log \frac{7{\cdot}6\mathrm{B}}{pa},$$

which is generally known as the Henderson-Hasselbalch equation.

To Hasselbalch, therefore, as consideration of this equation shows quite clearly, belongs the merit of having devised a very valuable method for determining indirectly the hydrogen-ion concentration of the blood; but see Adair (1925 *a*). It is comparatively easy to measure both the bicarbonate and the free carbonic acid of a particular sample of blood, and the ratio of these quantities gives the hydrogen-ion concentration at once.

It should not be forgotten, however, that the constant K_1 includes the first acid dissociation constant of carbonic acid, the equilibrium constant (which is unknown) of the reaction between CO_2 and water, the 'activity' coefficient of HCO'_3 and, possibly, the dissociation coefficient of $NaHCO_3$. The value obtained for pK_1 by Hastings, Sendroy, and Van Slyke (1928) is 6·10 approximately.

It seems desirable at this point to consider and criticize this method of Hasselbalch's and some other indirect means which have been used for estimating variations in the hydrogen-ion concentration of the blood. It is very remarkable how closely Hasselbalch's law holds for different kinds of blood and in blood-serum, in spite of great differ-

ences in the dissociation curves for CO_2. Figure 28 from Hasselbalch's paper (1917) shows (for fresh ox blood) the differences in the dissociation curves for serum, blood, and corpuscles. In spite of these great differences in the dissociation curves of blood and serum Hasselbalch's law holds good. He therefore applied it as a means of calculating the hydrogen-ion concentration of corpuscles and of abnormal blood. As an example of abnormal blood he took, from the paper by Christiansen, Douglas, and Haldane already referred to, experiments in which Douglas had flooded his blood with lactic acid

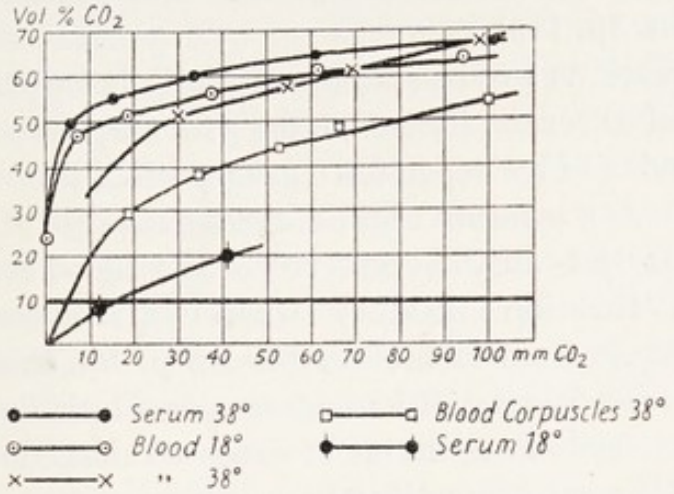


FIG. 28. CO_2 dissociation curves (from Hasselbalch, 1917).

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 10 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 0·12. 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 0·003, instead of 0·12, or only one-fortieth as much as calculated. From this example it would seem, at first sight, as was pointed out in the first edition of this book, to follow that Hasselbalch's method, when extended to abnormal blood, is unreliable. Further investigation, however, has thrown light on the discrepancy and has indicated that under certain conditions there may be temporarily an upset of the relations which normally exist between respiration and the hydrogen-ion concentration of the arterial blood. This matter will be fully discussed below (p. 113).

In recent years, as will be stated more fully below, 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 on p. 108 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 connexion between diminution in alkaline reserve or titration alkalinity and diminution in blood alkalinity. Moreover, it must not be forgotten that the greater part of the base which combines with CO_2 in the blood is removed from haemoglobin, hence the bicarbonate of plasma separated from its corpuscles is no measure even of the CO_2 binding power of that same plasma in contact with its corpuscles, still less is it a measure of the hydrogen-ion concentration of the blood.

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 will be shown in Chapter VI, 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 Hasselbalch (1917) 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. 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 will be mentioned on p. 95 (Barcroft, 1911; Barcroft, Camis, Mathison, Roberts, and Ryffel, 1914; Douglas, Haldane, Henderson, and Schneider, 1913). Later, however, Barcroft and others found at high altitudes a definite change in the constant, such that at any given oxygen-pressure there is increased saturation of the haemoglobin with oxygen (Barcroft, Binger, Bock, Doggart, Forbes, Harrop, Meakins, and Redfield, 1923). Dill and others (1931), however, fully confirm the observations of Douglas, Haldane, Henderson, and Schneider. The shift of the oxygen dissociation curve of haemoglobin is, moreover, clearly not a sufficiently delicate index to give reliable information about changes of hydrogen-ion concentration in the blood within the limits which are normally of physiological importance.

The relative diffusion pressures of any particular ion, in different solutions, can be measured by the differences of potential communicated to electrodes which, when dipped into the solutions, tend to give off the same ion. It has been found that an electrode of platinum saturated with hydrogen acts as if it were made simply of hydrogen, and by means of measurements of the potential differences obtained with such electrodes it is possible to measure the relative hydrogen-ion concentrations of two solutions. Such measurements are the ultimate standard of reference as regards hydrogen-ion concentration. Early attempts to measure the hydrogen-ion concentration of blood by this electrometric method did not serve to demonstrate any variations from neutrality. The details of electrometric titration were, however, greatly improved by Sörensen (1909 *a*, 1912), and particularly by Hasselbalch and Lundsgaard (1912). They published curves showing the variations of hydrogen-ion concentration with

variations of CO_2-pressure at body temperature in ox blood, and Lundsgaard (1912) repeated the experiments with human blood. Figure 29 shows graphically their results for blood and other liquids. They also showed that the hydrogen-ion concentration of blood as

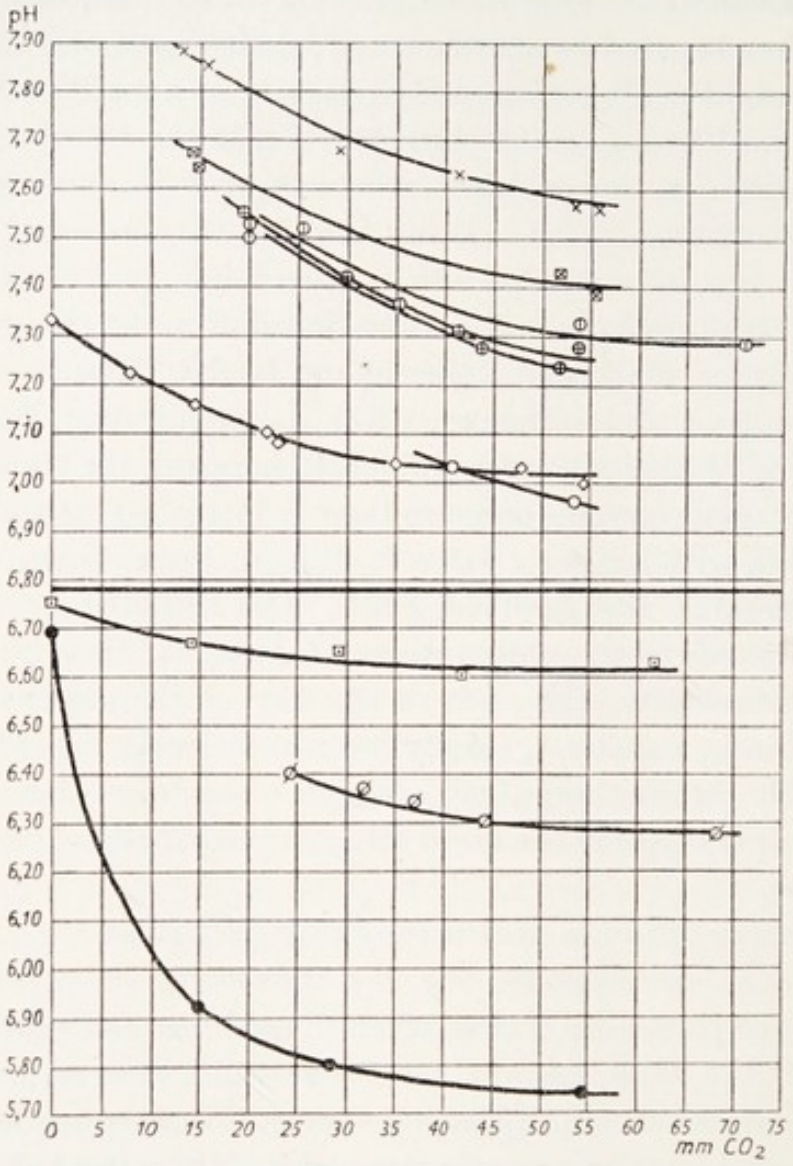


FIG. 29. ⊕ Blood, + Serum, ○ Corpuscles of same sample. ⊠ Blood, × Serum of another sample. / Blood of another sample. ⓘ Another sample of blood. Ø Same sample with acetic acid added. ◇ 8 parts M/15 Na_2HPO_4 and 2 parts M/15 KH_2PO_4. ⊡ Equal parts N/15 Na_2HPO_4 and KH_2PO_4. ● N/10 KCl solution.
The thick horizontal line indicates neutrality at 37°C.

determined by the ratio free H_2CO_3 to combined H_2CO_3 agreed with the measurements made with the hydrogen electrode.

A very full discussion of the Henderson-Hasselbalch equation is given by Warburg (1922) and he considers carefully the technique of the electrometric determination of hydrogen-ion concentration.

Lovatt Evans (1920–1) found that the pH of blood as determined colorimetrically by an indicator method (Dale and Evans, 1920–1) is as much as 0·2 higher than when determined electrometrically. He inclined to the opinion that the electrometric method is subject to error owing to the formation of formate from carbonate by catalytic action at the electrode, so that the pH of blood is actually higher by 0·2 than appears from the electrometric determinations. This conclusion is criticized by Warburg, who points out various sources of error in both the colorimetric and electrometric measurements of Evans and concludes that, with adequate precautions, the electrometric method gives accurate results for the pH of blood. Numerous investigations of the colorimetric method of determining pH of blood have been made (Cullen and Hastings, 1922; Hastings and Sendroy, 1924; Austin, Stadie, and Robinson, 1925), and the general conclusion to be drawn from them seems to be that the electrometric method, performed with adequate precautions, yields the most accurate results.

Bayliss, Kerridge, and Verney (1926) compared different methods of measuring the hydrogen-ion concentration of the blood. They found no systematic differences between the results given by (*a*) the hydrogen electrode, (*b*) the glass electrode, and (*c*) the Dale-Evans colorimetric method. They found the following probable errors for the three methods (mean of 3 or 4 observations) hydrogen electrode 0·003 pH, glass electrode 0·008 pH, and colorimetric method 0·011 pH.

Reference has already (p. 51) been made to the fact that blood is not a homogeneous system but consists of a corpuscular part, containing the haemoglobin, and a liquid part, the plasma.

Zuntz (1882) pointed out that when plasma or serum is separated from blood collected as it flows from a vessel, the corpuscles are capable of taking up, from an atmosphere of 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 is 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 (1895)

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 (1918) in particular has pointed out, to be practically impermeable to sodium and potassium ions, but permeable to chlorine and other ions. The necessary consequences of such a state of affairs were deduced by Willard Gibbs (1906), but his conclusions were largely neglected till Donnan (1911) (Donnan and Harris, 1911) investigated the problem. Donnan showed, both experimentally and on theoretical grounds, the distribution of concentrations on the two sides of a membrane which is permeable to some of the ions present but not to others. For instance, if on one side of the membrane, which is permeable to both Na' and Cl' as well as water, there is also present an anion, A', to which the membrane is impermeable, the following equilibrium is established

$$[Na]_1 . [Cl]_1 = [Na]_2 . [Cl]_2,$$

the products [Na].[Cl] on the two sides of the membrane being equal. But since the condition of electrical neutrality must hold, it follows that $[Na]_1 = [Cl]_1 + [A]$ and $[Na]_2 = [Cl]_2$. Therefore $[Na]_1 > [Cl]_1$ and $[Na]_2 . [Cl]_2 = [Cl]^2_2$. Hence $[Cl]_2 > [Cl]_1$, from which it follows that $[NaCl]_2 > [NaCl]_1$.

This conclusion of Donnan has been applied by L. J. Henderson (1928) and Van Slyke, Wu, and McLean (1923) to the blood, where the corpuscles are permeable to HCO_3 and Cl, but impermeable to Hb, K, and Na.

In Fig. 30, taken from L. J. Henderson's book *Blood*, the area *Bc* represents the concentration of cations (mainly potassium) in the corpuscles. The area *Hb* represents the concentration of ionized haemoglobin, i.e. of haemoglobin combined with part of the base *Bc*. *Ac* represents the concentration of inorganic anions ($Cl + HCO_3$) in the corpuscles. *As* and *Bs* represent respectively the anions ($Cl + HCO_3$) and the cations (mainly sodium) in the plasma.

Now it is well known that the corpuscles are permeable to water and that they shrink or swell when suspended in hypertonic or hypotonic solutions respectively. Hence $Bc + Ac = Bs + As$ approximately, since owing to its great molecular weight, the osmotic effect of *Hb* is relatively negligible.

Also a condition of electrical neutrality must be maintained, hence $Bc = Ac + Hb$ and $Bs = As$.

Further, since the corpuscles are impermeable to *Hb*, *Bc*, and *Bs* there must be a state of Donnan equilibrium with the result that

$$\frac{[A]_c}{[A]_s} = \frac{[\mathrm{Cl}]_c}{[\mathrm{Cl}]_s} = \frac{[\mathrm{HCO_3}]_c}{[\mathrm{HCO_3}]_s} = \frac{[H]_c}{[H]_s} = r.$$

Though these equations are only rough approximations and neglect several factors such as (1) the osmotic effect of haemoglobin, (2) the serum proteins, (3) the presence of divalent ions, etc., (4) 'activity coefficients' (p. 81), they permit of several important conclusions being drawn to a first approximation, as L. J. Henderson points out clearly.

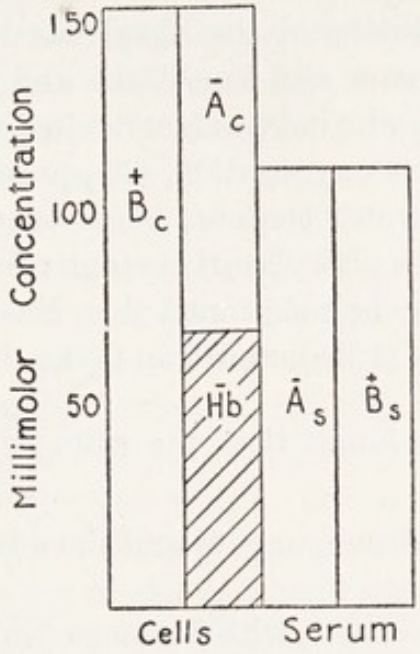


FIG. 30. Diagram of ion-equilibria in blood

Thus the total ionic concentration of the cells is greater than that of the plasma by the value $[Hb]$. The total concentration of anions (including *Hb*) in the cells is greater than the concentration of anions in the plasma by a quantity equal to half the concentration of *Hb*. The cations of the cells exceed the cations of the plasma by the same amount, but the concentration of anions in the corpuscles, excluding *Hb*, is less than the concentration of anions in the plasma by the same amount. It follows that the ratios of the last equation are all less than unity by the fraction $\frac{[Hb]}{2[A]_s}$. Hence, as Van Slyke has pointed out, the greater the concentration of ionized *Hb* in the cells (i.e. concentration of base neutralized by *Hb*) the greater the excess

of chloride and bicarbonate concentrations in the plasma over those in the corpuscles.

Also since, as we have seen (see p. 53), oxygenation of *Hb* makes it a stronger acid, i.e. increases the concentration of base bound by *Hb*, it follows that as the *Hb* is oxygenated Cl and HCO_3 pass out from corpuscles to plasma and the hydrogen-ion concentration of the plasma increases relatively to that of the corpuscles. Further, as the pressure of carbon dioxide increases the base bound by *Hb* diminishes and chloride passes into the cells. The observations of Gürber therefore are now seen to be in accordance with a theoretical explanation.

The physical chemistry of the blood has been worked out very fully by L. J. Henderson and Van Slyke and his colleagues (Peters and Van Slyke, 1931), who have in fact devised nomograms expressing the relations between oxygenation, CO_2-pressure, concentration of base bound by *Hb*, water content, bicarbonate, chloride, hydrogen ion, etc., of corpuscles and plasma respectively.

It should, however, be mentioned that Hastings, Sendroy, McIntosh, and Van Slyke (1928), and Van Slyke, Hastings, Murray, and Sendroy (1925) have found that the ratio $\frac{[HCO_3]_c}{[HCO_3]_s}$ is greater than the ratio $\frac{[Cl]_c}{[Cl]_s}$. This discrepancy is explained by Henriques (1929) by combination of Cl and HCO_3 with haemoglobin; but the point cannot be regarded as settled (Stadie and O'Brien, 1931).

It is desirable to add a few words of warning and explanation. In the preceding discussion of equilibria obtaining in the blood the expression 'concentration' has, following the prevailing convention, been used freely. Now Guldberg and Waage stated that the velocity of a chemical reaction is proportional to the 'active masses' of the reactants, and Nernst, in deriving his theory of concentration cells, stated that the 'solution pressure' of a metal dipping into a solution of one of its salts is balanced by the osmotic pressure of the cation in the solution and an electrostatic force. In applications of the mass action law it has become customary to assume that the 'active mass' of a solute is equivalent to its 'concentration', i. e. the number of gramme-molecules per unit volume, and Nernst replaced 'osmotic pressure' by 'concentration'. This substitution may serve reasonably

well for dilute solutions of electrolytes, etc., in water, but a little consideration will show that it is not applicable to fluids, such as blood, with which the physiologist has to deal. For instance, if $\frac{1}{10}$ mol of, say, cane-sugar is placed in a 1-litre measuring flask and water is added to the mark a solution is obtained in which the 'concentration' of sugar is said to be $\frac{1}{10}$ mol per litre. If, however, the same amount of sugar together with a handful of glass beads is placed in another 1-litre flask nobody would say that a solution of concentration $\frac{1}{10}$ mol per litre is obtained by adding water up to the mark.

Now it is commonly stated that the 'concentration' of sodium chloride in blood-plasma is about one-tenth molar, because chemical analysis shows that 1 litre of plasma contains about 6 gm. NaCl. But the proportion of water to NaCl in plasma is by no means the same as in a simple 0·6 per cent. solution of NaCl in water, because a litre of plasma contains not only NaCl and water but also many other solutes including proteins of high molecular weight. The proteins in fact play the same part as the glass beads mentioned above. The physiologically important quantity, with regard to NaCl, CO_2, or any other solute, is not, therefore, 'concentration' in terms of mols per litre but 'pressure', i.e. the pressure with which the substance tends to diffuse. Now this diffusion pressure is proportional—not to g.mol of the substance per litre—but to the ratio of the number of molecules of the substance to total molecules (see above p. 76). When, as in the case of blood, some of the molecules are relatively bulky (the molecular weight of proteins is of the order of several thousand) their number is small even though the absolute weight present is fairly large, and the actual diffusion pressure of, say, NaCl correspondingly exceeds the diffusion pressure of NaCl in a simple watery solution of the same 'concentration'. Failure to appreciate these considerations has led to much confusion with regard to the physiology of respiration and perhaps even more with regard to the relation of the chemical composition of the blood to renal activity. It is important therefore to bear in mind in discussing the physical chemistry of blood that the various equilibria relate to actual pressures of solutes in the blood, and that 'concentrations' in terms of, say, H-ion and water only are no more than first approximations. It is for these reasons that in this book we use the word 'pressure' in place of 'concentration' in referring to solutions of hydrogen ions and other solutes. Even in the case of very dilute solutions this is

necessary in physiological work where considerable amounts of proteins are present in the solution.

It will now be abundantly clear that the physico-chemical equilibria of the blood are such that the buffering of the plasma has an important effect in minimizing changes of hydrogen-ion pressure brought about by variations in CO_2-pressure, and that ionic exchanges between corpuscles and plasma have a still more important influence on this relation. It is also clear that an intimate relation exists between the oxygenation of the *Hb* and the CO_2 capacity and hydrogen-ion pressure of the plasma.

It cannot, however, be emphasized too emphatically that these physico-chemical considerations, important as they are, do not in themselves afford any adequate explanation of the regulation of reaction in the living body. It is perfectly true that, given a particular sample of blood, all these necessary relations can be worked out. The hydrogen-ion pressure, for instance, can be deduced from the ratio $H_2CO_3 : NaHCO_3$; but in the living body the composition of the blood is always varying and the pressures of H_2CO_3, $NaHCO_3$, etc., at any moment are determined by *physiological* reactions.

We must, therefore, now consider the physiological aspects of the hydrogen-ion pressure of the blood, its regulation and relations to respiration.

It was mentioned in Chapter I that the experiments of Geppert and Zuntz (1888) on the hyperpnoea following muscular contractions in animals showed a great diminution of 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 the presence of some acid substance 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 results; and the experiments of Haldane and Priestley on man brought us back, as shown in Chapter II, to CO_2 as the stimulus to the increased breathing. The improbability of any organic acid being the stimulus to the breathing seems in any case to be 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, if the breathing is stimulated by organic acids, how the air hunger of muscular exertion could be relieved, as it undoubtedly

is, by the 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. Haldane and Priestley 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. Consequently, although the pressure of CO_2 was perhaps actually higher in the arterial blood and caused hyperpnoea, the actual amount of CO_2 contained in the blood was much less. They 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. They had correctly divined the main cause of the greatly diminished proportion of CO_2 in the arterial blood, but not the whole cause.

In a series of experiments by Boycott and Haldane (1908) in a steel chamber on the effects of low atmospheric pressure on the alveolar CO_2-pressure they 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 (1908), working in conjunction with them, found the same thing, though in a much more marked and persistent degree, on returning to sea-level pressure after a stay on Monte Rosa. Galleotti (1904) 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 experiments made in Hoppe-Seyler's laboratory by Araki (1891, 1892, 1893, 1894) 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 (1877) experiments on acid poisoning, they concluded that the real stimulus to which the respiratory centre responds is the combined effect of carbonic and other acids on the reaction of the blood. It seemed that it was no longer possible to maintain the hypothesis of Haldane and Priestley that CO_2 acts specifically in exciting the respiratory centre. 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 sodium or potassium lactate thus formed had been excreted by the kidney, so that the body was deprived of alkali and the blood was left correspondingly less alkaline—a deficiency which could only be made up after some time.

This conclusion was further strengthened by the observation of Douglas and Haldane (1909 *b*), that after excessive muscular exertion the alveolar CO_2-pressure remains low for about an hour. They attributed this to the effect on the respiratory centre of lactic acid given off into the blood by muscles in which the work had been far in excess of the possible oxygen-supply. The correctness of this inference was shortly afterwards established by Ryffel (1909–10), who had meanwhile worked out a new and very convenient method of determining small amounts of lactic acid in blood and urine.

Winterstein (1911) suggested that changes in the H-ion concentration of the blood control the breathing, and later (1915) made experiments, the results of which support this view.

The methods of determining hydrogen-ion concentration in the blood were until 1911 still too crude to permit of testing these inferences by direct measurements, but the work of Sörensen and Hasselbalch, referred to above, shortly afterwards overcame this difficulty. At body temperature the point of neutrality corresponds to a pH about 6·78, as indicated by the thick line in Fig. 29. 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 in equilibrium with CO_2) shows this clearly. Thus sulphuric acid when pure and quite anhydrous is devoid of any acid properties and does not attack metals, because it is practically not ionized at all. This can be understood on the theory that ionization in aqueous solutions is brought about by reversible reaction with the water molecules.

In order to test whether it is really to difference in pH that the respiratory centre reacts normally, 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 are oxidized to sulphuric and phosphoric acids, 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 (1912) found that with the acid-producing meat diet the resting alveolar CO_2-pressure was 4.4 mm. lower, and he then proceeded to compare the pH of the blood in the two conditions. The results were as follows:

	Alv. CO_2-pressure mm. Hg	*pH of blood at 40 mm. CO_2-pressure*	*pH of blood at existing alv. 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 when the subject was on the meat diet was distinctly more acid than the sample taken when he was on the vegetable diet, but that at the existing alveolar CO_2-pressure the two values for pH were identical, at least within the limits of accuracy of the method of measurement. Hence the respiratory centre 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 (1911) found that on the Peak of Teneriffe the oxygen dissociation curve of human blood appeared to be normal, provided that the curve was plotted, not at the normal sea-level alveolar CO_2-pressure of about 40 mm. but at the existing resting alveolar CO_2-pressure. A similar result was obtained at a greater height by the Pike's Peak Expedition (Douglas, Haldane, Henderson, and Schneider, 1913), and also by Barcroft, Camis, Mathison, Roberts, and Ryffel (1914–15) on Monte Rosa. As will be shown in Chapter VI the oxygen dissociation curve of haemoglobin is shifted to the right or left with varying alkalinity, and the shifting is a moderately delicate index of the variation. Peters (Barcroft, 1914), working with Barcroft, has shown that the shifting with variations in CO_2-pressure depends on the shifting in 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 the 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. Subsequently Hasselbalch

and Lindhard (1915 *a*) made direct electrometric measurements of pH of the blood after the subject had been exposed in a steel chamber to low pressure for a sufficient time, and their measurements gave practically the same results. 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 most extreme panting.

As soon as the results of Hasselbalch and Lundsgaard were published, it was possible to estimate quantitatively the delicacy with which the respiratory centre responds to variations in the reaction of the blood: for the delicacy of the reaction of the centre to variations of CO_2-pressure was known from the previous experiments of Haldane and Priestley, 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 (1911), and Hasselbalch and Lindhard (1911) had meanwhile published experiments which seemed to indicate that the respiratory centre in man is commonly far less sensitive to CO_2 than Haldane and Priestley had found. The matter was therefore reinvestigated by Campbell, Douglas, Haldane, and Hobson (1913). They 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 Haldane and Priestley had obtained, so the calculation could be made accordingly.

A rise of 0·2 per cent. or 1·5 mm. in the CO_2-pressure of the alveolar and arterial blood causes an increase of about 100 per cent. in the resting alveolar ventilation, and from Fig. 29 it will be seen that this corresponds to a difference of 0·012 in pH. This difference, large as its physiological effect is, cannot be detected with certainty by the electrometric method or by indicators, and it 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. When one considers the sensitiveness of the respiratory centre to changes in the CO_2-pressure in the arterial blood, and also, as has been shown above, the minuteness in the changes of the hydrogen-ion concentration of the blood corresponding to these variations in CO_2-pressure owing to the great efficiency of the direct and indirect buffers of the blood,

the astounding delicacy of the relation between respiration and blood reaction becomes evident. No existing physical or chemical method of discriminating differences in reaction approaches in delicacy the physiological response of the breathing. Unfortunately, however, the quantitative significance of this fact has not yet been universally appreciated. There is still a tendency to treat the blood within the living body as if its reaction were not only variable during rest, as it is, but as if the variations detectable by the relatively insensitive chemical and physical methods which are alone available at present were always a true index of the changes in reaction to which the breathing is responding. One might as well try to cut delicate histological sections with a blunt carving-knife, as try to demonstrate the ordinarily very minute changes in blood reaction to which the breathing is responding in normal daily life by the existing physical and chemical methods. As will be shown below (p. 98), however, considerable changes in blood reaction, when not due to CO_2, may occur without these changes affecting the breathing more than slightly.

The observations outlined above, and particularly perhaps the work of Hasselbalch, seemed to make it clear that the original conception of Haldane and Priestley that breathing is regulated simply by the CO_2-pressure of the arterial blood must be given up. It appeared, however, that breathing is regulated by changes in the hydrogen-ion concentration of the arterial blood, and that this regulation is of the most remarkable refinement. The conception of the regulation of the breathing by variation in the hydrogen-ion concentration of the blood gained practically universal acceptance, but it was not long before observations began to accumulate which seemed to be incompatible with this theory. For instance, Lacquer and Verzar (1912) found that, for a given hydrogen-ion concentration, carbonic acid was more effective as a respiratory stimulant, than mineral acids when injected into animals. They came to the conclusion that carbonic acid exerts a specific effect independent of its properties as an acid, thus reverting to the view originally expressed by Haldane and Priestley. Hooker, Wilson, and Connett (1917) perfused the medulla with solutions of varying hydrogen-ion concentration and carbon dioxide tension. They found that a specimen of blood containing a high tension of CO_2 caused greater activity of the respiratory centre than another specimen of the same hydrogen-ion concentration but with a low tension of CO_2. They also concluded that carbonic acid

acts specifically on the respiratory centre. Scott (1918–19) carried out experiments in which decerebrate cats breathed CO_2 before and after intravenous injection of sodium bicarbonate. He found that the stimulation of respiration by CO_2 was equally effective irrespective of the hydrogen-ion concentration of the blood. Dale and Evans (1922) also observed the results of varying hydrogen-ion concentrations of the blood in different ways. They found that increased alkalinity of the blood brought about by injections of sodium bicarbonate did not cause apnoea, and they also came to the conclusion that CO_2 has a specific effect apart from its qualities as an acid.

Collip (1920–1) injected bicarbonate intravenously into a dog under ether and observed increase of respiration and rise of blood-pressure. He deduced a specific sensitivity of the respiratory centre to the HCO_3 ion.

Mellanby (1922) found that in anaesthetized animals injections of lactic acid and sodium bicarbonate caused considerable changes in the pH of the blood and relatively small changes in the respiration, while inhalation of CO_2 and oxygen lack caused large increase of ventilation and small change in the reaction of the blood.

Ege and Henriques (1926) compared the large increase in lung ventilation and small change in blood reaction when CO_2 is breathed with the much smaller increase of lung ventilation following the same change of reaction caused by injections of acid. They concluded that the action of CO_2 on the respiratory centre is specific and not due to hydrogen-ion change.

Heymans, Bouckaert, and Dautrebande (1930) also came to the conclusion, as a result of perfusion experiments, that it is the CO_2-pressure and not the hydrogen-ion concentration of the perfusion liquid which is the physiological regulator of the respiratory centre.

Christiansen, Douglas, and Haldane (1914) found that shortly after severe exertion the hydrogen-ion pressure of the arterial blood, as calculated from the Hasselbalch equation, was much higher than before, though the breathing was only slightly increased. J. B. S. Haldane, Linder, Hilton, and Fraser (1928), investigating the acidosis resulting from the ingestion of ammonium chloride, found that the pH of the blood fell by about 0·12 while the breathing was only about double instead of being eight times as great, as would have been expected if there were direct proportion between the hydrogen-ion pressure of the arterial blood and the breathing.

Gesell (1925, 1929) lays stress on the undoubted facts, which will be discussed later (p. 115), that the activity of the respiratory centre is influenced, apart from changes in hydrogen-ion concentration, by other factors, e.g. changes in body temperature, oxygen deficiency, etc. These considerations, together with the discrepancies which, as we have just seen, have sometimes been observed between blood reaction and breathing, together with the effects of circulatory changes, have led him to the conclusion that the essential factor in the regulation of the breathing is the metabolism of the respiratory centre itself.

The change in hydrogen-ion pressure in the arterial blood which accompanies hyperpnoea caused by breathing air containing CO_2 has been investigated by Douglas and Havard (1932). They determined directly the change in hydrogen-ion pressure in the blood by means of the glass electrode. They also determined the change of alveolar CO_2-pressure, and by means of the curve relating CO_2-pressure and pH calculated the change in hydrogen-ion pressure. They found that the direct determination agreed precisely with the calculated values. Thus an increase of 10 litres per minute in the total ventilation of the lungs was accompanied by a rise of about 2 mm. in the arterial CO_2-pressure and a fall of about 0·015 in the pH of the arterial blood.

All these observations seemed to be unassailable and also seemed to be incompatible with the hydrogen-ion theory of the regulation of respiration. This theory, however, was founded on such a large body of reliable evidence that it seemed almost inconceivable that it could be wholly erroneous. The experimental evidence therefore which was in existence about 1912–20 led apparently to a dilemma; but it was not long before a satisfactory explanation was obtained. Jacobs (1920 *a*, *b*) found that a saturated solution of CO_2 is far more toxic to tadpoles than are solutions of other acids of the same hydrogen-ion concentration. He also found that in the presence of sufficient bicarbonate to make the reaction of the solution almost neutral, the toxic properties of CO_2 were unchanged. Further, he compared the effects of CO_2 and other acids on protozoa and on the sense of taste in man. He concluded that undissociated carbonic acid penetrates the living cells much more readily than other acids or the hydrogen ion itself. In his second paper he found that intracellular acidity can be produced almost as effectively by a slightly alkaline solution of CO_2 and sodium bicarbonate as by a solution of CO_2 in distilled water.

Loeb (1922) found that weak undissociated acids diffuse readily through membranes.

We may thus conclude that it is in virtue of changes in the hydrogen-ion pressure of the arterial blood that CO_2 affects the respiratory centre, but that considerable changes in hydrogen-ion pressure produced in other ways may fail to cause comparable effects owing to failure of these changes to be communicated from the blood to the reacting tissue.

We can now consider the physiological importance of the amazing delicacy of the regulation of the reaction of the arterial blood. It was discovered by Christiansen, Douglas, and Haldane (p. 51) 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 pressure of the blood is also correspondingly prevented from rising. Accordingly the actual increase in hydrogen-ion pressure 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 very much more intelligible, as venous blood must be very little less alkaline than arterial blood.

In determining the hydrogen-ion pressure 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 (Peters, 1914). 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 evident therefore that the value obtained for the hydrogen-ion pressure is lower than that which exists in either arterial or venous blood in the living body. To investigate the amount of this difference Parsons (1917) adopted the method of determining the hydrogen-ion pressure, not in whole blood, but in its serum, of which the hydrogen-ion pressure is not altered when free oxygen is removed. Using this method, he found that in normal blood the pH at constant pressure of CO_2 at anywhere near the alveolar CO_2-pressure is greater by 0·038 in the oxygenated than in the reduced blood. Fig. 31 shows his results. From them and from Fig. 16 it is possible to calculate what the difference from 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 oxygen the difference would be 0·07, as shown in Fig. 32 from Parsons's paper. Assuming, however, that the mixed venous blood loses normally only about a fourth or less of its combined oxygen (p. 382), the

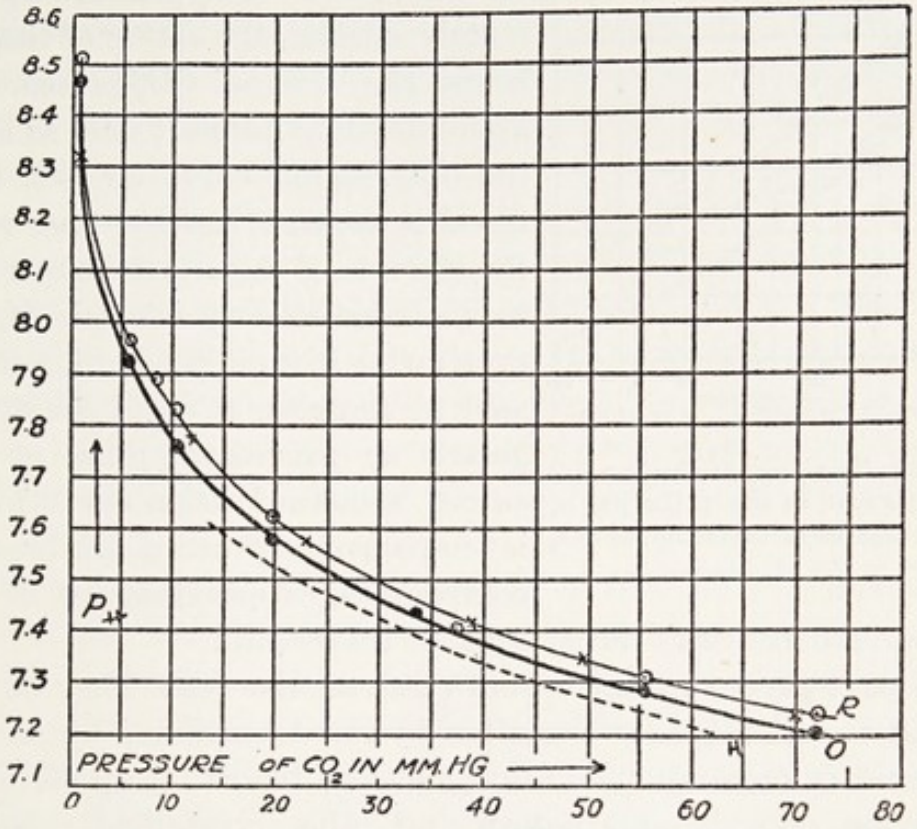


FIG. 31. Curve *R*, completely reduced blood. Curve *O*, fully oxygenated blood. ×, direct measurements on reduced blood without removal of corpuscles. *H*, Hasselbalch's curve.

difference is only 0·0175—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.

On the existing evidence it seems evident that during health the regulation of the reaction of the arterial blood is ordinarily carried out with a delicacy of which we can at present only obtain a real conception by physiological observations. This very exact physiological regulation of the pH of arterial blood becomes intelligible in view of the very small difference in pH between arterial and mixed venous blood. The foregoing discussions show that there are at least three distinct regulators of the reaction of the blood in the body, namely, 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 also approximately normal; and, so long as the dissociation curve for CO_2 in the blood is 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, a 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 the reaction of the tissues.

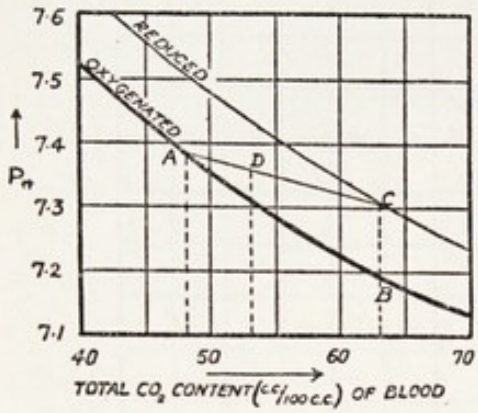


FIG. 32. The slope of the line AC shows the rate at which the pH of blood decreases as its content of CO_2 increases in the capillaries.

The part played by the kidneys also seems clear. They not only respond to the minutest variation 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 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 an acid poured out into the blood, the kidneys help to restore it to normal again.

The blood reaching the kidneys contains in health from 10 to 50 mg. of urea per 100 c.c. (Mackay and Mackay, 1927). Benedict and Nash (1921, 1926, 1929) found that the circulating blood only contains traces of ammonia and that there is more ammonia in the blood of the renal vein than in that of the renal artery. They concluded that the kidney forms ammonia from urea.

Krebs (1933) has shown quite clearly that the kidney is, next to the liver, one of the main sites of deaminization of amino acids. Amino acids are indeed the most important source of urinary

ammonia. If, in consequence of increased intake of acid, or of increased formation of acid in the body, as in diabetes mellitus, non-volatile acids are present in the blood, they exist in the form of their sodium salts. To the kidney falls the task of excreting this excess of acid without depleting the body of its store of fixed base. This it does by excreting the acids in combination with the ammonia derived from amino acids. The kidney thus rids the body of excess of acid without excessive rise of the acidity of the urine, but preserves the sodium of the blood. In so doing it acts as a most important regulator of the hydrogen-ion pressure of the blood. The toxic properties of ammonia preclude the possibility of its existence in appreciable amounts in the circulating blood. Thus the ammonia required for neutralization of excess acid is formed in the kidney, where it is immediately excreted, and not in the liver. Interference with the ammonia-forming function of the kidney leads to acidosis. Uraemic acidosis, indeed, is not a consequence of impaired renal secretion, but of impaired kidney metabolism, i.e. defective deaminization of amino acids.

If the proportion of available alkali in the blood is temporarily increased, the kidneys deal with the excess, and in this case less ammonia is formed. The action of the kidneys in regulating the reaction of the blood is slow compared with that of the lungs; but is also extremely delicate. As L. J. Henderson (1908) was the first to point out clearly, 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 total acid excreted titration must be employed, and in titrating alkaline urine the CO_2 liberated must be allowed to escape (Davies, J. B. S. Haldane, and Kennaway, 1920).

Until the work of Benedict and Nash was published it was generally accepted that 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. It was supposed that, by allowing more, or less, ammonia to enter the circulation the liver regulates the reaction of the blood in the manner already described, and the neutral ammonia salts are afterwards eliminated by the kidneys as being foreign substances. The observations of Benedict and Nash which seemed to show the absence of

ammonia from the circulating blood and its formation by the kidney led to neglect of the old teaching of Schmiedeberg.

The part played by the liver in the formation of urea was, however, investigated by Bollman, Mann, and Magath (1924), who perfected the operation for the removal of the liver in dogs. They found that the blood-urea always diminished greatly when urine was excreted, and did not increase when the kidneys were removed. They concluded that the production of urea in the dog is wholly dependent on the liver. Mann and Bollman (1928) found that absence of the liver prevents transformation of ammonia into urea, and that amino acids injected into liverless dogs do not cause increase of the blood-urea. They concluded that the liver is necessary for the deaminization of amino acids and the formation of urea, but that it is not concerned with the formation of ammonia from urea. Even so, the importance of the part played by the liver under normal conditions is evident enough. Like that of the kidneys the action of the liver is slow compared with that of the lungs, but quantitatively the effect of the activities of the two organs in preserving the acid-base balance of the body is of the utmost importance.

The importance of the liver as the site of formation of urea, and the nature of the reactions involved, was shown clearly by Krebs and Henseleit (1932) in a remarkable paper. They demonstrated that slices of liver tissue formed citrullin by combination of ornithin with CO_2 and ammonia derived from deaminization of amino acids. The citrullin so formed is then combined with a further molecule of ammonia to form arginin, which is finally split up into urea and ornithin by the enzyme arginase which is specially abundant in the liver.

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.

Having considered the regulation of the hydrogen-ion pressure of the blood in the normal body, under conditions generally assumed to be standard, and the remarkable precision of its physiological adjustment, together with the organs concerned, it will be well to consider how this joint regulation behaves when the action of one of the regulators is modified; and the case of modification of the lung regulation will be considered first. This regulation may be disturbed in various ways. In considering these we may direct attention first of all to the fact that, under abnormal conditions, the stimulus of anoxaemia

increases the breathing, and this disturbs the normal relation between the lung ventilation and the degree of stimulus of the respiratory centre owing to varying reaction of the arterial blood. The history of development of knowledge on this point is very instructive.

As shown in Chapters II and VII diminution of the oxygen pressure of the inspired air causes increased ventilation of the lungs, but 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 subjectively noticeable increase in the breathing. The effect on the respiratory centre of the very distinct degree of anoxaemia which is undoubtedly produced, in the manner explained in Chapter VIII, is almost entirely masked by the contrary effect due to extra washing out of CO_2 and consequent raising of the pH in arterial blood; but the fact that the alveolar CO_2-pressure is lowered, so that CO_2 is washed out, is in itself proof that the breathing is increased, though this increase may be subjectively inappreciable. But if exposure to the lowered oxygen-pressure is continued, not merely for perhaps an hour, but for days or weeks, the increase in breathing, as shown by a fall in the alveolar CO_2-pressure, is persistent for hours or days after the anoxaemia has been removed. The lowering of the alveolar CO_2 in consequence of exposure to even moderately low barometric pressures was brought out in full clearness by the investigation carried out in connexion with the Pike's Peak expedition by Miss FitzGerald (1913, 1914–15) on persons fully acclimatized at different altitudes. Figure 33 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? After the experiments, already referred to, of Boycott, Ogier Ward, and Haldane, it was fairly 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. No excess of lactic acid could be discovered by Ryffel (1909–10) in the urine, and hardly any in the blood, of persons exposed to low pressures

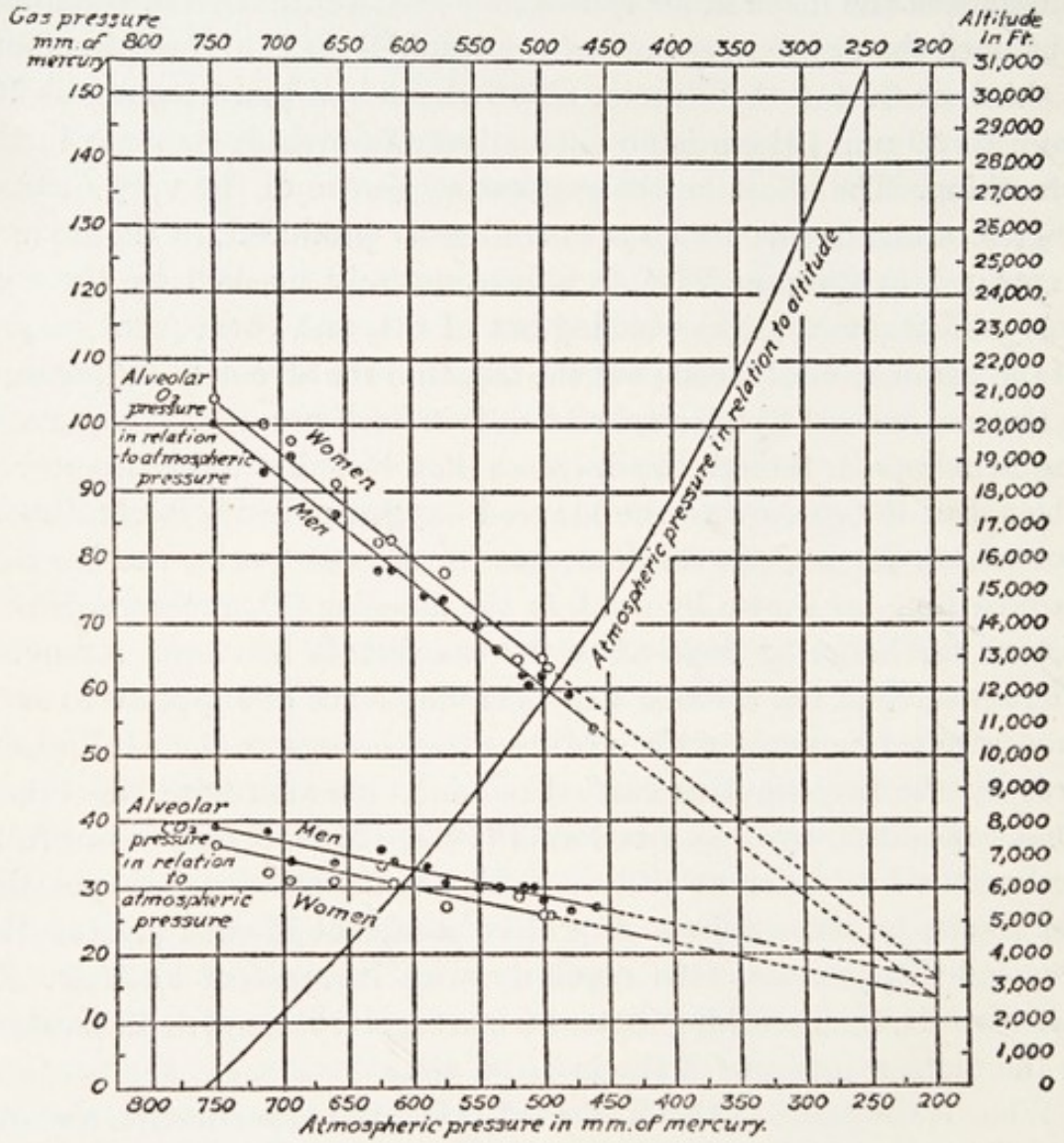


FIG. 33. Alveolar gas pressures in relation to barometric pressure or altitude.

in a respiration chamber or steel chamber, or indeed in persons at high altitudes; and no other abnormal acid could be discovered in the blood. Hence the theory of an acidosis due to accumulation of abnormal acids cannot be substantiated. In the report of the Pike's Peak Expedition the theory was adopted 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 (1915 *b*) as the result of experiments in a steel chamber. They found that the excretion of ammonia is distinctly 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 Haldane, Kellas, and Kennaway (1919–20), in which careful measurements were made of the excretion of acid and ammonia. They 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 was then revealed.

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 (1919, 1920) (Haggard and Henderson, 1920 *a*, *b*, 1921).

The increased excretion of alkali and diminished formation of ammonia lead gradually towards a compensation of the alkalosis with simultaneous relief of the anoxaemia, this relief being due to the 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, on Pike's Peak when air enriched with oxygen was breathed after acclimatization had been established.

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, pursuing 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. By the administration of acid or an ammonium salt of a strong acid the adaptation to a lowered oxygenation of the arterial blood could doubtless be hastened (p. 317).

There is no doubt therefore that the regulation of the respiration by slight variations of the hydrogen-ion concentration of the blood is liable to be modified by conditions which vary the oxygen-pressure of the blood (see Chapter VII).

A ready method of interfering temporarily with the regulation of the blood reaction by the lungs is forced breathing. This can be continued for a considerable time if it is employed in moderation. The physiological effects are, however, very striking and include sensations of numbness and tingling, and may eventually produce a condition of tetany and stupefaction. Leathes (1919) found that if forced breathing was continued for some time the urine became alkaline to litmus, and the titration alkalinity has been investigated by Davies, J. B. S. Haldane, and Kennaway (1920).

Lepper and Martland (1927) found that by forced breathing the pH of the blood could be raised by 0·20 to 0·24 in 10 to 15 minutes. On stopping forced breathing the pH returned to normal in 5 minutes. They found the rise in pH to correspond to changes in plasma bicarbonate and alveolar CO_2-pressure which were observed simultaneously.

The titration alkalinity of the urine is not so striking as after a large dose of sodium bicarbonate has been taken. Davies, J. B. S. Haldane, and Kennaway 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 disappeared completely from the urine, and this was also the case after forced breathing, although such a degree of forced breathing as was practicable did not

diminish appreciably the available alkali in the blood within 1½ hours. Henderson and Haggard (1918 *c*) 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. Collip and Backus (1920), moreover, found that, as might be expected from the change in distribution of acid and alkali between the plasma and corpuscles when the pH of blood is altered, the alkaline reserve of the plasma is distinctly diminished by forced breathing.

Another case of interference with the lung regulation of blood reaction is observed when an animal or man is placed 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 by Yandell Henderson and Haggard (1918 *a*). They made the very important and significant discovery that the acidosis thus produced gradually brings about a marked increase in the 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 Fig. 13, would occupy a higher position.

What is the significance of these changes which occur in the blood after forced breathing on the one hand or inhalation of CO_2 on the other? They occur much too quickly to be capable of explanation as due to an adaptive response by the kidneys and liver. The probability is, therefore, that they are due to exchange of anions between the tissues and blood in the manner discussed above, and are indicative, therefore, of very severe alkalosis or acidosis of the tissues. This explanation 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 of these investigators (Haggard and Henderson, 1919; 1920 *a*, *b*, *c*) brought out in striking

manner the fact 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 akalinity 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 suffering, on the one hand, from severe alkalosis although the 'alkaline reserve' or titration alkalinity of their blood was greatly diminished; and on the other hand they were suffering from severe acidosis although the 'alkaline reserve' was greatly increased.

It was these observations that led Yandell Henderson to the same conclusion that was reached by Haldane, Kellas, and Kennaway, 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.

It is unfortunate that great confusion has arisen with regard to the regulation of the reaction of the blood and its relation to the so-called alkaline reserve. It may therefore be useful to indicate explicitly the reasons for confining the use of the words 'acidosis' and 'alkalosis' to indicate *solely* deviations towards the acid or alkaline side respectively of the normal reaction or hydrogen-ion concentration within the body.

Acidosis and alkalosis have frequently been 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 (1917) 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 oxygenated blood-plasma in place of whole blood for the purpose. Though they stated clearly that variations in alkaline reserve are no direct measure of the variations in actual reaction of the blood, as was also shown very clearly by Hasselbalch and Warburg (1918), they, very unfortunately, as many think, proceeded to define 'acidosis' as being 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 the alkaline side of the reaction seems to be quite unjustifiable. The confusion has been increased by general failure to realize the extreme delicacy of physiological regulation of reaction, as compared with the comparative roughness of our present means of measuring directly changes in reaction. Thus in cases where there are all the physiological signs of acidosis, the available means of direct measurement may show no signs of the change; and hence it has often been assumed quite wrongly 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 which may combine in the body is in reality always in physiological use, and the most urgent symptoms of acidosis appear long before the alkaline reserve disappears.

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 (1914) produced a temporary true acidosis by flooding the blood with lactic acid produced by muscular anoxaemia during the heavy exertion of running several times up stairs. In this case two results followed. In the first place there was a heavy 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 $1\frac{1}{2}$ 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. The result was a very distinct acidosis; but reference to the calculations already made will show that the acidosis in the respiratory centre itself could not have been detected by any existing method of estimating the 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 nearly as efficient as normal blood. This is due to the fact that, as already explained in Chapter III, the haemoglobin and other proteins play an 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 (p. 14). In discussing these experiments Haldane and Priestley 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 Haldane 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 removed 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 kidneys. Had the acidosis been produced by a mineral acid it would probably have taken far longer to pass off.

The effect of muscular exercise on blood reaction and breathing was studied by Barr (1923). His results are given in the following

table, and from them and similar results he drew the conclusion that the respiratory centre is much less sensitive to changes of reaction in arterial blood than had been supposed and that there is no constant relationship between blood reaction and breathing which can be demonstrated. These conclusions of Barr cannot, however, in the light of all the evidence that has been discussed in this chapter,

GENERAL RELATION OF RESPIRATION IN H.E.H. DURING AND FOLLOWING EXERCISE

Time relation to Exercise	*Minute volume May 23rd litres*	*pH of arterial blood*		
		Apr. 14	*Apr. 5*	*Apr. 21*
Before	8·0	7·35	7·30	..
During last minute . .	83·5	7·27	..	..
1 min. after . . .	56·0	..	7·16	..
3 mins. after . .	34·0	..	7·15	7·19
15 „ . . .	11·0	..	..	7·23

be accepted. The explanation of Barr's results is to be found in the fact that there is a lag in the changes of hydrogen-ion concentration in the respiratory centre which follow changes in the arterial blood, and a temporary disharmony between changes in the blood and respiration (see Douglas and Havard, 1932).

Owles (1930) investigated the changes in the blood and alveolar air during exercise. He found that there was a critical metabolic level, i.e. an oxygen consumption of 1·8 litres per minute, or about eight times the resting value, below which there was no increase of blood lactate in consequence of the exercise, though above this level such an increase did occur. Correspondingly he found a fall in the CO_2-combining power of the blood above the same critical level but not below it. He concludes that in muscular work there is no output of lactic acid from the active muscles so long as the local adjustments of the circulation are adequate to prevent the occurrence of local areas of anoxaemia.

Disturbance of the blood reaction may be artificially produced by the ingestion of acids or alkalis, or even, to a slight extent, by varying the character of the diet. It requires a very large dosage 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 (variation 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 alkalis 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 can only 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 centre. There are no short cuts to decisions on the 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, the urine in man 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 often 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 (Palmer and Henderson, 1915). This result is now intelligible in view of the fact, already mentioned, that the kidneys themselves are the seat of formation of ammonia (Krebs, 1933).

Considerable new light is thrown on the causes of acidosis by experiments of J. B. S. Haldane (1921). 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 kidney forms ammonia 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 similar result was found to follow administration of calcium chloride (J. B. S. Haldane, Hill, and Luck, 1923).

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.

The ordinary processes of regulation of breathing are also modified by changes of body temperature. The rapid respiration which often occurs in fever is a well-known clinical phenomenon. In experiments, too, on the effect of muscular work on the respiration it is important to take precautions against rise of body temperature if misinterpretation of the results obtained is to be avoided.

Haldane (1905) observed the effect of moist heat on the body temperature and respiration. He found that as the temperature of the blood rose hyperpnoea set in, and that in consequence the alveolar CO_2-pressure fell. For instance, in one case with a rectal temperature of 99·7° F. the alveolar CO_2 was 5·65 per cent. When the temperature rose to 103·8° F. the alveolar CO_2 fell to 4·67.

Haggard (1920) observed the effect of immersion in a hot bath (43° C. for 20 minutes) and found that the alveolar CO_2 fell by about 0·7 per cent., but this fall was not compensated by decrease in the available alkali of the blood during the short period of the experiment.

Bazett and J. B. S. Haldane (1921) also investigated the effect of hot baths. They found that when the temperature of the bath was below 37° C. and the water constantly stirred respiration was not affected. In hotter baths hyperpnoea set in, and rather with rate of rise of body temperature than actual temperature. They found that the hyperpnoea was accompanied by faintness, mental confusion, etc., which were relieved by breathing either CO_2 or oxygen.

Koehler (1923) investigated the effects of hot baths in normal subjects and fever occurring clinically. In both he found lowering of hydrogen-ion concentration of the blood and of CO_2-combining

capacity. He also found that the symptoms were relieved by measures directed to reduce the alkalosis.

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 centre 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 centre must do its share, as well as the kidneys and liver, in compensating for these disturbances. Hence the alveolar CO_2-pressure cannot remain completely steady during rest. One of the causes of slight variation of the alveolar CO_2-pressure is the secretion of acid or alkaline digestive juices. It was found by Dodds (1920-1) that the alveolar CO_2-pressure rises distinctly soon after a meal and then falls below normal, subsequently returning rapidly. He found that the rise above normal amounted to about 4 mm. Hg $\frac{1}{2}$ hour after a meal and that the subsequent fall below normal was also about 4 mm. Hg culminating about $1\frac{1}{2}$ hours after the meal.

Bennett and Dodds (1921) 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. Dodds (1923) observed corresponding variation in the urinary excretion of acid and alkali after meals.

Cullen and Earle (1929) observed the diurnal variation in the pH of the blood. Their most constant finding was an increase from early morning to late evening which varied from 0·01 to 0·07 pH. This increase was not steady but was interrupted by fluctuations due to digestion, exercise, and other factors. The changes following digestion were not regular, but there was a definite tendency to increased pH- and CO_2-content after meals.

Brunton and Israëls (1930) failed, however, to observe variations in alveolar CO_2-pressure corresponding with varying activity of the digestive glands. It appears to be probable that there are considerable individual differences in this respect.

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 shown very clearly in some experiments of Hasselbalch (1912) alluded to above (p. 95); and he showed at the same time that the reaction of the urine varied in correspondence with the change in alveolar CO_2-pressure.

During starvation the body is living on what amounts to an acid-forming diet, and Higgins (1915) has shown that during starvation the alveolar CO_2-pressure falls. Higgins, Peabody, and Fitz (1916) showed that on a carbohydrate-free diet there is a striking fall in alveolar CO_2-pressure together with a very large elimination of oxybutyric and aceto-acetic acids by the kidneys, and an accompanying large increase in ammonia excretion and excretion of acid. There is evidence that these acetone derivatives may affect the body directly and not merely by causing change of hydrogen-ion concentration or oxygen lack (Hurtley and Trevan, 1915–16). Walinski (1926) found that in the course of starvation the alkaline reserve of the blood fell, but returned to its original value after one day on a carbohydrate diet. Perhaps an even more striking effect was obtained with a carbohydrate-free diet, which led to the formation within the body of a certain amount of aceto-acetic and β-oxybutyric acids, as in severe diabetes.

Some very interesting observations were made by Hasselbalch and Gammeltoft (1915) on the pH of the blood during and after pregnancy. 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 child-birth with the results shown in the accompanying table.

REACTION OF THE BLOOD IN EIGHT DIFFERENT WOMEN BEFORE AND AFTER CHILD-BIRTH

	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

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 favourable 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 fifty times as sensitive as the existing 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 to be produced without any measurable 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. It should never be forgotten, however, that, except by observation of physiological reactions, there seems to be at present no method of estimating in a reliable manner the small variations in pH which are of so much physiological importance. Hasselbalch, for instance, estimated that a difference of 0·03 in pH could be detected in single determinations by the electrometric method; but this, from a physiological point of view, is a very large difference, corresponding to an increase of 250 per cent. in the breathing.

As was shown above, a difference of 0·012 in the pH of the blood is sufficient to double the resting breathing, or to cause apnoea, as the case may be. 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 previously been assumed. By forced breathing we can, it is true, produce a greater difference in the pH of arterial blood. As will be shown in Chapter XII, 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 (1925) 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 the circulation ensue, but so much damage is done that it is impossible to restore the animal even when the pH of the blood is readjusted by administering CO_2, just as it is impossible to restore a patient who has suffered for a sufficient time from active 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 consequently the rise in pH in the tissues is minimized.

Consideration of the facts discussed in this chapter points therefore to the conclusion that all the available evidence indicates that practically speaking the regulation of breathing in man during rest under normal conditions is regulation of the tissue reaction. Further, this regulation is a physiological regulation which far surpasses in refinement any physico-chemical means by which we may attempt to follow its working in the body.

The physico-chemical equilibria in the blood afford, in themselves, no explanation of the regulation of the breathing. They merely facilitate physiological adjustments and help the reactions of the living body to varying conditions to maintain the internal environment within the narrow limits which alone are compatible with life and physiological efficiency.

V

THE NERVOUS CONTROL OF BREATHING

FROM the evidence discussed in the previous chapters it is clear that the regulation of respiration is fundamentally chemical, but it has long been recognized that the activity of the respiratory centre is also under the control of nervous influences. It is now necessary to discuss more closely the influence of nervous control on the breathing.

The rhythmic activity of the respiratory centre 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 as shown by Krogh and Lindhard (1913–14*b*), 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 centre, when not influenced 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 (1868*a*, *b*), 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 produced by an anaesthetic, and were so studied by Haldane and Mavrogordato (1916). They used a very simple arrangement which enabled them 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 bag of

air containing any required percentage of CO_2, they could observe the influence of hyperpnoea due to CO_2, and by suitable recorders connected with the far end of the bag and the gauge, the breathing and pressure could be recorded.

If expiration is interrupted by turning the tap, and all voluntary effort is suspended, the previous rhythm of the respiratory centre is interrupted by a prolonged expiratory phase, as indicated by the gauge. The expiratory pressure is at first slight and constant, but

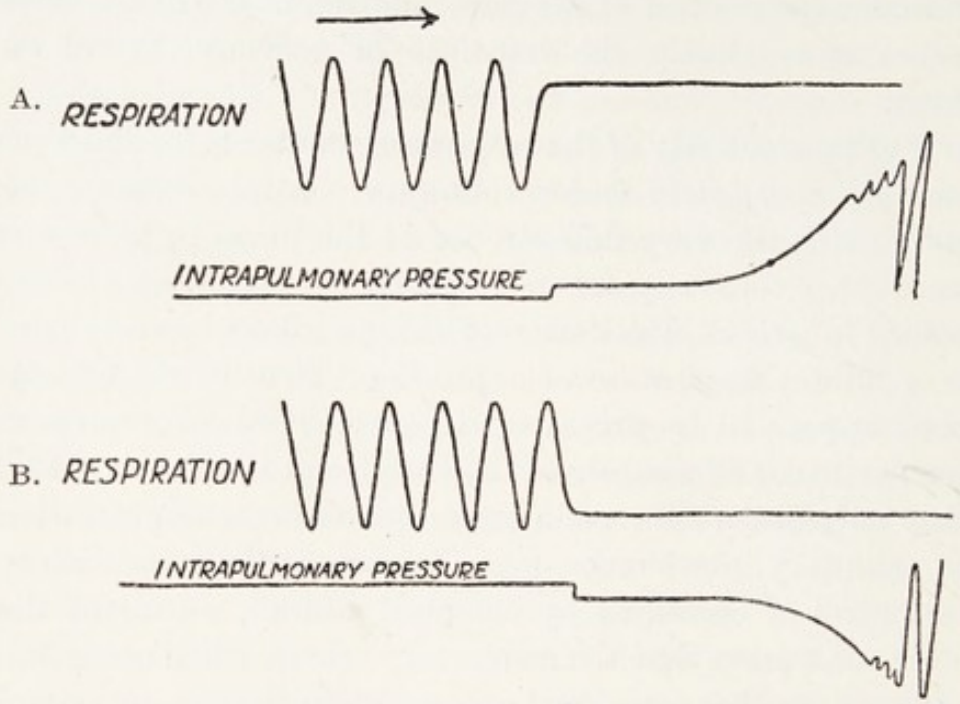


FIG. 34. Effects of interrupting natural breathing. A. Respiration interrupted during inspiration—near end. B. Respiration interrupted during expiration—near end. Respirations—inspiration up, expiration down. Intrapulmonary pressure—positive pressure down, negative pressure up.

afterwards rises gradually and at an increasing rate, until, if expiration is still prevented, there is at last an inspiratory effort as shown in Fig. 34 B. Similarly, if the breathing is obstructed during inspiration, there is a prolonged and increasing inspiratory effort followed by an expiratory effort (Fig. 34 A). 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 during ordinary breathing.

With interruption at the complete end of inspiration the expiratory phase begins at once as shown by the pressure gauge, the supposed apnoea of distension being thus non-existent. Similarly, at the

complete end of expiration the inspiratory phase usually begins at once in man; but there may be a delay at the end of expiration.

In order to study the respiratory movements with the nose and mouth perfectly free, Haldane and Priestley (1905) put the whole

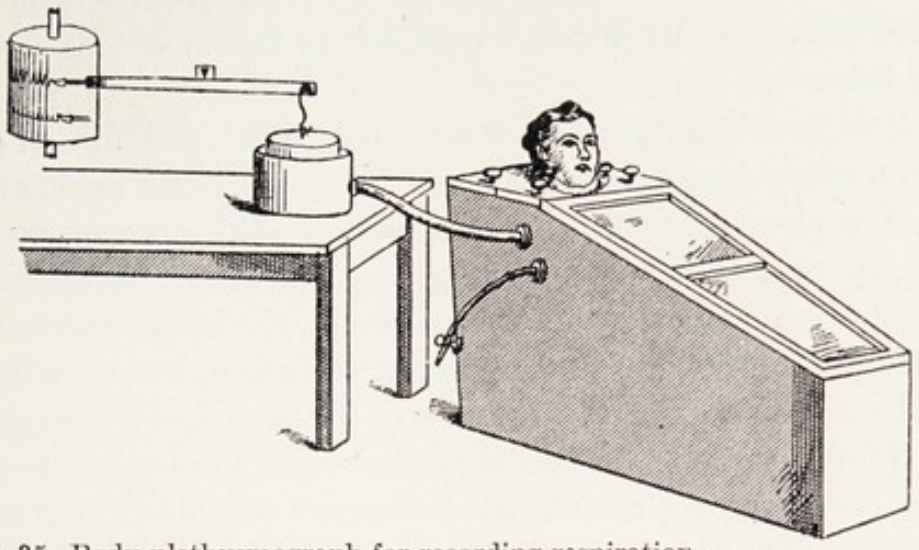


FIG. 35. Body-plethysmograph for recording respiration.

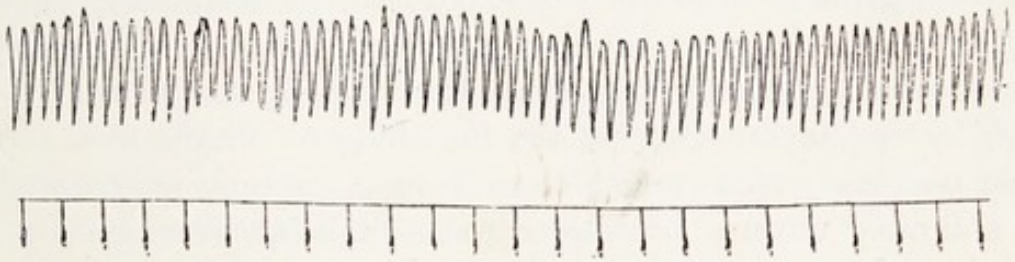


FIG. 36. Plethysmograph record of respiration. Subject J. G. P. Time-marker = 10 seconds. Read from right to left. Down stroke = inspiration.

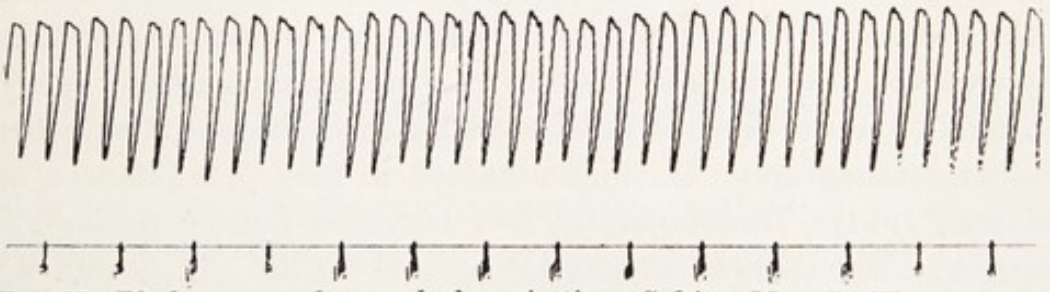


FIG. 37. Plethysmograph record of respiration. Subject Mrs. G. Time-marker = 10 seconds. Read from right to left. Down stroke = inspiration.

body, except the head, into a recording plethysmograph (Fig. 35). The record obtained showed accurately the movement of air into and out of the lung. One record in which inspiration follows sharply on the completion of expiration is reproduced in Fig. 36. The other record (Fig. 37), from a lady, shows a pause at the end of expiration.

From these records we can infer that, although inspiration in man usually follows sharply on the completion of expiration just as if the completion of expiration were a stimulus to inspiration, as Hering and Breuer thought, yet inspiration need not follow immediately. We can thus say that the completion of expiration permits inspiration, but does not excite it. Further evidence in favour of this view will appear below (p. 127).

Haldane and Mavrogordato found that, with interruption at the end of an extra deep inflation or deflation of the lungs during hyperpnoea, the phenomena described above are still more marked, the expiratory or inspiratory pressures being greater. If apnoea has previously been caused by forced breathing, the initial expiratory or inspiratory pressures are still produced as before, but only increase after a long interval, and the duration of the inspiratory or expiratory phase is much prolonged. The mounting up of the initial pressure is thus dependent on the accumulated chemical stimulus to the respiratory centre. 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 Fig. 34.

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 Figs. 38 and 39 which reproduce stethographic tracings obtained in man (Christiansen and Haldane, 1914). The subject at first breathed quietly through the branch 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 the pressure of about 3 inches of water. The consequence of this was that the lungs were suddenly distended with a large volume of air. It will be seen that after about half a minute the apparent pause in 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 the results shown in Fig. 39.

Fig. 40 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 fact that not only had no fresh air been introduced, but the volume of air in the lungs was diminished.

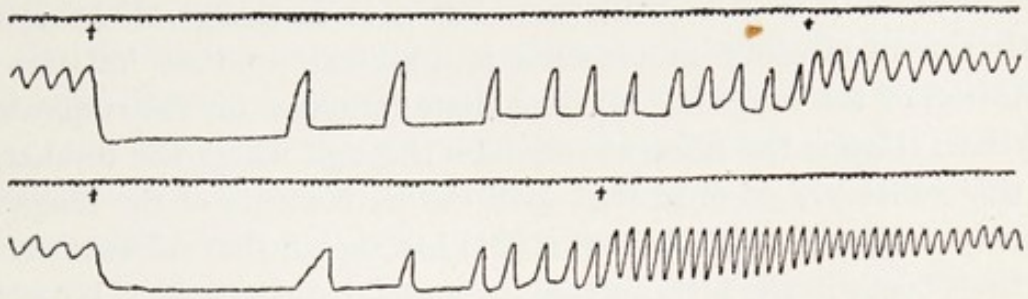


FIG. 38 (above) and 39 (below). Effects of prolonged distension of the lungs. To be read from left to right. Time-marker = seconds. Distension continued between the two crosses. In Fig. 38 pure air was used for distension; in Fig. 39 air containing 7·3 per cent. of CO_2 and 8·2 per cent. of oxygen.

The supposed apnoeic pause produced by inflation of the lungs is simply a prolonged expiratory phase. This effect is produced regardless of the chemical stimulus to the centre. Thus Haldane and Lorrain Smith (1893 *a*, *b*) showed that it is produced even when the lungs are distended with air containing 20 per cent. of CO_2, though the prolongation is much curtailed in such a case.

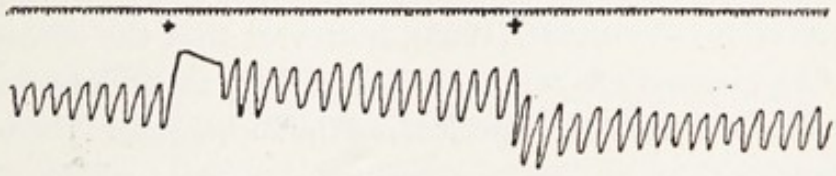


FIG. 40. Effects of partial deflation. Crosses show beginning and end of deflation. To read from left to right. Time-marker = seconds.

It is thus clear that the continuance of an inspiratory or expiratory discharge of the respiratory centre 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 centre does not naturally act independently of the lung movement, but inspiratory or expiratory discharge of the centre tends to go hand in hand with actual

inspiration or expiration, as if the centre were of one piece with the lungs. The term 'vagus apnoea' is evidently an entire misnomer, as prolonged expiratory phases cannot be called apnoea. Tracings which have apparently demonstrated the existence of apnoea are only one-sided, i.e. record only activity of inspiratory muscles, and are 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 centre 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 centre are co-ordinated with the movements of the lungs are conveyed by the vagi. Larsell (1921) has shown that afferent nerve-endings occur in the intrapulmonary bronchi and extend as far as the walls of the atria.

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 inspiration in particular taking on a dragging character, which, until the work of Schäfer, referred to below, was attributed entirely to the absence of the normal inhibitory effect conveyed through the vagi on distension 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 (1908), 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.

When, in addition to section of the vagi, the respiratory centre is also severed from its connexions above the medulla oblongata, the rhythmic discharges of the centre become still less frequent and may be inadequate to prevent death from asphyxia (Trevan and Boock, 1922; V. E. Henderson and Sweet, 1929). The centre is also affected by afferent stimuli from the respiratory muscles. This is indicated by the observation of Boothby and Shamoff (1915) 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. Coombs and Pike (1918 *a*, *b*) found that section of the vagi alone produced a slow and deep type of

respiration, while section of the cervical and thoracic dorsal roots caused diminished costal respiration, the action of the abdominal muscles being unchanged. Section of both vagi and posterior roots caused slowing of the breathing and diminished costal respiration, leading to dyspnoea and gradual cessation of the breathing. They (1922) also found that section of the vagi in cats produced slowing of the respiration, and that there was little recovery of the rate. If 6 to 18 days after section of the vagi the thoracic dorsal roots were also cut the movements of respiration were again seriously disturbed.

Schafer (1920 *a*) found that the slow breathing after section of the vagi is due largely to obstruction caused by laryngeal paralysis. He concluded that if such obstruction is prevented, the breathing is either unaltered or soon returns to a normal rhythm, and that this indicates the existence of constant afferent impulses in other nerves playing a part in the nervous regulation of respiration. Hammouda and Wilson (1932), however, find that in anaesthetized dogs the breathing after section of both vagi remains slow and deep for at least 36 hours, even when laryngeal obstruction is excluded by tracheotomy. They also fail to confirm the conclusion of Lumsden (1923–24) that movements of the air in the trachea play a part in producing afferent impulses in the vagi which affect the respiratory centre. They consider the expiratory phase in normal quiet breathing to be mainly passive and to consist of two parts—the first due chiefly to elastic recoil and lasting about 0·6 second, the second due chiefly to restoration of tone of the internal intercostal muscle which is inhibited reciprocally during inspiration. The second part is really a pause, and during it there is no movement of the thorax or of the air in the lungs. Hence inspiration is not initiated by increasing deflation of the lungs. Variations in rate of breathing they find to be due mainly to variations in the length of the second part.

Adrian (1926) recorded the electrical impulses in the peripheral part of the cut vagus and found that there was a well-marked respiratory effect. Oscillations occurred during both inspiration and expiration, but their frequency and amplitude were greatest at the height of inspiration and least at expiration. He points out that the most striking result is the absence of any sign of a renewed discharge of impulses at the moment when the lungs are most deflated. The expiratory impulses varied somewhat with the species of animal, but the explanation of this is not clear. By clamping the trachea

he showed that the state of expansion of the lungs is the effective stimulus to the vagal endings. He found no evidence that deflation of the lungs is an effective stimulus to vagal endings. Partridge (1932–3), using a Mathews's oscillograph, recorded the action potentials in the pulmonary branches of the vagus during the various phases of respiration, both normal and forced. She found that impulses are initiated by inflation of the lungs, but that there is no

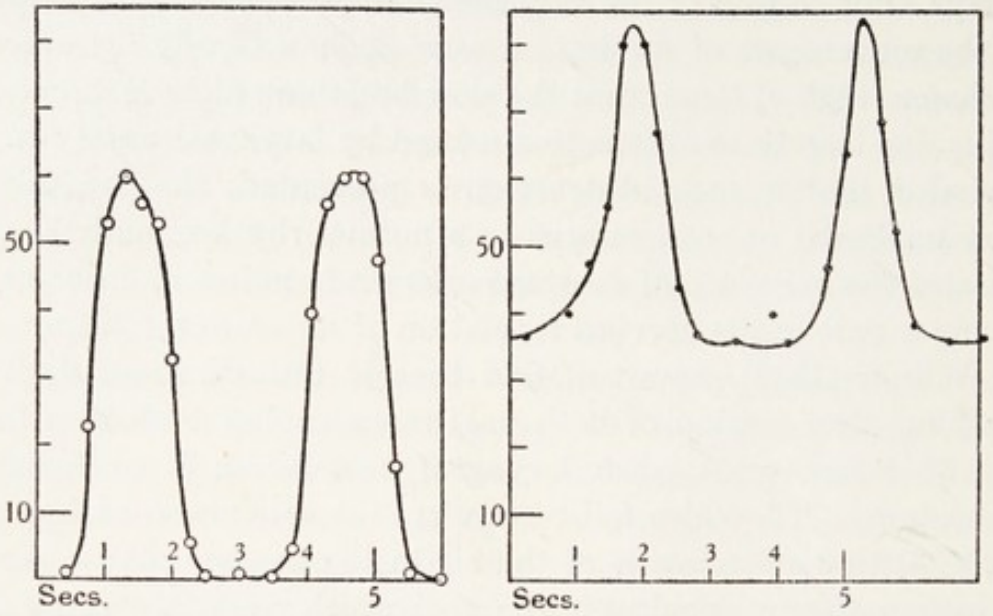


FIG. 41. Frequency of impulses in single fibres of the cat's vagus during normal breathing. Two preparations, both decerebrate.

evidence that even maximal artificial deflation stimulates pulmonary vagal endings. She also found no evidence that CO_2 acts on these nerve-endings.

Adrian (1933) succeeded in recording the impulses in individual fibres of the vagus. He showed that the afferent impulses do not all depend on distension of the lungs, but that some result from the heart-beat and other causes. Figure 41, taken from his paper, shows the frequency of impulses in single fibres of the cat's vagus during normal breathing. It will be seen that the frequency does not always fall to zero, doubtless on account of the impulses of non-pulmonary origin just mentioned and because the lung is not completely deflated during normal breathing. He found no evidence of any impulses due to deflation of the lung except in cases of deflation far greater than that which occurs in any ordinary breathing. It seems from these results that the afferent impulses passing up the vagus in normal breathing are purely inhibitory of inspiratory effort, and Adrian

points out that this suffices to account for the fact that the respiratory rhythm is quicker when the vagi are intact than when they are cut. He does not find that the afferent vagal endings are affected by CO_2 or want of oxygen.

We must now endeavour to correlate the facts relating to the 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 distension of the lungs to a certain point and a consequent inhibitory impulse transmitted up the vagi. The experiments of Head (1889), in which the movements of a slip of the diaphragm, the most prominent inspiratory muscle, were recorded, showed that this inhibition produces an instant relaxation of the diaphragm. If the vagi had been frozen the relaxation was greatly delayed and, even after the delay, was at first very imperfect. The inhibition of inspiration initiates an expiratory phase, which continues until it also ceases on deflation to a certain point. 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, and this corresponds well with the above-described experiments on man. If, with the vagi intact, the breathing is partially obstructed, inspiration or expiration is continued till either act is complete. The influence transmitted through the vagi initiates expiration, therefore, and its disappearance permits inspiration; and the centre persists in the inspiratory or expiratory phase till the vagus gives the signal which terminates the phase existing at the moment. The centre behaves as if it always remembered the last signal; and the analogy between any act dependent on memory and the duration of the inspiratory and expiratory phases of the breathing is evident. We are reminded equally of the 'refractory period' in the phases of cardiac and other muscular activity.

Where the 'chemical' regulation of the respiratory centre exerts its preponderating influence is in determining the extent to which inflation of the lungs must extend in order that the Hering-Breuer reflex shall appear, and also the vigour and consequently the rapidity of the inspiratory and expiratory movements. Thus an increased CO_2-stimulus causes increased depth of breathing, since a greater degree of inflation of the lungs is required before the stimulus becomes effective, and similarly a greater degree of deflation occurs

before reduction of the Hering-Breuer stimulus 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 travelled by the chest walls. The net result is thus, ordinarily, increase in depth without diminution in frequency. But if the frequency 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 a 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 exertion 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 (p. 218), is a very important abnormal symptom.

It is evident that the existence of the Hering-Breuer reflex tends to prevent excessive distension of the lungs during breathing. Such distension might cause injury to the alveoli, and gradual production of the condition known as emphysema. The danger resulting when distension is not controlled by the Hering-Breuer reflex is strikingly shown by certain fatal accidents which have occasionally occurred during the use of an apparatus for enabling men to escape from a submarine which has sunk, and which are discussed fully on p. 358.

In man and several species of animals the internal carotid artery shows a dilatation at its origin. In 1924 and subsequent years H. E. Hering (1927) carried out a series of researches on this sinus, and our views as to the nervous control of the breathing have had to be reconsidered since his discovery that the carotid sinus is a source of afferent impulses which have important reflex effects. The possibility of a reflex control of the respiration by the carotid sinus was first investigated by Moissejeff (1926–7), Koch (1931), and Koch and Mark (1931); and Heymans and his colleagues (Heymans, Bouckaert, and Regniers, 1933) have published a number of papers on the part played by the carotid sinus in the control of the respiration and circulation. They found that impulses originating in the carotid sinus are transmitted to the respiratory centre and modify its activity. The afferent nerve-endings in the carotid sinus are affected by a

variety of stimuli. For instance, Heymans and Bouckaert (1930) find that, when the carotid sinus with intact nerve-supply is perfused, increase of blood-pressure causes reflex apnoea, while decrease of blood-pressure causes reflex hyperpnoea. They conclude that changes in the activity of the respiratory centre brought about by changes of blood-pressure and blood-flow in the cephalic circulation are due to carotid reflexes and not to changes in the cerebral blood-supply. The afferent nerves concerned are the carotid sinus nerves and the depressor fibres of the vagus, and these normally transmit tonic inhibitory impulses to the respiratory centre. This particular reflex control of the respiratory centre explains the apnoea produced sometimes by injections of adrenaline. Heymans and Heymans (1926) find that variations of the CO_2-content of the circulating blood influence the respiratory centre by means of a peripheral reflex mechanism, the afferent impulses from which are conveyed to the centre by the vagus nerves. Heymans, Bouckaert, and Dautrebande (1930 *a*, *b*) find that afferent nerve-endings in the carotid sinus are stimulated directly by lack of oxygen and also by excess of CO_2 in the blood passing through the sinus. They also find in particular that it is changes in the CO_2 rather than changes in hydrogen-ion concentration in the perfusion of blood which has a stimulating effect. Selladurai and Wright (1932) also find that, in the decerebrate cat, stimulation of respiration is wholly reflex and is due to impulses from the carotid sinuses and vagi.

Schmidt (1932 *a*, *b*) repeated the work of Heymans and his colleagues and extended it. He concluded that the carotid sinus reflexes are necessary for the maintenance of normal blood-pressure, but not for the maintenance of normal breathing. He does not consider that the CO_2-tension or pH of arterial blood have any important effect on the nerve-endings in the carotid sinus whereby the breathing is controlled. He thinks, however, that the hyperpnoea of anoxaemia is caused reflexly by stimulation of the nerve-endings in the carotid sinus brought about by want of oxygen in the arterial blood. De Castro (1927–8), as a result of histological investigation of the carotid sinus and carotid body, had previously suggested that the nerve-endings in the sinus might be sensitive to pressure changes and those in the carotid body to chemical changes in the blood.

Gemmill and Reeves (1933) pointed out that the experiments of Heymans and his colleagues and those of Schmidt had all been done

on anaesthetized dogs which were still under the effects of severe operative procedure. They denervated the carotid sinus, or removed the carotid sinus and carotid body, in dogs which had been trained to breathe through respiratory valves and which were allowed to recover completely from the operation. Unlike the authors mentioned above they found that the response of dogs to changes in the CO_2-pressure in the inspired air was unaffected by the operation. They therefore concluded that response to CO_2 is solely dependent on the respiratory centre and not on the carotid sinus at all.

They also tested the response of their dogs to anoxaemia caused by breathing pure nitrogen. Before operation, with the carotid sinus and body intact, the response was great hyperpnoea. After operation the hyperpnoea did not occur at all. Their deduction was that the effect of anoxaemia on the respiratory centre, unaffected by anaesthesia or acute operation, was almost wholly depressor. In marked contrast, however, is the effect of anoxaemia on the carotid nerve-endings which are stimulated and reflexly cause hyperpnoea.

On the whole it seems that the reflex control of the breathing by chemical stimulation of the carotid nerve-endings has not been established, at any rate as regards CO_2. In respect of oxygen it has perhaps hardly been proved that the hyperpnoea of anoxaemia is a carotid reflex effect apart from changes in the circulation.

The response of the breathing to an abnormal resistance was investigated by Davies, Haldane, and Priestley (1919). For recording the depth and frequency of breathing they used the recording 'concertina' described on p. 208 (Fig. 58). As a resistance to the breathing they used sometimes partly-closed taps, the effects of which could be thrown in suddenly by closing alternative inspiratory and expiratory air-passages. In place of these taps they also used sometimes cotton-wool resistances, since with these 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.

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 slower, and after several breaths the breathing settles down to a rhythm in which the respirations are deeper and correspondingly less frequent. With a considerable resis-

tance the frequency is often reduced to a fourth of the normal rate, while the depth is almost correspondingly increased (Fig. 42). 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 owing to the vagus influence. 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 breathing. With excessive resistance the initial slowing and deepening of the breathing is followed by a phase in which the rate increases and the depth diminishes owing to fatigue and anoxaemia. This effect is discussed on p. 138.

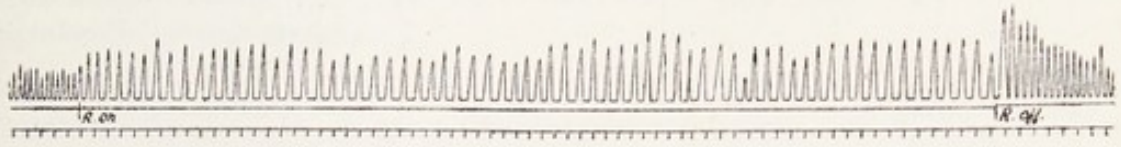


FIG. 42. Effects of resistance. In this and subsequent figures inspiration = upstroke. Time-marker = 10 seconds. To be read from left to right.

When slowing of the breathing is due to resistance the compensation of diminished frequency by increased depth is less perfect than Haldane and Priestley found it to be without resistance. This is due to the extra work of the respiratory muscles and so greater stimulus of the respiratory centre by CO_2. Hence the alveolar CO_2-percentage rises considerably with resistance to breathing. The table on p. 134 shows the rises observed 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 centre, increases the depth of breathing, so a slight diminution in alveolar CO_2-percentage diminishes the depth. It was discovered independently by Liljestrand, Wollin, and Nilsson (1913) in Sweden and by Yandell Henderson (1914) in America 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

Subject	*Alveolar CO_2-percentage*		*Resistance in cm. of H_2O*		Remarks
	Normal	*During resistance*	*Inspiratory*	*Expiratory*	
J. S. H.	5·40	5·34	4½	1½	Slight cotton-wool resistance. Breathing slowed
J. G. P.	5·60	5·80	4½	1½	Same as above
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	,,	,,	Same as above
,,	,,	6·21	,,	,,	,, ,,
,,	,,	6·26	,,	,,	,, ,,
,,	,,	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

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 natural breathing.

These phenomena are completely intelligible on the theory that the limits within which inflation or deflation of the lungs governs 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 centre 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 centre tends indirectly to govern artificial respiration unless the latter is of a specially vigorous kind.

That the centre responds, even during apnoea, with tonic contraction of the diaphragm after 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 centre to the Hering-Breuer stimuli is possibly as much depressed as its excitability to CO_2, in which case the artificial respiration may well become excessive. Experiments by Adrian (1933) indicate, however, that the Hering-Breuer reflex is very little affected by anaesthetics or other influences, such as failure of oxygen, which might have been expected to abolish it.

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 centre 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 centre 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 centre' (p. 9) 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 connexion with any efferent nerves supplying respiratory muscles, discharges of the centre through these nerves continue, as shown by the rhythmical contractions of the muscles, although all the other nervous connexions upwards and downwards have been severed.

It is also now clear that the activity of the centre depends upon the composition of the circulating blood, 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 aerated or less aerated in the lungs.

It has been suspected that although respiratory stimuli depend on the composition of the blood passing to 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 (1888), who severed all the nervous connexions between actively working muscles and the medulla, 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 connexion between the lungs and the centre did not affect the response. Haldane and Lorrain Smith (1893 *a*) 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. The possible initiation of afferent impulses affecting the respiratory centre by changes in the blood passing through the carotid sinus has been mentioned above (p. 131).

No definite anatomical group of nerve cells has been defined at the position occupied by the respiratory centre, and the exact meaning which ought to be attached to the expression 'respiratory centre' is still doubtful. Lumsden (1923) postulated the existence of an apneustic centre, at the level of the striae acusticae, controlling inspiration; an expiratory centre just below this level; a higher centre, in the upper half of the pons, controlling the two former centres, and a more primitive gasping centre at the apex of the calamus scriptorius. Trevan and Boock (1922) also suggest the existence of a primitive respiratory centre in the pons (see also Trevan, 1916). Teregulow (1929) and V. E. Henderson and Sweet (1929), however, do not find evidence of the existence of a respiratory centre other than that in the medulla. The importance of the red nucleus in controlling and co-ordinating muscular contraction is well known and the intimacy of the relations of the medullary respiratory centre with other parts of the central nervous system cannot be doubted, but it seems desirable to exercise great caution in postulating the existence of a variety of definite centres having sharply defined functions and controlling different aspects of the respiratory movements. Still, the central paths for the innervation of inspiratory and expiratory movements must be different, though it is not possible to

state definitely in what sense the centre itself is double. The excitation of the centre by chemical stimuli probably depends more upon the character of the blood supplied to it than on substances generated by its own local metabolism, though Gesell (1929) has attributed preponderating importance to the latter. Thus the temporary diminution of blood-supply in fainting does not produce the same prompt effect on the centre as changes in the arterial blood owing to imperfect aeration in the lungs. In this respect the centre is very well suited to fulfil the function of taking a part in controlling the *quality* of the general arterial blood-supply to the body. The *amount* of arterial blood supplied is controlled in other ways.

Like other parts of the central nervous system, the respiratory centre can easily be fatigued; and, as will be explained later, fatigue of the respiratory centre is of great importance in practical medicine. Fatigue of respiration was studied by Davies, Haldane, and Priestley (1919), 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 centre 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. Fig. 43 is a tracing which shows this change. Fig. 44 shows a similar change produced, not by resistance alone, but by the combined effects of resistance and the increased breathing due to muscular work.

It will be shown later that even a slight deficiency in the oxygenation of the arterial blood greatly favours the development of fatigue symptoms in the respiratory centre. But addition of oxygen to the air does not prevent the development of fatigue due simply to great extra work thrown on the respiratory centre. When the breathing is quite free, and the oxygenation of the blood normal, fatigue does not show itself at all readily, 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

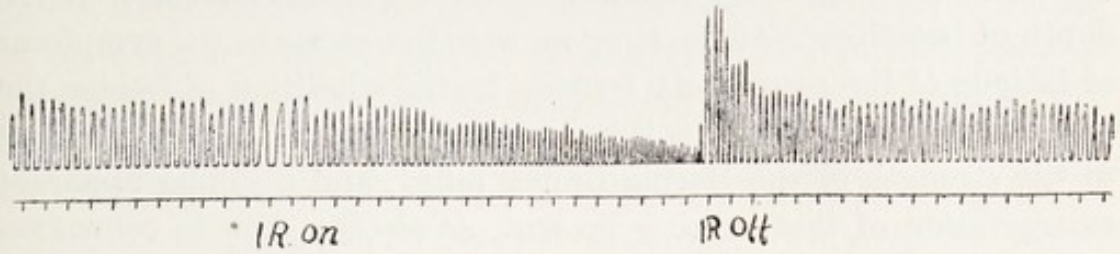


FIG. 43. Effects of heavy resistance. To be read from left to right.

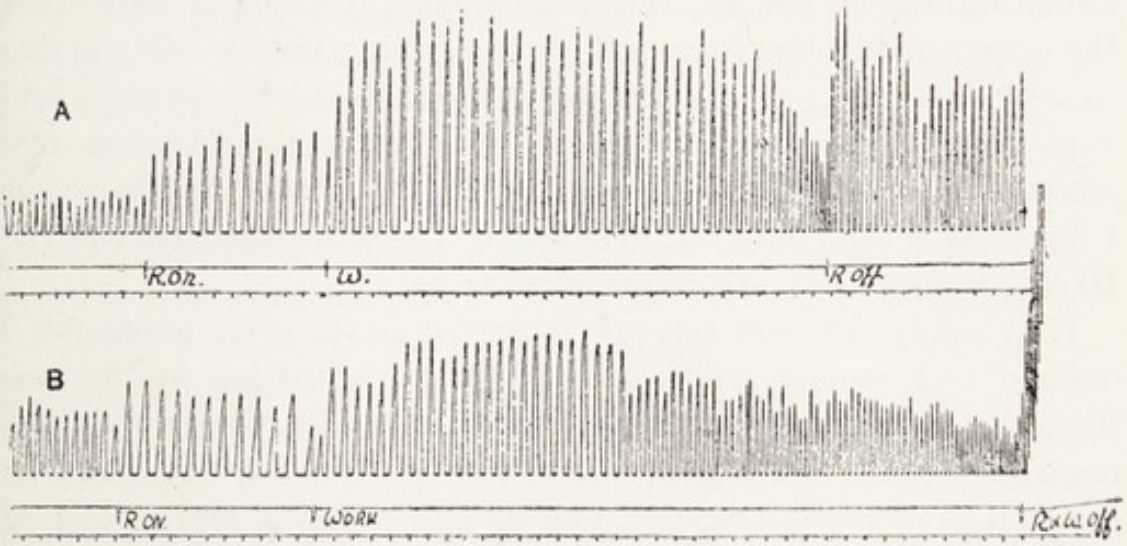


FIG. 44. Effects of resistance and gentle work. To be read from left to right.

exertion was a common and prominent symptom. Their breathing was investigated by Haldane, Meakins, and Priestley (1918–19 *b*) and they found a marked deviation from normality in its regulation. In many of these persons the frequency of breathing was 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 centre, and on extra exertion these patients were liable to lose consciousness with asphyxial symptoms, just as in ordinary over-fatigue of the centre. 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 centre. 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 connexion 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 centre, rather than to any real increase in the inhibitory Hering-Breuer discharges up the vagus nerves. It is thus only the weakness of the centre that enables the Hering-Breuer reflex to gain the upper hand.

If we apply the same general conception to the other exaggerated reflexes and general failure of nervous co-ordination 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 the 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 connexion with various incidents of warfare 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 apparently having been weakened by toxic influences. In the same way ordinary fatigue of the respiratory centre 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 effect of the shallow breathing characteristic of neurasthenia or fatigue of the respiratory centre 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 quite healthy persons a comparatively small resistance suffices to produce shallow breathing and rapid exhaustion of the respiratory centre, though in others 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 connexion 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 centre begins to be excited may be altered by various abnormal conditions which have been discussed in Chapter II and III and will be considered 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 has pointed out, ether in low concentrations, or by massive afferent nervous stimuli (Henderson and Scarborough, 1910). 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 (Collingwood and Buswell, 1907) and the breathing is commonly so much diminished that the arterial blood becomes markedly blue. These facts are of great importance in connexion with the use of anaesthetics. Henderson showed also that morphia affects the chemical more than the nervous afferent threshold of the respiratory centre.

VI

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 when the partial pressure of oxygen in the atmosphere, with which it is in contact, is diminished. At the same time the colour of the haemoglobin changes from bright scarlet to a dark purple. The oxyhaemoglobin, as the dissociable compound with oxygen is called, 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. Haemoglobin is contained in the corpuscles to the extent of about 30 per cent. of their weight. Adair (1923–4) has shown that this great solubility can be accounted for if the haemoglobin is present as a salt of potassium. On liberation from the corpuscles haemoglobin can, generally speaking, be crystallized out from solution with comparative ease by the help of cold and of substances which diminish its solubility. It is, however, very liable to chemical change, so that attempts to purify it are very apt to produce changes in its properties. There is considerable variation in the form of the crystals obtained from the blood of different animals (Reichert and Brown, 1909) and in the ease with which they crystallize out.

The fact that the properties of haemoglobin vary in samples of different origin has been known for a long time. The haemoglobin of birds was, moreover, believed to contain phosphorus, but this has been disproved. None is present in the haemoglobin of birds or mammals (Inoko, 1894; Abderhalden and Medigreceanu, 1909). It is only comparatively recently, however, that deeper insight into the nature or consequences of the differences in structure of different haemoglobins has been obtained. These investigations are discussed later in this chapter in connexion with the question of the differences of chemical behaviour shown by samples of blood of different origins. Meanwhile, it may be pointed out that the haemoglobin molecule always contains iron. Further, 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, of course, in simple physical solution, on saturation with oxygen instead of air. An exactly equal volume of carbon monoxide or nitric oxide is taken up in chemical combination on saturation with either of these gases. It was shown by R. Peters (1912) that haemoglobin, on saturation with oxygen, combines with one molecule of oxygen for each atom of iron present in the haemoglobin. There is in fact no shadow of doubt that the combination is a chemical one. Nevertheless attempts, which ignored well-ascertained facts, were made some years ago to explain the combination of oxygen and CO_2 in blood as being due to adsorption.

Haemoglobin not only enters into dissociable chemical combinations with oxygen, carbon monoxide, and nitric oxide, but also in the 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 (1865) methaemoglobin, which gives off no oxygen on exposure to a vacuum. This substance, which crystallizes in a similar form to oxyhaemoglobin but has a dull brown colour in acid solution and a brownish-red colour in alkaline solution, with a characteristic spectrum in both cases, was thought by Hüfner to take up in its formation from haemoglobin just as much oxygen as oxyhaemoglobin. On the other hand, it oxidizes reducing agents much more rapidly 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 colour and spectrum. But if free oxygen is present the colour and spectrum of oxyhaemoglobin appear, since the ammonium sulphide reacts 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 quite a long time as oxyhaemoglobin.

While investigating the action of poisons which form methaemoglobin in the living body Haldane (1897–8) noticed that when ferricyanide and certain other reagents act on oxyhaemoglobin

to form methaemoglobin fine bubbles are liberated, and on further investigation the gas liberated was found to be oxygen. He then measured accurately the oxygen liberated, and found that the volume of oxygen liberated by ferricyanide immediately before applying the mercurial blood-pump agreed exactly with the volume liberated by the pump alone. 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 c.c. liberated from the haemoglobin of 100 c.c. of blood and measured dry at 0° C and 760 mm.

By blood-pump alone from blood saturated with air	18·18
By ferricyanide and blood-pump from blood saturated with air . .	18·20
By ferricyanide and blood-pump from blood saturated with CO . .	18·07

From their behaviour, it appears that oxyhaemoglobin and CO-haemoglobin are molecular compounds in which the molecules of 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 solution. When haemoglobin is converted into methaemoglobin the new molecule formed has lost the 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 ferricyanides, and can be measured in the gaseous form by a simple method described by Haldane (1900). If it is the fact, as found by Hüfner, that methaemoglobin contains the same proportion of oxygen as oxyhaemoglobin, but with the atoms of oxygen separately combined, the reaction of oxyhaemoglobin with ferricyanide might be supposed to occur in accordance with the equation

$$\mathrm{Hb}\begin{matrix}\diagup\mathrm{O}\\ \quad|\\ \diagdown\mathrm{O}\end{matrix} + 4\mathrm{Na_3Fe(CN)_6} + 4\mathrm{NaHCO_3}$$

$$= \mathrm{O_2} + \mathrm{Hb}\begin{matrix}\diagup\!\!\diagup\mathrm{O}\\ \quad\\ \diagdown\!\!\diagdown\mathrm{O}\end{matrix} + 4\mathrm{Na_4Fe(CN)_6} + 4\mathrm{CO_2} + 2\mathrm{H_2O}.$$

But Roaf and Smart (1923) and Quagliariello (1923) brought forward evidence that methaemoglobin contains only half as much oxygen

as oxyhaemoglobin. In this case the reaction might be expressed by the equation

$$\mathrm{Hb}\begin{matrix}\diagup \mathrm{O} \\ \\ \diagdown \mathrm{O}\end{matrix} + 2\mathrm{Na_3Fe(CN)_6} + 2\mathrm{NaHCO_3} =$$
$$= \mathrm{O_2} + \mathrm{HbO} + 2\mathrm{Na_4Fe(CN)_6} + 2\mathrm{CO_2} + \mathrm{H_2O}.$$

Their deductions from experimental results have, however, been criticized by Conant and Scott (1926), who have shown very clearly that the oxidation of haemoglobin or oxyhaemoglobin to methaemoglobin involves only one hydrogen equivalent of oxygen. The reaction is, indeed, analogous to the oxidation of ferrocyanide to ferricyanide and may be represented by the equation

$$\underset{\text{Oxyhaemoglobin}}{\mathrm{Na_3X(O_2)}} + \mathrm{Na_3Fe(CN)_6} \rightarrow \underset{\text{Methaemoglobin}}{\mathrm{Na_2X}} + \mathrm{Na_4Fe(CN)_6} + \mathrm{O_2}.$$

It appears to be proved, therefore, by the careful work of Conant and Scott that strictly speaking there is no available oxygen as such in methaemoglobin any more than there is in ferricyanide. In any case, however, the volume of oxygen liberated by the action of the ferricyanide is exactly equivalent to that originally present in combination as oxyhaemoglobin.

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. It also had the advantage of avoiding the error caused in blood-pump measurements by gas adsorbed on the surface of the glass. This error becomes of increasing importance as the volume of blood and the capacity of the pump are reduced.

The ferricyanide method, however, introduced another source of error due to the comparatively long time required to complete an analysis, since it has been found that a slow process of oxidation, wrongly attributed by Haldane originally to bacterial action, may go on in mixtures containing blood and ferricyanide. This makes the results of a determination of the oxygen content of blood by the ferricyanide method tend to be too low. Litarczek (1928) showed that the main factor determining this auto-oxidation was the lipoid content of the blood or serum, and that both haemoglobin and ferricyanide can act as catalysts for the oxidation of serum lipoids.

It was found by Woodhouse and Pickworth (1930) that auto-oxidation during a blood-gas analysis by the ferricyanide method could be reduced greatly by buffering the mixture adequately at pH 7·5 by means of a phosphate mixture. Even so the absorption of the oxygen liberated by the ferricyanide is not entirely prevented. The amount of this absorption is variable, doubtless because of the variable amount of lipoids in blood, and may be inappreciable when only 1 or 2 c.c. of blood are used for the analysis. In the ferricyanide method as first introduced 20 c.c. of blood were used, so that the time required for the liberation of all the oxygen was relatively great. This would tend to increase the error due to auto-oxidation. As mentioned on p. 43 Haldane and Barcroft (1902) introduced an improved form of apparatus which permitted an analysis to be carried out on only 1 c.c. of blood, and later Haldane (1919–20) still further increased the delicacy of the method by the use of a form of apparatus in which the oxygen liberated was measured at constant pressure.

Van Slyke (Peters and Van Slyke, 1932) introduced a method in which the oxygen liberated from blood by ferricyanide is at once boiled off by reducing the pressure and is measured either volumetrically or manometrically, the latter method being the more accurate. This method doubtless avoids the error of the simple ferricyanide method due to auto-oxidation, and Van Slyke has shown by measurement of the nitrogen evolved that it does not introduce any appreciable error in consequence of liberation of gas adsorbed on the glass. Van Slyke and Stadie (1921) carried out comparative determinations on five bloods by their volumetric method, using water to lake the blood, and Haldane's method. The differences in the results given by the two methods were somewhat variable (see table on p. 147), but on the average the results by Haldane's method were 1 volume per cent. lower than those given by Van Slyke's method. They attributed this discrepancy to difference in the laking solutions used, since, when they used 1 per cent. Na_2CO_3 solution instead of water to lake the blood in their apparatus they got low results corresponding to those they obtained with the Haldane apparatus using Na_2CO_3. Haldane (1899–1900 *b*) had, however, definitely given up the use of Na_2CO_3 because he found that the blood was apt to be incompletely laked when it was used. He reverted to the use of dilute ammonia and subsequently, as stated in the first edition, added a pinch of saponin to ensure complete laking.

Price-Jones (1931) made careful measurements of the oxygen capacity of twenty different bloods, using in each case both Haldane's method and Van Slyke's. He found that on the average Van Slyke's method gave an oxygen capacity 0·47 per cent. higher than Haldane's method, the differences varying between −0·07 and +0·85. He concluded that the difference is not statistically significant. Simultaneous haemoglobin determinations with a Haldane haemoglobinometer agreed well with the Van Slyke figures for the oxygen capacity.

OXYGEN CAPACITIES OF A SERIES OF BLOODS DETERMINED BY VAN SLYKE AND STADIE'S AND BY HALDANE'S METHOD

No.	*Van Slyke and Stadie's method*	*Haldane's method*	
	vol. per cent. O_2	vol. per cent. O_2	per cent. of capacity by Van Slyke and Stadie's method
1	21·78	19·80	90·9
2	21·84	20·84	95·4
3	19·37	19·62	101·2
4	19·62	18·75	95·6
5	15·29	14·30	93·6
		Average	95·3

One of the first discoveries made with the ferricyanide method was that the colouring power of haemoglobin or any one of its molecular compounds with gases varies exactly as its capacity for combining with the 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 (Haldane and Lorrain Smith, 1899–1900).

That oxygen capacity and depth of colour run parallel also in various anaemias and other pathological conditions was shown by Morawitz and Röhmer (1908). Douglas (1910) showed that even during the rapid regeneration of haemoglobin after considerable loss of blood, this also holds, and Meakins and Davies (1925) have confirmed the observation in a striking manner for the blood of normal individuals and of patients suffering from a variety of diseases. The table on p. 148 is taken from p. 28 of their book.

At the time when the ferricyanide method was introduced there existed several well-known forms of 'haemoglobinometer'. Of these

Disease	*Hb*	*O_2 capacity determined by Haldane's method*	*O_2 capacity cal. from Haemoglobinometer results*
		Per cent.	Per cent.
Normal	104	19·20	19·24
,,	105	19·60	19·42
,,	102	18·84	18·87
,,	102	18·89	18·87
,,	102	18·90	18·87
,,	93	17·16	17·20
,,	94	17·25	17·39
,,	94	17·15	17·20
,,	96	17·73	17·76
,,	93	17·20	17·20
,,	96	18·19	17·76
Normal diluted	61	11·95	11·30
,, ,,	40	7·44	7·40
,, ,,	15	2·64	2·77
Goitre	109	20·07	20·16
,,	113	20·84	20·90
Aur. fibrill.	112	20·78	20·72
,,	78	14·48	14·43
,,	94	17·31	17·39
,,	94	17·31	17·39
,,	98	18·16	18·13
Aortic disease	83	15·43	15·35
Chronic bronchitis	95	17·63	17·58
,, ,,	97	18·08	17·94
Emphysema	110	20·27	20·35
,,	110	20·27	20·35
,,	111	20·51	20·55
,,	108	20·04	19·98
,,	109	20·24	20·16
,,	110	20·40	20·35
Pneumonia	95	17·51	17·57
,,	97	17·83	17·94
,,	79	14·70	14·69
,,	82	15·16	15·17
,,	82	15·12	15·17
Myocarditis	86	15·84	15·91
Asthma	114	21·25	21·09
,,	114	21·26	21·09

the apparatus of the late Sir William Gowers was by far the most convenient. In his method 20 cubic millimetres of blood, obtained from a prick of the skin, are introduced into a small graduated tube and diluted with water until the depth of colour is the same as that of a standard solution of picrocarmine in another similar tube. The depth of colour of the picrocarmine solution is that of average normal human blood diluted to 1/100th; and the graduated tube gives the strength of colour of the blood under examination in terms of this

normal standard. One defect of the method was that the picrocarmine standard was arbitrary, since it was determined from observations on the blood of only one individual. Another was that the colour of the picrocarmine solution is not the same spectrally as that of the blood solution. As a consequence of this both the depth and the quality of the tint 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 colour match for one person is not the same as that for another person, even in the same light. To remedy these defects Haldane (1900–1) substituted for the picrocarmine a 1 per cent. solution of blood of the average oxygen capacity of the blood of adult men (18·5 c.c. of oxygen per 100 c.c. of blood as determined by his original ferricyanide method) and introduced other improvements.

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 colour 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, if hermetically sealed in a tube with adequate precautions, 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 the blood; and the accuracy of any particular instrument can be controlled at once by blood-gas analysis. Certain ever-recurring criticisms of the instrument are based almost entirely on want of acquaintance with the physiological principles of colorimetric methods, or of the chemical facts on which the method is based. Since the introduction of Gowers's method with the improvements outlined above, a large number of different forms of haemoglobinometer have been devised. Few, if any, of these, however, approach the Gowers-Haldane haemoglobinometer with regard to accuracy and convenience combined, and the results given by many of them are grossly inaccurate.

The oxygen capacity of the blood used for making the standard was, however, determined by the original ferricyanide method using 20 c.c. of blood. As was shown above (p. 147) the figure so obtained is possibly slightly too low. Moreover, 100 per cent. on the scale was made to correspond to an oxygen capacity of 18·5 per cent., which was found to be the average for the bloods of 24 males whose ages ranged from 16 to 62. In more recent years, however, a number of observations have been made, chiefly in America, which seem to indicate that the average oxygen capacity of the blood of healthy males is somewhat higher (Peters and Van Slyke, 1931; Price-Jones, 1931). Price-Jones found that the average haemoglobin percentage (Haldane haemoglobinometer) of 100 healthy men in London was 105·42 with a standard deviation of 3·92, while the figures for 100 healthy women were 98·26 and 4·42. He does not, however, state that his haemoglobinometer was calibrated. He made similar observations on 20 healthy medical students and laboratory workers, determining the oxygen capacity of their blood by both Haldane's and Van Slyke's methods and the haemoglobin by means of Haldane's haemoglobinometer. He found the mean oxygen capacity was 20·67 by Van Slyke's method and 20·2 by Haldane's. The average haemoglobinometer reading was 112·25. The reason for the difference between the London and Boston results has not been determined with certainty, but Price-Jones suggests that it may be due to the greater use of motor-cars in America and chronic CO absorption from the exhaust gases.

Unpublished observations by Douglas and Priestley (1934) have shown that readings with the original Haldane haemoglobinometer agree closely with the oxygen capacity as determined by Brodie's blood-gas apparatus and Haldane's constant pressure instrument. Their readings were taken about 6 minutes after spilling the ferricyanide and remained quite steady for a further 4 minutes. There was thus no evidence of appreciable absorption of oxygen.

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. Dreyer, Bazett, and Pierce (1920), for instance, have found that diurnal variations of 10 per cent. in the haemoglobin percentage are common and that 30 per cent. may be reached; but Price-Jones (1931) in 100 observations on his own blood

taken in the mornings and afternoons of successive days found a mean value of 104·9 per cent., with variations between the extreme limits 100 per cent. and 108 per cent. There was no significant difference between the morning and afternoon values. There are also variations associated with age and sex; and pathological variations may be very marked and significant. As regards age and sex Haldane (1900–1) 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 long been known that, when an oxyhaemoglobin solution is overheated or treated with various simple reagents, the oxyhaemoglobin decomposes into a coagulated protein and a deeply coloured, brown substance soluble in alcohol and certain other solvents and known as haematin. Haematin contains 8·7 per cent. of iron, and the coagulated protein is free from iron. The formula $C_{34}H_{34}N_6O_5Fe$ was assigned to haematin. By the action of reducing agents the haematin loses oxygen and the colour of the solution changes to a deep purple, with a corresponding change of spectrum, which was described by Stokes (1864) at the same time as he described the spectra of haemoglobin and oxyhaemoglobin. To this reduced haematin Hoppe Seyler (1871) gave the very suitable name haemochromogen, as he believed it to be the parent substance of the colour of haemoglobin and its varied derivatives. Thus haemoglobin came to be regarded as a compound of haemochromogen with a protein; also haematin came to be regarded as an oxygen compound of haemochromogen, while compounds of haemochromogen with carbon monoxide and nitric oxide were also described.

This conception was confirmed by the fact that the oxygen capacity of haemoglobin varies as its colouring power, and by the discovery of Peters (1912), already referred to, that there is a fixed and simple relationship between the oxygen capacity and iron content of haemoglobin, one molecule of combined oxygen corresponding to one atom of iron. Till the work of Peters it had seemed very doubtful whether there is a fixed and definite relationship between the iron content and oxygen capacity of haemoglobin. Bohr (1909 *a*), indeed, thought that he had obtained evidence of the existence of marked variations in this relation, and further that it actually differed in arterial and

venous blood. The doubts on this subject turned on the reliability of the methods used for determining iron and were dispelled when Peters used a wholly reliable method.

There were other considerations which pointed in the same direction. Examination of the colours and spectra of the various direct derivatives of haemoglobin and haemochromogen revealed a striking general correspondence. Methaemoglobin and haematin have very similar colours and spectra, which differ in a more or less similar manner in acid or alkaline solutions, and give a similar red colour and corresponding spectrum on addition of hydrocyanic acid. With carbon monoxide haemochromogen gives the same colour and spectrum and takes up the same volume of carbon monoxide as haemoglobin. With nitric oxide compounds also there appears to be a correspondence. Thus Haldane (1901) found that the red colour of raw salted meat was due to the presence of NO-haemoglobin, formed by the action on haemoglobin of the reduction product of the nitre which is mixed with the salt; and the colour is still red after the meat is cooked and the NO-haemoglobin broken up to yield a haemochromogen compound. NO-haemoglobin is also found *post mortem* in poisoning by nitrites. Between haemoglobin and haemochromogen there is also more or less of a correspondence; but oxyhaemochromogen, the molecular oxygen compound of haemochromogen, is missing, and it seemed that haematin is so readily formed from haemochromogen in the presence of oxygen that oxyhaemochromogen cannot exist.

All these observations have been made intelligible in consequence of the researches of many workers during recent years on the chemistry of haemoglobin and related compounds. Thus Nencki, Willstätter, H. Fischer, Küster, Papendieck, Schumm, and others have investigated the remarkable group of substances known as porphyrins, and the outcome of their work has been the establishment of the chemical constitution of these bodies, the climax being the synthesis of a porphyrin by Fischer and Klarer (1926). It has been shown definitely that porphyrins are all built up on the basis of four pyrrhol groups linked together with various side chains attached. Consequently there are a number of different porphyrins, some of them occurring in nature, others having been made in the laboratory. These porphyrins are in several ways remarkable substances, and among other properties they have the power of sensitizing the tissues to the action of light (Hausmann, 1911; H. Fischer, 1916; Meyer-Betz,

1913). Porphyrins occasionally occur in the body in abnormal amounts, either in consequence of taking certain drugs or as a congenital abnormality. The consequences are serious, and, in congenital cases, manifest themselves as a condition known as Hydroa aestivale (McCall Anderson, 1898; Garrod and Mackey, 1921–2, 1925–6). The interest of porphyrins, however, from the point of view of respiration arises from other remarkable properties.

It has long been known that, by the action of strong acids, the iron could be removed from oxyhaemoglobin leaving the substance known as haematoporphyrin. Laidlaw (1904) showed that the same porphyrin could be prepared readily from reduced haemoglobin by the action of weak acids, and he found also that porphyrins have the power of combining not only with iron but also with copper or cobalt, and other observers have subsequently prepared a whole series of metalloporphyrins in which the place of iron is taken by other metals such as nickel, tin, silver, sodium, etc. Only three of these compounds, however, are capable of being oxidized and reduced, namely, those containing cobalt, iron, or manganese. R. Hill (1925) showed that metallic derivatives of haematoporphyrin show two-banded spectra which fall into three classes, resembling the spectra of (1) acid haematoporphyrin, (2) oxyhaemoglobin, and (3) haemochromogen.

Teichmann (1853, 1857) described the formation of characteristic crystals when blood was heated with glacial acetic acid and sodium chloride, and this reaction acquired importance as a test for blood. The name haemin was given to the substance of which the crystals are composed, and the work of Willstätter and M. Fischer (1913), H. Fischer and Ziele (1929), and Küster (1925) has shown that it is a compound of a particular porphyrin, namely protoporphyrin, iron and chlorine. Treated with caustic soda it loses chlorine and is converted into alkaline haematin which forms a brown-coloured solution. The spectrum of this solution shows a single indefinite absorption band between the C and D lines. On acidifying the solution a substance known as acid haematin is obtained, which is soluble in ether, the solution having a four-banded spectrum which resembles that of methaemoglobin. It was supposed until a few years ago that, on treating an alkaline solution of haematin with reducing agents, a substance called reduced alkaline haematin was formed, and that this body was identical with Hoppe Seyler's haemochromogen. Bertin-Sans and Moitessier (1893) and Dilling (1910), however,

threw doubt upon the accuracy of this conclusion, and the matter was investigated by Anson and Mirsky (1925), who showed clearly that haemochromogen, a substance showing a very characteristic two-banded spectrum, is not simply reduced alkaline haematin, but is a compound of the base, obtained by acting on haematin with caustic soda and reducing agents, with a nitrogenous substance. Anson and Mirsky named the base so obtained 'haem' and showed that the nitrogenous body combined with it to form haemochromogen might be any one of a number of substances, including proteins (native or denatured), amino acids, amines, ammonia, pyridine, nicotine, etc. There are, therefore, many different compounds which may be called haemochromogen.

The chief reason which led Anson and Mirsky to distinguish between haematin and the base they supposed to combine with globin, etc., to form haemochromogen was that, apparently, the solubility of 'haem' and haematin were markedly different. It was shown by Keilin (1926), however, that this supposed difference in solubility is apparent, not real, and depends upon the presence or absence of a protective colloid. Haemochromogens therefore are compounds of reduced haematin and a nitrogenous substance. The affinity of different nitrogen-containing bodies for haematin varies very greatly, and in this respect one of them, namely globin, far surpasses all the others. It is also a matter of great physiological importance that the haematin-globin compound is far more soluble than haematin itself. The combination with globin therefore makes haematin, with its remarkable properties, available to play a most important part in the physiological processes of the body.

Anson and Mirsky also found that, in a mixture containing haemochromogen and globin, haemoglobin was formed reversibly on suitable adjustment of the reaction. They suggested that haemoglobin was formed by a process of polymerization, and asserted that in all haemoglobins occurring in nature the iron-containing (haematin) fraction of the molecule is identical. R. Hill and Holden (1926), however, showed that haematin and denatured globin react to form haemochromogen, while haematin and undenatured globin form, on suitable adjustment of the hydrogen-ion concentration, methaemoglobin, from which haemoglobin can be prepared by reduction, and so oxyhaemoglobin by subsequent oxygenation. Hill and Holden also found that undenatured globin will react with various metallic

derivatives of haemato-and meso-porpyhrin as well as with the iron derivative of protoporphyrin. They thus showed the existence of haemoglobins which contain the same globin molecules but differ from one another as regards the iron-containing group. The evidence as to differences in the globin part of the molecule and their physiological importance will be referred to below (p. 168).

In view of the work just discussed it may be taken to be definitely established that haemoglobin is chemically a compound of haematin and globin. Elementary analyses (Oppenheimer, 1924) have given the following results for haemoglobin from various species:

C	. .	52·47	to	54·75	per cent.
H	. .	6·83	,,	7·39	,,
N	. .	16·09	,,	17·35	,,
S	. .	0·40	,,	0·86	,,
Fe	. .	0·335	,,	0·59	,,
O	. .	20·12	,,	22·50	,,

The simplest approximate formula, therefore, which can be ascribed to haemoglobin is about $C_{712}H_{1130}N_{214}O_{245}S_2Fe$, which corresponds to a molecular weight of 16,700. Weymouth Reid (1905–6) concluded from measurements of osmotic pressure that the true molecular weight must be a multiple of this—his results indicated that the multiplying factor is 3. More recently careful measurements of the osmotic pressure of haemoglobin solutions have been made by three different methods. Adair (1925*b*) has made direct measurements, taking very careful precautions to exclude sources of error, and has obtained the result that a 1 per cent. solution of haemoglobin has an osmotic pressure of 3·2 mm. Hg or less. This corresponds to a molecular weight of 68,000.

Svedberg (1926) has carried out elaborate measurements of the sedimentation of haemoglobin solutions when rapidly centrifuged. He was thus able to calculate the molecular weight and obtained a result in exact agreement with that of Adair.

Northrop and Anson (1929) measured the rate of diffusion of haemoglobin through disks of sintered glass or alundum and were thus able to calculate the diffusion coefficient and deduce from this, by means of Einstein's equation, the molecular weight. They obtained a value $68{,}500 \pm 1{,}000$.

It seems certain therefore that in the reactions between O_2 and CO with haemoglobin the gases react with a haemoglobin molecule containing four atoms of iron and having a molecular weight of about

70,000. Before entering upon a discussion of these reactions, however, a few further words should be said about the porphyrin complex in the haemoglobin molecule. The great physiological interest of the haemoglobin in the blood depends upon its capacity for reacting reversibly with oxygen, so that it is enabled to take up oxygen in the lungs and carry it to the tissues. Clearly, however, such transport of oxygen could have no physiological value unless there is some means by which the tissues can utilize the oxygen brought to them.

As long ago as 1884 MacMunn described a respiratory pigment, widely distributed through the animal kingdom, which he called 'myohaematin'. He thought that this pigment was independent of haemoglobin. A controversy arose between MacMunn and Hoppe-Seyler, who regarded 'myohaematin' as being haemochromogen derived from haemoglobin. No agreement was reached and 'myohaematin' ceased to arouse any interest. About 1925, however, Keilin was investigating the respiration of parasitic insects and worms, and in the course of this work he confirmed the existence of 'myohaematin' and found that it was of wider distribution and even greater importance than had been supposed by MacMunn. Keilin showed that the pigment occurs not only in a great number of species of animals but also in plants and bacteria and yeasts. He preferred to give it the non-committal name of cytochrome. He found that it had a characteristic spectrum which showed four absorption bands, three of which were narrow and the fourth a good deal wider and fainter and actually consisting of three narrow bands close together. The position of these bands was very constant in different species, but the relative intensity varied quite definitely. Keilin also showed that the pigment can be oxidized and reduced, and that the spectrum disappears on oxidation. Oxidation of cytochrome is inhibited by potassium cyanide (at least partially); reduction is hindered by urethane, etc. (narcotics).

On further investigation Keilin found that the simplest explanation of the spectrum of cytochrome is to suppose that the pigment consists of three haemochromogens each with its distinct two-banded spectrum. This hypothesis is supported by the composite nature of the third faint band of the spectrum and by a considerable amount of collateral evidence.

In a later paper (1928–9) Keilin investigated in further detail the

part played by cytochrome in the processes of oxidation going on in the cell and showed that it acts as a carrier in two types of activating mechanism.

The porphyrin compounds are therefore of the utmost importance in the processes of respiration. Firstly, the haemochromogens—cytochrome—are essential in making oxygen brought to the cell available for the processes of cellular metabolism; secondly, the compound of haematin with native globin—haemoglobin—enables oxygen to be taken up from the air in the lungs and makes possible its transport to the tissues and discharge there, so that cytochrome is reoxidized and is thus able to maintain the cycle of cellular respiration.

We must now inquire into the transport of oxygen by the blood and the part played by haemoglobin in this process. It is important to bear in mind that oxygen is present in two states, namely, in simple solution and in chemical combination as oxyhaemoglobin.

The amount of oxygen present in simple solution in blood varies in accordance with Henry's law of solution of gases in liquids. It depends therefore upon the solubility of oxygen in blood and upon the partial pressure of oxygen in the atmosphere with which the blood is in equilibrium. The solubility of oxygen in blood is, of course, less than its solubility in water, owing to the presence of other substances, and Bohr (1905) found that at body temperature 2·2 c.c. of oxygen (measured at 0° C and 760 mm. Hg) go into simple solution in 100 c.c. of blood when the partial pressure of oxygen is one atmosphere. The solubility of oxygen in blood is, therefore, about 8 per cent. less than its solubility 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 11·5 per cent., or 87 mm. Hg. Hence the amount of free oxygen dissolved in 100 c.c. of a man's arterial blood is only about 0·24 c.c. (measured at 0° C and 760 mm. Hg), while about 18·5 c.c. are present in combination with haemoglobin as was shown above. It is evident, however, that the oxygen in simple solution is of great importance, for it is the immediate source from which the tissues obtain their oxygen-supply and, as already pointed out, Paul Bert found that the physiological action of oxygen or any other gas depends upon its partial pressure. From the standpoint of physical chemistry the 'partial pressure' of a gas in solution is simply the vapour 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, as shown on page 76, the vapour pressure of a substance in solution, or of the solvent itself, varies directly with the diffusion pressure of the substance in solution. It is owing to differences in diffusion pressure that water and substances dissolved in it tend, independently of active 'secretory' pressures, to pass in one direction or another in the living body as as they do outside it.

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 it is an index of the diffusion pressure of the gas; 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. We have just seen that the oxygen dissolved in the blood is the immediate source of supply to the tissues and that its all-important partial pressure is determined initially by the partial pressure of oxygen in the alveolar air. As oxygen is absorbed by the tissues, however, the amount dissolved in the blood would decrease rapidly, as also the partial pressure, unless it were replaced by dissociation of oxyhaemoglobin. Hence it is clear that in order to understand how the oxygen-pressure of the blood is regulated we must know the connexion between dissociation of oxyhaemoglobin in the blood and fall in oxygen-pressure. In other words, we must know the 'dissociation curve', as it is called, of oxyhaemoglobin in the blood.

The history of the growth of knowledge on this subject is somewhat curious. Paul Bert (1878) made some rough determinations with the pump of the amounts of oxygen in dog's 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. Hg, 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 about half its oxygen.

The subject was taken up again by Hüfner (1890), who used a solution of oxyhaemoglobin crystals in decinormal solution of caustic soda. As a result, partly of experiments, and partly of calculation, he obtained a very symmetrical curve, according to which oxyhaemoglobin does not lose half its oxygen till the oxygen-pressure is reduced to 2·6 mm. Hg. 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.

Loewy and Zuntz (1904) published further experiments with defibrinated human blood giving results much nearer to those of Paul Bert, but indicating considerable differences in the dissociation curves of the blood of different individuals.

Bohr (1904) had meanwhile taken up the subject. His results confirmed those of Paul Bert in the main, but were particularly important in that they showed for the first time that the oxygen dissociation curves of blood or haemoglobin solutions have a very peculiar shape, with a double bend (cf. Fig. 45), and that the curve for a haemoglobin solution differs considerably from the curve for blood. This fact led Bohr to conclude that the haemoglobin in blood, which he called 'haemochrome', differs chemically from crystallized haemoglobin. Bohr also found that the dissociation curve is affected by variations in the concentration of the haemoglobin, i.e. the number of grammes of Hb per 100 c.c. of solution.

Bohr, Hasselbalch, and Krogh (1904) then made the important discovery that the oxygen dissociation curve of haemoglobin or 'haemochrome' is greatly influenced by the partial pressure of the CO_2 present (Fig. 45), the CO_2 helping to expel oxygen from its combination. This fact has the important consequence that, as the blood in the body takes up CO_2 in its passage through the capillaries, oxygen is liberated from the oxyhaemoglobin more readily than would otherwise be the case.

The investigation of the dissociation curve of oxyhaemoglobin was then taken up by Barcroft (1914, 1928) and his pupils, and they made a number of important advances with the help of one form or another of the ferricyanide apparatus.

Barcroft and Camis (1909–10) 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 oxyhaemoglobin, and they also confirmed the observations of Bohr,

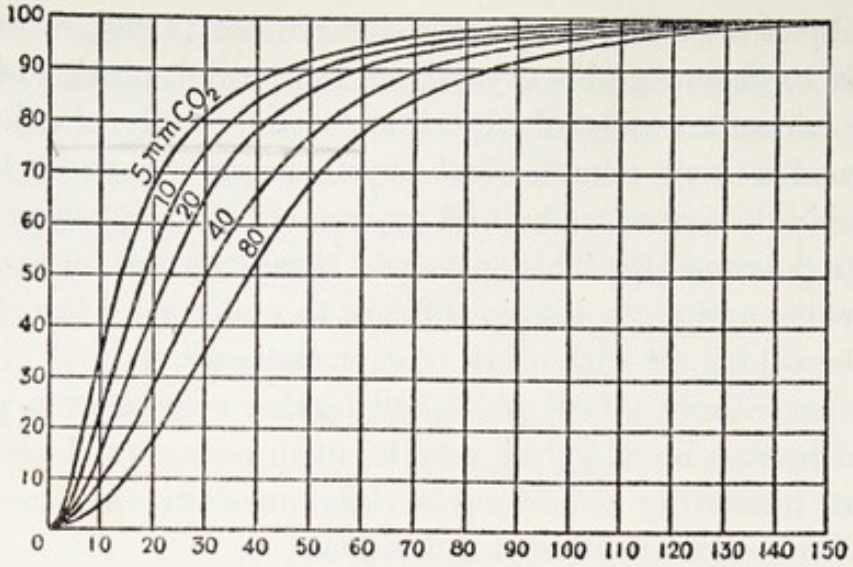


FIG. 45. Curves representing the percentage saturation of haemoglobin with oxygen at different partial pressures of oxygen and CO_2. Dog's blood at 38° C. Ordinates = percentage saturation with oxygen; abscissae = partial pressures of oxygen in millimetres of mercury. (Bohr, Hasselbalch, and Krogh.)

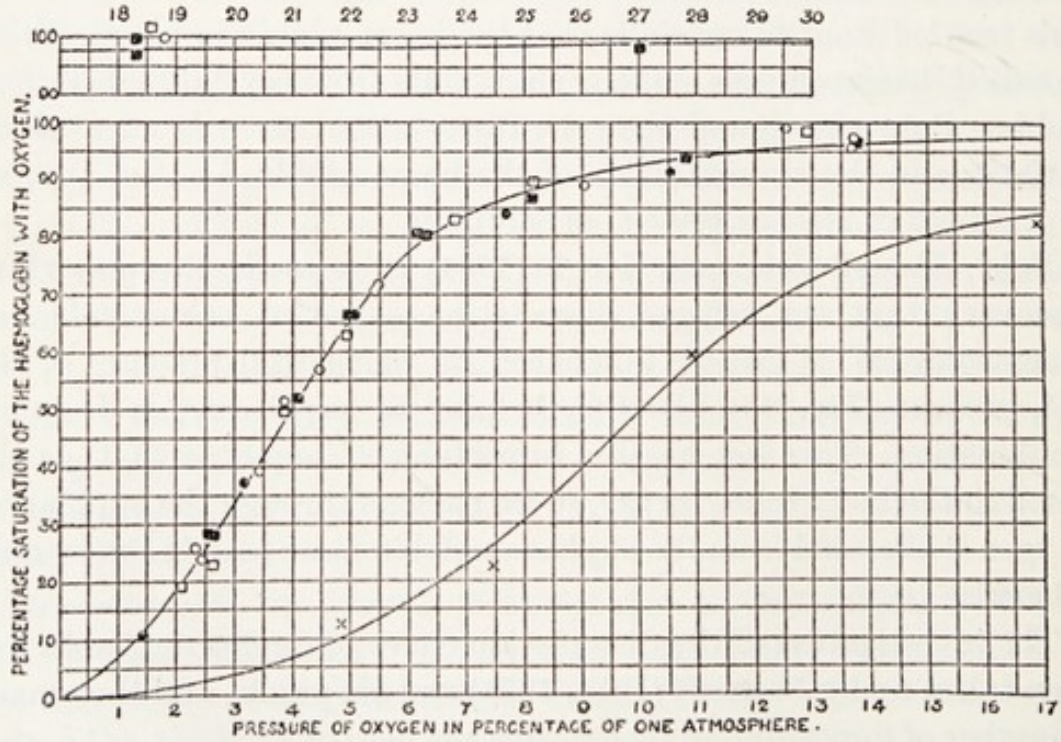


FIG. 46. Dissociation curves of oxyhaemoglobin in presence of 40 mm. pressure of CO_2 at 38° C (1 per cent. of an atmosphere = 7·60 mm. pressure).

○ 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.

Hasselbalch, and Krogh on the effect of CO_2. They did not, however, fully appreciate the effect of hydrogen-ion pressure on the dissociation curve and did not control it in their experiments on the effect of salts. Hence there is some doubt as to how far the changes they observed were due to neutral salts and how far they were due to changes in reaction. When all the salts are removed from a dilute solution of oxyhaemoglobin by dialysis (Barcroft and Roberts, 1909–10) the dissociation curve becomes a rectangular hyperbola, as was the curve found by Hüfner for a solution of oxyhaemoglobin in decinormal caustic soda (p. 159). Barcroft and Camis found that when dialysed dog's haemoglobin was dissolved in a salt solution of the same composition and concentration as in human red corpuscles the dissociation curve 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 (1910–11) (see also Barcroft 1911) 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 alkalis 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 pressure of the blood; and they have used it for this purpose.

Barcroft and Poulton (1913) 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 (p. 164), namely, to alter a simple constant in the equation to the curve, or in other words to change the affinity of haemoglobin for oxygen. Barcroft and Means (1914) showed, however, 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 variation in the hydrogen-ion pressure of whole blood

that the mathematical form of the dissociation curve is sensibly unaltered.

The form of the dissociation curve of the oxyhaemoglobin in human blood at body temperature and with a constant pressure of 40 mm. of CO_2, as in average alveolar air, was worked out by Barcroft, and his results for one individual (Douglas) were approximately confirmed by Douglas and Haldane, working with a different apparatus. Fig. 46 shows the curves given by the bloods of Douglas and Haldane in a very exact series of observations at 38° C., with the individual observations marked. Their curves, as will be seen, are sensibly the same; but Barcroft (1914) has found that the curves of different individuals may vary very distinctly. With the blood of Douglas and Haldane, 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. These experiments were performed at 38° C. as other observers had used this temperature; but at 37° C. the curve shown in fig. 46 would be pushed by about 4 per cent. to the left, so that half-saturation would occur at an oxygen-pressure of 29·2 mm. Hg instead of 30·4. With that of other individuals, and the same pressure (40 mm.) of CO_2, half-saturation may, according to Barcroft, occur as at low an oxygen-pressure as 24 mm.

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 takes 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 pressure of the blood are of essential importance in connexion with the oxygen-supply of the tissues.

Paul Bert (1878) and Hüfner (1889, 1890) showed that the oxygen in chemical combination in whole blood is given off more readily when the temperature of the blood is raised. Barcroft and King (1909–10) later determined the dissociation curves of blood and oxyhaemoglobin solutions at various temperatures. They found that

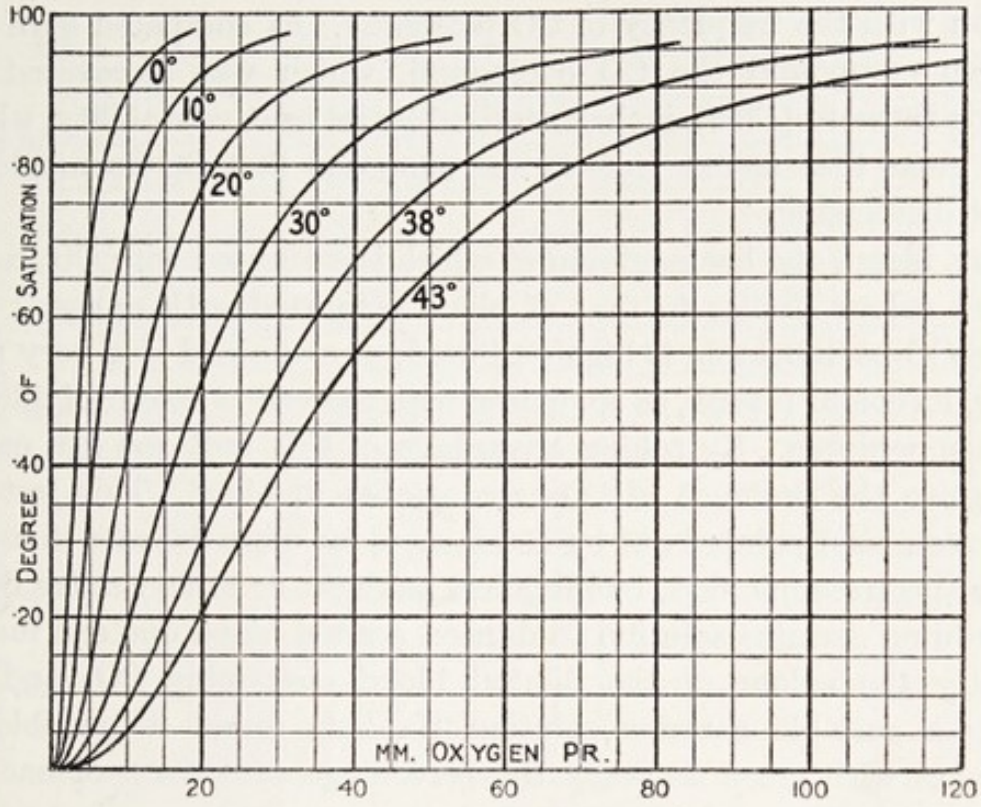


FIG. 47. Calculated oxygen dissociation curves of human blood, at different temperatures, and exposed to a CO_2 concentration which would have given a pressure of 40 mm. Hg at 38° C. Plotted in terms of oxygen-pressures at the actual temperatures involved.

rise of temperature has a great influence on the curve, so that the rate of dissociation of human blood at 41° C. is 1·7 times the rate at 36° C. Brown and A. V. Hill (1922–3) also investigated the effect of temperature, and give curves showing the great change in the dissociation curve of human blood between 0° C. and 43° C.; see Fig. 47. It is to be noted that change of temperature does not alter the character of the curve; it only affects the scale of co-ordinates in one direction. In other words it appears that, if oxyhaemoglobin dissociated in accordance with the simple law of mass action (which in fact it does not), the effects of changes of temperature could be accounted for simply by change in the dissociation constant. We

have seen on p. 161 that a similar effect is produced by changes in the CO_2-pressure of whole blood.

Haemoglobin, as already mentioned, forms specially coloured 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 connexion with the frequency of CO poisoning. As compared with the oxygen compound the CO compound, which was discovered by Claude Bernard (1858), is characterized by its relative stability, which is so great that at one time it was supposed that CO-haemoglobin is not dissociable.

Any blood, the haemoglobin of which is saturated with CO, has a scarlet colour similar to that of blood saturated with oxygen; but if the CO-haemoglobin is highly diluted, or examined in a very thin layer, its colour is pink, as compared with the yellow colour of diluted oxyhaemoglobin. By taking advantage of this fact one can easily recognize the presence of CO-haemoglobin in blood. This test, as has often been pointed out by Haldane, 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 match exactly the colour of the diluted blood containing CO, and by using a suitable carmine solution Haldane found it possible to estimate with great accuracy the percentage saturation of haemoglobin with CO.

With the help of this method Douglas and Haldane worked out the dissociation curve for the CO-haemoglobin of human blood at 38° C.—in the absence, of course, of oxygen, but in the presence of varying partial pressures of CO_2 (Douglas, J. S. Haldane, J. B. S. Haldane, 1912). The results are shown in Fig. 48.

These curves, like the curves for the oxyhaemoglobin of human blood in Fig. 46, are drawn freehand. On comparing them it will be 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 constant. It thus appears that the effect of substituting CO for O_2, and of varying the partial pressure of CO_2 in blood is only to alter a simple constant in the equation to the curve. The observation of Barcroft and Poulton that variations in the partial pressure of CO_2 have the same effect on the dissociation curves of oxyhaemo-

globin and CO-haemoglobin was mentioned on p. 161. In the case of Barcroft's blood it required 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.

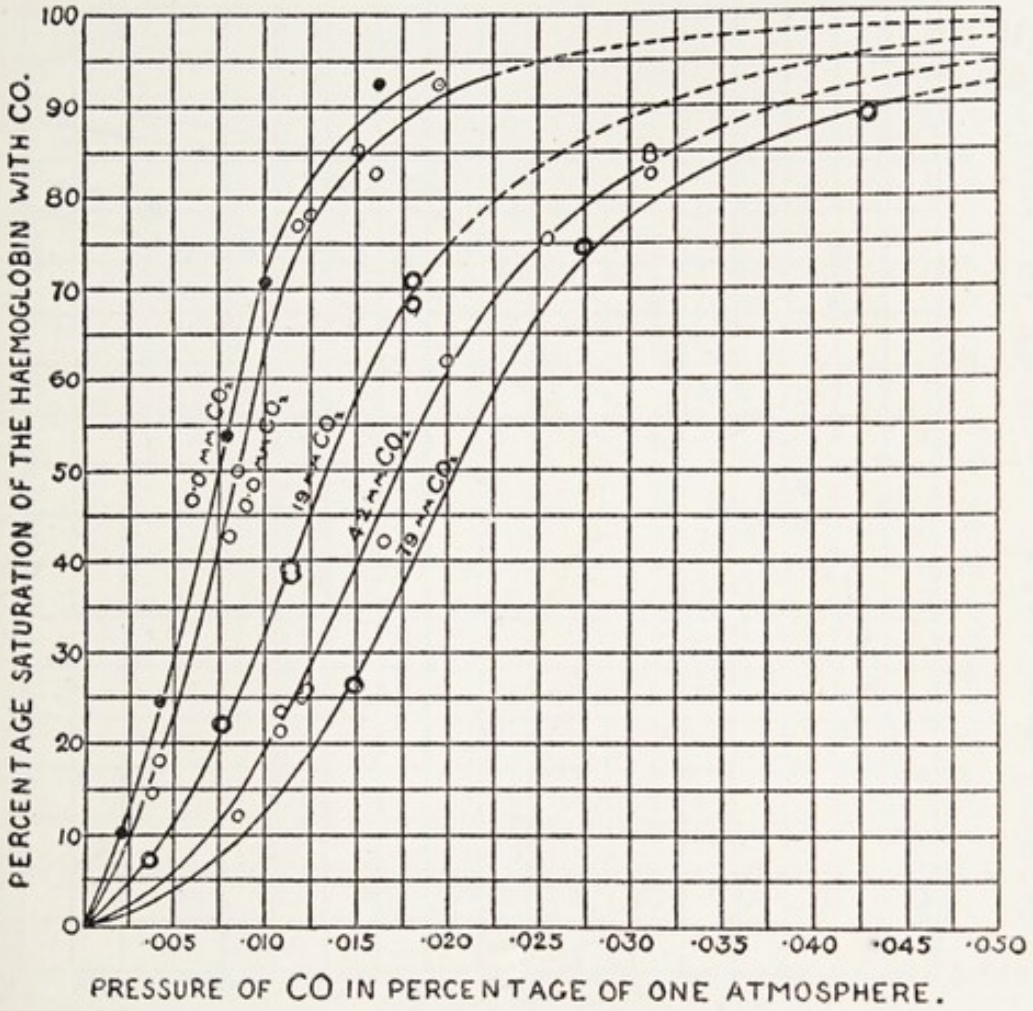


FIG. 48. Dissociation curves of CO-haemoglobin in absence of oxygen at 38° C and with various pressures of CO_2. ○ Blood of C. G. D. ● Blood of J. S. H.

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. Haldane (1895 *b*) found 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. Fig. 49 shows curves obtained by Douglas, Haldane and Haldane (1912) with undiluted blood at body temperature from two persons and two mice.

It will be seen that in each case the curve is a rectangular hyperbola, corresponding to the simple reversible reaction

$$HbO_2 + CO \leftrightharpoons HbCO + O_2.$$

Thus for Haldane's blood the proportions of HbCO to HbO_2 are 1 : 1

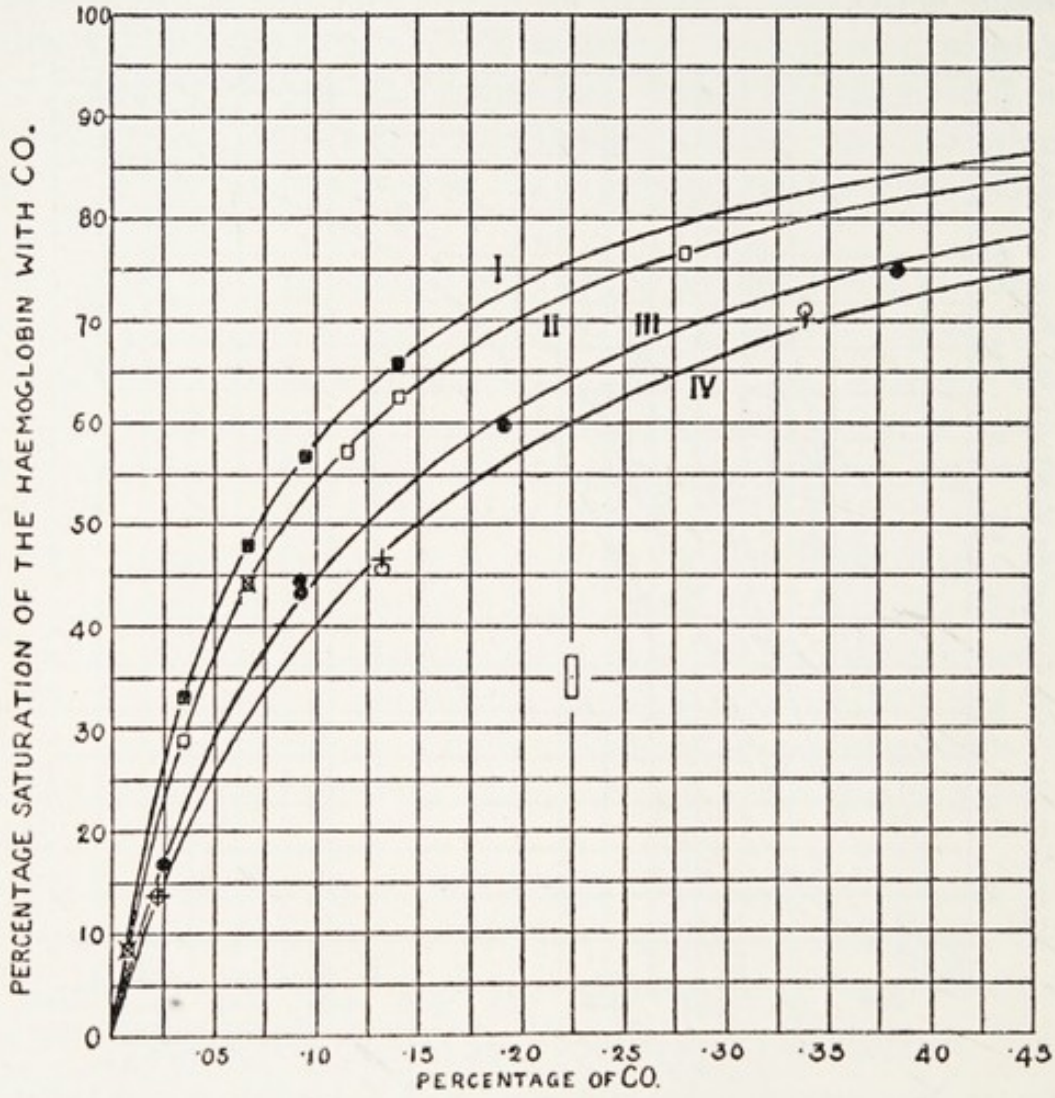


FIG. 49. Dissociation curves of CO-haemoglobin in presence of air (20·9 per cent. O_2) at temperature of 38° C. I. Blood of J. S. H. II. Blood of C. G. D. III. Blood of mouse A. IV. Blood of mouse B. The crosses indicate points determined in the presence of 40 mm. pressure of added CO_2.

with 0·07 per cent. of CO, 2 : 1 with $2 \times 0{\cdot}07$ per cent. of CO, 3 : 1 with $3 \times 0{\cdot}07$ per cent. of CO, etc. For each kind 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.

When the percentage of CO in the air is kept constant and the percentage of oxygen is varied, the curve is again a rectangular hyperbola, provided that the percentage of CO is sufficient to saturate the haemoglobin completely in the absence of O_2. This is shown in the upper curve of Fig. 50. The two dotted curves are

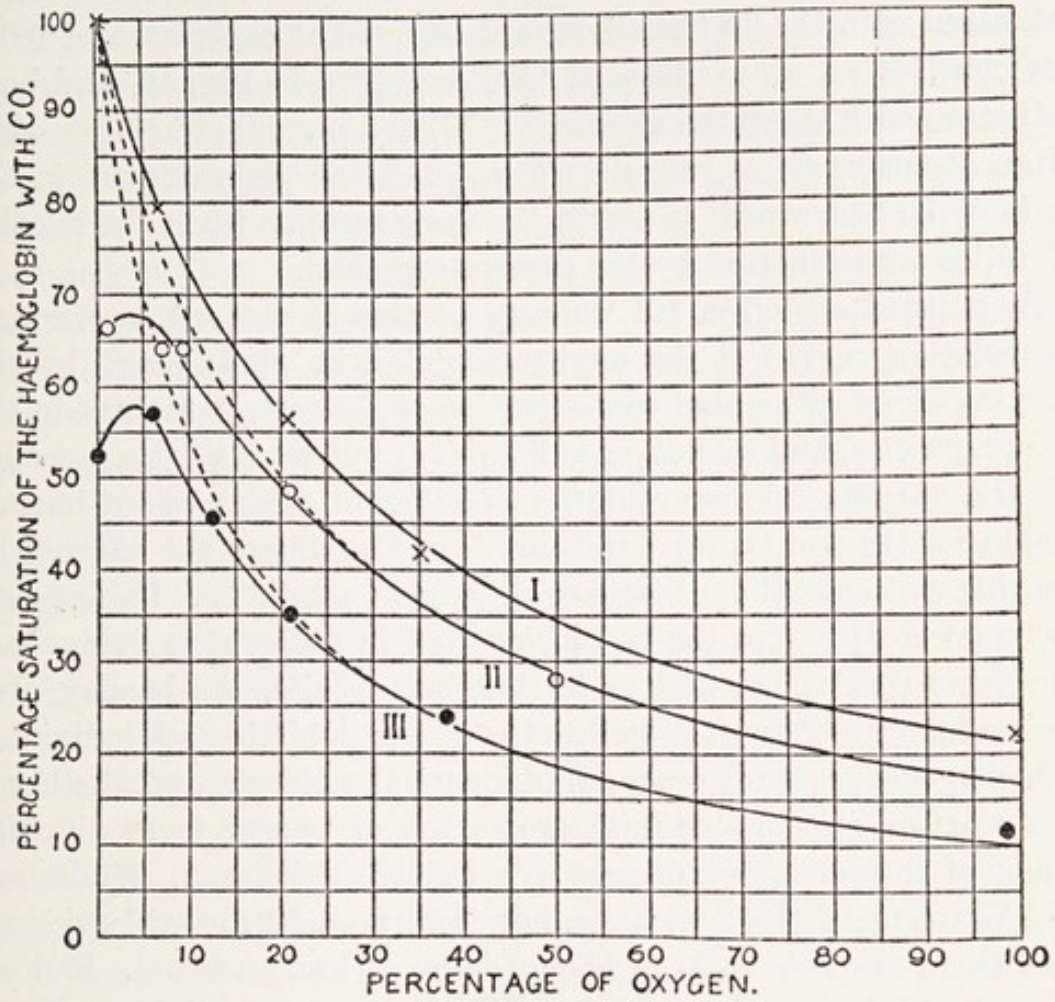


FIG. 50. Dissociation curves of CO-haemoglobin in presence of constant percentage of CO and varying percentage of oxygen, at atmospheric pressure. I. Blood of J. S. H.: CO = 0·0945 per cent. II. Blood of mouse C: CO = 0·090 per cent. III. Blood of mouse D: CO = 0·0635 per cent.

drawn on the same assumption. Actually, however, in these cases the percentage of CO was not enough to cause complete saturation in the absence of O_2.

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 partial pressures, what we have really determined is the relative affinities of the haemoglobin for CO and O_2. In Haldane's blood the haemo-

globin is equally divided between CO and O_2 when the partial pressures of CO and O_2 are as 0·07 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 0·017 per cent. of an atmosphere of CO, as shown in Fig. 48, 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 Fig. 46. 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 pointed out on p. 161 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 Fig. 49 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 homogeneous and is made up of identical molecules, or whether it is a mixture in some definite proportion of two or more different kinds of molecule, we do not yet know. Brinkman, Wildschut, and Wittermans (1933–4) have, however, brought forward evidence that there are two kinds of haemoglobin in human blood. It does, in fact, appear to be fairly certain that each individual has a specific kind of haemoglobin just as he has a specific nose. Whenever the haemoglobins of Douglas and Haldane have been investigated their specific differential characters have appeared to be sensibly the same. It seems pretty certain that, since the ratio of oxygen capacity to both colouring power and amount of iron in haemoglobin is constant, the difference in the haemoglobin molecule in different bloods of one species is due to the protein and not to the haemochromogen fraction of the molecule. The same statement almost certainly applies to the haemoglobins of different species, but the observations of R. Hill and Holden, quoted on p. 155, should be borne in mind. It is not surprising that the globin parts of the haemoglobin molecules

of different individuals of the same species should differ, for Todd (1930–1) has shown that the red corpuscles of chickens of the same clutch can be distinguished from one another by immunological reactions. There are, however, as yet no data to indicate precisely the nature of the differences between the haemoglobins of different individuals.

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 in sufficient pressure to saturate the haemoglobin, it is clear that if 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 solution 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 by some method the percentage saturation of the haemoglobin with CO, and calculate the percentage of CO present (Graham and Haldane, 1934). 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 described on p. 267, 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 Haldane found that when the combined pressure of O_2 and CO is 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 the peculiar hump shown on the lower two curves in Fig. 50 and in greater detail in Fig. 51. 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 phenomenon has also been discussed mathematically by A. V. Hill (1921), and it explains a very anomalous fact noticed by Haldane and Lorrain Smith (1897–8)—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

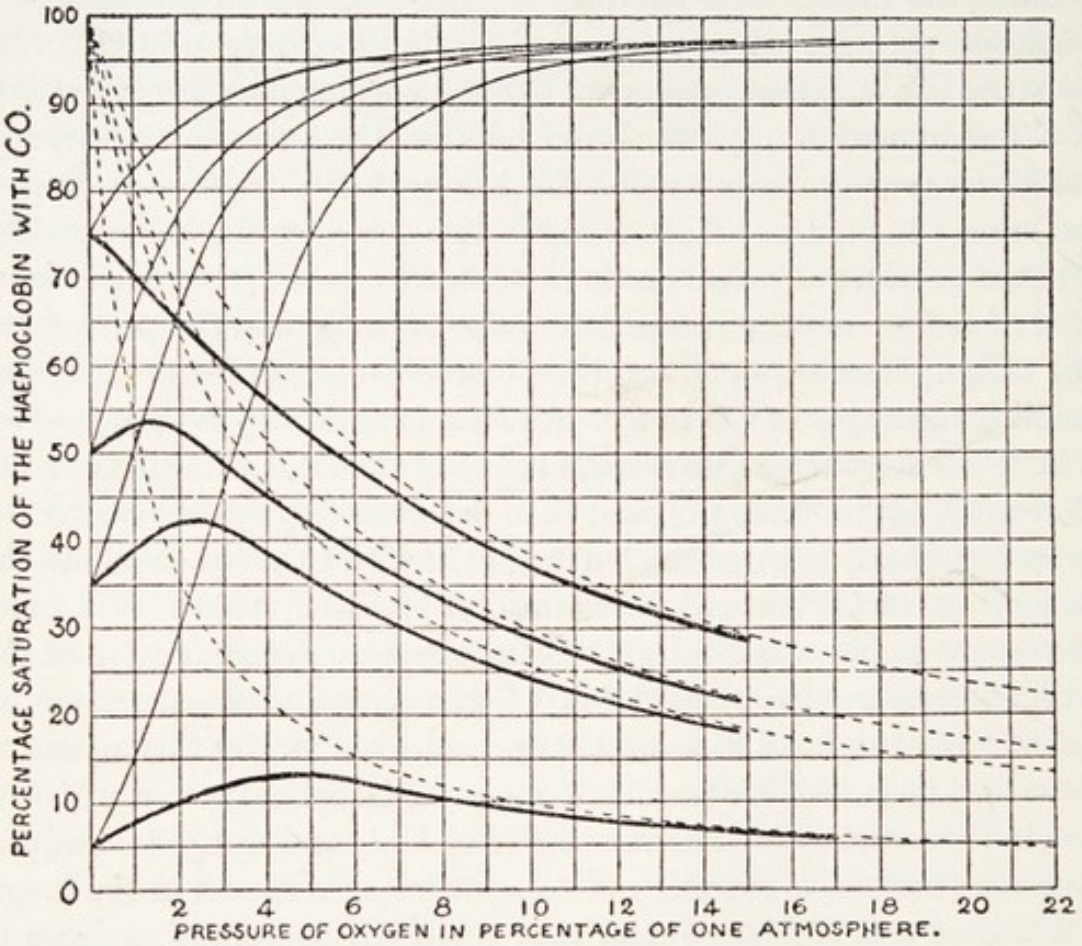


FIG. 51. Calculated dissociation curves of Hb-CO in blood at 38° C and in presence of 40 mm. CO_2 with 4 constant pressures of CO and varying pressures of oxygen.

not make them worse. They 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 Haldane and Lorrain Smith were then quite at a loss to understand why at very low oxygen-pressures the CO seemed to do no harm.

The explanation of the anomalous humps in the curves on Figs. 50 and 51 is easy enough in view of the peculiar double-bended form of the simple dissociation curves of oxyhaemoglobin and CO-haemoglobin in the whole blood. When CO is present at a pressure insufficient to saturate the blood and the 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 Fig. 51. These curves are calculated on the theory that the proportion of oxyhaemoglobin to CO-haemoglobin is exactly what is required in view of the relative known 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 (Fig. 50) show actual observations. There is indeed 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 Fig. 50. The great significance of this in connexion with the explanation of CO poisoning will be referred to later.

It remains to discuss the explanation of the facts outlined above, namely:

(1) The dissociation curve for a dilute dialysed solution of oxyhaemoglobin is a rectangular hyperbola.

(2) In strong solutions or in the presence of salts the curve is modified and assumes a remarkable double inflexion.

(3) The same statements apply to the dissociation curves of CO-haemoglobin.

(4) Change of reaction towards acidity diminishes the affinity of haemoglobin for O_2 or CO, and, in the presence of salts, in such a way as may be explained by change in a simple constant in the equation of the curve; but in the absence of salts in a way which implies also change in the mathematical form of the curve.

(5) Oxygenation of haemoglobin causes increase in the hydrogen-ion pressure of the solution.

(6) Rise of temperature also diminishes the affinity of haemoglobin for O_2 or CO in a way which can be explained by change of a simple constant.

(7) When blood is exposed to a mixture of O_2 and CO and the pressure of either gas is varied while that of the other is kept constant, the dissociation curve is a rectangular hyperbola provided that the pressure of the gas which is kept constant is

sufficient to saturate the haemoglobin completely when the other gas is absent.

(8) When blood is exposed to a mixture of O_2 and CO, the combined pressures being insufficient to saturate the haemoglobin, the dissociation curve for varying pressures of either gas ceases to be a rectangular hyperbola and acquires a remarkable hump.

At the beginning of this century it was generally believed that the dissociation and re-formation of oxyhaemoglobin in blood could be represented by the reaction $Hb + O_2 \rightleftharpoons HbO_2$, with an affinity factor which remained the same before and after the reaction, so that the dissociation curve, when saturation of the haemoglobin with oxygen was plotted against pressure of oxygen, was a rectangular hyperbola as it was definitely represented to be by Hüfner. Thus if we were dealing with an uncomplicated reversible reaction between molecules of Hb and of O_2 we could represent the balance between Hb and HbO_2 molecules by the expression $\frac{[Hb] \times [O_2]}{[HbO_2]} = C$, where [Hb], [$O_2$], and [$HbO_2$] represented the relative numbers of each of those kinds of molecules present, and C was a constant.

It would, or at least it need, make no difference if there were aggregation, so that molecules of Hb_2O_4, Hb_3O_6, Hb_2, and Hb_3 were present, if we also had Hb_2O_2, Hb_3O_2, Hb_3O_4. For we could regard the combinations and the dissociations by heat as occurring at the relatively small part of each molecule concerned with taking up of oxygen. These parts could behave in the same way whether the far greater globin part of each molecule was united to the globin of another molecule or not. We know that crystals which have been formed as oxyhaemoglobin retain their crystalline form although they have ceased to behave towards oxygen or in their spectrum as oxyhaemoglobin, so that aggregation in the crystalline form has no close relation with the state of the part of the molecule which combines with oxygen.

Thus we should be justified in treating, so far as dissociation of the oxygen is concerned, a solution of oxyhaemoglobin or reduced haemoglobin as if it contained only molecules of Hb and HbO_2 in solution, whether or not these molecules were actually aggregated together. In other words, we could disregard the aggregation, or the real molecular weight of the haemoglobin molecules.

The discovery by Bohr in 1904 (p. 159), that the actual dissociation curve, whether for blood or for a solution of oxyhaemoglobin crystals in distilled water, is very far from being a rectangular hyperbola, proved that the dissociation cannot be a simple monomolecular reaction proceeding according to the law of mass action.

Bohr's own attempt to explain the shape of his curve was based (p. 159) on the supposition that when oxyhaemoglobin splits off its oxygen it also dissociates further, forming what he called, not reduced haemoglobin, but reduced 'haemochrome', and globin. He assumed that 2 molecules of oxygen for 1 of haemochrome are concerned in its reduction, thus altering the dissociation curve in the direction found by experiment. No other evidence than the peculiar shape of the curve, has, however, appeared in support of Bohr's haemochrome theory, so that it never became generally accepted.

A further attempt to explain the curve was made by A. V. Hill (1910) on the basis that the simple rectangular hyperbola, which would be given by the reaction $Hb+O_2 \rightleftharpoons HbO_2$, is altered by combination of the molecules to form aggregates represented by Hb_2O_4, Hb_3O_6, and Hb_2, Hb_3, Hb_4, etc., but not intermediate molecules such as Hb_2O_2, etc. (Cf. Adair, 1925 *b*.) Hill devised an equation based on the theoretical influence of this kind of aggregation and giving approximately most of the experimental curve. This curve, however, shows an acute bend at the bottom, which was not found in the experimental curves published from Copenhagen, Oxford, or Boston.

The principle involved in Hill's theory was accepted by Douglas, Haldane, and Haldane (1912) as no other theory presented itself at the time. In order, however, to bring the equation into better agreement with the experimental curve as they had found it, they modified the theory in such a way that it assumed greater aggregation of reduced haemoglobin than of oxyhaemoglobin. This was certainly a very improbable assumption, as they felt; but they could see no other way to explain the curve.

Hill's explanation starts from what was formerly the very natural assumption that a molecule of fully oxygenated haemoglobin, not aggregated, is HbO_2. In view of Adair's experiments, however, we seem to be driven to the conclusion that the unaggregated molecule is HbO_8, in which case Hill's theory, or any modification of it, becomes meaningless. In any case Hill's assumption that when haemoglobin

molecules aggregate together they do not each combine with oxygen just as they would without aggregation seems very improbable. There seems to be no reason to believe that in the event of aggregation we could not, for instance, have aggregated molecules represented by Hb_2O_2, as well as Hb_2O_4, and Hb_2. Moreover Hill's equation, as stated, does not give the whole curve correctly; and the theory leaves unexplained the effect of varying hydrogen-ion pressure and the effect of deoxygenation on the dissociation curve of bicarbonate. We must, it seems, abandon Hill's explanation, and assume that the molecule HbO_8 parts with its oxygen molecule by molecule, in which case, as we shall see immediately, when anything acting as base is either almost absent or present in great excess the dissociation curve may be practically a rectangular hyperbola.

It was pointed out in Chapter III that the dissociation of CO_2 from blood equilibrated with diminishing pressures of CO_2, is affected, as found by Christiansen, Douglas, and Haldane (1914), by the degree of oxygenation of the haemoglobin; also that Parsons (1919–20) showed that the curves determined experimentally by Christiansen, Douglas, and Haldane for both oxygenated and reduced blood correspond to the theoretical hyperbolas which would result if a single protein were competing with carbonic acid for the available base. In the body, however, the affinity of haemoglobin for base is diminished in proportion as the blood is reduced, so that the actual curve of bicarbonate dissociation passes from the hyperbola for oxygenated blood to the hyperbola for reduced blood, and thus comes to describe what appears to be practically a straight line.

Now, as shown on p. 161, it was first established by Barcroft and Roberts that, when a dilute solution of oxyhaemoglobin is thoroughly dialysed, its dissociation curve is a rectangular hyperbola. Thus, in the absence of anything which can act as base, the oxyhaemoglobin dissociates in accordance with the reaction $Hb + O_2 \rightleftharpoons HbO_2$, with a constant affinity between oxygen and haemoglobin.

If we assume that when an oxyhaemoglobin molecule loses its oxygen its affinity for base is diminished, while at the same time, if it loses base its affinity for oxygen is diminished, we can explain the actual dissociation curves of haemoglobin solutions for both oxygen and CO_2. When, as in a dialysed solution, there is no base to lose, the affinity of haemoglobin for oxygen cannot change, so that the dissociation curve is, or may be, a rectangular hyperbola as found by

Barcroft and Roberts. When, on the other hand, base is present in great excess, as in Hüfner's experiments, the haemoglobin does not lose base when reduced, and again its affinity for oxygen remains unaltered. Hence, in this case also, the dissociation curve, as Hüfner found, is a rectangular hyperbola.

When base is present, in not too great excess, the mean affinity of the haemoglobin molecule for oxygen must, however, diminish in proportion as the haemoglobin is reduced, and therefore loses base. As a consequence the curve, if we trace it downwards, bends farther and farther away from the rectangular hyperbola which would result if the affinity for oxygen remained the same as for fully oxygenated blood, and comes nearer and nearer the rectangular hyperbola which would result if the affinity for oxygen remained the same as with completely reduced blood. At the very top and the very bottom the curve is thus practically a rectangular hyperbola, the hyperbola at the top having, however, its vertical asymptote much closer to the zero point than the hyperbola at the bottom. The bending away from the first hyperbola, or towards the second hyperbola, would, if we were dealing simply with dissociation of HbO_2, reach its maximum rate at half-saturation, thus tending to produce a symmetrical curve more or less similar to that first shown clearly in the papers of Bohr, and Bohr, Hasselbalch, and Krogh.

It will be seen at once that the same theory explains the effect of diminishing oxygenation on the dissociation of bicarbonate in blood. This effect, as was shown and figured by Christiansen, Douglas, and Haldane, can be represented by at any rate something near to a straight line within physiological limits, with a slope much steeper than would be the case if the affinity of haemoglobin for base remained constant during the dissociation. Owing to the affinity of haemoglobin for base diminishing in proportion as the blood is reduced, the actual curve of bicarbonate dissociation passes from the curve of the hyperbola for oxygenated blood to the hyperbola for reduced blood, and thus comes to describe what would seem to be practically a straight line. We can say that reduced haemoglobin acts less as an acid in blood than oxyhaemoglobin, as is implied in saying that its affinity for base is less strong.

The theory also explains at once the fact that, as the pressure of CO_2 increases, the doubly bent oxygen dissociation curve becomes more and more open, as shown by Bohr, Hasselbalch, and Krogh

and by Douglas, Haldane, and Haldane for the CO dissociation curve (p. 164). With increase in the pressure of CO_2 or, as Barcroft and Orbeli (p. 161) have shown, with addition of acid to the blood or reduction of its available alkali, the availability of alkali for combination will diminish, so that both haemoglobin and oxyhaemoglobin will have less alkali and the dissociation curve as ordinarily represented will open out and move to the right, though still possessing its characteristic doubly bent form. The influence of carbonic and other acids added to the blood will, moreover, depend on the change in hydrogen-ion pressure which they produce, as shown experimentally by Barcroft and Murray (1923).

We can also explain why, when both oxygen and CO are present at such a combined pressure as to be capable of saturating the haemoglobin completely, the dissociation curve for either CO or oxygen respectively, with the oxygen or CO-pressure constant, is a rectangular hyperbola, uninfluenced by change in reaction, as was finally shown accurately and completely by Douglas, Haldane, and Haldane (1912). In this case the affinities of both oxygen and CO for haemoglobin are constant, since no alkali is lost by the saturated haemoglobin, so that nothing but a rectangular hyperbola can result from it, in accordance with the equation

$$\frac{[HbCO]\times[O_2]}{[HbO_2]\times[CO]} = C \text{ (a constant)},$$

when $[HbCO]+[HbO_2]$ remains the same. When the combined pressures become insufficient to saturate the haemoglobin the curve ceases to be a rectangular hyperbola, and finally begins to show the characteristic hump figured by Douglas, Haldane, and Haldane, on one side of which the presence of CO actually helps saturation with oxygen or vice versa. The theory renders these phenomena easily intelligible.

With some of the known facts, the theory, as stated simply above, is not yet in agreement; and it does not give at all satisfactorily the lower part of the actual dissociation curve of oxyhaemoglobin in blood. In the first place it seems to be definitely established by the investigations of Adair (p. 155) on the osmotic pressures given by dialysed solutions of oxyhaemoglobin and reduced haemoglobin that the molecular weight of haemoglobin is four times that which it would be if only one molecule of oxygen or one atom of iron were

present in a molecule of oxyhaemoglobin. Oxyhaemoglobin is therefore HbO_8, and not HbO_2. When, therefore, a solution of dialysed oxyhaemoglobin shows a rectangular hyperbola as its dissociation curve, it must dissociate in the successive stages $HbO_8 - O_2 = HbO_6$; $HbO_6 - O_2 = HbO_4$; $HbO_4 - O_2 = HbO_2$; and $HbO_2 - O_2 = Hb$. In the absence of base the result will be a rectangular hyperbola according to the theory; but this would not be the case if the dissociation were not in the successive stages represented.

In the second place we have to account for the fact that with strong solutions of dialysed haemoglobin the dissociation curve is no longer a rectangular hyperbola, but begins to show signs of the double inflexion. It seems to us that this is most naturally explained by the assumption that since haemoglobin itself can act as a feeble base, and not merely as a feeble acid, it unites to an appreciable extent with itself in strong solutions, the compound thus formed having a similar effect on the affinity for oxygen as a compound with an ordinary base. The presence of this compound does not, however, affect the osmotic pressure, which, according to Adair's results, increases steadily with concentration. This raises an interesting question connected with unstable union of enormous molecules such as those of haemoglobin with a molecular weight of about 70,000. When two such molecules become attached to one another at one point, such as the iron-containing part of the molecule, they will still, presumably, continue to perform vibratory movements as wholes independently of one another; and as osmotic pressure depends upon movements of molecules as wholes we should hardly expect it to be appreciably diminished by the attachment of a proportion of them in this way.

Since we have to deal with the series of compounds HbO_8, HbO_6, HbO_4, HbO_2, and Hb, the further question arises whether at each stage of this dissociation the affinity of haemoglobin for oxygen and for base is equally diminished. The answer to this question is furnished by an analysis of the dissociation curve. The dissociation curves obtained with different methods with blood, by Bohr and his pupils for oxyhaemoglobin, by Douglas, Haldane, and Haldane for CO-haemoglobin and oxyhaemoglobin, and by Bock, Field, and Adair (1924) for oxyhaemoglobin, are all practically identical in shape when the relative values of the abscissae are allowed for; so we may provisionally assume that this general shape is correct.

If, now, it were the case that in each step of the dissociation of oxygen from the HbO_8 of arterial blood the affinity of oxygen for the remainder of the molecule was equally diminished, we could from the theory calculate the whole of the curve if we knew two experimentally determined points sufficiently separated from one another. When, however, we calculate the curve on this assumption, it is found that at one part or another the calculated curve diverges very distinctly from the experimentally ascertained curve. If, for instance, we calculate from the experimentally ascertained values at 90 per cent. and 50 per cent. saturation, the bottom of the curve is too much straightened out, so that at, for instance, 10 per cent., or 20 per cent. saturation the calculated oxygen-pressure is very considerably too low, although above 50 per cent. saturation there is close agreement between calculated and observed points. Thus we are driven to the conclusion that as oxygen molecules are successively split off from haemoglobin the effect (in the presence of base) of each successive loss of an oxygen molecule on the affinity of oxygen for haemoglobin becomes increasingly great. Hence we cannot calculate the whole curve by any simple formula, though we can calculate satisfactorily the prolongation of the upper part of the curve, at over 95 per cent. saturation, where experimental determination becomes uncertain.

From the same considerations it would seem also that the dissociation curve of bicarbonate in the living body is not in reality the almost straight line figured by Christiansen, Douglas, and Haldane, but a distinctly curved line, bending more and more upwards, not downwards, as is often represented in an exaggerated form. The only intermediate determination which they made supports this conclusion, but further data are not yet available.

Assuming the validity of the theory put forward above, the dissociation curve of the oxyhaemoglobin in blood is of great interest to physical chemists owing to the fact that though the reaction can be expressed at all stages by an equation representing the combination of haemoglobin or partly oxygenated haemoglobin with a single molecule of oxygen, the affinity factor is not constant, but is altered at each stage in the percentage dissociation as an indirect consequence of the dissociation. This indirect consequence is presumably due to the properties of the iron-containing part of the molecule.

Apart from the influence of different salts or different reactions, the haemoglobin, not only of different species, but also of different

individuals of the same species, varies considerably as regards its relative affinities for oxygen and CO, as was definitely shown by Douglas, Haldane, and Haldane (1912). This variability must be attributed to differences in the make-up of the globin part of the molecule; and if the globin make-up influences the affinity of haemoglobin for CO, it must also influence its affinity for oxygen. Many further data bearing on this point are brought together by Barcroft (1928) in the second edition (Part II) of his book on *The Respiratory Function of the Blood*. Macela and Seliskar (1925) have, for instance, working under his direction, shown that with a temperature as much as 20° C. lower the dissociation curve of oxyhaemoglobin in frog's blood is practically the same as in human blood at 37° C., whereas human blood at the same lowered temperature would give an entirely different curve. Differences in the globin part of the molecule seem to be mainly responsible for what appear to be the great differences in affinity of oxygen for haemoglobin in different animals.

On the theory which has been stated the specific characters in the reactions of haemoglobin towards oxygen and bicarbonate depend upon two separate peculiarities of haemoglobin. In the first place, the affinity of haemoglobin for base diminishes when the haemoglobin is reduced, and in the second place, the affinity of haemoglobin for oxygen diminishes as base is removed from the molecule. The coincidence of these two properties depends on the specific properties of the iron-containing part of the molecule. We can imagine the existence of one of these peculiarities without the other. Thus we can imagine the affinity for oxygen diminishing with removal of base without the affinity for base diminishing with removal of oxygen, or vice versa.

The peculiar and extraordinarily characteristic chemical properties of haemoglobin have evidently been seized upon and developed in the course of natural selection in consequence of the very great physiological advantages resulting from them as regards transport of oxygen and CO_2 between primitive gills or lungs and tissues, and the possibilities thus opened out for large-sized and at the same time extremely active animals. We can sum up these advantages by saying that with a comparatively low pressure of oxygen and high pressure of CO_2 in the lungs, so that moderate lung-ventilation suffices, a satisfactorily high pressure of oxygen, low pressure of CO_2, and even hydrogen-ion pressure over the whole body, can be maintained in the tissues without excessive circulatory effort.

In order to realize this we have only to consider the effort in breathing or circulation which would be required if the affinity of haemoglobin for oxygen and alkali, or the affinity for either of them, remained constant during the dissociation of oxyhaemoglobin. We can hardly imagine that, if the affinity of haemoglobin for oxygen remained constant during the dissociation of oxyhaemoglobin, a satisfactory supply of oxygen, and at sufficient pressure, would still be available for the tissues. Even if it were, the removal of CO_2 and regulation of hydrogen-ion pressure would be quite unsatisfactory. The pressure of CO_2 in the tissues would have to mount very high, varying also greatly in different tissues, together with the hydrogen-ion pressure; and if the rate of circulation or breathing were so increased as to remedy this state of matters, the energy expended in circulation or breathing would be altogether excessive except with very restricted metabolism. Supply of oxygen and removal of CO_2 are linked together physiologically, and it is useless to think of them as if this were not the case.

Fuller understanding of the physiology of the carriage of oxygen and CO_2 by the blood cannot be attained without knowledge of the co-ordination of circulation and lung ventilation. Discussion of this matter must, however, be postponed to Chapter XII.

VII

THE EFFECTS OF WANT OF OXYGEN

IN the higher organisms, as Paul Bert (1878) first pointed out, the immediate cause of death of the body as a whole is practically always want of oxygen, due to failure of either the circulation or the breathing. This fact arises from the circumstance that the body has hardly any internal storage capacity for oxygen, but depends from moment to moment on its supply from the air. We can deprive the body for long periods of its external supplies of food or even of water, or we can prevent for some days the excretion of urinary products, without causing death. We can even obstruct the removal of CO_2 for some time, 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 oxygen at sufficient pressure in the body is in the lungs. In virtue of this small store—about 400 c.c. of oxygen—breathing can be prevented for about $1\frac{1}{4}$ minutes in a man at rest, and previously breathing normally, before urgent symptoms of oxygen-want appear. The factors which determine the ability of a man to hold his breath voluntarily are partly psychological, partly physiological. The latter again include anoxaemia and accumulation of CO_2. Some experiments by Schneider (1930) illustrate their effect and the results of varying the store of oxygen in the lungs. The results of his observations on twenty subjects were as follows:

After a moderate inspiration the breath could be held for 30 to 105 seconds.
After a very deep inspiration the breath could be held for 45 to 123 seconds.
After forced breathing for 2 minutes the breath could be held for 65 to 260 seconds.
After 3 deep breaths of pure oxygen the breath could be held for 130 to 340 seconds.
After forced breathing and 3 deep breaths of O_2 the breath could be held for 210 to 842 seconds.

On one occasion another man held his breath for 913 seconds (15 min. 13 sec.) after forced breathing and inhalation of oxygen. Vernon (1909) found that after forced breathing with oxygen he could hold his breath for as long as 8 min. 13 sec. It is clear from these figures that ability to hold the breath voluntarily is very largely dependent upon the store of oxygen in the body.

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. Haldane and Lorrain Smith (1893 *a*) found that even with quiet breathing of pure hydrogen, so that some time was needed to wash out the lungs, complete loss of consciousness was produced within 50 seconds without the least warning. Even when the oxygen-supply, though not entirely cut off, is insufficiently free, the ill effects develop rapidly and may very soon become serious. Moreover, after restoration of the oxygen-supply, it may be a long time, if ever, before recovery is complete. Hence few things are of more importance in practical medicine than the causes and effects of want of oxygen.

Want of oxygen in the tissues supplied by the systemic circulation may be produced either by deficiency in the available oxygen in the arterial blood, or by abnormal slowing of the circulation, with the result that so much of the available oxygen is used up that the oxygen-pressure in the systemic capillaries falls unduly low and the supply to the tissues is therefore hampered.

The tissues may also be deprived of oxygen in consequence of circumstances affecting the dissociation of oxyhaemoglobin, even though the arterial blood reaching them is saturated to a normal extent. Defective charge of oxygen in the blood is, therefore, not identical with defective supply of oxygen to the tissues, though unfortunately the two conditions are often not clearly distinguished from one another.

It will be convenient to consider first the effects of want of oxygen and to discuss afterwards in Chapter VIII the various ways in which it may be produced.

The effects of causing an oxygen deficiency in the tissues 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 (Fig. 46).

The effects in the two cases are not, however, identical and, for the reason which is explained in Chapter X, a given reduction in partial pressure of oxygen is less effective in causing anoxaemia if

resulting from diminution of total barometric pressure than if it was brought about by lowering of the percentage of oxygen in the air breathed at normal atmospheric pressure.

The effects of oxygen deficiency on the breathing have already been touched upon in Chapter II but must now be discussed more 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 upon the breathing is produced at the time; and this effect differs according as the reduction is brought about 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 the breathing. In the course of several minutes, however, the increase diminishes markedly. This phenomenon and the causes of it were described and investigated by Haldane and Poulton (1908). They 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. The initial considerable washing out of CO_2 had, however, the effect of diminishing the stimulus to the respiratory centre so that after a short time the extra lung ventilation and therefore also the extra discharge of CO_2 from the blood began to fall off. When this stage was reached the lung ventilation was greater than normal, and thus the alveolar CO_2-pressure was less than normal. At the same time the alveolar oxygen-pressure fell from the level at which it was maintained during the initial excess breathing, since the rate of absorption of oxygen remained undiminished, while the lung ventilation decreased as just described. The drop in alveolar oxygen-pressure tended, of course, to increase the symptoms of want of oxygen and thus increase the 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, they 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 diminution caused apnoea, just as when pure air is breathed at normal atmospheric pressure. It was evident, therefore, that the alveolar 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 VIII, 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 or hydrogen-ion pressure 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 distension 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 of want of oxygen on the respiratory centre 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 be only valid under conditions otherwise normal.

The fact that normal conditions tend to be maintained during life is one basis of biological science. Apart from this fact physiology would be a mere chaos of unconnected 'bio-physical' and 'biochemical' 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 normal individuals. Some respond by increased breathing much more readily 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 alveolar oxygen percentage. In some persons a lowering by as little as 5 per cent. in the oxygen percentage of the inspired air will increase the breathing noticeably, but in most persons a lowering of at least 7 per cent. (i.e. from 20·93 to 14) is needed to produce a noticeable effect, while in others very little effect is produced before consciousness is lost from want of oxygen. It is thus for many people peculiarly dangerous to pass into an atmosphere in which the oxygen percentage is very low or to attain to a very great height in a balloon or aeroplane, since increased breathing may give very little warning, particularly if the change is gradual, so that the extra CO_2 is blown off insensibly.

It was discovered by Yandell Henderson (1908 *b*) 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 even a single breath. It may even be impossible to start the breathing again by supplying CO_2 in the inspired air. To produce this effect the artificial respiration must be performed forcibly by means of a suction and exhaust-pump, since it is evident from what has been said already in Chapter V that the control of the chest movements by the Hering-Breuer reflex during artificial respiration produced by ordinary means prevents excessive washing out of CO_2.

This important experiment shows that when the CO_2-pressure is reduced below a certain point in the respiratory centre the latter ceases to respond to even an excessive degree of want of oxygen, and evidently soon becomes severely damaged, just as it is by extreme want of oxygen. The apnoea produced in the ordinary way by voluntary forced breathing is terminated, as shown in Chapter III, by the combined stimulus of CO_2 and want of oxygen, and in some persons the oxygen saturation of 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 the aforesaid 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 the case of J. S. H. 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 increased breathing, by washing out CO_2, checks this increase very quickly, so that the net result after a time is only a small increase. When the anoxaemia is only slight this net increase of breathing will be practically inappreciable subjectively, and this, as has been shown in Chapter III, 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 in Chapter VIII, 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, though a similar deficiency in the absence of the excess of CO_2 would produce a definite 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 (1898) imagined, the effects of high altitudes 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 shown by Haldane, Meakins, and Priestley (1918–9 *a*)

is chiefly manifested as an increase in the *frequency* of the breathing. The respective effects of variation in frequency and depth of breathing, which are physiologically important, will be considered in the next chapter.

Aggazotti (1918) suggested the use of a mixture of oxygen and CO_2 by mountaineers above a height of 13,000 feet. Schneider, Truesdell, and Clarke (1926) investigated the effect of adding CO_2 to the inspired air at barometric pressures corresponding to heights varying from sea-level to 30,000 feet. They found that addition of 8 per cent. of CO_2 to the inspired air raised the oxygen tension of the alveolar air about 1·3 mm. at 30,000 feet.

A further complication in the effects of anoxaemia and forced breathing on the respiratory centre and the body as a whole is introduced by the fact that, as Bohr discovered (see p. 159, and Fig. 45), 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 would otherwise be, but on the other hand the blood holds its oxygen so firmly that the oxygen-pressure in the tissues falls lower than it otherwise would. There may thus be considerable oxygen want in the tissues ('anoxia', Peters and Van Slyke) though there is no 'anoxaemia', and the blood is almost as red as usual. The existence of this oxygen deficiency in the tissues is only revealed by the immediate physiological effect of raising the alveolar oxygen-pressure (Haldane, 1919).

On reducing, in a steel chamber, the atmospheric pressure to half an atmosphere there is quite an appreciable permanent increase in the breathing, and consequent drop in alveolar CO_2-pressure caused by anoxaemia, but, in the case of J. S. H. 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 will only be sufficient to saturate the haemoglobin of the blood to the extent of about 60 per cent. if the pressure of CO_2 is that of normal alveolar air (Fig. 46). Blood with this percentage of saturation would be very strikingly blue. Owing to the diminished pressure of CO_2 the saturation is actually much higher, and this accounts for the colour of the lips being nearly normal. The existence of

considerable oxygen want in the tissues is, however, revealed at once by the effect of adding oxygen to the inspired air; for vision and hearing are at once strikingly improved and the breathing diminished. The degree of blueness of the lips is thus only a rough index of oxygen want in the tissues. It is the diminution in the pressure and available amount of free oxygen in the blood which is functionally important as regards the oxygen supply of the tissues, whether or not the amount of reserve oxygen combined with haemoglobin is also diminished.

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 the arterial blood with oxygen can be only very slightly increased by the lowering of the alveolar CO_2-pressure. The oxygen-pressure of the venous blood must in consequence be lower, so that oxygen want in the tissues may 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 the normal alveolar CO_2-pressure, were only half saturated, a lowering of the alveolar CO_2-pressure would increase considerably the saturation of the haemoglobin of 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 in consequence of a fall in alveolar CO_2-pressure. Practically speaking, therefore, the Bohr effect, i.e. 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. This diminution of cyanosis may mask the existence of a very serious state of affairs. On the other hand, the converse effect due to the 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 is always 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 oxygen-pressure in the alveolar air. Hence the saturation of the haemoglobin is increased from about 95 to almost 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 reduced enormously in the arterial blood and to a less extent in the venous blood, since the circulation, as will be shown later (p. 389), 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. It was discovered by L. Hill and Flack (1910) that when the forced breathing is with oxygen instead of with air the symptoms 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 oxygen want in the tissues, 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 oxygen deficiency in the tissues caused by the Bohr effect. The subject will be discussed further at p. 387.

It is a very interesting fact that in many persons forced breathing does not produce apnoea at all, although in such people the breathing is regulated in accordance with the alveolar CO_2-pressure, just as in others. This fact was investigated by Boothby (1912–3) while he was working with Haldane. He found that at the end of continuous forced breathing for one or for 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 oxygen want to the tissues 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 tested by Haldane. His power of

voluntarily holding a deep breath was greatly increased by forced breathing of air, but natural apnoea did not occur.

Owing, in part, 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. Haldane (1924) showed that animals in a semi-conscious 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 change in the percentage saturation of the blood with carbon monoxide. A still more striking effect was produced by simply adding CO_2 to the air inspired during CO poisoning. Bohr's observations furnish a partial explanation of why a rise in the alveolar CO_2-pressure without alteration of the alveolar oxygen-pressure 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 symptoms of oxygen-want. A still more important fact is that the circulation-rate will also be increased, as will appear at p. 389.

It is evident, therefore, that there is considerable scope for the therapeutic use of CO_2 in conditions of oxygen want of all kinds, whether or not these conditions are due to imperfect oxygenation of the arterial blood. Indeed, this method of treatment has been in use for a considerable time in cases of gassing in pits and blast furnaces, though it was used quite empirically and without understanding of the physiological principles involved. A sod was cut out of the turf or a shallow hole scraped in the ground and the unconscious patient was placed with his face downwards in the hole and his head covered over. It would seem that any beneficial effects resulting from this method of treatment were due to increase in the CO_2 in the inspired air.

The importance of the therapeutic use of addition of CO_2 to the air inspired in cases of carbon monoxide asphyxia, ether or alcohol intoxication, anaesthesia, and respiratory failure due to other causes, e.g. asphyxia neonatorum, has been emphasized by Yandell Henderson (1924, 1928), and efficient forms of apparatus are now available by means of which oxygen-CO_2 mixtures in any desired proportions may be administered safely.

Though, as shown above, an important and early consequence of want of oxygen is increase in the respiration, it is found that, 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 has frequently been 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 increased only slightly, 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 (1898), 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 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 (Fig. 52). Sometimes the middle breath of the group is deepest, sometimes the last breath (Fig. 53), or sometimes the breaths are about equal in depth. Sometimes the periodicity only shows itself by periodical recurrence of single deep breaths.

The general explanation of this periodic breathing has already been given in Chapter III. That this explanation is the correct one is shown by the fact that, as seen in Fig. 52, on adding oxygen to the inspired air the periodicity disappears. This experiment was carried out repeatedly by Douglas, Haldane, Henderson, and Schneider (1913) on Pike's Peak and never failed. Mosso had attempted to carry it out, but got a negative result owing to a defective method of administering oxygen.

As already seen, periodic breathing can be produced easily at ordinary barometric pressure by suitable means. As the barometric pressure is reduced the periodic breathing is produced more and

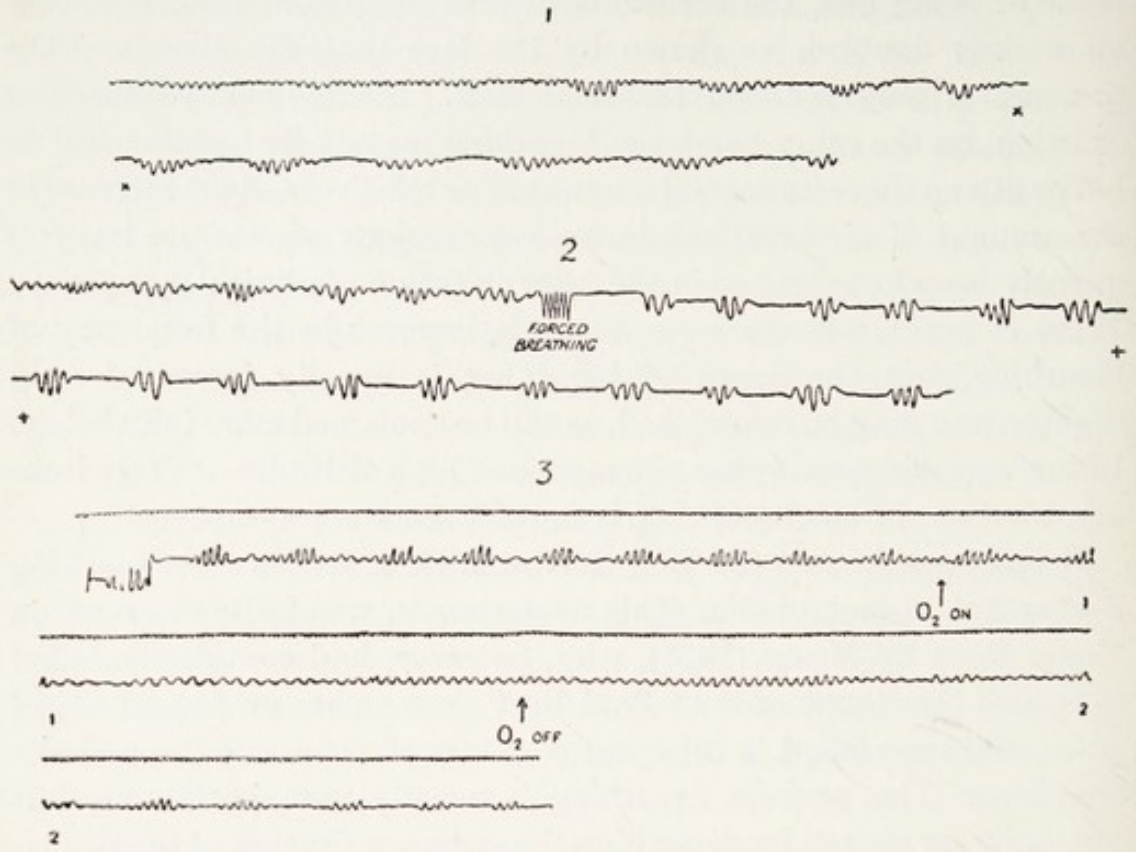


FIG. 52. Tracing 1. (Stethograph) Douglas, July 12. Evening of arrival on Pike's Peak. Natural periodic breathing.

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

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

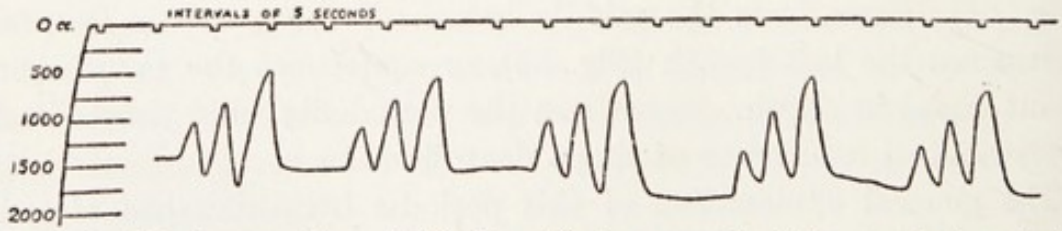


FIG. 53. Henderson, August 13. Quantitative record of the respiration during periodic breathing. Inspiration upwards.

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 even during perfect health.

The special characters of the increased breathing caused by anoxaemia were studied by Haldane, Meakins, and Priestley (1918–9 *a*). 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 effects of excess of

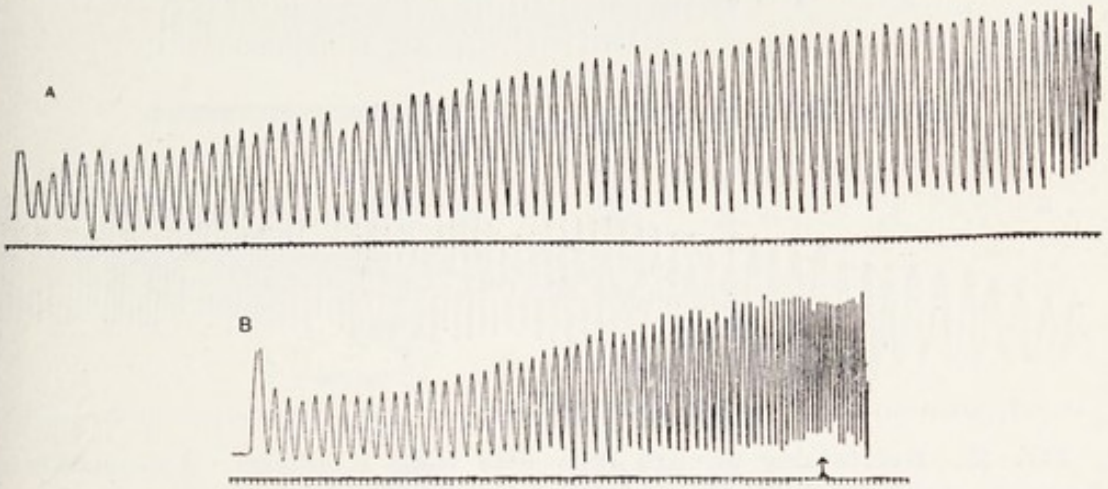


FIG. 54. (A) Rebreathing—Concertina filled with oxygen—CO_2 accumulating. (B) Rebreathing—Concertina filled with air—CO_2 accumulating. Time-marker = 2 seconds. Arrow shows point where lips were distinctly blue.

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 the case of J. S. H., for instance, when the breathing was pushed, in short experiments, to as much as seemed bearable, 131 litres per minute, with a depth of 1·98 litres and a frequency of 66 per minute, were breathed when the effects of excess of CO_2 and anoxaemia were combined; and only 81 litres, with a depth of 2·69 litres and a frequency of 30 per minute, when the only stimulus was excess of CO_2.

Fig. 54 shows quantitatively the effects of rebreathing a small volume (about 2 litres) of air or oxygen from the recording concertina described on p. 208. It will be seen that the increase in frequency was much less when the effects of anoxaemia were cut out by the oxygen.

Fig. 55 (A) shows the effect on the same subject of similar rebreathing when the accumulation of CO_2 was prevented by interposing

a layer of soda lime. It will be seen that the frequency increases, but not the depth. Fig. 55 (B) shows the effects on another subject, whose respiratory centre 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

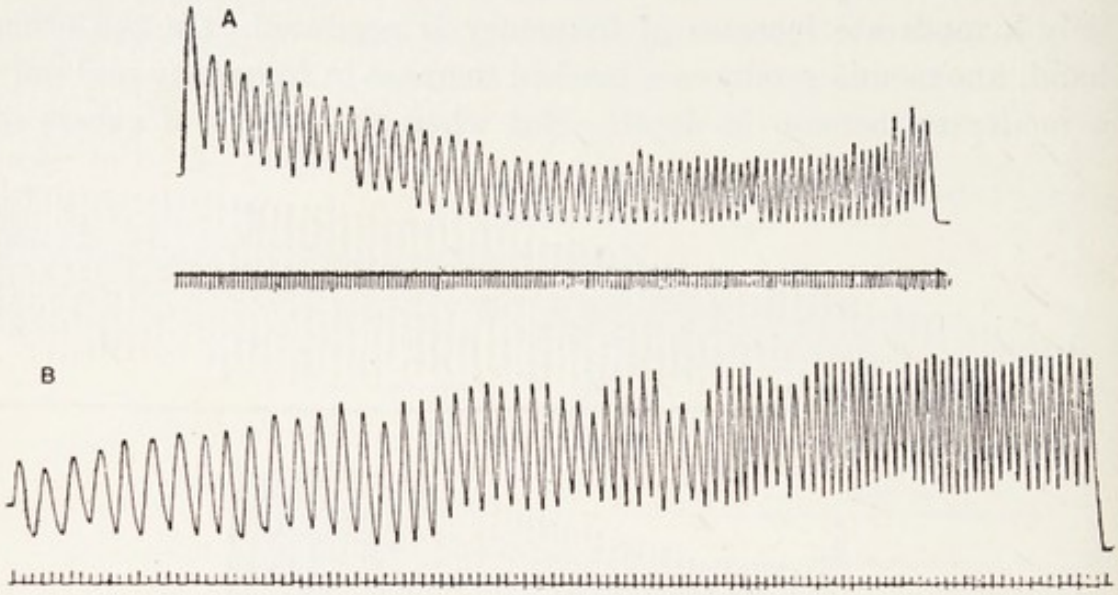


FIG. 55. Rebreathing through soda lime from concertina. Time-marker = 2 seconds. (A) Subject Cpl. M. (B) Subject J. S. H.

experiments such as these, the increased breathing, as already explained, is mainly due to the necessity of removing from the body a large amount of pre-formed CO_2 which has become an excessive charge in the body owing to the effects of anoxaemia in lowering the threshold of CO_2-pressure.

Figs. 56 and 57 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 Fig. 56 (B) and Figs. 57 (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

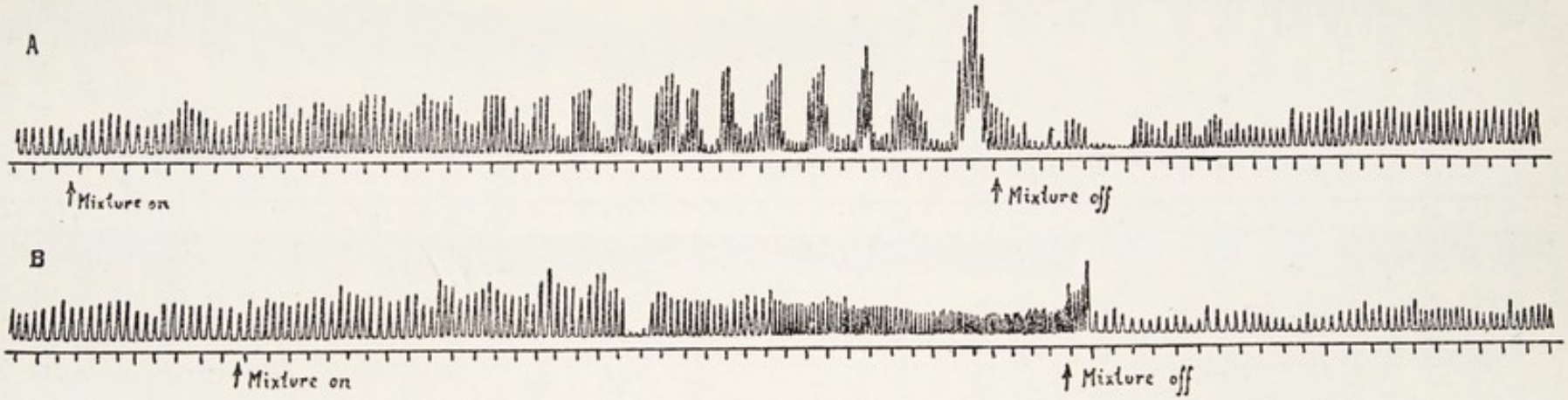


FIG. 56. Subject J. G. P. Time-marker = 10 seconds. (A) Breathing 10·33 per cent. oxygen. (B) Breathing 9·59 per cent. oxygen.

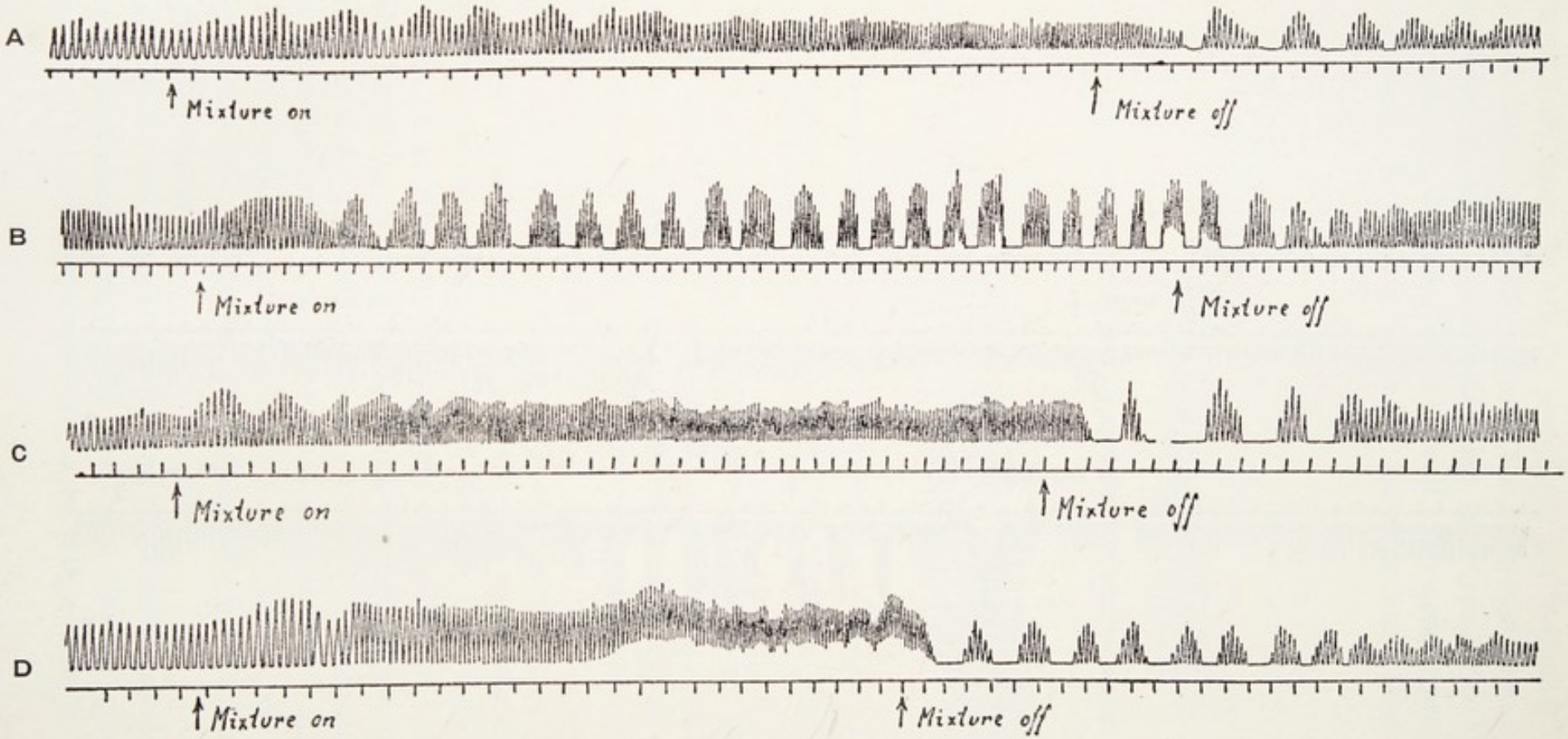


FIG. 57. Subject J. S. H. Time marker = 10 seconds. (A) Breathing 11·19 per cent. oxygen. (B) Breathing 11·05 per cent. oxygen +0·7 per cent CO_2. (C) Breathing 10·64 per cent. oxygen. (D) Breathing 9·84 per cent. oxygen.

resistance; and after a time asphyxial symptoms were usually impending owing to the ineffectiveness of the shallow breaths. When the experiments were made the effects of fatigue caused by resistance had not been investigated, and there is now no doubt that the slight resistance due to the apparatus, combined with the effects of anoxaemia on the respiratory centre, accounted for the especially rapid failure of breathing shown in the figures. When the breathing is quite free, as in a steel chamber at low pressure, failure of the respiratory centre does not occur nearly so readily, but the difference is only one of degree; and failure of the respiratory centre, as shown by shallow and frequent respiration, is the inevitable result of serious arterial anoxaemia. With the increasing shallowness of the breathing the arterial anoxaemia increases, owing to causes discussed in Chapter VIII. This hastens the failure of the respiratory centre; 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 air breathed. Our knowledge of the effect of want of oxygen on the circulation is thus imperfect as yet. It will be discussed more fully in Chapter XII. For the moment it will suffice to state that, 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, there is at first an increase of the frequency, and apparently also in the strength of the heart-beat. This indicates an increase in the circulation-rate. But just as in the case of the respirations, the frequency and vigour 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 respiration 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 centre 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 due at bottom to the same cause as the falling off in the initial depth and frequency of breathing. With further increase in the anoxaemia the heart-beats, like the respiration, become more and more feeble. 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 colour of the skin depends upon (1) the amount of blood in the capillaries, and (2) the degree of saturation of this blood with oxygen. Hence in clinical observation it is important to bear in mind that, if the small vessels are poorly filled, the colour of the skin and mucous membranes will be pale rather than blue, even though the blood is very poorly charged with oxygen.

The bluish colour 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 colour may be produced by the action of poisons which produce methaemoglobin and other coloured decomposition products in the blood. Such conditions, which are of course quite exceptional, and can be distinguished quite easily, will be referred to in Chapter VIII. 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 on p. 217, is far more frequent than has commonly been supposed. Parts of the skin may be blue from the 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 the circulation. According as there is much or little blood in the capillaries the colour is full or unsaturated. Thus in extreme cyanosis the lips may be either almost black or only leaden grey; and in slight cyanosis the colour may be either a full or pale purplish red. If anoxaemia

is produced rapidly or in such a way that CO_2 is not removed in excess, as in asphyxia, the vessels are congested and a deep blue or plum-coloured cyanosis is produced. If, however, anoxaemia is produced gradually and so that CO_2 is removed in excess, as in phosgene poisoning, the superficial vessels are poorly filled owing to depression of the vasomotor system, and the skin is pallid and takes on a greyish-blue or leaden colour. It is particularly important that such a condition should not escape recognition since it is evidence of an even graver state than that which is indicated by plum-coloured cyanosis.

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 of the partial pressure of oxygen in the blood in 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 (Fig. 46), not a direct measure of the former effect. When, however, the latter 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 (1914) 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 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 aeroplanes, 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 judgement are much impaired, and anoxaemic persons become subject more or less to irrational fixed ideas, and to uncontrolled emotional outbursts. Muscular co-ordination 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 being first paralysed, then the arms, and finally the head. The senses are lost one by one, hearing being apparently the last to go. The sense of pain seems to be lost early and to return late during recovery from the anoxaemia. 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. Also patients beginning to come round after administration of nitrous oxide for extraction

of a tooth are sometimes aware of the dentist's manipulations though entirely without any sensation of pain.

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, Haldane has always been quite confident of his own sanity, and it was only afterwards that he realized that he could not have been in a rational state of mind.

An experience of this kind was in a steel chamber in which Dr. Kellas, who was an experienced climber in the Himalayas and had exceptional powers of resisting anoxaemia, was with Haldane (Haldane, Kellas, and Kennaway, 1919–20). The pressure had been reduced to 320 mm., and as J. S. H. could no longer write or make any observations he handed the notebook to Kellas, who afterwards told J. S. H. that he remained sitting, but always answered Kellas's questions quite deliberately and confidently, and insisted on the pressure being kept at 320 mm. This went on for an hour and a quarter, of which time Haldane could afterwards remember absolutely nothing. At last Kellas obtained his assent to raising the pressure to 350 mm., after which Haldane took up a mirror to look at his own lips, but Kellas observed that for some time he looked at the back instead of the front of the mirror. Haldane had, however, begun to realize that they had been as long at the low pressure as they had intended and agreed to a rise to 450 mm. On reaching this pressure his mind had cleared and he noticed a return of feeling and power in his arms and legs. After coming out of the chamber he could vaguely remember taking up the mirror but nothing before that after handing over the notebook. They had no intention of staying at so low a pressure that it was quite impossible for Haldane to take notes, and so his persistence was quite irrational. Kellas was much bluer than Haldane was during the stay at 320 mm., but could still write quite well, read the barometer, and manage the regulating tap; but whether he was quite normal mentally seems rather

doubtful. Perhaps he shared to some extent Haldane's irrational desire to continue the experiment: otherwise it would seem probable that he would have noticed how abnormal Haldane's condition was. Both observers were at the time unacclimatized to low pressures.

This personal experience illustrates some of the peculiar dangers associated with atmospheres which produce anoxaemia, 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 aeroplane 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, Haldane 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 judgement. A man suffering from anoxaemia will usually go on, and insist on 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 on 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 behaviour is very abnormal for a few minutes after recovery. One of Haldane's acquaintances has twice knocked persons down on waking up from a short loss of consciousness caused

by anoxaemia; and Haldane's own behaviour 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 his 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 called 'mountain sickness'. This is a condition in the typical form of which there is nausea, vomiting, headache, sometimes diarrhoea, 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 much of the CO has 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 generally begins about 8 to 12 hours after the beginning of the exposure. 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 a common condition during illness. At present we can only guess at the nature of the slight temporary pathological changes of which the symptoms of mountain sickness are 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. For a reason which will be explained in Chapter VIII 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 haemorrhages in the brain have been described, and Mott has found small multiple haemorrhages. 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 broncho-pneumonia 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 centre becomes very easily susceptible to 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 centre 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 centre 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 VIII, 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 centre. When death from anoxaemia occurs at very high altitudes (as, for instance, in the case referred to in Chapter X, of the balloonists, Tissandier and Croce Spinelli) it is evidently failure of the respiratory centre 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 VIII, 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 centre 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 V, may be produced. 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 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 in many chronic cases of valvular heart disease, emphysema, etc.

The fact that cyanosis, as stated above, 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.

VIII

THE CAUSES OF ANOXAEMIA

ANOXAEMIA may be 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.

Anoxaemia in the above sense, which of necessity implies also a degree of oxygen-want in the tissues, may be brought about in three main ways, viz. owing to (1) defective saturation of haemoglobin with oxygen in the lungs, the haemoglobin being itself normal; (2) defect in the charge of available oxygen in the arterial blood owing to diminution of physiologically efficient haemoglobin; and (3) defective circulation, so that the passage of blood through the capillaries is so slow that the available oxygen is used up to an excessive extent, or arterial blood leaving the heart becomes mixed with venous blood, as in some types of congenital heart disease.

Of these causes the first may be brought about in two ways, i.e. it may result from defective partial pressure of O_2 in the alveolar air or from hindrance to the passage of oxygen from the alveolar air to the blood.

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 that alveolus. For the purpose of the present discussion we may assume provisionally 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 sight 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. This assumption is made all the more probable by 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 indeed generally done, 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 aerotonometer (Chapter IX) is nearly always lower, and sometimes considerably lower, than the average alveolar oxygen-pressure; but various explanations of this difficulty were formerly adopted by Haldane and others.

A new and important light was thrown on the whole subject in the course of a study by Haldane, Meakins, and Priestley (1918–9 *b*) of the 'neurasthenia' produced by gassing and other causes during the War. As mentioned in Chapter VII, the breathing in these patients is abnormally frequent and shallow, particularly on exertion. It was found also 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 on the effects of shallow breathing in normal persons, and for this purpose we devised the apparatus shown in Fig. 58. The subject inspires through the mouthpiece and inspiratory valve from the recording 'concertina'. The bottom of this moves upwards with the inspiration, and records the movement by means of an inked pen on the drum. During expiration the bottom comes down on to a movable stop, and by moving this upwards and fixing it by means of a screw the maximum capacity of the concertina can be reduced to any extent desired. The descent of the bottom of the concertina during expiration is brought about as follows. The expired air passes out by a rubber expiratory valve which offers a very slight resistance to its passage. The expiratory pressure so produced is communicated by means of a small side tube to a tambour, the movement of which, as shown, closes an electric circuit. This circuit includes the coils of an electro-magnet which, on being energized, instantly lifts a valve and admits air freely into the concertina, which at once refills itself, the weight of the bottom being so adapted as to ensure this.

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 to any extent desired, and a continuous record is obtained at the same time of the depth and frequency of respiration. With the concertina fully open ordinary records of the breathing are obtained, and moreover any

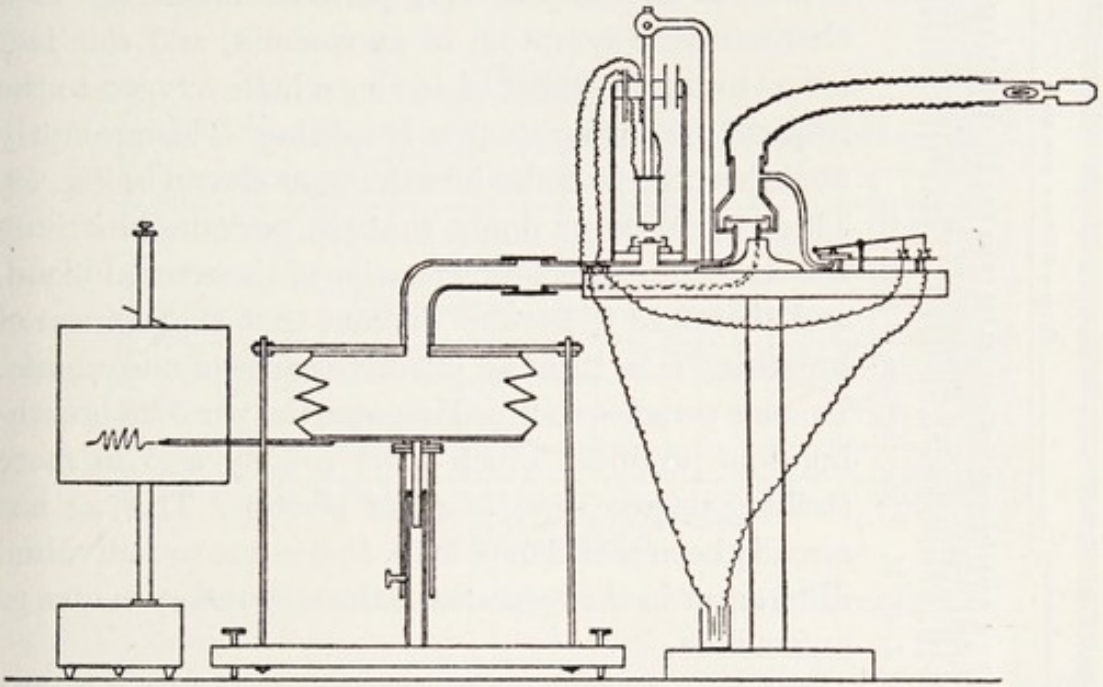


FIG. 58. 'Concertina' apparatus for continuous record of respiration.

gaseous mixture can be supplied through a glass cylinder which encloses the electro-magnet and valves. 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 very 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, since, naturally, the Hering-Breuer reflex has not given the signal for expiration. Also, since the apparatus does not control the depth of expiration, this must be adjusted voluntarily to correspond with the depth of inspiration permitted. With a little practice, however, the breathing goes quite easily, and

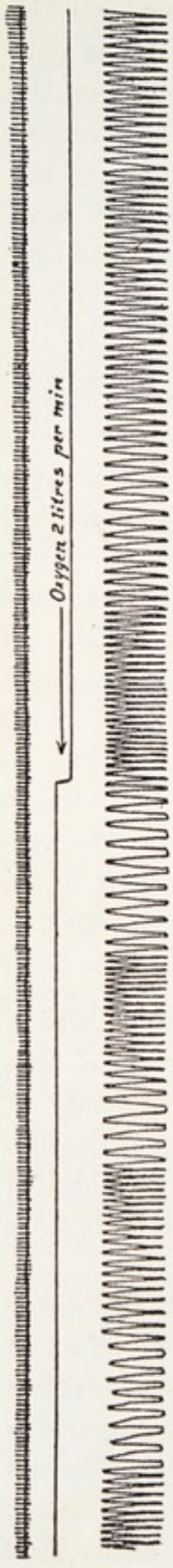


Fig. 59. Subject J. G. P. Time-marker = seconds.

it is found that the frequency increases in proportion as the depth is diminished. When the depth is greatly diminished the breathing becomes very frequent—one hundred or more a minute.

On observing the breathing when the depth was gradually and progressively limited, we found that the breathing became periodic very readily. As already explained in Chapter III, periodic breathing is a characteristic symptom of anoxaemia, and this fact led us to try the effect of adding a little oxygen to the inspired air during shallow breathing. This promptly abolished the periodic breathing, as shown in Fig. 59. There could be no doubt that the periodic breathing was due to imperfect oxygenation of the arterial blood, and therefore it became evident that shallowness of breathing is in itself an effective cause of anoxaemia. In some persons, such as Haldane, the periodic breathing was produced much more readily and in more striking degree than in other persons. This, as has already been mentioned on p. 184, is due to individual differences in the response of the respiratory centre to anoxaemia.

We thought at first 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 surprised to find that in the deepest alveolar air the oxygen percentage, so far from being lower, was actually higher than usual. There was thus definite anoxaemia, 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. The anoxaemia, of course, was another factor operative in increasing the total ventilation.

On considering this remarkable state of affairs, we bethought ourselves of some anatomical observa-

tions collected by Professor Sir Arthur Keith (1909). He showed 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 Japanese fan. The parts nearest the moving chest-wall (for instance, the diaphragm) expand first, and other parts follow; those near the roots of the lungs expanding least. It follows from this that different parts of the lungs are rather unevenly ventilated, and in shallow breathing this inequality of ventilation of different

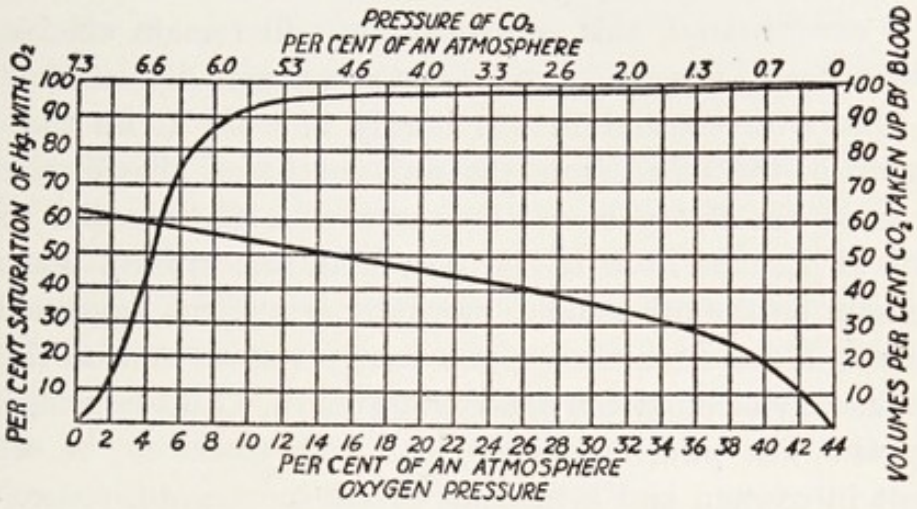


FIG. 60. Dissociation curves of blood for CO_2 and oxygen.

parts of the lungs is accentuated. Under such conditions only certain parts of the lungs will expand at all efficiently, and on account 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 under-arterialized and over-arterialized blood. To understand what the results of this mixture will be, we must refer to the respective dissociation curves for the oxygen and CO_2 present in blood, taking into account also the action of oxygen in expelling CO_2 from venous blood, as shown by the curve in Fig. 16. For convenience sake the two relevant curves are plotted together in Fig. 60, taken from our paper. A consideration of the CO_2 dissociation curve shows at once that over-ventilation in some parts of the

lungs will wash out CO_2 from the blood in the same proportions as the corresponding under-ventilation fails to wash it out in other parts, for throughout the region of physiological pressures the curve is practically a straight line. As long, therefore, as the total alveolar ventilation is normal, the mixed arterial blood coming from different parts of the lungs will be normal as regards its content of CO_2. Deficient removal of CO_2 from some portions is exactly compensated by excess removal from other portions. Even when, owing to shallow breathing, the inequality of ventilation of different parts of the lungs is accentuated, this compensation will remain efficient. On the other hand, a consideration of the oxygen dissociation curve shows that over-ventilation will hardly increase at all the charge of oxygen in the blood from the well-ventilated alveoli, since this blood is on the flat part of the curve with the alveolar oxygen-pressure at perhaps 16 to 18 per cent. of an atmosphere. The under-ventilation, on the other hand, of some parts of the lungs will leave the venous blood from these parts nearly venous and on the steep part of the oxyhaemoglobin dissociation 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.

These considerations thus afford 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 oxygen-pressure of the mixed alveolar air gives directly 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 discussed above. It is probable indeed that in some way or other the air-supply is proportioned to the blood-supply under normal conditions, whether by regulation

through the muscular coats of the bronchioles or regulation through the blood distribution; but it is also certain that this adjustment is only an approximation.

Unfortunately our knowledge of the pulmonary circulation and its regulation is very limited. Indeed, until recent times it was generally assumed that pulmonary vasomotor nerves play no important part in the regulation of the blood-flow through the lungs, despite the existence of a number of observations which indicated clearly that the pulmonary vessels were under the control of the nervous system (Bradford and Dean, 1889 *a*, *b*; 1894), François Franck (1895 *a*, *b*), Plumier (1904 *a*), Weber (1910), and Schafer (1920 *b*).

Definite evidence of pulmonary vasomotor effects was subsequently obtained by various observers. Plumier (1904 *b*), Tribe (1914), and Le Blanc and Wijngaarden (1924) found that pulmonary vaso-constriction followed stimulation of sympathetic nerves. The same result was obtained by Cavazzani (1891) on stimulating the vagus. Dilatation of the pulmonary vessels, on the other hand, was observed by Le Blanc and Wijngaarden on stimulating the vagus and by Cavazzani on stimulating the cervical sympathetic. Daly and von Euler (1932) have carried out a most careful investigation of the vasomotor nerve-fibres of the lungs and have found that both vasoconstriction and vasodilatation may be obtained by stimulation of the thoracic and cervical vagi and vago-sympathetic nerves. These observations, however, only afford evidence of the existence of control of the pulmonary circulation by the nervous system and throw no light on local adaptation of the circulation to variations in the ventilation of different parts of the lungs. Churchill and Agassiz (1926), however, have observed that distension of the capillaries in a given portion of the lungs may be attended by an increase in the corresponding air space, and Wearn, Barr, and German (1926–7) have made direct observations of the pulmonary capillaries through windows in the chest-wall, the pleura being kept intact. They found that the number of open capillaries in a given region varied and that pressure on the abdominal aorta resulted in the opening up of pulmonary capillaries which had previously been closed. They were unable, however, to detect any relation between variations in the oxygen and CO_2 percentages of the inspired air and the state of the capillaries. Löhr (1924), on the other hand, found that the circulation-

rate through the isolated lung increased when CO_2 was added to the inspired air. Drinker, Churchill, and Ferry (1926) were, however, unable to confirm this observation.

Such observations as these, however, throw little light on the adjustment of the circulation to the ventilation in different parts of the lung. There is some evidence, however, that, as stated above, this adjustment is only an approximation. For instance, the fact that in animals the aerotonometer gives a lower arterial oxygen-pressure than the alveolar oxygen-pressure (Chapter IX) is most naturally explained on the theory that the adjustment is only approximate, and there are various other facts that 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 (1908) discovered, however, that if the lungs are filled with oxygen first the breath can be held for two or three times as long; also that the alveolar CO_2-percentage is then 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 expired 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.

	After holding breath		*Time held in seconds*	*After three breaths of oxygen*		*Time held in seconds*	*Breathing expired air from bag*		*Time held in seconds*	*Breathing oxygen from bag*		*Time held in seconds*
Subject	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

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 Haldane (1909 *b*) repeated the observations, but in such a way as to have great variations in the alveolar oxygen percentage. It was 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 the proportion 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 air runs down to 10 or even 8 per cent. The results were therefore very mysterious at the time, and Douglas and Haldane 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 centre. 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 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 inspiration, 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 was demonstrated by Meakins and Davies (1920). They found that on holding a deep breath of air for 40 seconds the haemoglobin of the arterial 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 carried out by Douglas and Haldane is very instructive in this connexion. As already mentioned in Chapter III, the alveolar CO_2-percentage rises high above its normal value before the end of an apnoea after forced breathing with extra oxygen. They observed how high the alveolar CO_2-pressure went when there were varying pressures of oxygen in the mixed alveolar air at the end of the apnoea produced by two minutes of forced breathing. Their results were plotted in Fig. 61. It will be seen that

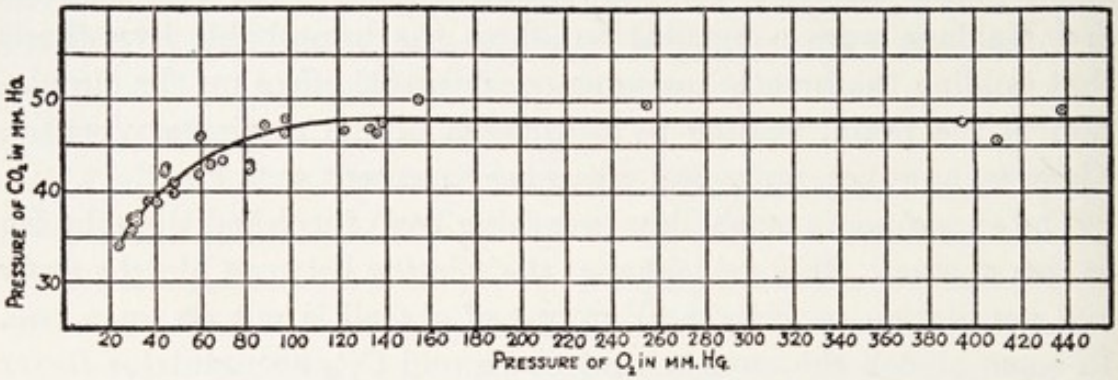


FIG. 61. Alveolar CO_2 during breath holding after inhalation of oxygen.

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 were 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 of the different alveoli.

Judging from aerotonometer 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 shows 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 (1914) described in the oxyhaemoglobin dissociation curves of different individuals.

The periodic breathing produced by shallowness of the respiration differs strikingly from the periodic breathing produced by anoxaemia in normal persons. As will be seen from Fig. 59, the periods are much longer, and in this respect resembled closely the 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.

Ordinary clinical Cheyne-Stokes breathing is evidently a symptom of anoxaemia due often to the shallow breathing which characterizes a failing respiratory centre. This failure may be that of approaching death, since the anoxaemia itself tends to hasten the failure of the centre, as already explained on p. 205. 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 colour 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 centre, 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 centre, and consequently impending danger from anoxaemia. The frequent and shallow breathing in some cases of 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 connexion with what has

just been said. In this connexion it is very desirable 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 centre is seen in neurasthenia and various other forms of disease; but failure of the respiratory centre 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 on p. 140, assumes exaggerated influence, owing to the failure of the respiratory centre. 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 centre, the effects of the oxygen are rapid and prompt, and have been so in cases which have chanced to come under our 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 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 favours 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.

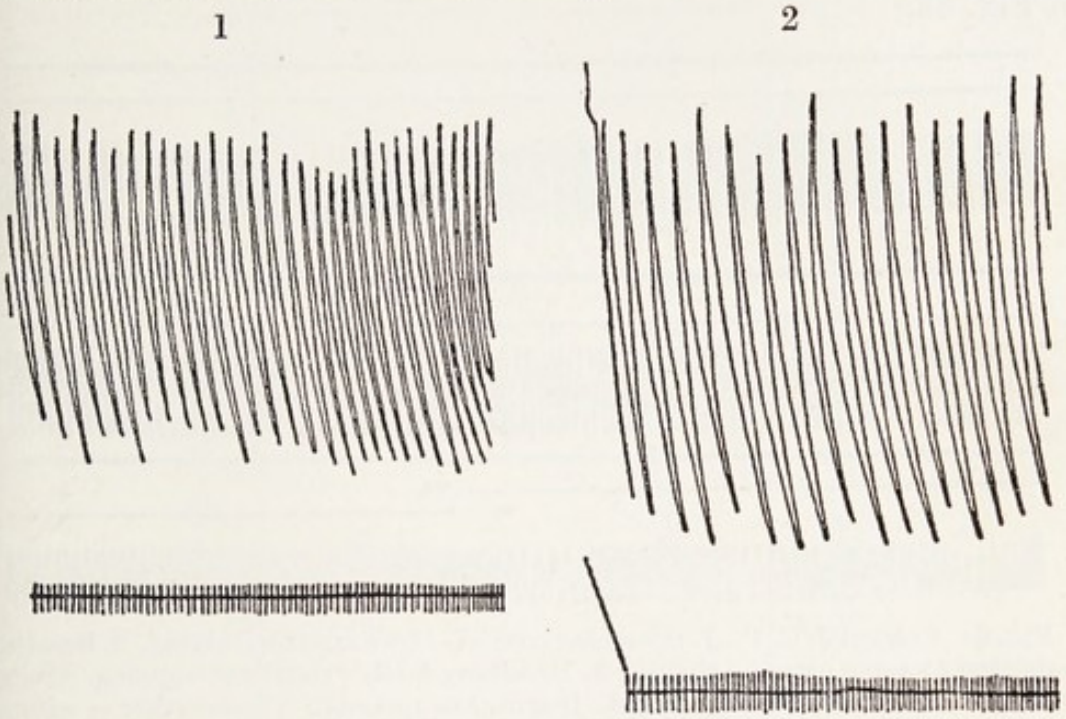


FIG. 62. Subject J. S. H. Rebreathing in and out of a 50-litre cylinder. Time-marker = 2 seconds. 1. Sitting. 2. Lying.

In Haldane's 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 Fig. 62). 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 photographs which we took to show the position of the diaphragm favoured 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 V. 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 the case of Haldane 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 Fig. 63.

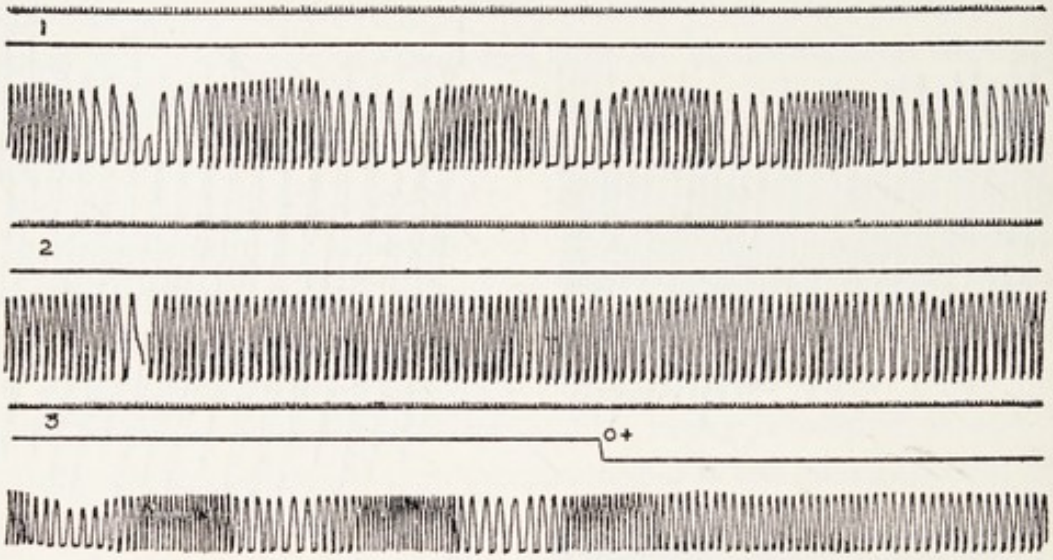


FIG. 63. Subject J. G. P. 1. Breathing restricted by concertina—lying. 2. Breathing restricted to same extent—sitting. 3. Breathing further restricted—sitting. Oxygen given at +. Curves read left to right. Inspiration upstroke. Time-marker = seconds.

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 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 centre, 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.

Restricted depth of breathing from any cause, including the after-effects of gassing and various other conditions, may become very dangerous if any considerable muscular exertion is attempted, as

the anoxaemia may cause fatal heart-failure. The attention of one of us was directed to this in connexion with the sudden death of a man during a bicycle ride several days after he had been slightly gassed, the after-effects having been described by him as tightness of the chest, as if something was hindering its expansion.

Defective distribution of air in the lung alveoli is, of course, only one of the causes of defective oxygenation of the arterial blood; but this has been dealt with first, not only because it is of very great

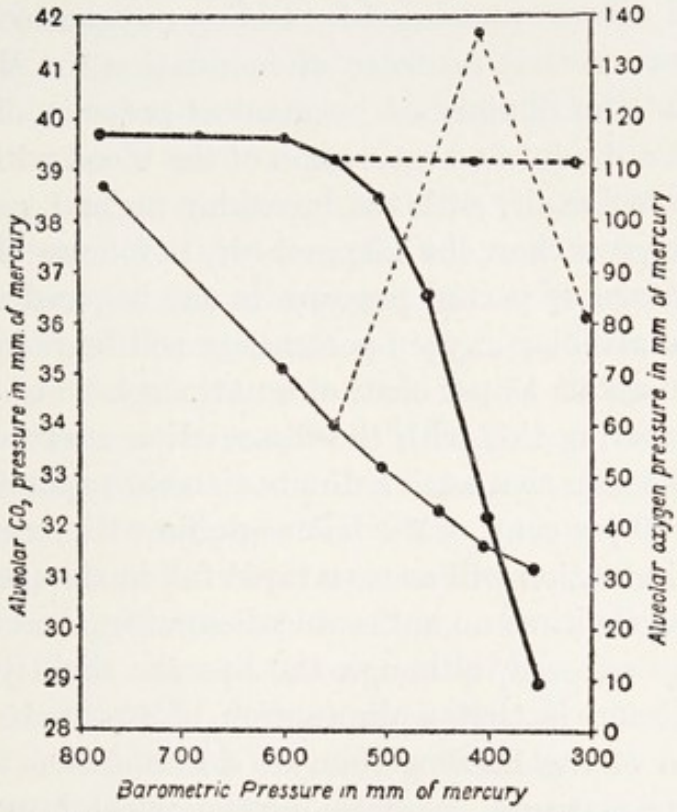


FIG. 64. Effects of diminished barometric pressure on the alveolar gas-pressures. The thick lines show the alveolar CO_2-pressure, and the thin lines the alveolar O_2-pressure. The dotted lines refer to the experiment in which oxygen was added to the air.

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 VII, 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. Fig. 64, from a paper by

Boycott and Haldane (1908), 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 they 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 (1898) contention 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 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 colour. 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 be quite measurable physiological responses, which will be discussed in succeeding chapters.

The truth is that 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 in unacclimatized persons is distinctly lower than corresponds to the oxygen-pressure of the alveolar air.

Haldane and Poulton found that when a small quantity of air—about 6 litres—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 VII. 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 Haldane's 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 (Haldane, Kellas, and Kennaway, 1919–20). As a rule no very serious symptoms are experienced at once 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 Haldane, are soon very seriously affected in the manner described in Chapter VII, 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 connexion with the effects of lung-irritant poison gas during the war. It was evident from the first cases which Haldane saw in April 1915 that there was 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-coloured 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, Haldane found that there was no abnormal pigment present, so that the blue colour 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 colour 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 the lungs oedematous, so that they did not allow oxygen to pass inwards at a normal rate. To judge by the increased breathing there was also much disturbance in the excretion of CO_2 by the lungs; and the great distension of the veins and other signs in the chlorine cases pointed in this direction also.

In cases of poisoning by phosgene and other lung-irritants used later, the symptoms of irritation of the air-passages were much less prominent and there were no signs of hindrance to excretion of CO_2. The anoxaemia is produced gradually in these cases and at the same time CO_2 is removed in excess. The general symptoms therefore are those of anoxaemia accompanied by CO_2 deficiency, and thus differ markedly from the symptoms of chlorine poisoning just described. This was particularly true in the less severe cases or in those seen early, when there was no evident oedema of the lungs. Thus, in cases of phosgene poisoning, the symptoms of acute anoxaemia were shown, at first, 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 distension of the lips and veins with blood, and the cyanosis was thus of the leaden or grey type previously described, just as in cases of slowly advancing anoxaemia from other causes. In death from gradual CO poisoning, for instance, there is no extra distension of the lips or veins with blood, although, of course, the lips are not grey but light pink. Death, in the phosgene and similar cases, seems to have been due finally to failure of the respiratory centre, 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 favourable cases of ordinary croupous pneumonia the lips remain of a good colour, 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) Haldane was told that cases of early 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 Haldane and his colleagues, in the report of the Pike's Peak Expedition, to advocate the continuous employment of 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 was confirmed by Gross (1919), 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 (see Fig. 65). 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 centre 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 been shown directly by Stadie (1919), who examined 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 (1919), 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 centre 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, it may be hoped, already sufficiently 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

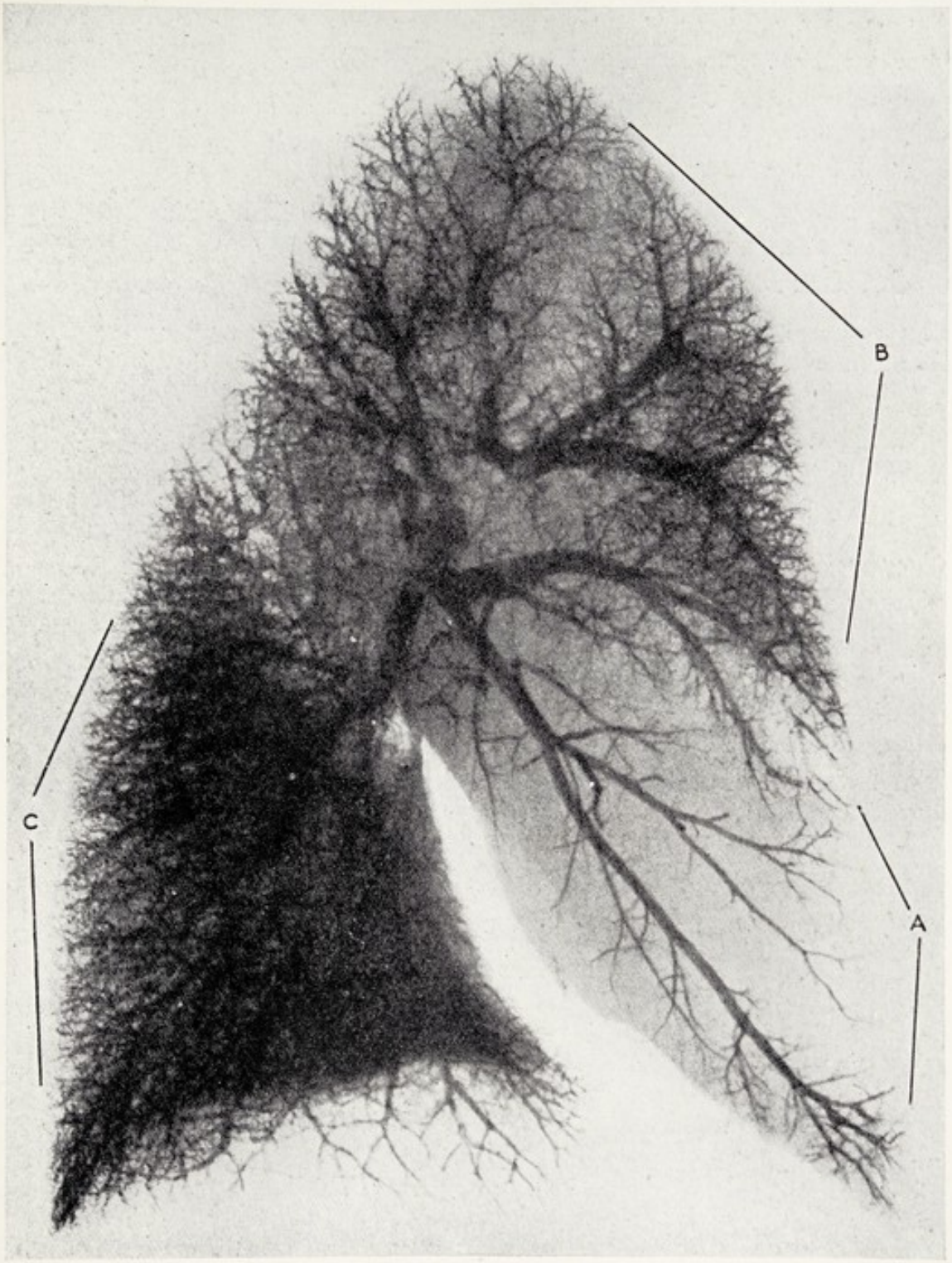


FIG. 65. X-ray photograph of barium-injected lung from a case of lobar pneumonia. (*After Gross.*)

A. Consolidated area—grey hepatization. The main vessels, though constricted, are patent. The finer vessels have been entirely occluded.

B. Consolidated area—red hepatization. The main vessels are constricted and the finer vasculature is less dense than in the normal lung.

C. Healthy lung tissue except for compensatory congestion. The main and finer vessels are both conspicuously dilated.

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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 to above—a very simple method of administration will suffice. A small cylinder of oxygen furnished with an indiarubber 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 connexion 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 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 get hardly 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 XI. 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. Haldane 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 to need. The effects of continuous oxygen inhalation with this apparatus on the arterial blood in pneumonia and bronchitis have been investigated by Meakins (1920, 1921). He found that with 2 litres 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 litres 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 litres a minute, and the cyanosis and orthopnoea disappeared. In a normal man the saturation rose from 95·6 to 98·1 per cent. on giving 2 litres a minute.

The oxygen administration apparatus designed by Haldane is shown in Fig. 66. It consists of: (1) an oxygen cylinder provided with an easily worked 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 litres 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 the face-piece 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

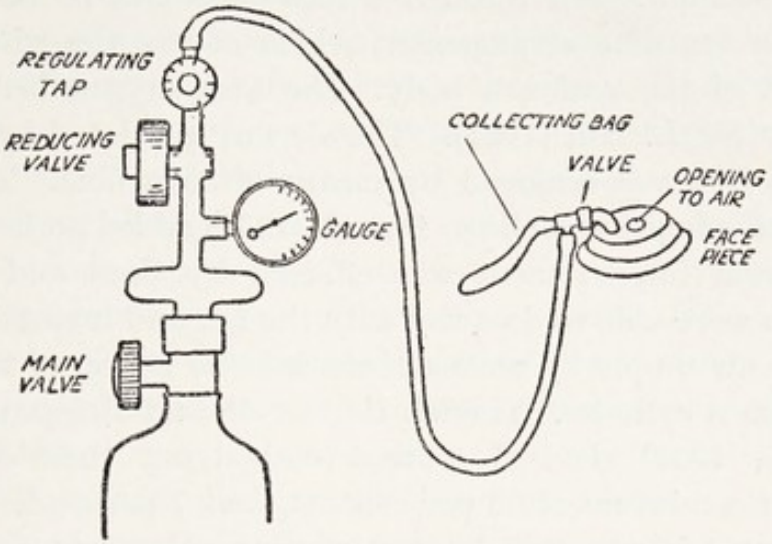


FIG. 66. Apparatus for administering oxygen.

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 litres a minute or whatever greater or less amount suffices. With a delivery of 2 litres a minute a 40-foot cylinder would last nearly 10 hours.

While there is no question of the economy and efficiency of this apparatus there is one drawback to its use. The face-piece is somewhat apt to become displaced during sleep, and it is often found that patients in need of oxygen are at first apt to be intolerant of any form of mask or face-piece, but usually soon overcome their objection.

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 Stoke-on-Trent and at Cambridge under Barcroft's direction (Barcroft, Hunt, and Dufton, 1919–20). Similar chambers were used at Guy's Hospital, and in America. Favourable 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 V and VII. There are, however, serious objections to

the general use of such chambers. In the first place the costs of installation and maintenance are considerable, and in the second place there is danger owing to the risk of fire. It is, perhaps, not generally realized how great this danger is. Many materials which in ordinary air cannot be ignited become extremely inflammable in air enriched with oxygen.

The disadvantages inherent in the use of an apparatus by which oxygen is administered through a face-piece can be obviated by means of a tent-like arrangement which covers the whole of the upper part of the patient's body. The first oxygen bed-tent was devised by Sir L. Hill (1921). The air was circulated by means of a fan and CO_2 was removed by means of soda lime. There was, however, no adequate cooling. Barach (1931) added an ice-box, and another great improvement was effected by Cecil and Plummer (1930) who were able to do away with the fan and maintain circulation of the air simply by means of the injector action of the oxygen issuing from a cylinder. Yandell Henderson and Haggard (Yandell Henderson, 1932) devised a tent embodying these principles. Oxygen (or a mixture of 93 per cent. O_2 and 7 per cent. CO_2—sold as 'carbogen') is admitted by a regulating valve into a wide tube leading from the top of the tent. The oxygen enters at a pressure of about 4 pounds per square inch and, mixing with the warm air from the top of the tent, forces it along the wide tube to a vertical, double-walled, metal cylinder which is filled with ice. From the bottom of this cylinder the mixed, cooled gases are led by a wide tube into the lower part of the tent where they escape by a series of holes, and are inhaled by the patient. The warm expired air rises to the top of the tent and is again forced through the cooler. The oxygen in the tent is thus maintained at about 45 to 55 per cent., and, if carbogen is used, the CO_2 reaches about 4·5 to 5 per cent. The temperature in the tent when pure oxygen is used keeps at about 10 to 14° F. below the room temperature. If carbogen is used the temperature in the tent is kept at about 4 to 8° F. below that of the room. In Barach's and Cecil and Plummer's apparatus the CO_2 of the expired air was absorbed. Poulton (1933) found that considerable economy of oxygen was effected by keeping the cooling mechanism separate from that for the removal of CO_2.

In connexion with the subject of the administration of oxygen it may be well to say a few words about artificial respiration. The

need for the efficient performance of artificial respiration in cases of suspended breathing due to various causes is now generally recognized. Two efficient methods have been devised, namely, those of Silvester and Schafer. The latter has, in several respects, undoubted advantages, and is in general use. It is found to be very efficient and can be continued for hours if necessary. If Schafer's method of artificial respiration is applied to a normal individual who voluntarily suspends his breathing it will be found that it is quite easy to maintain a rhythmic flow of six litres per minute of air or more into and out of the lungs. If, however, the subject voluntarily over-breathes until he has washed out so much CO_2 that apnoea ensues on stopping the over-breathing, a very remarkable phenomenon will be noticed if artificial respiration is attempted during the apnoea.

It will be found that a feeling of board-like rigidity is encountered on attempting to compress the subject's thorax and that it is impossible to cause the entry of any air at all into the lungs. Evidently the Hering-Breuer reflex acts as a most efficient protection against over-ventilation when artificial respiration is attempted on a conscious subject. It is not, however, known for certain that the Hering-Breuer reflex remains effective in states of complete unconsciousness with cessation of breathing. Hence the possibility of producing acapnia by over-vigorous application of artificial respiration to a deeply comatose patient should be borne in mind, and if the procedure has to be continued for long it would seem wise to supply a 5 per cent. mixture of CO_2 with air if possible.

Of recent years not a few cases of complete or almost complete paralysis of the respiratory muscles in consequence of attacks of anterior poliomyelitis have occurred. In such cases the preservation of life depends on the maintenance of effective artificial respiration for periods of weeks or months. This obviously cannot be achieved by means of the ordinary methods. To deal with such cases Drinker and McKhann (1929) devised an apparatus which has proved highly efficient in practice. It consists of a large metal cylinder big enough to contain a bed on which the patient lies. His head protrudes through a soft rubber diaphragm in one end-wall of the cylinder. This diaphragm is adjustable so that it makes an air-tight joint with the patient's neck without causing discomfort. By means of electrically driven blowers and appropriate valves the pressure inside the cylinder is changed alternately from about -12 to -18 cm. water

negative pressure to normal atmospheric pressure. It is found that when the surface of the patient's body is exposed to such a negative pressure air enters the lungs through the nose and mouth. When the pressure in the cylinder is restored to atmospheric pressure the elastic recoil of the thorax drives out the air again. Artificial respiration can thus be maintained most efficiently for months if necessary. Both the depth and rate of breathing are under the control of the attendant and can be measured and recorded. Positive pressures are found to be quite unnecessary and the negative pressure should be limited to that amount which is just necessary to prevent cyanosis.

The Drinker apparatus is made in this country by Messrs. Siebe, Gorman & Co., who have introduced various modifications which have increased its efficiency and lowered its cost.

While the value of such apparatus in cases of paralysis of the respiratory muscles cannot be overestimated, the treatment of cases of drowning, etc., should always be carried out by applying artificial respiration by Schafer's method and not by the use of any mechanical apparatus. If reliance is placed on such apparatus invaluable time may be lost if it is not immediately available and its inexpert use may cause serious damage.

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 Haldane and Priestley, Haldane's alveolar CO_2-pressure rose only by 0·13 per cent. in place of an expected rise of about 0·8 per cent., if the increased breathing had been due to CO_2 alone; while in the case of Priestley (who was in much better physical training than Haldane) the rise was 0·44 per cent. in place of an expected rise of about 0·56. Haldane has since then frequently found that his 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 on p. 30. The absence of a rise in Haldane when ordinary air is breathed is not due to the formation of lactic acid referred to in Chapter IV. He found in 1917, however, that there is a well-marked rise when a little oxygen is added to the inspired air. The failure of his 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 construction work on the Blackwall Tunnel under the Thames. At the existing air-pressure the alveolar oxygen-pressure would have $3\frac{1}{2}$ times its normal value. In breathing nearly pure oxygen while wearing a mine rescue apparatus, Haldane shares 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 L. Hill and Flack (1910) published a number of observations on the apparent effects of oxygen before and after muscular exertion. Many of their observations were concerned with the 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. We are 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 physiological advantage as regards performance of work over a man who has simply breathed air. Douglas and Haldane (1909 *c*) found 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 on p. 355, 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 unintelligible.

A clear and striking light has been thrown on this subject by the work of Briggs (1920–21). 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.

PERCENTAGE CO_2 IN EXPIRED AIR

Work in foot-pounds per minute	*Subject A*		*Subject B*	
	Breathing air	*Breathing oxygen*	*Breathing air*	*Breathing oxygen*
Pedalling with brake off	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

The reason why anoxaemia is absent in persons who are in good training will be discussed on p. 287.

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 cause of this anoxaemia will be discussed on p. 285.

A possible explanation might perhaps suggest itself, and seemed indeed, to be suggested in Chapter XI of Barcroft's book, *The Respiratory Functions of the Blood* (1914). 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 it is only within recent years that means have been found of measuring it. Hartridge and Roughton (1926–7) have, however, devised a method of measuring, with the help of the reversion spectroscope, the rate of uptake of oxygen by haemoglobin solution and have shown that it is too rapid to account for the anoxaemia of muscular exercise. Roughton (1932) and Dirken and Mook (1931) have compared the rate at which oxygen is taken up by simple solutions of haemoglobin with the rate at which it combines with the haemoglobin in a suspension of red corpuscles. They find that the rate of combination of oxygen with haemoglobin in the corpuscles may be reduced by as much as 75 per cent. or more as compared with the rate at which it combines with haemoglobin in simple solution.

We can form some conception of how great the rate of absorption of oxygen by the lungs must be 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 (1908, 1909) 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 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 found experimentally.

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 VI. Haldane's interest in carbon monoxide rose out of his connexion with coal-mining, as it had become evident to him that carbon monoxide poisoning was

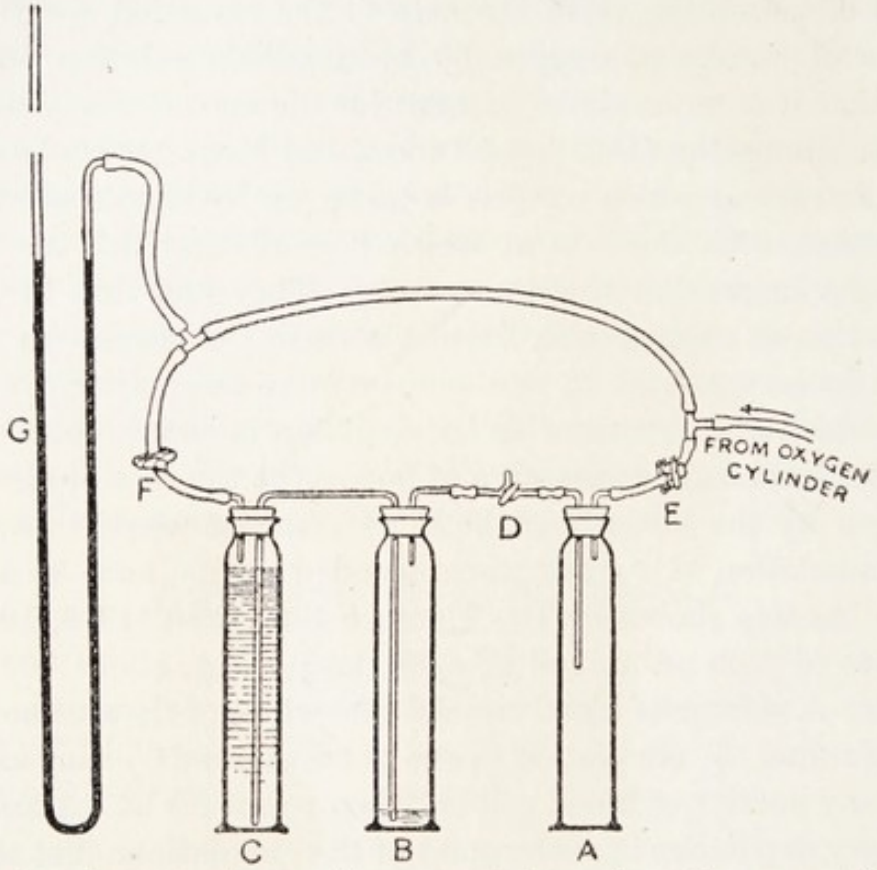


FIG. 67. Apparatus for exposing mouse to atmosphere of oxygen and CO.

a common occurrence, and he 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 that of causing anoxaemia, and Haldane's (1895 *a*) first experiments were made with a view to elucidating this matter.

He devised the following experiment (Fig. 67). 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 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.

Haldane's 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 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 c.c. of blood, which is about as much as is ordinarily taken from the blood as it passes through the tissues (p. 382).

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 seems to have no appreciable physiological action except that of producing anoxaemia. It appears to be, physiologically speaking, an indifferent gas like nitrogen, hydrogen, or methane, and, like these gases, only to act physiologically by cutting off the supply of oxygen. Its only specific physiological action, so far as we are aware, is that it has a slight garlic-like odour. It is not an 'odourless 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 seem at first sight to pay no more attention to CO than to nitrogen. Thus Haldane 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 (Haldane, 1899–1900 *a*; M. Krogh, 1915). It is true that Fenn and Cobb (1932) state that CO is oxidized by frog's muscle. They found that, when the muscle, immersed in Ringer's solution, was in contact with an atmosphere of 79 per cent. CO and 21 per cent. O_2, gas was absorbed more quickly than when air was used. They give no evidence, however, that they allowed for the fact that CO is much more soluble than nitrogen, nor did they apparently take into account combination of CO with cytochrome, which is referred to below. Hence their conclusion that CO is oxidized by muscle does not seem to be justified on the evidence. CO 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 cause 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 imperilled. If there were only one clinical lesson derived from a perusal of this book, it is to be hoped it would be that anoxaemia is a very serious condition, the continuance of which ought to be prevented if at all possible.

Although, as just explained, CO appears at first sight to have practically no physiological effect apart from its action in paralysing the oxygen-carrying power of haemoglobin, it has been shown that this view is not wholly correct. Warburg (1926) found that when more than about five times as high a pressure of CO as of oxygen was present the oxygen consumption of yeast was diminished; and J. B. S. Haldane (1927) showed that under similar conditions symptoms of want of oxygen appeared in germinating cress, moths, and rats. It thus seems that when the pressure of CO becomes much greater than that of oxygen the CO combines with, and thus paralyses, a substance which is required in the consumption of oxygen by living tissues. The probable connexion of these experiments with those of Keilin, referred to on p. 156, will be evident.

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 Haldane's case 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 $\frac{14}{300} = 0{\cdot}047$ per cent. of CO is breathed continuously for a sufficient time. If the percentage is 0·0235 per cent. the final saturation will be only one-third, and if the percentage is 0·012 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, although it holds good with extremely low percentages of CO, is profoundly modified with higher percentages by the intervention of active secretion of oxygen inwards by the lungs.

It is evident also that in air abnormally poor in oxygen a given percentage of CO will generally become more poisonous, and in air abnormally rich in oxygen less poisonous. This Haldane verified experimentally on animals. It remained to ascertain in man what effects corresponded to a given saturation of the haemoglobin; and this he ascertained by experiments on himself (1895 *b*), using for the purpose the carmine titration method referred to on p. 164.

Haldane found in these experiments that no particular effect was observed until the haemoglobin was about 20 per cent. saturated. At about this saturation any 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 any exertion 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, 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. With saturations above about 25 per cent. headache and nausea often follow exposure to CO, and with saturations above 35 per cent. this effect is very marked. The nausea, vomiting, and extreme depression are similar to those of mountain sickness (p. 203).

Shortly after these experiments Haldane (1896 *a*) 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 the heart's action is impaired through want of

oxygen, so that it is unable to 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 centre 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, when anoxaemia is caused by low partial pressure of oxygen leading to imperfect oxygenation of the haemoglobin, though normal in amount and quality, there will be marked response by the respiratory centre, even though the degree of anoxaemia is insufficient to affect the heart seriously. With CO poisoning, however, a degree of anoxaemia which is enough to affect the heart is reached before the respiratory centre responds. This points clearly to the very important conclusion that it is practically speaking to the oxygen-pressure of the *arterial* blood that the respiratory centre responds. The blood which bathes the receptor end-organs (or whatever else is sensitive to the respiratory chemical stimuli) of the respiratory centre must therefore be blood which has, under normal conditions, 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 centre 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 to be probable, *a priori*, that the respiratory centre should be continuously sampling and controlling the gas-pressures of the *arterial* blood. 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 on 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 centre does not rapidly fail in the same manner as it does when the arterial oxygen-pressure is very low, as explained in Chapter VII. 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 other modification of its properties, 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 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 used to go 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 (Douglas, J. S. Haldane, and J. B. S. Haldane, 1912) 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. Fig. 68, from a paper by J. B. S. Haldane (1912–13), shows the alterations in the dissociation curves of the oxyhaemoglobin with varying percentage saturations of the blood with CO. It will be seen, for

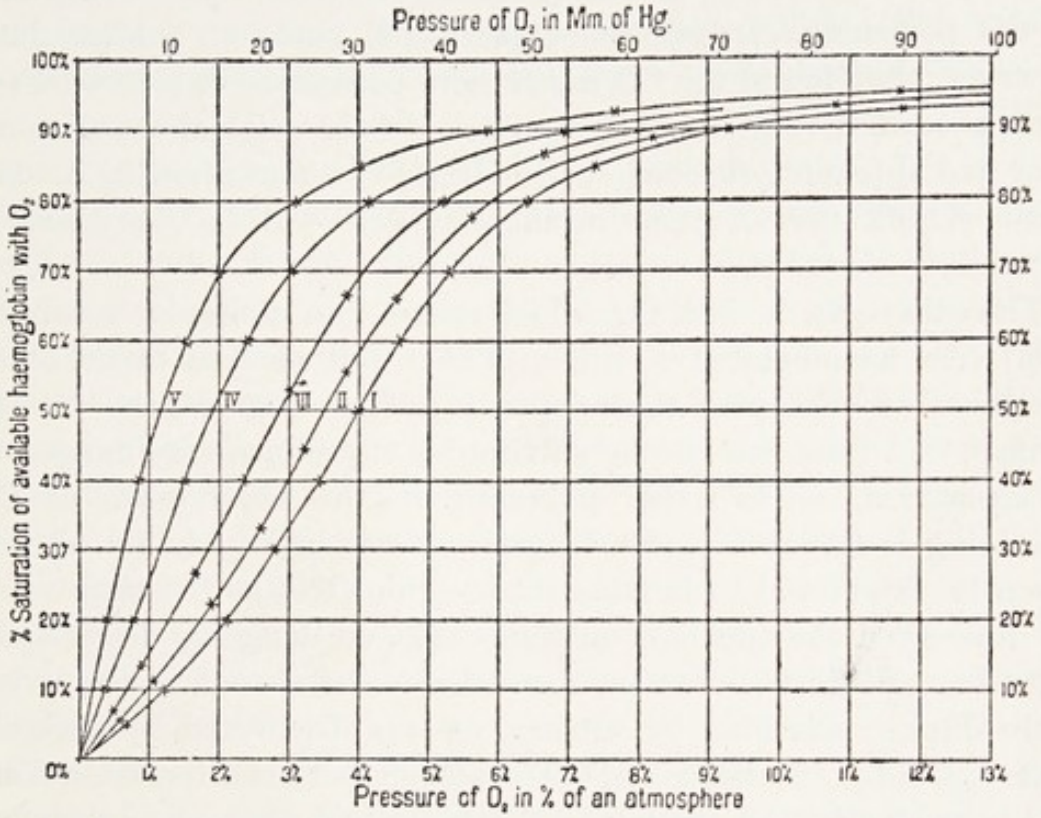


FIG. 68. Curve I, 0 per cent. saturation with CO; II, 10 per cent.; III, 25 per cent.; IV, 50 per cent.; V, 75 per cent.

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 Haldane and Lorrain Smith (1896) made on the effects of continuously breathing a definite percentage of CO all the experiments were made on themselves, and in a series which was more or less continuous from day to day. From the results of these experiments they estimated that it required about 0·06 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 at a later date, however, they found the CO much more poisonous, so that 0·04 per cent. produced very severe symptoms. In the original experiments they had apparently become 'acclimatized' without knowing it. The great significance of this 'acclimatization' will be discussed in succeeding chapters.

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 Humphry 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 Haldane (1897); 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 (p. 152).

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 diphtheria treated with chlorate of potash the blood con-

tained 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 Haldane. As ferricyanide does not penetrate the walls of the red corpuscles, and chlorates do not do so in the animals they were using, they used chiefly nitrites for the experiments; and they 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 they then, as soon as serious symptoms began to develop after administration of the dose, placed the animals in compressed oxygen. The result was 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, they 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. They also found that the methaemoglobin and NO-haemoglobin soon disappeared, leaving the blood quite normal, if death was averted. The methaemoglobin was simply reduced back again, just as on the addition of a reducing agent to a methaemoglobin solution outside the body, and then reoxygenated in the normal way. It was also evident that the reduction process was constantly going on and tending to neutralize the poison even while 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. Fig. 69 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 colour, and the arterial blood becomes, therefore, very dark, as in ordinary cyanosis. This form of cyanosis may become very marked indeed without serious real symptoms of anoxaemia being present. Thus in acute poisoning by dinitrobenzol

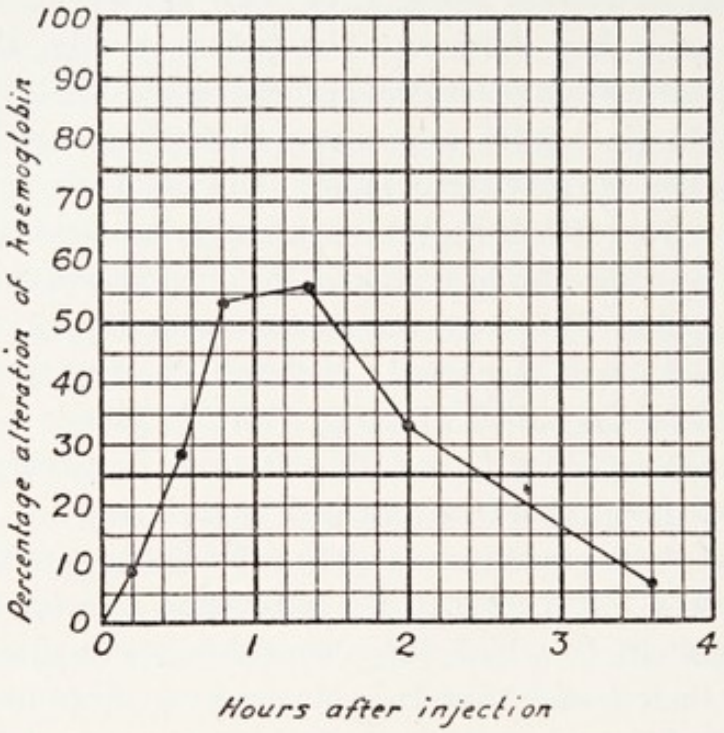


FIG. 69. Methaemoglobin due to sodium nitrite.

(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.

The fact that in nitrite poisoning the whole of the blood becomes red after death raises the question whether a similar production of NOHb is ever observed *post mortem* in man apart from cases where nitrite has been introduced into the body from outside.

Cases recorded by Banham, Haldane, and Savage (1925) seemed to indicate that nitrite poisoning may result from nitrites produced in the body by infecting organisms, and that such an organism played a very prominent part in the 'influenza' epidemic of 1918.

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 coloured

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 colour 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 coloured decomposition products are present the normal blood solution will be pinker, as the CO does not combine to give a pink colour 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 arsenuretted 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 (1900).

It was found by Miss FitzGerald (1910) that in ordinary cases of anaemia there is no appreciable diminution in the alveolar CO_2-pressure. As has been shown more fully in Chapter VI, 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 III, 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 on p. 390) 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 on p. 393.

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 XII. 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 anoxia in the tissues, together with an 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 thin curve in Fig. 19, while the CO_2-pressure will rise along the thick line in Fig. 16. 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 comparatively 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 will be obtained from the application of measures directed to increase the blood-volume. This matter is discussed in Chapter XII.

As will be pointed out in Chapter XII, 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.

IX

OXYGEN 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, or always behave, towards the respiratory gases as any very thin non-living moist membrane would behave? Or may 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 assumption 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 will be useful, before discussing oxygen secretion by the lungs, to give some account of oxygen secretion as it is now well known to exist in the swim-bladder of fishes and elsewhere.

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 gas, 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 re-establish its position of unstable equilibrium; and conversely if the small 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 (1877) 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 helplessly 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 on the other hand it succeeds in reaching the surface it immediately swallows air. Evans and Damant (1928–9) have shown that Cyprinoid fishes can inflate their swim-bladders either by swallowing air, or far more slowly, by secreting a gas rich in oxygen. 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 (1807) 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 analyse the gas, and having introduced 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 analysing 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. 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 (1896), in connexion 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 got in mostly 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 $136 \times \frac{84{\cdot}6}{100} = 115$ atmospheres, while the oxygen-pressure in the sea-water was not more than 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 has just been 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 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

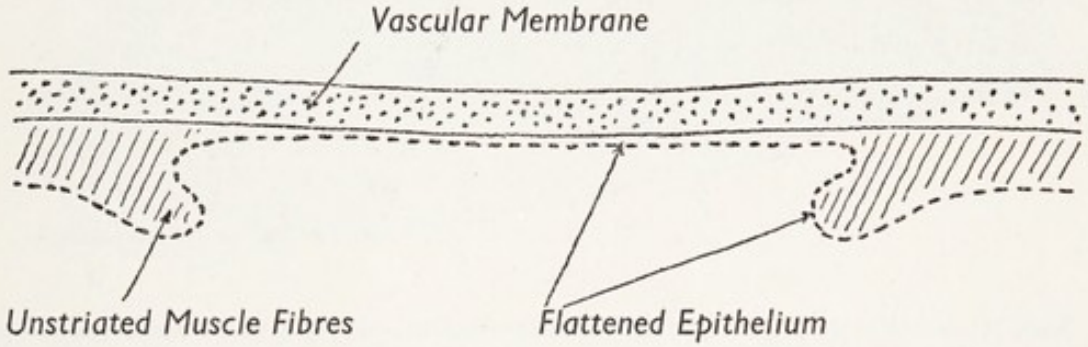


FIG. 70. Diagram of arrangement of 'oval'.

Bohr (1894) showed that the secretion after emptying the swim-bladder by puncture ceases after the branch of the vagus supplying the swim-bladder is cut. Dreser (1892) meanwhile had 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 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 (1903) that in fishes with a closed swim-bladder there is an oval window-like area on the dorsal side of the swim-bladder (Fig. 70). 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 diffuse freely into the blood capillaries, where, as already

seen, 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 per cent. of an atmosphere, as it is in sea-water; so that 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

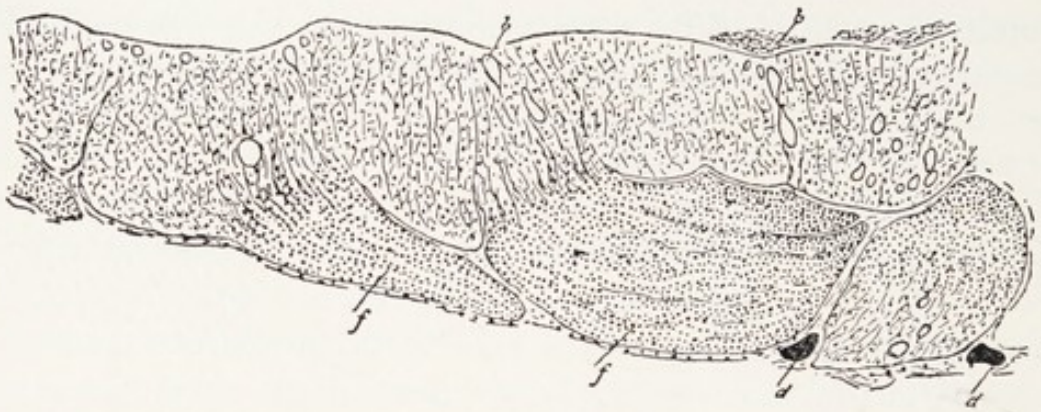


FIG. 71. Section through secreting gland of swim-bladder of *Sciaena aquila*, showing the epithelial body and underlying layer of capillary network (*f*) with gas bubbles distending the gas ducts of the epithelial body (Jäger).

'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 relaxation 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 walls 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' (Figs. 71 and 72), or else a convoluted layer of columnar epithelium (Fig. 73). In the glandular structure ducts containing gas may be seen (Figs. 71 and 72) 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.

Beneath the glandular structure is a mass of red blood-vessels,

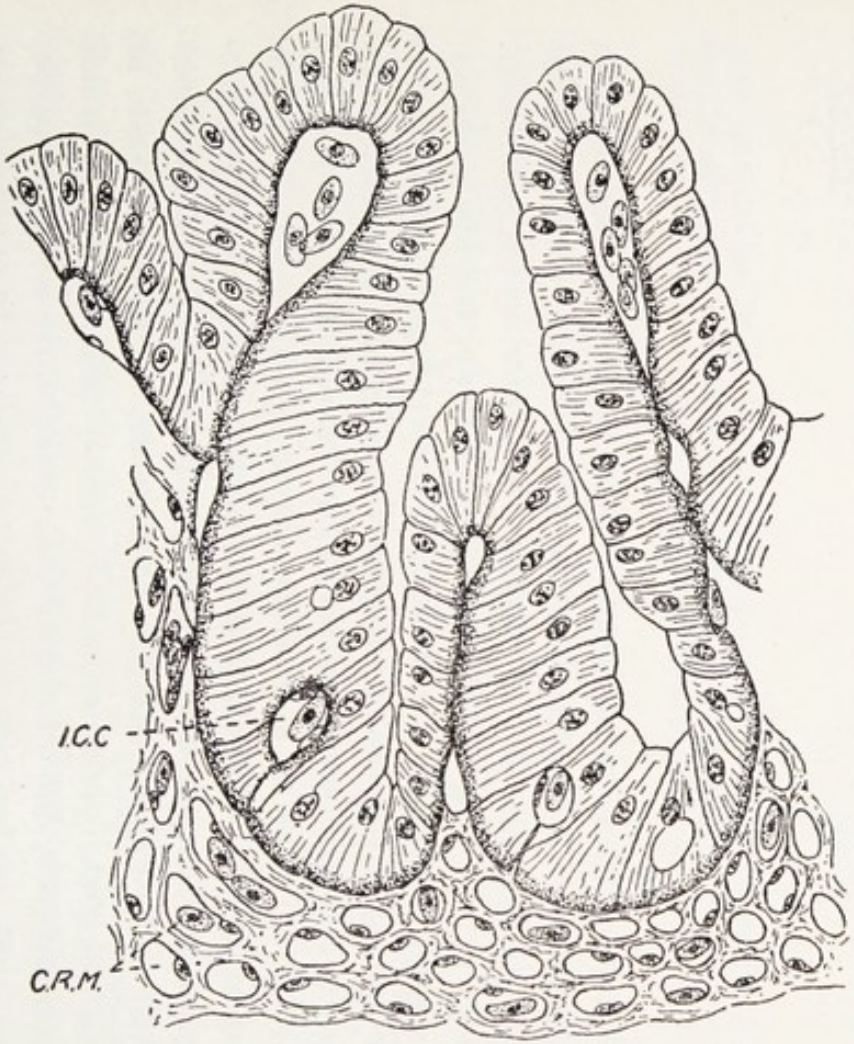


FIG. 73. (×330) Folds of the swim-bladder epithelium of *Gobius niger*. C.R.M., capillaries of the *rete mirabile*. I.C.C., intracellular capillary (Woodland).

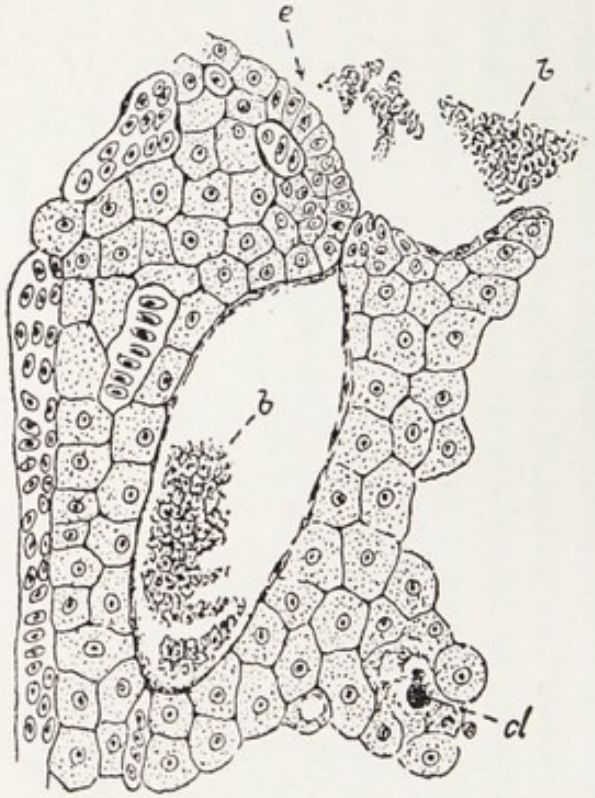


FIG. 72. More highly magnified portion of epithelial body shown in Fig. 71. A distended gas duct, with surrounding secreting cells (Jäger).

forming a structure which attracted the attention of anatomists hundreds of years ago (Redi, 1684) and came to be known as a *rete mirabile*. The arrangement of the blood-vessels in this 'red body' was studied by Woodland (1911), 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 (Fig. 74). What is the significance of this? The arrangement reminds

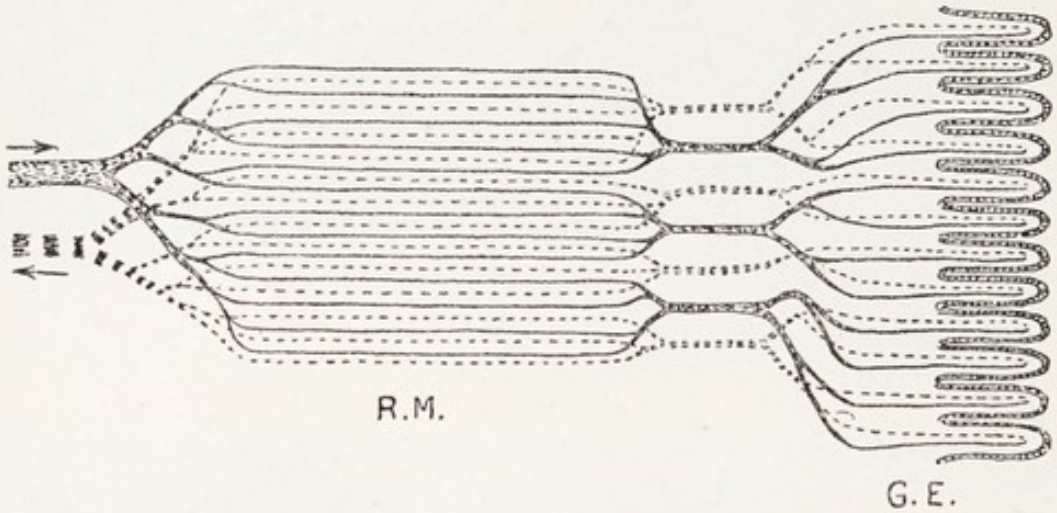


FIG. 74. Diagram of circulation in *rete mirabile* of eel. R.M. *rete mirabile*. G.E. gland epithelium. Arterioles and arterial capillaries continuous lines. Venules and venous capillaries interrupted lines (Woodland).

us of that in a regenerating furnace, where the heat carried away in the waste gases is utilized to heat 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 an explanation can now be suggested. It was discovered by Barcroft and King (1909–10) 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 mainly dependent, not on fall 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 hypothesis is supported by the existence in the arterial capillaries of a very peculiar thickened endothelium figured clearly by Woodland (Fig. 75).

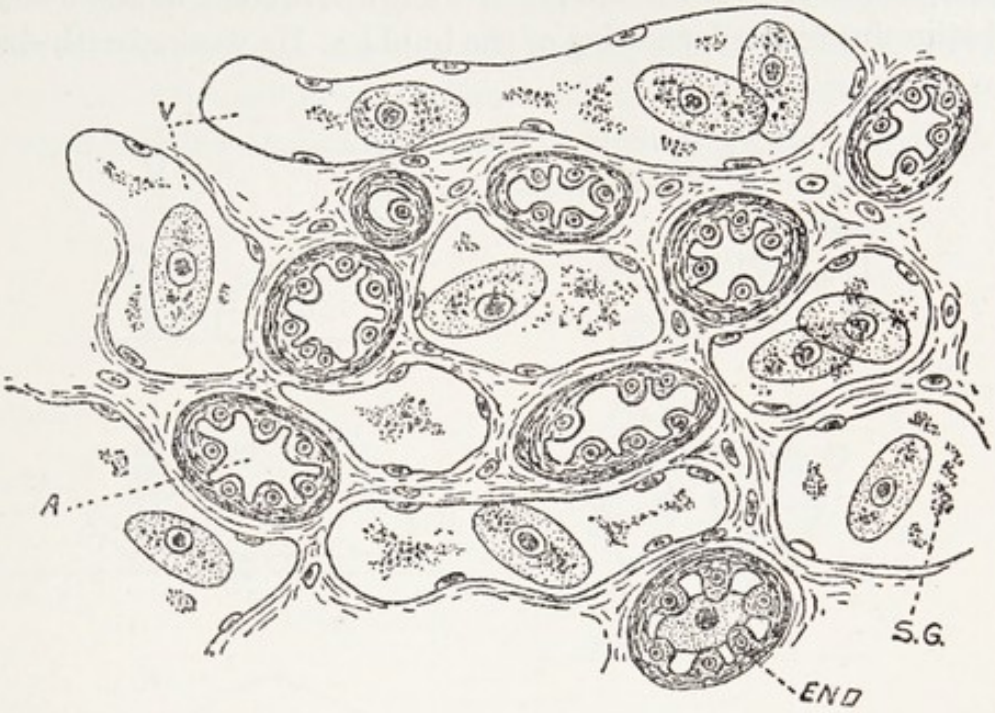


FIG. 75. (× 1000) Transverse section through anterior end of *rete mirabile* of *Gobius niger*, showing the peculiar endothelium (END) of the arterial capillaries (A) as compared with the venous capillaries (V) (Woodland).

Another very interesting case of gas secretion occurs in *Arcella*, 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 (Fig. 76). 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

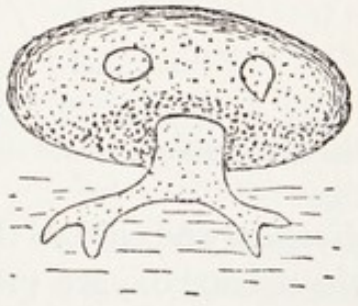


FIG. 76. *Arcella* raising itself by developing bubbles. Two bubbles visible through shell, and pseudopodia projecting through lower opening.

disappear again. The occurrence of these phenomena was described many years ago by Engelmann (1869 *a*, *b*), who brought forward clear evidence that the bubbles consist, mainly at least, of oxygen. More recently Dr. Bles (1929) took up the subject again at Haldane's suggestion, as it looked as if oxygen-want was in some indirect way the real stimulus to the formation of the bubbles. He worked with *Arcella*

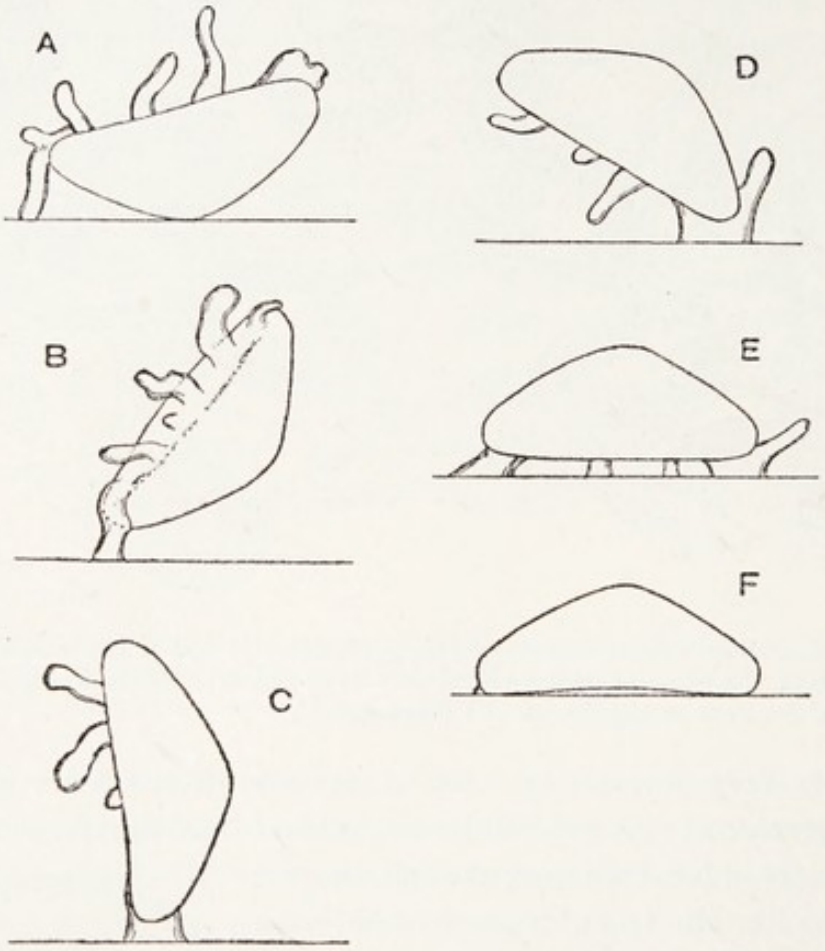


FIG. 77. Side view of a reversed *Arcella*, showing movements of its pseudopodia, and the use of one of them to right itself (Bles). (From *Quart. Journ. Micr. Sci.*, vol. 72.)

discoides and elicited the very interesting fact that quite a 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 (Figs. 77, 78, 79). 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. Although these observations were made some

years before the publication of the first edition of this book and were there referred to, they were not published in full till after the death of Dr. Bles. They were subsequently edited by Keilin and published in 1929.

Before going farther 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

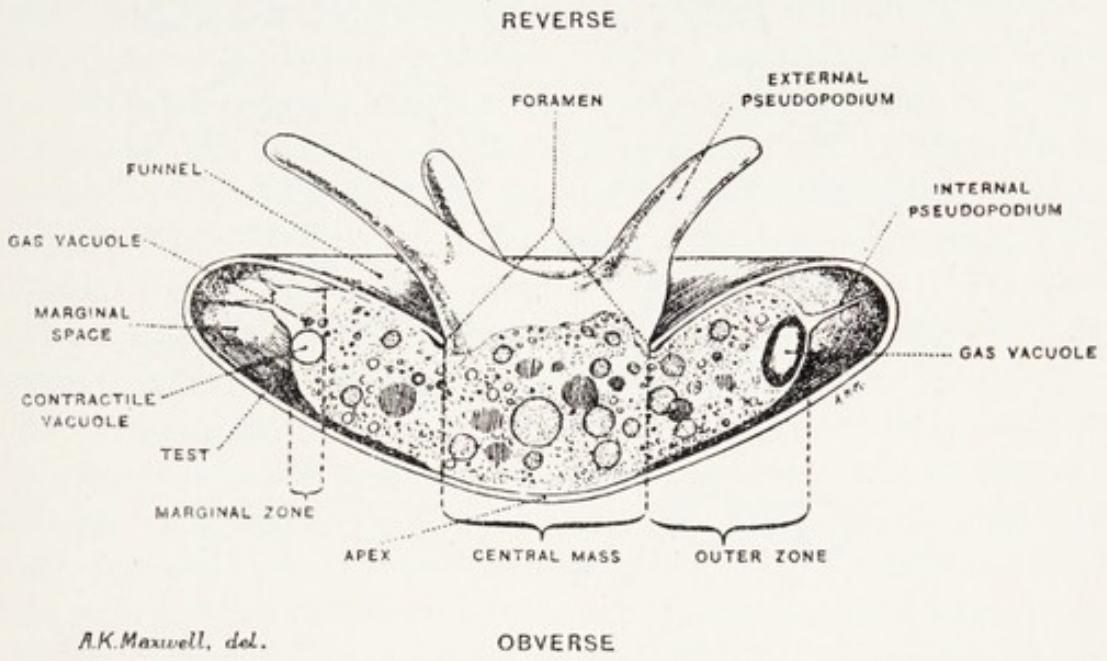


FIG. 78. A diagrammatic optical section of *Arcella* (Bles). (From *Quart. Journ. Micr. Sci.*, vol. 72.)

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° C. 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.

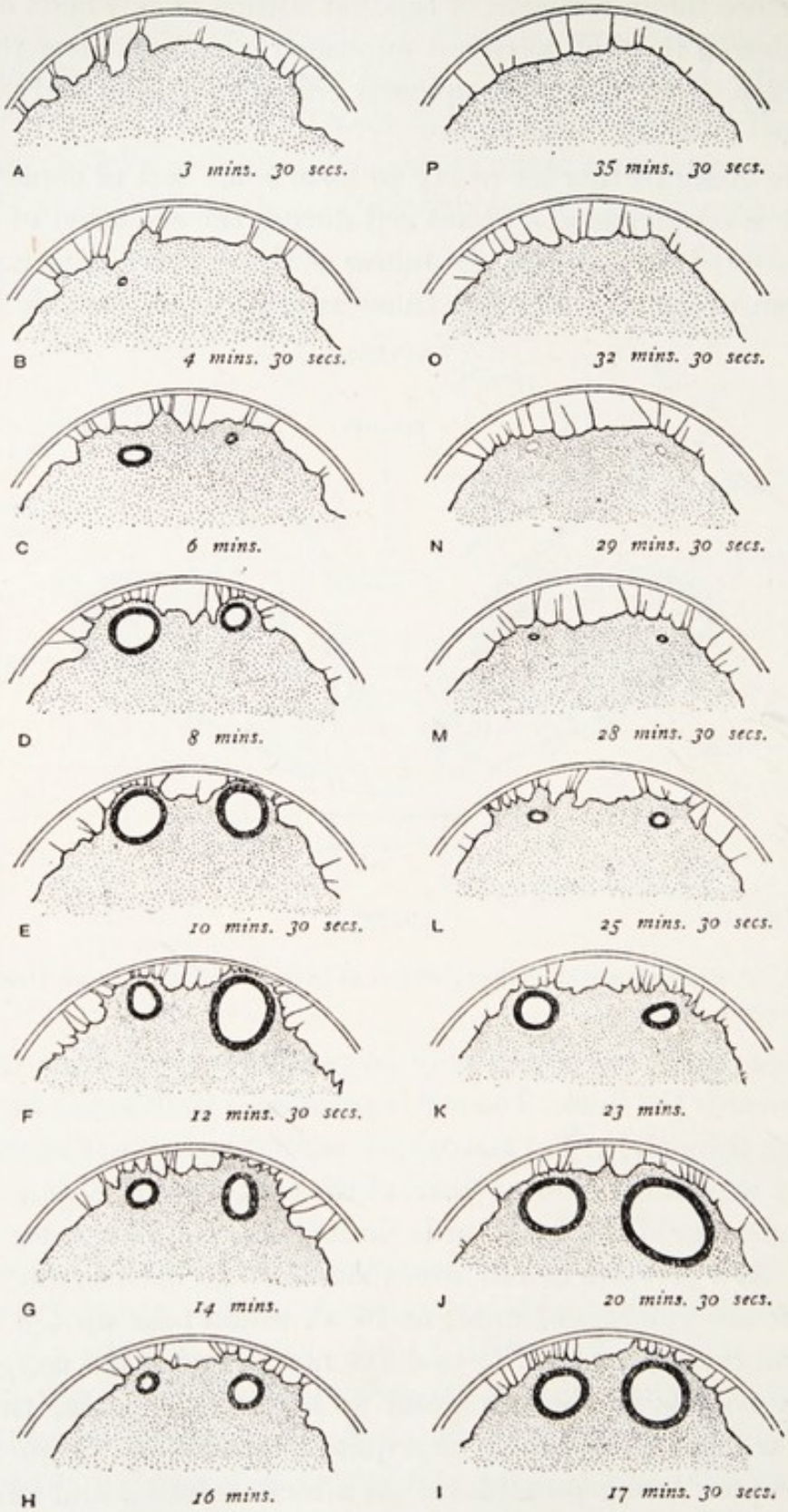


FIG. 79. Diagrams of the marginal zone of a reversed *Arcella*, showing the condition of the marginal protoplasm before, during, and after the appearance of two gas-vacuoles. Times from moment of reversal (Bles). (From *Quart. Journ. Micr. Sci.*, vol. 72.)

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 epithelium lining the swim-bladder 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 water, 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 tissue 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. A century ago Johannes Müller (1830), at the end of his famous memoir on secreting glands, 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 at which he was grasping 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 a century of careful experimental investigation that mechanical theories of secretion are impossible, as was evident enough to the genius of a great biologist like Müller, 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 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 paralyse the oxygen secretion at once by reducing the concentration of, for instance, calcium ions in the cell environment.

In a secreting cell the rate of secretion, other conditions being favourable, 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. In the swim-bladder and various other glandular structures the process is under nervous control. 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, but unless this pressure becomes greater than the surrounding mechanical pressure no gas will be liberated as such. 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 water, 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 materials, so that, for instance, an intestinal cell which takes up fatty acid may deliver fat on the other side, or a cell may take up and transform sugar 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 likely that the bubbles, for the development of which a high internal oxygen-pressure will be needed, occur in interstices of enclosed liquid in the living substance. Assuming all this, however, it still does not describe the manner in which the various activities are co-ordinated and remain so in the bringing about of actual secretion. It is only the conception of life, which, as pointed out in the Preface, fills this gap.

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 (1911) showed, however, in a beautiful series of experiments, that there is no gas secretion, and believed that there is 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 could be kept the same as that of the atmosphere, and hence less than the hydrostatic pressure of the water. The gas-pressures inside and outside the bladders would thus be the same.

Damant (1924–5), however, has brought forward what appears to be conclusive evidence that *Corethra* adjusts its buoyancy by contracting or relaxing the walls of the air-sacs. He found no evidence for passage of water into or out of the bladders.

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 this purpose Pflüger devised an instrument which he called the aerotonometer, its object being to measure the partial pressures or tensions of the 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 aerotonometer 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 by 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.

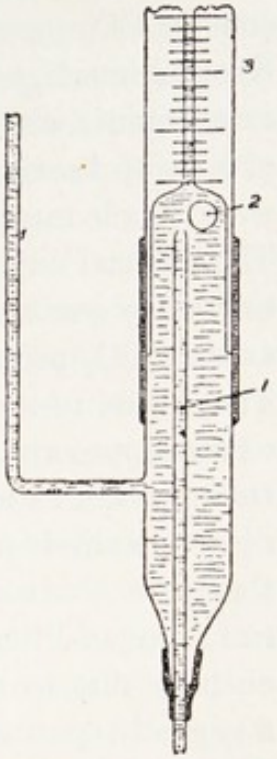


FIG. 80. Krogh's micro-aerotonometer, showing inlet and outlet for blood, lower part of measuring tube, and air bubble.

The conclusion drawn from the actual experiments by Pflüger and his pupils (1871–3) 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.

The question was taken up again by the late Professor Christian Bohr of Copenhagen, one of Ludwig's pupils (1891). Bohr improved the aerotonometer, 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 (1896) of Liège soon afterwards made a further series of experiments, all of which seemed to tell in favour of Pflüger's interpretation.

About fifteen years later the aerotonometer 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 aerotonometer, 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 analysed 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 (see Fig. 80).

Before his death Bohr published some experiments made with Krogh's aerotonometer 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 (1910 *a*), the results of a careful series of experiments on animals under conditions which were much more nearly normal than in any previous experiments. The arterial oxygen-pressures were 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 favour 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	*Pressure of CO_2 in*		*Pressure of oxygen in*	
	alveoli	*blood*	*alveoli*	*blood*
1·36–1·43	3·6	3·7	12·0	10·0
2.10–2·12	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 farther, a fallacy should be pointed out in the interpretation of the aerotonometer 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 on p. 53. 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. This conclusion is certainly correct; and it agrees, as he points out, with all the indications given by the work of Haldane and Priestley (1905) 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 Haldane was just beginning the serious study of mine gases and the physiological effects of vitiated air, and Bohr's results interested him greatly. A year or two later Haldane and Lorrain Smith made a visit of several weeks' duration to Copenhagen and carried out some research work in the laboratory under Bohr's direction, thus learning a great deal which they could not have learned in England about existing methods of blood-gas investigation, and, far more important, getting into personal touch with Bohr himself. It is fitting to acknowledge the indebtedness of Haldane and Lorrain Smith, and indirectly of other physiologists in Great Britain and America, to Bohr and the Copenhagen School of Physiology.

The difficulties of the aerotonometer method of determining the oxygen-pressure of arterial blood were at that time very evident, and Haldane cast about in his mind for some better method. Soon afterwards he began the investigation of carbon monoxide in connexion with its occurrence in mines; and the results of this investigation, and the colorimetric method of blood examination which he worked out during the investigation, suggested a new means of attacking the problem which Ludwig had originally proposed.

The general principle of this method has already been explained in Chapter VI and depends on the fact that within wide limits the relative amounts 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 respective affinities for 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 should

therefore only be 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-pressure calculated from a knowledge of the relative affinities of the two gases for haemoglobin, as determined outside the body. If the oxygen-pressure in the blood leaving the lung capillaries is the same as that in the alveolar air, the percentage saturation with CO of the blood in the rest of the body will become the same as that of blood saturated directly with air containing the same percentages of CO and oxygen as in the alveolar air; but if there is active secretion of oxygen inwards the percentage saturation of the blood will be correspondingly lower.

The method seemed simple in principle, but it turned out to be as full of pitfalls as the use of the blood-pump, aerotonometer or spectrophotometer. The chief of these were found to depend upon (1) the assumption that Hüfner's oxyhaemoglobin dissociation curve, then and for many years later quoted in every text-book, 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 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 also probably some errors in the colorimetric titrations owing chiefly to failure to take precautions, which subsequent experience showed to be necessary, against decomposition of blood solutions during long experiments.

The first experiments were made by Haldane and Lorrain Smith (1896) on men, the subject of the experiments 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 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 led Haldane to form the conclusion that, in these experiments, he and Lorrain Smith had become acclimatized

more or less to want of oxygen by frequently breathing CO, so that at the time they were no longer ordinary normal subjects. They 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 they were surprised to find that the former percentages were too high for them, and they suspected that there must have been some error about the percentages breathed in the first series of experiments. On reconsidering the matter, however, Haldane was quite unable to see how there could have been an error about the percentages breathed. It now seems practically certain that he and Lorrain Smith had become acclimatized and had consequently developed during the experiments a considerably higher arterial oxygen-pressure than normal persons would have had, or than they themselves would have had, if they had not absorbed so much carbon monoxide as in fact they did during the experiments, and thus become somewhat short of oxygen.

Their next experiments (1897–8) were on various small animals—chiefly mice. Such small animals are specially convenient, as their 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 surprise to Haldane and Lorrain Smith, as they had expected that when oxygen was breathed, active secretion of oxygen inwards would cease. The fact that apparently it did not do so ought to have aroused their suspicions of the correctness of the measurements. The phenomena observed when the oxygen percentage or the barometric pressure was diminished led them, apart from the measurements, to conclude that secretion of oxygen inwards became more active; but in their estimations of oxygen-pressure they were depending on the substantial correctness of Hüfner's dissociation curve and, when this curve was subsequently found to be totally incorrect, their estimations 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 the work of Haldane and his colleagues as described in Chapter VI. Douglas and Haldane (1912 *a*) then took up the old subject again, but with far more complete knowledge of the material they were dealing with. Professor Krogh had also kindly informed Haldane in a letter of some experiments he had made (subsequently published, 1910) showing that in the blood of a rabbit the relative affinities for haemoglobin of oxygen and CO were different from those in the blood of the ox; and Douglas and Haldane found, as already mentioned on p. 168, 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.

It was necessary, therefore, to modify the method. Each animal was exposed for a sufficient time to a definite percentage of CO in a bottle and was then drowned *in situ*. Some of its blood was then placed, undiluted and at body temperature, in the saturator and was thoroughly saturated in the presence of some of the same mixture of air and CO that the animal had been breathing. The percentage saturations with CO in the haemoglobin of 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 first table on p. 271 shows the results.

On looking down this table it will be seen that as long as the percentage of CO did not exceed about 0·03, or the percentage saturation of the blood did not rise above about 28, 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.

The old experiments with oxygen, which had puzzled Haldane and Lorrain Smith so much, were then repeated. The results were as shown in the second table on p. 271.

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, how-

Animal used	*Percentage of CO*	*Duration of exp. in minutes*	*Percentage saturation of haemoglobin with CO*		*Arterial oxygen-pressure in percentage of existing atmosphere*[1]
			In vivo	*In vitro*	
Mouse	0·016	60	26·2	17·2	12·2
,,	0·0165	50	26·7	19·5	13·9
,,	0·018	45	26·0	18·5	13·5
,,	0·019	33	19·7	12·5	12·1
,,	0·025	43	25·6	17·6	13·0
,,	0·046	40	29·1	22·7	15·0
,,	0·053	40	37·7	30·2	16·2
,,	0·100	32	45·0	43·0	19·3
,,	0·129	31	56·4	56·3	20·8
,,	0·198	—	57·6	56·5	20·0
,,	0·213	13	59·1	75·5	44·7[2]
,,	0·244	12	67·3	71·7	25·7[2]
,,	0·255	60	60·1	62·8	23·3
,,	0·260	25	67·0	64·7	18·9
,,	0·262	20	66·4	73·7	28·2
,,	0·275	25	66·5	76·9	35·9
Rabbit	0·029	140	28·0	18·7	12·4
Same rabbit	0·191	150	58·2	56·0	19·1

[1] Calculated without reduction for aqueous vapour in the alveolar air.
[2] Mouse died.

ever, 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 the average, different in mouse-blood from what they are in human blood, or in the ox blood which was then taken as a fixed standard. This led Haldane and Lorrain Smith 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

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*[1]	
		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

[1] Calculated without reduction for aqueous vapour.

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 re-calculates 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 is no evidence of active secretion of oxygen inwards, but that with higher percentages of CO there is 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 on p. 238, are simply those of oxygen-want: moreover, the secretion did not occur 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 on p. 157, 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 centre is excited, nervous impulses pass down secretory fibres in the vagus nerve and excite secretion in the lungs. Haldane and Lorrain Smith tested this hypothesis and found that when the respiratory centre was excited by excess of CO_2 there was not the slightest rise in the arterial oxygen-pressure. Hence the secretion has no direct connexion with the ordinary activity of the centre in producing respiratory movements; and the stimulus to secretion is not a hydrogen-ion stimulus.

Haldane and Douglas also made a series of determinations on man. In view of the results of the mouse experiments they were anxious to work with low percentages of CO; but if they had used the old method of Haldane and Lorrain Smith, it would have taken so long before equilibrium was reached between the CO in the air and that in the blood that the experiment could hardly have been completed during a winter daylight. They 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 be established very quickly. The method finally adopted was as follows (see Fig. 81).

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 calibre

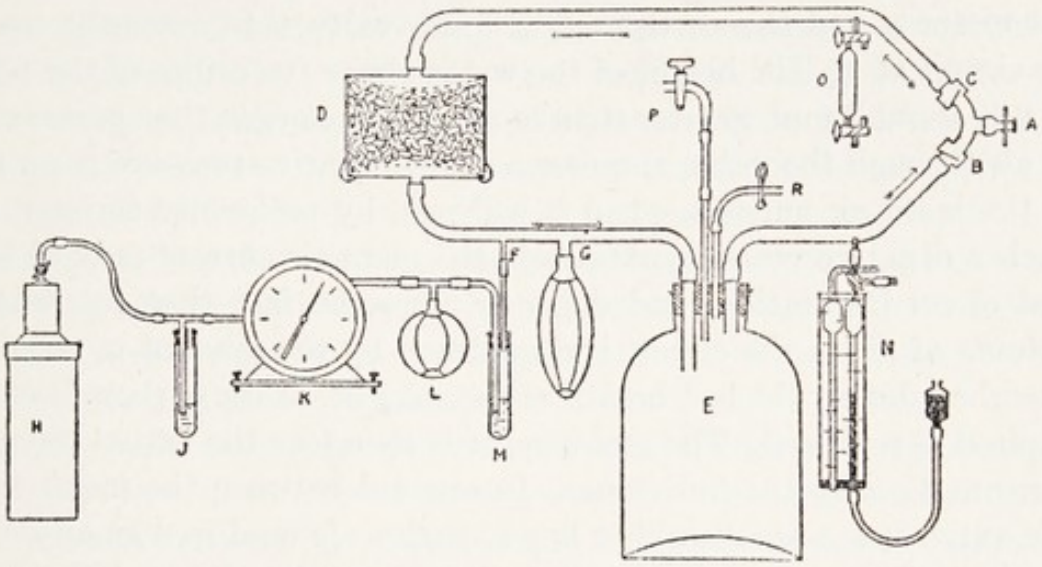


FIG. 81. Apparatus for determining the arterial oxygen-pressure in man.

to the tin vessel D which is filled with small fragments of solid caustic soda and is made of such a size (diameter 23 cm., depth 12 cm.) 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 litres capacity, which is connected by another pipe with the inspiratory valve B. The entrance and exit pipes of E are so arranged 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 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 each 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-supply shall be pure; the small amount of nitrogen contained in ordinary cylinder oxygen renders its use inadmissible. In all the later experiments, therefore, oxygen made by the action of water on 'oxylith' in the generator H was used. 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 J to air, 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 thus passes out to air through the valve J, unless a slight negative pressure is set up in the main air current, when it will pass by preference through M. Such a negative pressure obtains in the main air current 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 during the last breath of the subject, as the carbon dioxide 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 provision 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 ensure 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.

It was 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 re-established 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 the apparatus is about 15 litres, and it may therefore be presumed that the whole of it goes through the alveoli of a resting adult subject in three minutes. Douglas and Haldane 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 their experiments varied on different occasions from twenty minutes to one hour. So far as they 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 they adopted as a rule a period in excess of this as a matter of precaution. In their earlier experiments they passed about 2 c.c. 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 they gave it up, and the respiration apparatus thereafter always contained air free from CO at the beginning of the experiment.

Analyses of the inspired air were made several times during the course of the experiment, as it was naturally important for their 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. Of this blood 0·05 c.c. was then introduced into the saturating vessel in the manner described in their 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 filled as soon as possible 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 complete.

Their first experiments on man were taken up with determining the arterial oxygen-pressure under as normal conditions as possible, and they especially wished to guard against the effects of deficiency of oxygen. They 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 table printed on p. 278.

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.

They 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 they 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 CO_2 in the alveolar air had precisely its normal value, namely, 5·6 per cent. when measured dry, and there is therefore no reason to suppose that the alveolar air samples were other than normal.

EXPERIMENTS ON ARTERIAL OXYGEN-PRESSURE OF MEN

		Inspired Gases in per cent.														
		5′ after start		*15′ after start*		*Just before alveolar sample taken*		*Into saturator at finish*		*alveolar air gases*		*Percentage saturation of haemoglobin with CO*		*O_2-pressure of arterial blood in per cent. of existing atmosphere; not corrected for moisture.*	*O_2-pressure of arterial blood in per cent. of O_2-pressure of alveolar air.*	
Date	*Subject*	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	*In vivo*	*In vitro*			
14.12.10	C. G. D.	19·54	0·05	19·75	0·00	..	..	20·55	0·08	(13·6)	(5·6)	23·1	17·2	14·2	(104·4)	Normal oxygen atmosphere. Rest.
16.12.10	,,	22·50	0·04	..	..	..	..	22·07	0·15	15·38	5·63	23·0	16·0	14·1	91·6	
17.12.10	J. S. H.	19·57	0·02	19·72	0·02	..	..	19·75	0·06	12·46	5·51	23·5	16·6	12·8	102·7	
20.12.10	,,	21·70	0·07	21·47	0·07	..	..	21·34	0·16	14·13	5·51	23·2	15·8	13·2	93·4	
21.12.10	,,	25·85	..	25·38	..	..	..	22·39	0·11	14·62	5·63	22·2	17·1	16·2	110·8	
23. 5.11	C. G. D.	21·78	0·02	21·13	0·10	22·64	0·13	23·19	0·20	(15·7)	(5·6)	23·85	16·35	14·45	(92·0)	
29. 5.11	,,	19·79	0·29	19·80	0·33	20·22	0·32	20·17	0·35	14·06	5·64	23·7	17·6	13·9	98·9	
														Mean	99·1	
22.12.10	C. G. D.	28·00	..	28·58	0·03	..	..	27·88	0·11	21·65	5·47	23·2	19·0	21·7	100·2	High oxygen atmosphere. Rest.
24. 5.11	J. S. H.	32·73	0·20	31·86	0·13	31·20	0·16	30·19	0·16	23·46	6·01	23·5	18·5	23·1	98·5	
11. 1.11	C. G. D.	12·27	0·02	12·56	0·02	..	..	11·79	0·18	5·98	4·93	21·7	16·0	6·9	115·4	Low oxygen atmosphere. Rest.
13. 1.11	,,	12·82	0·02	13·61	0·03	..	..	13·34	0·11	6·99	4·78	23·0	17·7	8·5	121·6	
16. 1.11	,,	11·47	0·04	11·27	0·04	10·71	0·12	10·26	0·18	6·40	3·48	22·9	21·6	8·2	128·1	
23. 1.11	J. S. H.	12·03	0·00	12·00	0·01	11·19	0·04	11·74	0·12	5·53	4·74	23·1	16·4	6·2	112·1	
10. 2.11	J. S. H.	21·10	0·21	21·00	0·44	18·46	0·57	18·42	0·58[1]	12·82	5·39	23·3	20·9	16·0	124·8	Moderate work with one arm. — Normal oxygen.
11. 2.11	,,	21·19	0·24	..	..	20·56	0·84	21·43	0·80[2]	15·11	5·33	22·7	21·6	19·9	131·7	
27. 2.11	C. G. D.	21·88	0·11	21·84	0·11	20·66	1·30	20·53	1·11	15·49	5·69	23·4	24·0	20·9	135·0	Severe work with one arm. — Normal oxygen.
26. 4.11	J. S. H.	17·95	0·33	17·94	0·38	17·68	0·36	18·05	0·36	11·64	5·22	21·1	18·1	14·9	128·0	
27. 4.11	C. G. D.	22·32	0·96	22·88	0·90	23·49	1·07	24·12	0·82	19·38	4·43	24·25	24·75	24·8	128·0	
8. 2.11	C. G. D.	12·50	0·02	..	..	12·87	0·38	14·72	0·24[3]	10·20	3·30	23·5	23·9	15·1	147·6	Moderate work with one arm. Low oxygen.

[1] CO_2 added to saturator to 7·02 per cent.
[2] CO_2 added to saturator to 4·70 per cent.
[3] CO_2 added to saturator to 4·64 per cent.
The figures in brackets are calculated values.

Having thus obtained 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, Douglas and Haldane were naturally anxious to test the matter farther 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 they 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 they 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 CO_2-percentage. Both the subjects noticed distinct hyperpnoea for some time after beginning to breathe into the respiration apparatus, and that this was accentuated on the slightest movement. The face remained of a distinctly bluish colour 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 observed once or twice, indicating that the want of oxygen had induced a real hyperpnoea, which had lowered the general CO_2-pressure in the body considerably.

The calculation of the 'arterial' oxygen-pressure from the data afforded by these experiments is performed as follows: let x be the percentage saturation of the blood with CO *in vivo*; let y be the percentage saturation of the same blood *in vitro* when in equilibrium with the air in the saturator, and suppose that the percentage of oxygen in this air is 20·9. Then, since the percentage of CO in the air in the saturator must have been identical with that in the alveolar air when complete equilibrium of concentration of CO had

been reached between the blood and the alveolar air, the oxygen-pressure (P) in the blood leaving the lungs would be given by the equation $P = 20{\cdot}9 \times \frac{y}{100-y} \times \frac{100-x}{x}$ if the arterial blood were fully saturated with oxygen and CO, and if the air in the saturator contained the same percentage of CO_2 as the alveolar air.

This, however, is not the case, and consequently it is necessary to apply a correction to the figure calculated by the above equation. This correction, which is particularly important in experiments with low percentages of oxygen, is obtained as follows:

If the tensions of CO and oxygen are together sufficient to saturate the haemoglobin completely the respective percentage saturations with the two gases will, as described in Chapter VI, be proportional to the partial pressures of the two gases. Hence, if we assume that the haemoglobin is completely saturated (in the absence of CO_2), the curve indicating the percentage saturation with CO, when the CO-pressure (as in the experiment) is constant and the oxygen-pressure is varied, will be a rectangular hyperbola (Fig. 50). It is found, however, that the actual curve (the haemoglobin being incompletely saturated) is not a hyperbola but runs as the lower curve in Fig. 51. Suppose the blood of the subject of the experiment was found to be 22 per cent. saturated. This value on the hyperbola corresponds to a partial pressure of 7·8 per cent. of an atmosphere, and on the actual dissociation curve to a partial pressure of 6·8 per cent. This figure gives the correct arterial oxygen-pressure.

It is necessary, therefore, in order to obtain the arterial oxygen-pressure to know the COHb dissociation curve of the blood of the subject (*a*) calculated on the assumption of complete saturation with a constant CO-pressure equal to that found in the alveolar air and a varying oxygen-pressure but no CO_2-pressure, and (*b*) determined for the same constant CO-pressure, varying oxygen-pressure, and a CO_2-pressure of 40 mm. Hg.

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. It was therefore decided to make use of work with only one arm. This enabled the work to be pushed 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 was 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 this could be done in physiological units by observing, by means of the small gas-meter, the effect on the oxygen consumption of the subject per minute. What is termed 'moderate work' in the table on p. 278 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 it was found sufficiently tiring when it was performed with one arm only, and kept up for half an hour at a time.

The lower part of the table on p. 278 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 mm. and 15·6 mm. above the oxygen-pressure of the *inspired* air (allowing for aqueous vapour).

In the last experiment in 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 colour due to the low oxygen, and became of a normal red colour. It was also noticed many years ago by Loewy (1895) that slight muscular exertion produced a marked improvement in the subjective symptoms of want of oxygen in a steel chamber at low atmospheric pressure. The results of Douglas and Haldane on the arterial oxygen-pressure during muscular exertion furnish an evident clue to the meaning of these observations.

In Chapter VII reference has been made to some of the results of the Pike's Peak Expedition (Douglas, Haldane, Henderson, and Schneider, 1913). One of the objects of this expedition was to determine whether the want of oxygen due to the rarified air at 14,000 feet did not produce active secretion of oxygen inwards. The method used by Douglas and Haldane at Oxford was employed with every precaution against errors. The results obtained were quite unmistakable. It was found that as soon as acclimatization to the low barometric pressure was established the 'arterial' oxygen-pressure became considerably higher than that of the alveolar air. The table on p. 283 shows the 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' oxygen-pressure was only about 15 per cent. above the alveolar oxygen-pressure, whereas three days later, after acclimatization, the excess was 100 per cent.

If we were to calculate the percentage saturation of the arterial blood in these observations from the arterial oxygen-pressure as given by the carbon monoxide method, it would appear as if the mixed arterial blood must have been almost as highly saturated with oxygen as at normal atmospheric pressure. This inference would, however, be quite unjustifiable; and there can be no doubt that even after acclimatization the body is still reacting to some degree of anoxaemia, since otherwise there would be no stimulus to explain the responses of acclimatization. What the carbon monoxide method gives is not the oxygen-pressure of the mixed arterial blood, but the average oxygen-pressure of the blood leaving the alveoli. The two

Date	*Subject*	*Alveolar air Gases per cent.*		*Percentage saturation of blood with CO*		*O_2-pressure of arterial blood in percentage of the existing atmosphere without allowing for aqueous vapour*	*O_2-pressure of alveolar air in mm. Hg (at 37° moist)*	*O_2-pressure 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

values differ considerably owing to the facts discussed on p. 291, and at low atmospheric pressures the difference must be considerably exaggerated. In spite of the high oxygen-pressures given by the carbon monoxide method the mixed arterial blood after acclimatization on Pike's Peak must have had a quite considerably lower oxygen-pressure than at sea-level, though the fall was not sufficiently great to produce appreciable cyanosis.

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 Haldane and Lorrain Smith made jointly on themselves—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 they were not acclimatized against anoxaemia.

It is easy to see the physiological advantage of oxygen secretion as a defence 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 there was an enormous secretory pressure such as has never been found experimentally. It can thus be readily understood why there is no secretion during rest under normal conditions, as the experiments clearly showed to be the case. It was only during work that the experimental results showed secretion. During work, however, the venous blood returning to the heart is much more venous, and as a consequence the blood in the less completely ventilated parts of the lungs will tend to be less completely saturated with oxygen than during rest. In consequence the mixed arterial blood will tend to become less saturated. Secretion can therefore help greatly against this state of affairs, which may also be contributed to by incomplete

attainment of equilibrium between the gas-pressures in the alveolar air and the blood.

It must be pointed out that the experiments which Douglas and Haldane 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. It was known already that the stimulus to oxygen secretion came from oxygen-want of the tissues. It was known 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 there was no index of what the fall might be in the absence of secretion. They 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 the original experiments of Douglas and Haldane, and those on Pike's Peak, were carried out, a good deal of evidence, both direct and indirect, has accumulated in confirmation of the conclusions drawn from these experiments. This evidence must now be considered. In Chapter VIII we summarized the very clear physiological evidence 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 IV: 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, which is the physiological indication of the presence of lactic acid in the blood. 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 shown directly by the fact that a very moderate increase in the oxygen percentage of the air breathed relieves the symptoms.

The observations of Harrop (1919) also are very significant in this connexion. He determined 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 exertion. The deficiency found in the blood just after exertion is far greater than could be accounted for by experimental error.

Douglas and Haldane (1922) found that during work the blood-flow does not increase in anything like the same proportion as the general metabolism, with the result that the oxygen-pressure of the mixed venous blood falls considerably, particularly since it contains a very large proportion of blood from the active muscles. The stimulus to secretion must, apparently, be some substance produced in the tissues, and particularly in active muscle.

Strong confirmation of this is afforded by the fact that in experiments on unacclimatized persons at low pressure in steel chambers the symptoms and the colour of the lips are greatly improved by moderate work, as with a hand ergometer. The observations of Loewy mentioned above (p. 282) in this connexion were strikingly confirmed by Schneider and Clarke (1925), and would seem to be very difficult to interpret if oxygen secretion does not occur.

In ordinary persons not in good physical training a very moderate diminution in the atmospheric pressure is quite sufficient to cause a noticeable excess of hypernoea 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 Briggs (1920–1), described on p. 234, 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 favour 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 centre and central nervous system as already described in Chapters VII and VIII. In persons who are in good physical training these effects are in abeyance because, as one part of physical training, the lung 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, 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 occurs whether a man takes exercise or not.

In this connexion may be mentioned the result of an experiment which Haldane made 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. Haldane therefore shut himself 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. The experiment was then terminated 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. There was no trace of mountain sickness or any other symptom of anoxaemia, and Haldane's lips were just as red as usual, though from other experiments described in Chapter VII it was known that without acclimatization he would have broken down hopelessly in the existing atmosphere. A laboratory attendant who afterwards went into the chamber along with Haldane 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 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 IV.

In a series of experiments carried out by Haldane, Kellas, and Kennaway (1919–20) these two effects were separated. One of the 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, whose exposures are discontinuous. The effects produced before acclimatization on Haldane, Kellas, and others, by an exposure to 320 or 330 mm. Hg barometric pressure, are described in Chapter VII. To obtain acclimatization the method of exposure for 6 to 8 hours to atmospheric pressures of 500, 430, and 360 mm. on three successive days was used. It was found, however, that the 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 morning. There was also no lasting increase in haemoglobin percentage. It appears, therefore, that any acclimatization obtained under such circumstances must be due to increased power of oxygen secretion.

These experiments show that there was marked acclimatization, which, however, was limited in amount. When unacclimatized, Haldane 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 the subjects of the experiment stayed at 315 mm. for a considerable time, during which, though they were distinctly

blue, Haldane 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 J. B. S. Haldane acted as an unacclimatized control. He entered the chamber and stayed for some time at 366 mm.; but after 2 hours he was so much affected that he had to be let out. His breathing had become increasingly rapid and shallow, and he had gradually sunk into a partially stupefied 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 ascend to high altitudes pretty frequently, must be capable of acquiring some degree of acclimatization. Acclimatization under such conditions was noted long ago by Glaisher in connexion with his occasional high balloon ascents. An equal degree of acclimatization can undoubtedly be maintained in a similar manner by good physical training. At heights of about 20,000 feet an airman in good physical 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 VIII renders an airman totally incapable of going to any appreciable height without an oxygen apparatus.

Since the first edition of this book was published a great deal of information about acclimatization at high altitudes has accumulated as a result of the experience of the members of various expeditions to the Himalayas.

Somervell, a member of the 1922 Everest Expedition, records (Bruce, 1923) that the first effect of altitude, noted on the way to Base Camp (16,500 feet), was breathlessness. A few members of the expedition had headaches and attacks of vomiting, and at 17,000 feet Cheyne-Stokes respiration was noted when lying down. After a few weeks all ill effects, save breathlessness, disappeared. When harder work on the mountain was begun the effects of acclimatization became still more evident. Thus Somervell found his first ascent from Camp 3 (21,000 feet) to the North Col very exhausting, but after a few days at this camp he found he could do the same climb quite easily. Later Somervell felt quite comfortable at 26,000 feet, even when his pulse was 180 and his respirations 50 to 55 per minute while climbing.

Odell records (Norton, 1925) that during the second Everest

Expedition he found no benefit from breathing oxygen at 25,000 to 26,000 feet during his second ascent to 27,000 feet.

Careful observations with regard to acclimatization were made by Raymond Greene during the Kamet Expedition of 1931. He writes (Smythe, 1932) that breathlessness and Cheyne-Stokes respiration were noted on first reaching Base Camp (15,800 feet), but these symptoms passed off after one night. As increasing height was gained above Base Camp a steady increase of respiratory symptoms occurred, and though as much time as possible was given to acclimatization, it was not until Kamet had been climbed that the climbers found themselves able to move quickly without laboured breath. Later, however, the party were conscious, on the second part of the expedition, of a greater degree of acclimatization, so that they could climb at 20,000 feet at almost Alpine speed.

During the 1933 Everest Expedition Raymond Greene again made important observations on acclimatization. This expedition was the first to lay down a policy of careful acclimatization and to abide by it. They found absence of serious respiratory difficulty throughout. Little distress was felt during exercise, and of the fourteen climbers thirteen reached the North Col without undue distress. The other was ill and had to return. Above the North Col there was a general increase of respiration, but not to the extent of serious embarrassment. There were no cases of mountain sickness among the porters, whose acclimatization was as notable as that of the climbers. The appetites of all were good, headaches were uncommon, and most of the men slept well throughout, except sometimes during the first night at a new camp. One climber, for instance, at Camp 6, slept for 13 hours.

This expedition was provided with an oxygen apparatus weighing only $12\frac{3}{4}$ lb. It proved its value in the treatment of pneumonia and of frost-bite, but was never used by the climbers.

It was pointed out in Chapters VII and VIII 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. Meakins and Davies (1920) 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 (p. 162). In Haldane's case the saturation was 94·3 per cent. This is not much lower than 96 per cent., the saturation which would be expected if his 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 aerotonometer 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 Haldane as probably due, either to a process of rapid but slight oxidation of the blood itself, or to a little blood getting through the lungs without exposure to alveolar air. It is clear now, however, that there is no need to invoke these hypotheses, since our shallow breathing experiments, and the neurasthenia cases, showed clearly enough why the mixed arterial blood is not fully saturated with oxygen to the alveolar pressure. But why does not the carbon-monoxide method show this? A little consideration will make the reason evident. The carbon monoxide method gives the average oxygen-pressure of all the portions of arterial blood leaving the different 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 VIII, from the average of the oxygen-pressures in the portions of blood leaving the different alveoli. This, however, is the 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 when pure air is breathed at ordinary atmospheric pressure) that diffusion equilibrium is established between alveolar air and blood. In fact the 'arterial' oxygen-

pressure given by the carbon monoxide method is really an average which is higher than the true oxygen-pressure of the mixed arterial blood as determined directly. For the purpose 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 is far more reliable than the aerotonometer 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 aerotonometer results, it may perhaps be pointed out that if they were accepted as evidence they would completely wreck the diffusion theory. For, if diffusion equilibrium is not obtained even 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 and on Kamet (p. 313) the lips remained quite red during hard muscular work.

Consideration of the dissociation curve of oxyhaemoglobin will show 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 at these heights 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. It was formerly thought possible to calculate this time indirectly from the rate of absorption of CO, and Bohr (1909) and later A. and M. Krogh (1910*b*) and M. Krogh (1914–15) made such calculations. Haldane and Graham (quoted by Haldane, 1927), however, showed that the method was fallacious. Their results indicated that the diffusion rate of oxygen is considerably greater than had previously been supposed.

All the facts, 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. Its absence is probably also an important factor under pathological conditions, though on this subject our knowledge is still very imperfect, owing to lack of observations. The most relevant observations are those of Lorrain Smith (1897–8). His experiments, when due allowance is made for the errors already referred to in the calculations, showed that a severe infection paralysed 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 XI) 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 on p. 225.

It appears that febrile infections at high altitudes are extremely dangerous. Thus the unfortunate death of Dr. Kellas on the first Everest Expedition seems to have been due to his unsuspected loss of acclimatization while he was suffering from an attack of dysentery. His death occurred while he was being carried over a pass of, comparatively, no very great altitude.

Reference has been made above to the fact that persons may apparently become partially acclimatized to CO, and this is quite intelligible in view of the existence of increased oxygen secretion as a factor in acclimatization to low pressures of oxygen. Argyll Campbell (1929–30*a*) and later Esther Killick (1933) have shown

experimentally that mice, rabbits, rats, guinea-pigs, and birds become partially acclimatized to CO, so that they can tolerate a considerably higher percentage of this gas in the air.

As already mentioned, the aerotonometer 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 centre responds to the slightest increase or diminution in the alveolar CO_2-pressure, and the quantitative correspondence between rise in alveolar CO_2-pressure and response of the respiratory centre, 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.

Apart from this there seem to us 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 Haldane (1914). (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 Haldane's experience with self-contained mine-rescue apparatus, and similar devices, he has often been struck with the greater sensitiveness to CO_2 of himself 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 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 (p. 109).

The tissue elements in which oxygen secretion occurs might either be the alveolar epithelium or the capillary endothelium or both. As regards the former, we could hardly suppose that it would be capable of active secretion if it were true that, as has been commonly represented, the epithelial layer consists for the most part of plates containing no nucleus. According to the recent very careful investigations of Haynes (1934), however, all the living cells contain nuclei and are capable of active reactions. There is therefore no reason to suppose that they are not capable of secretion. On the other hand, it seems on the whole more probable that the secretory activity is localized in the endothelial cells of the capillaries, since they are in direct contact with the blood, and there is some reason to suspect that endothelial capillary cells elsewhere in the body possess active secretory capacities.

We must now consider the criticisms which have been directed against the conclusion that the lungs secrete oxygen. Barcroft (Barcroft, Cooke, Hartridge, Parsons and Parsons, 1919–20) stayed for 6 days in a chamber in which the oxygen percentage of the air was allowed to fall, until it became about 11 per cent. (84 mm. Hg). At the end of the experiment he made analyses of his alveolar air and of the gases of blood withdrawn from his radial artery. He found that the arterial blood *in vivo* contained less oxygen both during rest and work than did samples of the same blood exposed to alveolar air *in vitro*.

This fact is, however, no evidence against secretion of oxygen by the lungs, for it is clear that Barcroft had not become acclimatized and that consequently secretion was not to be expected. Moreover, some of the experimental figures are difficult to interpret, and Barcroft seems to have been ill, for his body temperature rose on the last day. This, as mentioned on p. 293, is a circumstance which prevents oxygen secretion.

Barcroft's main objection to secretion is, however, founded on the results of the expedition to Peru in 1922, when the party stayed for some time at Cerro de Pasco at an altitude of 14,200 feet—almost identical with that of Pike's Peak. In the report of the expedition (Barcroft, Binger, Bock, Doggart, Forbes, Harrop, Meakins,

and Redfield, 1923) are given measurements of the oxygen-pressures of arterial blood made by a modification of Krogh's aerotonometer method both at ordinary atmospheric pressure and at 14,000 feet. These measurements indicated that there was never any great disparity at rest between the oxygen-pressures in the alveolar air and mixed arterial blood. From this Barcroft concludes that there was no indication of oxygen secretion at 14,000 feet. His results, however, are inconsistent with those of Fredericq (1896) and A. and M. Krogh (1910 *a*), and moreover, conflict with the observations of Meakins and Davies (1920) on the degree of unsaturation of normal human arterial blood. Fredericq pointed out that in the aerotonometer equilibration occurs very slowly with arterial blood, and criticized Bohr's results on the ground that insufficient time was allowed for equalization to occur between the pressures of oxygen in the blood and the bubble of air. Barcroft had in fact never tested the method as regards this point with arterial blood, and it would seem that his results cannot be accepted as being reliable.

Barcroft also argues against secretion on the ground that the dissociation curve of oxyhaemoglobin changes in such a way at 14,000 feet that the blood would, at a given pressure of oxygen and the existing alveolar CO_2-pressure, take up more oxygen from air at low barometric pressure than normal blood. Even if this were so, the taking up of oxygen by the tissues would not be facilitated, for the more easily the blood takes up oxygen in the lungs, the more tightly will it hold on to it in the tissues. Further, the alleged shift in the dissociation curve seems to be very doubtful, for it is at variance with previous results of Barcroft (1911), on the Peak of Teneriffe and on Monte Rosa, and with the particularly careful observations of Douglas and Haldane on Pike's Peak. Later results too of Dill and his colleagues (Dill, Edwards, Fölling, Oberg, Pappenheimer, and Talbott, 1931) also indicated that the dissociation curve does not change at high altitudes.

As regards the cyanosis observed during the Andes expedition in both members of the expedition and natives we may refer to pp. 313, 314.

X

EFFECTS OF LOW ATMOSPHERIC PRESSURES

VERY low atmospheric pressures are met with on mountains or high plateaux and in ascents by balloons or aeroplanes to great altitudes. Mountain sickness, the symptoms of which are included in the characteristic effects of low atmospheric pressures, was known long before the facts about the composition and pressure 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 (1878). He also was the first to carry out a thorough investigation of the condition. His experiments on animals and men showed clearly that the physiological effects produced by low atmospheric pressure are simply the result of diminished partial pressure of oxygen. The nature of these effects and the manner in which they are produced have been described generally in Chapters VII and VIII in connexion with the symptoms and causes of anoxaemia. The subject of low atmospheric pressure and its effects has acquired increasing importance of recent years owing to the increasing use of aeroplanes, and it is necessary to discuss the matter in greater detail, particularly in view of the fact that erroneous ideas still persist.

Real insight into the effects of low atmospheric pressures dates, as said above, from the very important work of Paul Bert. It will be convenient therefore to summarize here the experimental results from which he drew the very important conclusion that the physiological actions of oxygen and other gases depend on their partial pressures. In doing so it will be necessary at the same time to 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 air breathed, Paul Bert proved that if the initial 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 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. It is unfortunate that, despite the very definite results of Paul Bert, an idea still persists that reduction of mechanical pressure itself produces serious physiological effects.

Paul Bert found on the other hand that when the partial pressure of oxygen was raised to the dangerous limits referred to in Chapter XI, death was due to oxygen poisoning or hastened by it; and the results suggest that increase of 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, a subject which will be discussed in Chapter XII.

Fig. 82 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

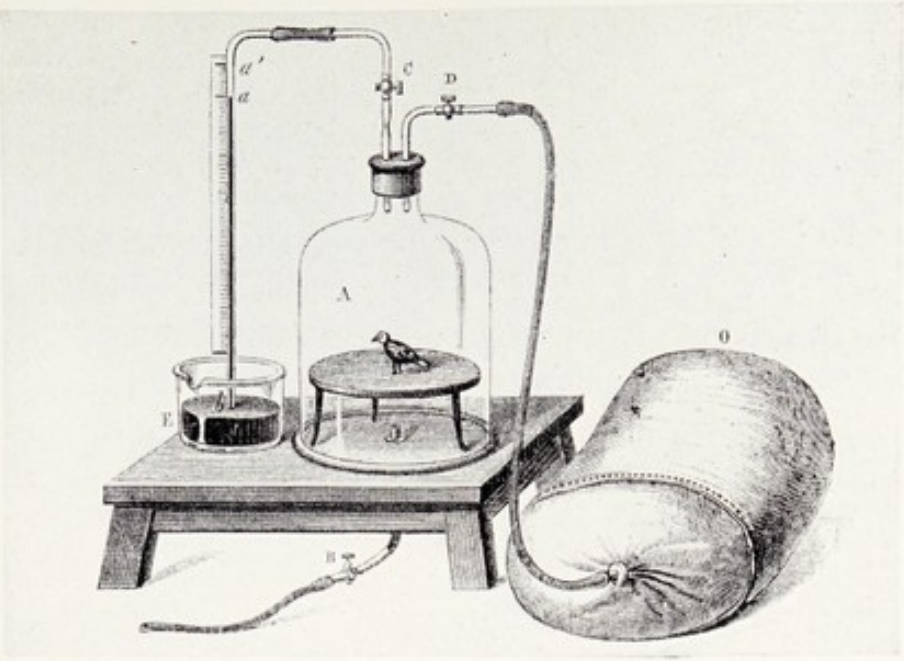


FIG. 82. Paul Bert's apparatus for showing the effects of varying low pressures of oxygen and CO_2. The tap B is connected with an air-pump, and D with a bag of oxygen or nitrogen, while C connects with a mercury manometer.

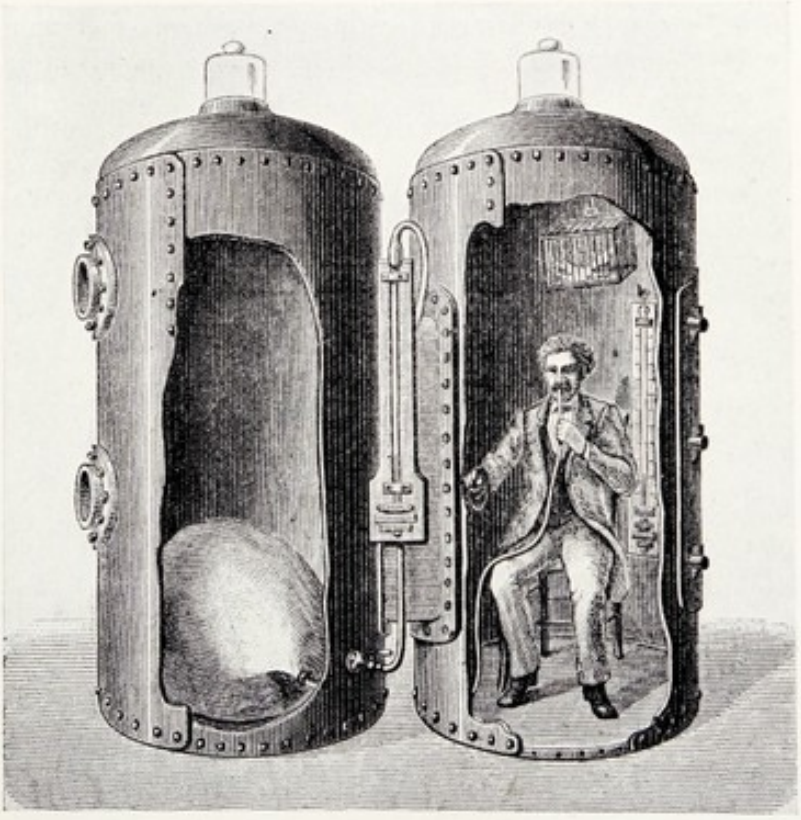


FIG. 83. Paul Bert's twin steel chambers for studying in man the effects of very low atmospheric pressures with respiration of oxygen.

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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.

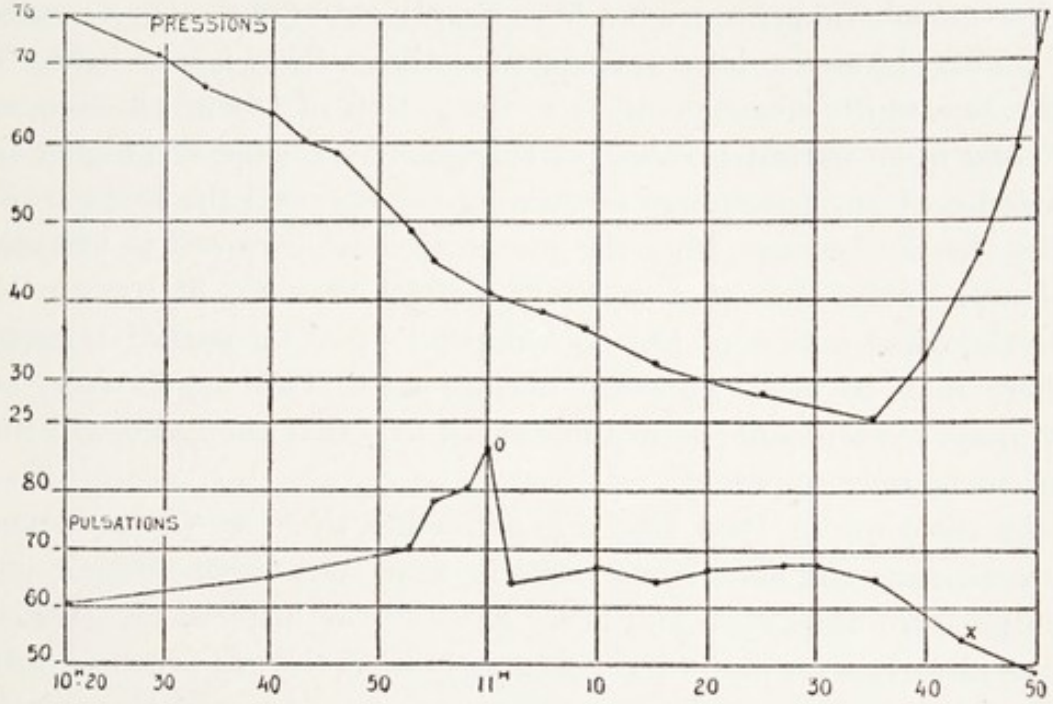


FIG. 84. Tracing showing Paul Bert's pulse-rate during a decompression experiment in his steel chamber. Upper line = barometric pressure in centimetres. Lower line = pulse-rate. At 0 the breathing of oxygen was begun and continued till the end of the experiment.

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 Fig. 83. 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. Fig. 84 is a diagram showing the variations of pressure in one 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 VII. Paul Bert observed these symptoms accurately. He noted the sudden increase in apparent brightness of light and loudness of sound, the return of powers of memory and of intellectual powers, etc. His observations have since been frequently confirmed, and nothing in subsequent investigations has shaken his 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 partial pressure of this gas alone, since the higher the pressure of an atmosphere containing CO is raised the less harmful does the CO become, from the causes already discussed in Chapters VI and VIII. But at a constant partial pressure of oxygen the physiological action of CO does depend upon its partial pressure. There may be other apparent exceptions to Paul Bert's rule, but we may be confident, as in the case of CO, that they also will turn out to be only apparent.

At the time of Paul Bert's experiments there was no means of investigating the alveolar air, and he took into direct account only the pressure of oxygen and other gases in the inspired air. But we have already seen that what really matters is the gas-pressure 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 vapour is constantly rising. At a barometric pressure of 47 mm. no air at all would enter the lungs, since the pressure of aqueous vapour 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 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 animals from want of oxygen should have coincided so closely with a threshold oxygen-pressure in the inspired air. The probable reason of this has already been referred to in Chapter VII, and is as follows: 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 neighbourhood 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 (Fig. 82) 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 vapour 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 III and VI, 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 counter-

balancing 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 (pp. 190, 437). 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 Haldane 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 pressure depend on the lowering of the oxygen-pressure, the theory was prominently brought forward by Mosso (1898) 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. 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 to the inspired air. Acapnia

may thus be looked on as a contributory 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 became clear through the work of Haldane, Kellas, and Kennaway (p. 288) and independently along closely similar lines by that of Haggard and Yandell Henderson (1920 *a*, *b*).

Mosso held to his acapnia theory till the time of his death, and it was quite in vain that Haldane himself endeavoured to persuade him that Paul Bert was right. This theory was for a time widely accepted, but Zuntz, Loewy, Müller, and Caspari (1906) placed the main facts in true perspective in an account of investigations carried out at high altitudes in the Alps.

Not only, as stated above, have the physiological effects of low barometric pressure been recognized for many years, but evidence has also accumulated that a process of adaptation also occurs. 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, and Paul Bert suggested that the tissues gradually become accustomed to a smaller supply of oxygen in the blood and perhaps become more economical in their use of oxygen. While there is still no experimental evidence of the validity of this theory, there are facts, which will be discussed later, which point in the direction of this explanation. However this may be, it is known definitely that there are other factors concerned in the process of acclimatization. Paul Bert himself suggested that the oxygen capacity of the blood might become increased at high altitudes; and this he afterwards verified by actual examination of blood taken from animals living at high altitudes.

Viault (1890, 1891) showed that the number of red corpuscles per unit volume of blood and the oxygen content are increased at high altitudes, and Müntz (1891) that the percentage of iron is increased. Various subsequent observers have clearly established 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 red corpuscles in the blood. An extensive and accurate series of observations on the increase in haemoglobin was carried out in connexion with the Pike's Peak Expedition by Miss FitzGerald (1913) on persons

living permanently at different altitudes in the Rocky Mountains and elsewhere in America. Fig. 85 shows graphically the average results obtained at different altitudes.

It will be seen from this figure that on an average the percentage of haemoglobin varies inversely with the barometric pressure, and that even quite small diminutions in barometric pressure are effective

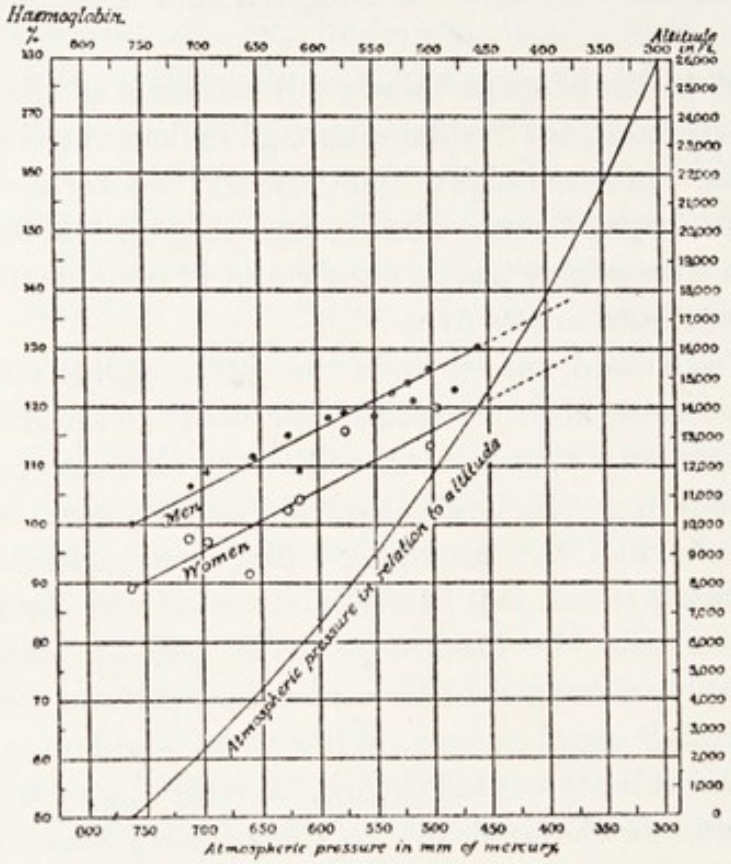


FIG. 85. Average haemoglobin percentages in persons living permanently at different altitudes (FitzGerald).

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 considerably. Thus among the persons acclimatized on the summit of Pike's Peak (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. On Pike's Peak the increased haemoglobin percentage was found to run parallel with the increased number of red corpuscles per c.mm. of blood. Very careful observations were made on this point.

The Royal Society physiological expedition to the Andes (Barcroft *et al.*, 1923) confirmed and extended these results. Their observations were made on themselves and also on Europeans and natives who had been resident at high altitudes for years or in some cases all their lives. They found too that the increase in the erythrocytes is roughly proportional to the increase in haemoglobin; while new formation of red cells was indicated by the large percentage of reticulated cells in the blood.

Both the Pike's Peak Expedition and the Andean Expedition found an initial diminution of the blood-volume followed by an increase.

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 Adèle Bornstein (1911), who kept the animals at a pressure of about three atmospheres or 2,280 mm. Hg in the Elbe tunnel at Hamburg during its construction. She found that the 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.

Argyll Campbell (1926–7) exposed rabbits to high percentages of oxygen for prolonged periods, e.g. four weeks, and found that their haemoglobin and red corpuscles were much diminished. In one case four weeks' exposure to about 55 per cent. oxygen reduced the number of red cells per c.mm. from 5·5 millions to 3 millions.

It appears, therefore, that the haemoglobin percentage is regulated generally in relation to the oxygen-pressure in the arterial blood, and rises or falls accordingly, as this pressure is diminished or increased.

Further confirmation is to be found in the fact, which has been noted by various observers, that after return to sea-level from high altitudes the number of red cells and the haemoglobin percentage return more or less gradually to their previous level. For instance, Hingston (1921–2) brought down dwellers in high altitudes in the Himalayas, who had never been below 3,300 metres, and found that, as in ordinary subjects, the red blood cell count (normally very high) dropped to 5·99 millions at 2,500 metres.

It is easy to see what the physiological advantage will be, other things being equal, of a rise in the haemoglobin percentage at low atmospheric pressures. As the blood passes through the systemic capillaries, its oxygen-pressure will fall more slowly than usual in consequence of the greater charge of oxygen carried by the arterial blood. Hence, although the arterial oxygen-pressure is considerably below normal, the venous oxygen-pressure will not be correspondingly lowered. It will in fact be much more nearly normal than the arterial oxygen-pressure, so that the lowering of the oxygen-pressure in the tissues is diminished. The fact that there may be much more available oxygen in the arterial blood at high altitudes than at sea-level 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, of which the oxygen-pressure in the venous blood is the most reliable index.

Argyll Campbell (1928) concluded that no physiological advantage arises from the increased haemoglobin percentage at high altitudes. He based this conclusion on the fact that, when the oxygen-pressure in the tissues is reckoned as equal to that which is finally reached in gas injected into the tissues, no reduced fall in this pressure due to the increased haemoglobin percentage can be found. This fact is doubtless correct, but appears to us to be evidence that the method of inferring the available oxygen-pressure in tissues from that of gas which is present in them is unreliable. The oxygen-pressures in gas which is present as such in the tissues will be somewhere between those in the arterioles and first capillaries reached by the blood, and in the last capillaries and venules. Hence, if the former oxygen-pressure is low, as is always the case at low atmospheric pressures of air, the oxygen-pressure of the free gas will be low, quite apart from what is physiologically important, namely, the pressure of oxygen in the venous blood leaving the tissues. Hence we cannot accept Argyll Campbell's reasoning as regards uselessness of increased haemoglobin percentage at low barometric pressures, nor, in general, can we accept as reliable the method, which he has used for judging the available gas-pressures in the tissues, though in some cases this method may give most useful indications.

It has gradually been clearly established over a number of years 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 made by Zuntz, Loewy, Müller, and Caspari (1906) of the volume of air breathed and respiratory exchange at high altitudes, and, as mentioned on p. 93, was made quite clear by the experiments of Boycott and Haldane (1908) and Ogier Ward (1908) on the alveolar air at low atmospheric pressures. The latter observers 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 centre. This diminution in the 'fixed' alkalinity of the blood had already been detected by titration. Barcroft (1911) 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 to the same direction. The phenomena accompanying the diminution of fixed alkalinity of the blood did not, however, correspond with those accompanying excess of lactic acid in the blood. Ryffel (1909–10) was unable to detect any excess of lactic acid in the blood during exposure to low atmospheric pressure. Further, Christiansen, Douglas, and Haldane (1914) found that a considerable acidosis due to the accumulation of lactic acid could be produced by doing heavy muscular work. On cessation of the work this acidosis disappeared within an hour, while a similar degree of reduction of the fixed alkali content of the blood resulting from acclimatization to oxygen-want is only restored after a period of weeks.

In view of such of these facts as were known at the time the members of the Pike's Peak Expedition drew the conclusion 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. They suggested the hypothesis that the anoxaemia must influence the kidneys specifically in this direction.

The Anglo-American Pike's Peak Expedition was planned with the special object of studying acclimatization to the oxygen deficiency caused by the low pressure of the air at high altitudes. Pike's Peak (14,100 feet) was selected because it was possible, not only to get apparatus and supplies to the summit easily by the cog-wheel

railway, but also to live there without experiencing the disturbing effects of cold and hardship. The members of the expedition were thus enabled to watch in themselves the progress, which was very striking, of acclimatization, and to observe the effects 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 the excessive removal of CO_2, the haemoglobin passing through the lungs will also combine more readily with oxygen, in consequence of the Bohr effect already often discussed. It might thus appear as if a simple increase in breathing were the natural adaptative response to low atmospheric pressures. But a mere increase in breathing without the changes already referred to in the blood defeats itself quickly in consequence of the lowered alveolar CO_2-pressure, and consequent tendency towards apnoea; and the Bohr effect is practically useless, since, though it increases the saturation of the arterial blood with oxygen, it at the same time lowers the oxygen-pressure in the tissues. Hence, although at first the breathing is distinctly increased by the anoxaemia, the increase is limited by the alkalosis which is produced at the same time, and this alkalosis is not relieved till the adaptive changes in the blood have developed. Meanwhile, the effects of imperfect distribution of air in the alveoli are necessarily exaggerated greatly, so that the arterial blood becomes very imperfectly saturated, and the lips and face are correspondingly blue.

It is during the period before the essential adaptations have taken place that the unpleasant symptoms of mountain sickness occur. In the course of two days or more, however, these symptoms usually pass off if the altitude is not too great; and thereafter the breathing is only slightly increased further, as was found on Pike's Peak (Fig. 86) by analyses of the alveolar air.

Further light was afterwards thrown on the process of acclimatization by Hasselbalch and Lindhard (1915 *a*, *b*; 1916 *a*, *b*) in a series of observations during which they remained for a number of days in a steel chamber at a 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. Hasselbalch and Lindhard also found

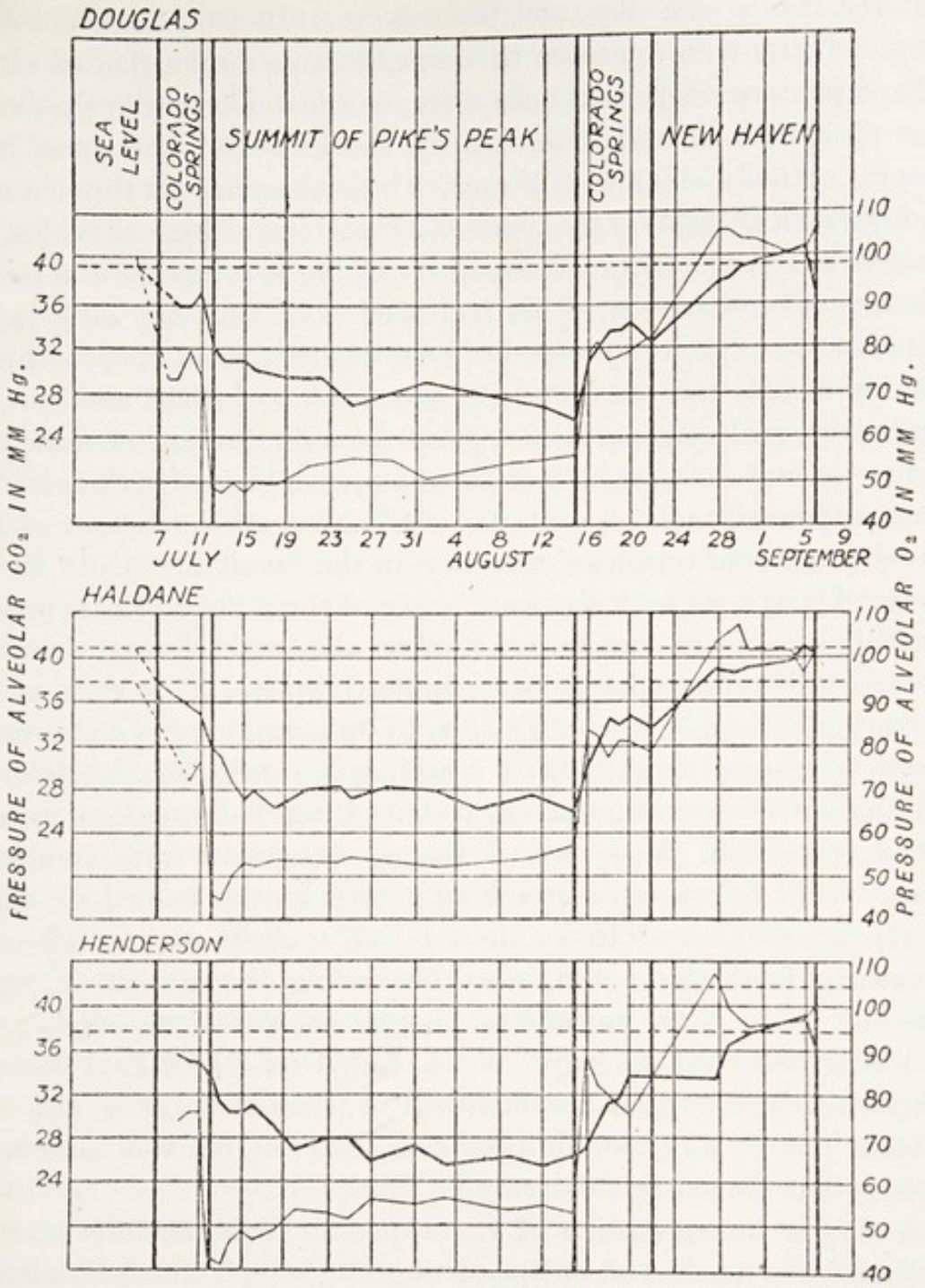


FIG. 86. Pressure of CO_2 and oxygen in alveolar air of three members of the Pike's Peak Expedition at about sea-level (Oxford and New Haven), at Colorado Springs (6,000 feet), and on Pike's Peak (14,100 feet). Thick line = alveolar CO_2-pressure, and thin line = alveolar oxygen-pressure. Interrupted lines = normal alveolar CO_2 and oxygen-pressures at sea-level.

that the excretion of ammonia in the urine is distinctly diminished; and they interpreted this as indicating that the very slight acidosis, which they presumed to be the cause of the increased breathing, was due to diminished formation of ammonia in the body.

Later, Haldane, Kellas, and Kennaway (1919–20) found, as stated on p. 107, 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 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 VI. 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, 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 was 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 the anoxaemia prevents this.

A similar interpretation of the apparent slight acidosis at high altitudes was reached on independent grounds by Yandell Henderson (1919). As already mentioned on p. 109, he and Haggard (1918 *c*) made the very important discovery that with prolonged and very excessive ventilation of the lungs (thus producing great alkalosis) the available alkali or 'alkali 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 ends is implied, but only a tendency of the living body to maintain its normal standards. The justification for this mode of interpretation, together with the demonstration that it constitutes the necessary scientific basis for physiology, has been stated in the Preface to this edition.

In connexion with the Pike's Peak Expedition Miss FitzGerald (1913, 1914–15), as mentioned in Chapter IV, 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 lower altitudes in South Carolina. The average results are shown in Fig. 87. The results for men and women are given separately, as men have a higher average alveolar CO_2-pressure than women, as mentioned on p. 34. It will be seen that within the limits of atmospheric pressure investigated, the average CO_2 and oxygen-pressures fall proportionally to the lowering of the atmospheric pressure. To judge from these results the alveolar oxygen-pressure at the height of 28,000 feet reached by the 1924 and 1933 Everest Expeditions would, after acclimatization, be only about 25 mm., and the CO_2-pressure about 19 mm. No actual figures have been obtained as yet for such high altitudes, but in the 1933 expedition samples of alveolar air, obtained from himself by Raymond Greene at 22,700 feet and analysed by Douglas, gave a CO_2-pressure of 19·3 mm. and an oxygen pressure of 38·8 mm., which results fall nearly on Miss FitzGerald's curve.

Acclimatization would be a very incomplete process if it depended solely on the increase of haemoglobin and of breathing observed at high altitudes. In fact it is always observed that, in spite of the increased breathing and coincident increased saturation of the arterial blood owing to the resulting alkalosis, there is at first very distinct cyanosis when persons go from a low to a high altitude. On Pike's Peak this was very striking, though it was noticeable that

in different persons the degree of cyanosis varied greatly. Local cyanosis owing to the slowing of the circulation through vessels constricted owing to cold is, of course, well known, but this source of fallacy was carefully excluded, and there could be no doubt that on

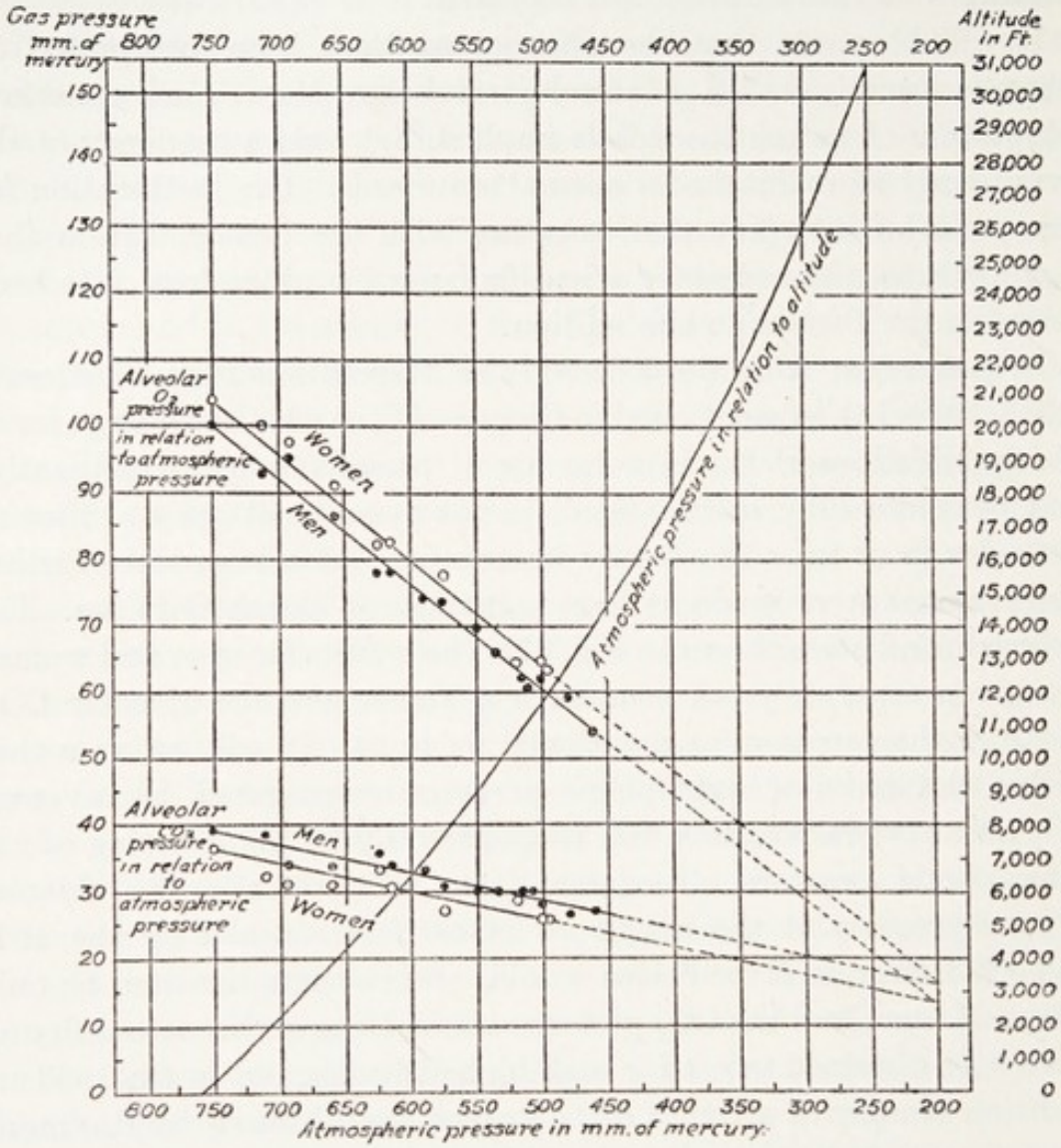


FIG. 87. Alveolar gas-pressures in relation to barometric pressure or altitude.

Pike's Peak cyanosis due to deficient saturation of the arterial blood with oxygen was a constant phenomenon in those newly arrived. The fact that there was so much cyanosis although the mean alveolar oxygen-pressure, as observed, was about 50 mm. Hg—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 is explained in Chapter VIII, the oxygen-pressure of the mixed arterial blood is very appreciably

below that of the mixed alveolar air, and particularly at low atmospheric pressures. The cyanosis, as was observed on Pike's Peak, commonly disappears after a day or two, or longer, of mountain sickness, and is thereafter absent both during rest and in any ordinary exertion. Most careful observations were made on this point. In persons, however, who have reached a high altitude by gradual stages, as in the Everest Expedition, there may apparently be little or no cyanosis, and certainly no mountain sickness. For instance, the members of the 1924 Everest Expedition were able to spend the night at 27,000 feet without any symptoms of mountain sickness whatever. Among the party also of four Europeans with the Duke of the Abruzzi, 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 published 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. Hg) does not produce mountain sickness' (Filippi, 1912). Mountain sickness and its accompaniments were considered to be in reality 'phenomena of fatigue'. The writer of this account was, however, 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.

In the Mount Kamet Expedition of 1931 very careful observations as to cyanosis were made by Dr. Raymond Greene on persons acclimatized up to an altitude of 24,000 feet, far higher than that of Pike's Peak. No traces of cyanosis could be observed either during rest or during exertion.

The experiences of members of these mountaineering expeditions may be contrasted with that of Hasselbalch and Lindhard (1916*b*) in their steel chamber. They started, altogether unacclimatized, from the sea-level air pressure of Copenhagen and only reduced the pressure 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, precordial pain, and feelings of asphyxia during the night, that they had to raise the pressure to 584 mm. Hg (about 7,000 feet). An experience of Haldane's, mentioned on p. 287, is also remarkable as showing the

difference between the reactions of the acclimatized and unacclimatized to low oxygen-pressure.

One of the most interesting results of the Andes Expedition was the discovery that the permanent local inhabitants showed quite marked cyanosis, and it appeared also that this entirely disappeared when they happened to journey to a much lower altitude. In spite of the cyanosis they were well and fit, in this respect resembling what may often be observed in chronic cases of emphysema and heart affections when extra exertion is avoided. It seems probable, therefore, that after a sufficient time the tissues of the body may become acclimatized to a low oxygen-pressure, in accordance with the suggestion made by Paul Bert.

With regard to the phenomena observed on Pike's Peak it should be remembered that those ascending this mountain started from a height of about 6,000 feet and were thus partially acclimatized, otherwise their symptoms would undoubtedly have been more severe than they actually were.

It is clear that acclimatization is a gradual process and that further reactions are involved in addition to those already noticed. In seeking to determine the nature of these further factors it is obviously desirable to inquire whether any change occurs in the oxygen dissociation curve of the blood during acclimatization. This point was investigated by Barcroft (1911), who found that on the Peak of Teneriffe at altitudes of 7,000 and 11,000 feet, the oxygen dissociation curves of the blood of several individuals, determined at the CO_2-pressures of their alveolar air at low altitudes, were identical with the curves at sea-level at the CO_2-pressures of the alveolar airs at normal barometric pressure. These results were confirmed by Barcroft, Camis, Mathison, Roberts, and Ryffel (1914–15) on Monte Rosa and also by Douglas and Haldane (1913) on Pike's Peak. Later too, Dill, Edwards, Fölling, Oberg, Pappenheimer, and Talbott (1931) made a series of careful observations on the oxygen dissociation curve of human blood after complete acclimatization at 10,000 feet and after ten days' stay at 14,000 feet. They also found that when the hydrogen-ion concentration was constant the oxygen dissociation curves were not altered by acclimatization and remained sensibly the same as at sea-level.

It would seem therefore to be established conclusively that the process of acclimatization does not include any change in haemo-

globin whereby it becomes capable of taking up more oxygen, *ceteris paribus*, at low pressure. This conclusion is, however, contradicted by the results obtained by Barcroft and his colleagues during the expedition to the Andes. They found that at 14,200 feet the oxygen dissociation curves of the blood of members of the expedition shifted definitely to the left, i.e. showed increased saturation for any given pressure of oxygen. The dissociation curves of the natives agree with those of the members of the expedition after acclimatization, but the dissociation curves of Anglo-Saxon residents did not differ appreciably from sea-level curves. The shift of the dissociation curve which was found was explained by Barcroft (1923, 1925) as being a necessary consequence of the increased proportion of haemoglobin in the blood. The argument is that a given rise of CO_2-pressure causes a shift of a definite quantity of chloride-ion from the plasma into the corpuscles. The effect of this on the reaction of the corpuscles and, therefore, on the oxygen dissociation curve must depend on the amount of haemoglobin in the corpuscles. The greater the amount of haemoglobin and base combined therewith in the blood the less will be the change of intracorpuscular reaction caused by a given chloride shift into the corpuscles. This argument, however, does not seem to be borne out by the work of Warburg (1922) and was not investigated quantitatively by Barcroft. It is noticeable also that the apparent change in dissociation curves was not found in the case of the Anglo-Saxon residents at Cerro. Since the observed shift of the curve was not found in all cases, and since it conflicts with all the other observations quoted above, it would seem to be unsafe to accept the apparent facts as having been correct, and suspicion naturally falls on the thermometer used. If, moreover, the shift in the curve had been a real one, it would apparently have been of no physiological advantage, since it would have hindered the dissociation of oxygen in the tissues.

There is, however, one further factor to be considered. In Chapter IX the quantitative evidence is given that at high altitudes after acclimatization the lungs actively secrete oxygen inwards, even during rest, and that were this not so the immunity from symptoms of mountain sickness among acclimatized persons would be wholly 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. What remains is, however, insufficient to produce any appreciable cyanosis. In this connexion 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.

In the Report of the Andes Expedition and in his more recently published book (1925) Barcroft still adheres to the old belief that there is no active oxygen secretion by the lungs, so that active oxygen secretion is not a factor in acclimatization. But it seems to us that in view of all the experimental and other evidence this belief must be abandoned finally.

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 on p. 114.

There is indeed some evidence in favour of this supposition. Adlersberg and Porges (1923, 1925), on the Jungfraujoch (11,343 feet), found that administration of acid ammonium phosphate increased the alveolar oxygen tension and the oxygen saturation of the capillary blood. Greene (1932) during the expedition to climb Mount Kamet took small doses of ammonium chloride and thought that the effect was beneficial. Douglas, Greene, and Kergin (1933) investigated the matter experimentally. They compared the general condition and capacity to do muscular work at a pressure of 347 mm. Hg in a steel chamber with and without the administration of ammonium chloride. They found that after treatment with ammonium chloride the subject showed a lower alveolar CO_2-pressure and a higher oxygen-pressure. There was also definitely a slighter degree of cyanosis after the ammonium chloride, together with a slower pulse-rate and a greater capacity to perform muscular work. They conclude that the process of acclimatization to low barometric pressures is definitely accelerated by the administration of ammonium chloride.

The question of acclimatization has assumed new interest, owing to the recent great extension of the use of aeroplanes at high altitudes. The great advantage of good physical training seems evident in this connexion. 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 aeroplanes to low atmospheric pressures. The limitation was distinctly evident in the experiments, mentioned on p. 288, 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 great improvements in the construction of aeroplanes and their engines, heights even greater than those reached in balloons before 1932 have been reached in aeroplanes. 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 seems 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 (1871) account of the symptoms observed was very full and valuable. 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. He then found that his arms and legs were paralysed, 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

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FIG. 88. Sivel, Tissandier, and Crocé-Spinelli in the car of the *Zenith*. Sivel is 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.

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 $11\frac{1}{2}$ 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 paralysed. He then, with great presence of mind, got hold 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 Croce-Spinelli, Sivel, and Tissandier in 1875, and resulted in the death of the two former (Bert, 1878). 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. Croce-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. Fig. 88 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 metres, but his voice was paralysed, 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 Croce-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 Croce-Spinelli were dead. Tissandier had great difficulty in letting go the anchor and landing safely, but succeeded. Fig. 89 indicates diagrammatically the course of the balloon. The maximum height was given by an automatic recorder.

It was clear that all three had been paralysed 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. Haldane has experienced it 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 aeroplanes 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 about 30,000 feet; and finally, in 1901, Berson and Süring reached about 36,000 feet (11,000 metres), with a barometric pressure of 180. 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 co-operation of the Austrian physiologist, von Schrötter, and the latter in his book (1906) describes not only these 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.

Berson and Süring used steel oxygen cylinders from which a constant stream of oxygen came to them through a tube which could be

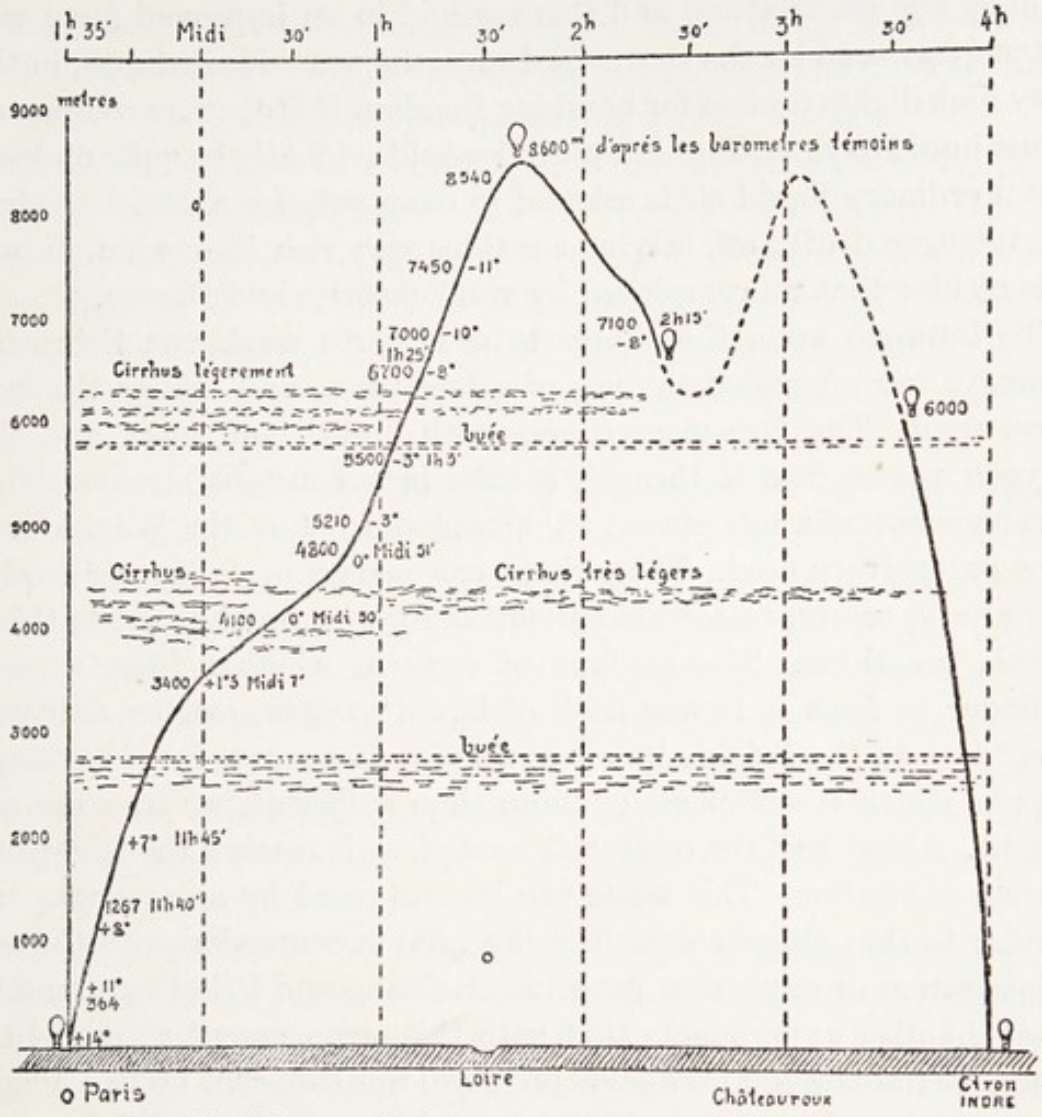


FIG. 89. Diagram of the voyage of the *Zenith*, April 15, 1875.

held 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 liquified gas 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 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 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 aeroplanes 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 (Fig. 66) in connexion with the administration of oxygen to patients. Haldane and Priestley found in steel-chamber experiments that with this arrangement about 1 litre a minute (measured at sea-level pressure) was sufficient up to a height of 28,000 feet during rest; but at least 2 litres were needed for such exertions as an aeroplane 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, however, matter so much. It is nevertheless evident that the greater the height the more does the unavoidable waste of oxygen become with this arrangement. The airman is probably only consuming about $\frac{1}{2}$ litre a minute (measured at ordinary atmospheric pressure), but to enable him to inspire nearly pure oxygen he would need about 30 litres a minute, measured at the existing pressure.

A height as great as Berson and Süring reached in a balloon was attained in 1920 in an aeroplane by Major Schroeder of the American army air service. He, however, also became unconscious and had a very narrow escape. How it was that the oxygen-supply became insufficient has not been reported. On September 16th, 1932, Flight-Lieutenant C. S. Uwins reached a height of 43,976 feet in an aeroplane, M. Lemoine attained 44,277 feet on September 28th, 1933, and Commendatore Donati 47,358 feet on April 11th, 1934.

A height reckoned as 45,000 feet by the internationally adopted altimeter scale represents a barometric pressure of 110 mm. Hg. If an airman were breathing normally at this height the oxygen-pressure in his alveolar air, even if he were breathing pure oxygen, would be only about 23 mm. Hg, since 47 mm. of the pressure would be due to aqueous vapour, 40 mm. to CO_2, and only the residue, i.e. 23 mm., to oxygen. This would produce asphyxial symptoms at once; but actually his breathing would be much increased from want of oxygen. This would reduce the pressure of CO_2, and correspondingly increase that of oxygen, so that for the time he would probably have an alveolar oxygen-pressure of 40 mm. Hg or more, and might retain consciousness, particularly if he were in good physical training and had corresponding powers of oxygen secretion in his lung capillaries. His position would, however, be one of constantly increasing danger in proportion as CO_2 was removed from his body. A barometric pressure of 110 mm. Hg (45,000 feet) would seem to be the extreme limit of safety however much oxygen is supplied.

Figure 90 shows the relation of barometric pressure to height as represented in the internationally adopted altimeter graduation, which is derived from the following equations:

$$\frac{P_0}{P} = \left(\frac{288}{288 - 1{\cdot}98H}\right)^{5{\cdot}256} \text{ from 0 to 36,090 feet,}$$

and $$H - 36{\cdot}090 = 47{\cdot}900 \log_{10} \frac{P_{36,090}}{P} \text{ beyond 36,090 feet,}$$

where H is the height in thousands of feet.

P_0 is the ground pressure.

$P_{36,090}$ is the pressure at 36,090 feet as calculated by the first of these formulae.

P is the pressure at the height H.

It should not be forgotten, however, that this relation depends upon

an assumed rate of fall of the temperature of the air near the earth's surface. This obviously varies with locality and season, so that barometric pressures actually met with at known heights do not always correspond to points on the curve. It is found, however, that the curve represents with fair accuracy average conditions over the whole world.

Miss FitzGerald (1913) gives a table which shows close agreement between the observed heights at a number of places in different parts of the world and the heights calculated from the formula (Zuntz, 1906):

$$\log b = \log B - \frac{h}{72(256{\cdot}4+t)},$$

where B = barometric pressure at the lowest level
b = barometric pressure at the upper level
h = difference of height in metres
t = the mean temperature of a column of air of height h.

When the mean temperature t is assumed to be 15° C., the heights, of more than 15,000 feet, calculated from the barometric reading by this formula exceed those calculated from the I.C.A.N. formula by increasing amount as shown in Fig. 90.

It is difficult to see how the addition of CO_2 to the inspired oxygen could be of service at extreme heights, although at moderate heights 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 millimetre 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 (1905) has shown 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.

It was pointed out in the first edition of this book that, 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

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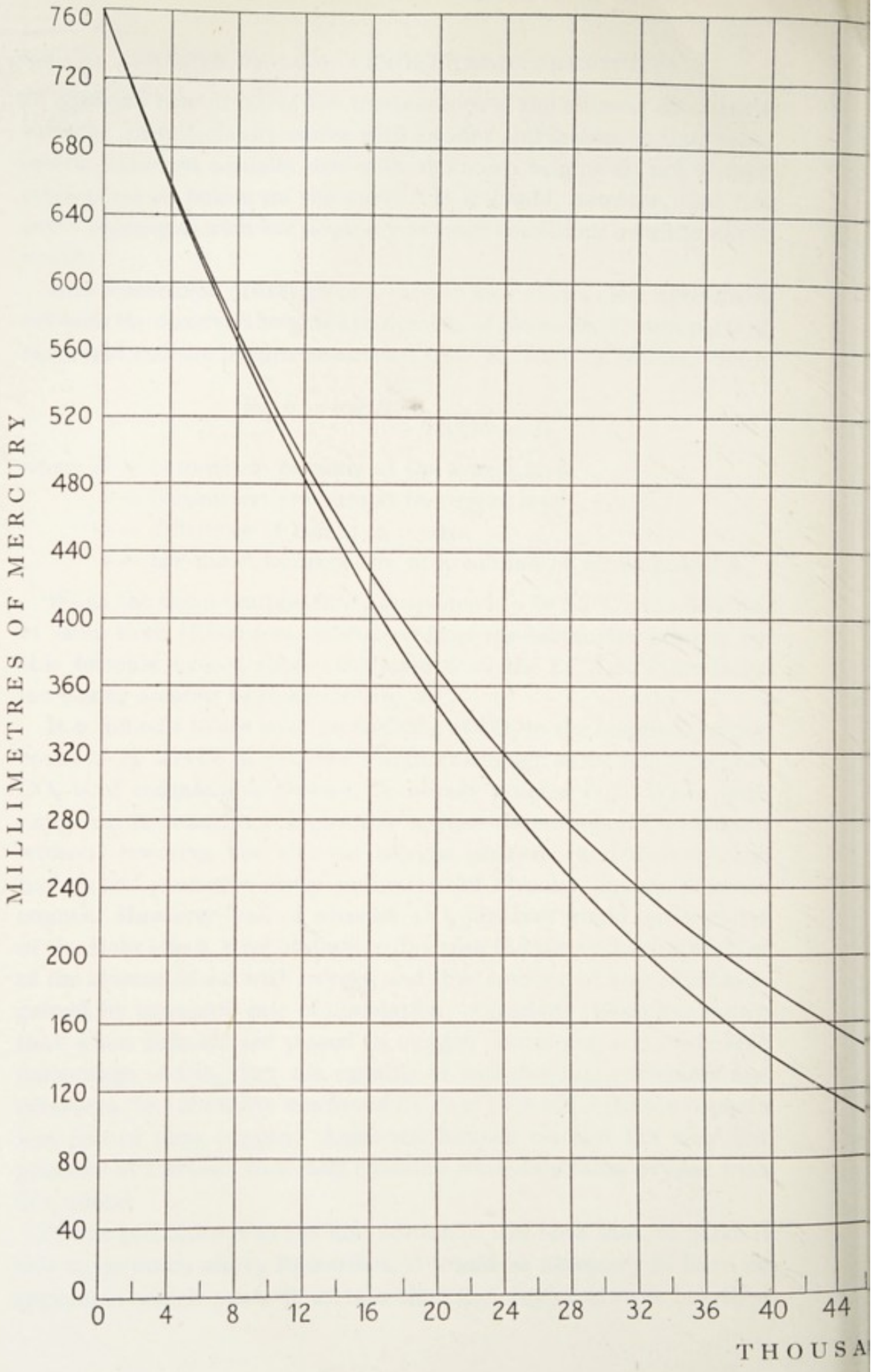
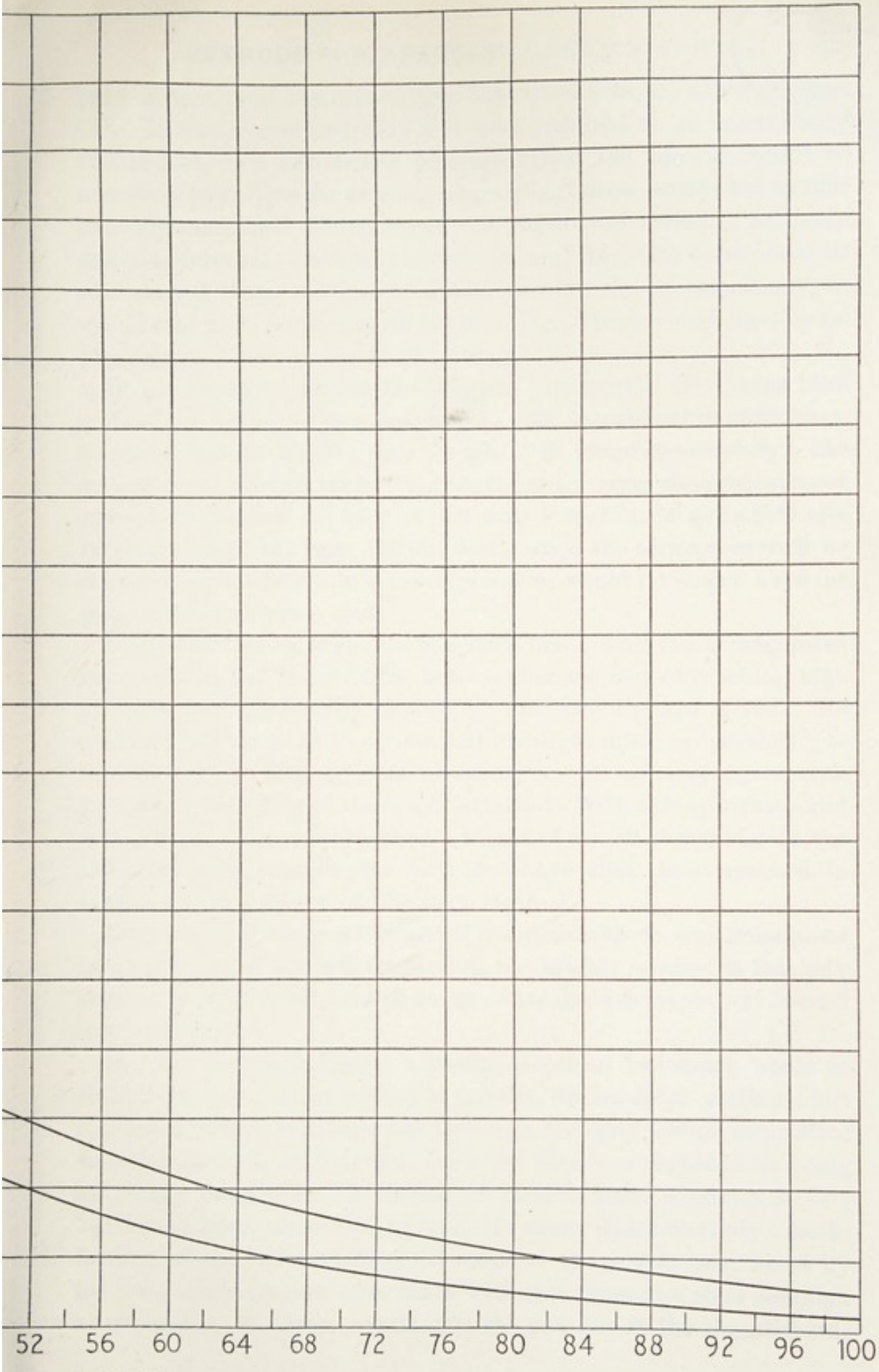


FIG. 90. Curves showing rela

The upper curve is calculated from the formula given by Zu

The lower curve is calculated according to the



barometric pressure to height.

wy, Müller, and Caspari, assuming a mean temperature of 15° C.

conventional law assuming standard conditions.

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pure oxygen, or at any rate oxygen not mixed with any other gas than CO_2. It was also stated that if it were required to go much above 40,000 feet, to a barometric pressure below 130 mm., it would be necessary to enclose the airman in an airtight dress, somewhat similar to a self-contained diving dress, but capable of resisting perfectly safely an internal pressure of about 130 mm. Hg. This dress could be so arranged that even in a complete vacuum the contained oxygen would still have a pressure of 130 mm. Hg. There would then be no physiological limit to the height obtainable.

In his ascent to 44,000 feet Flight-Lieutenant C. F. Uwins used a standard service oxygen apparatus, with improvised modifications to enable him to breathe pure oxygen if he found it necessary. The arrangement worked perfectly, but, being an improvisation, was not suitable for general use; nor as just stated would it be quite safe at a pressure below 130 mm. (40,000 feet), since the airman, even if he retained consciousness to a lower pressure, would no longer have his judgement and senses clear.

Until 1933 no experiments had been made with the arrangement suggested in the first edition, but another method of reaching high altitudes was successfully applied by Professor Piccard in 1932. He enclosed the aeronaut in a spherical metal chamber or 'gondola', as he called it, so that he was breathing air at ordinary barometric pressure irrespective of the height attained. With this apparatus and a very large balloon he reached a height of about 55,000 feet on the altimeter scale, and higher altitudes have since been reached in Russia and in America by the same method.

On account of the great weight of the metal sphere, and consequent enormous size of the balloon needed, the heights reached in this way are somewhat limited, and there are other disadvantages which need not be discussed.

In 1933 Mr. Mark Ridge, a young American balloonist, wrote to Haldane to say that he wished to use the 'diving-dress' method; but could not obtain permission to test it in the only low-pressure steel chamber existing in America, since the plan was regarded as being extremely dangerous. On behalf of Messrs. Siebe, Gorman & Co., Sir Robert Davis undertook to make the dress, which was only a modification of the self-contained diving-dress previously introduced by his firm. Experiments were made with this dress in a steel chamber at the works. In these experiments the pressure in the chamber was

reduced on successive days until finally a pressure of only 17 mm. Hg was reached. Mr. Ridge experienced no abnormal symptoms whatever. The oxygen-supply was automatic with a delivery of about 1 litre a minute measured at atmospheric pressure, and the carbon dioxide was absorbed continuously by an automatic arrangement. These appliances were so arranged that the subject's face was quite free. The pressure in the chamber could not be got any lower, since the excess of oxygen was constantly escaping into it. Caution was exercised in these experiments in case symptoms of compressed-air illness (p. 333) should occur, although they were by no means expected. The blood and tissues of the subject were saturated with air at ordinary atmospheric pressure before the experiment, and if, under this condition, the pressure in the dress were reduced to 150 mm. Hg, as would be the case with a complete vacuum in the chamber, the same effect would be produced as by decompression of a diver whose blood had been saturated at an excess pressure of 4 atmospheres. If proper precautions were not taken such a decompression might be dangerous. In the actual experiments, however, the subject was breathing pure oxygen, and had been doing so for some minutes before the decompression started. This precaution was taken to ensure also that the dress was thoroughly washed out with pure oxygen. During the time, about half an hour, before he reached the lowest pressure on each day, he was also breathing pure oxygen. He was kept for a considerable time at about the lowest pressure reached, to watch for any symptoms of bubbles in the tissues.

These experiments show quite clearly that the dress could be used for either balloon or aeroplane ascents without any limit to the height attainable with safety, and there is also great economy of oxygen and in consequent weight of gas containers with this method as compared with those hitherto used.



FIG. 91. Diving-dress, front view, with life-line and air-pipe, which is connected with the helmet behind.

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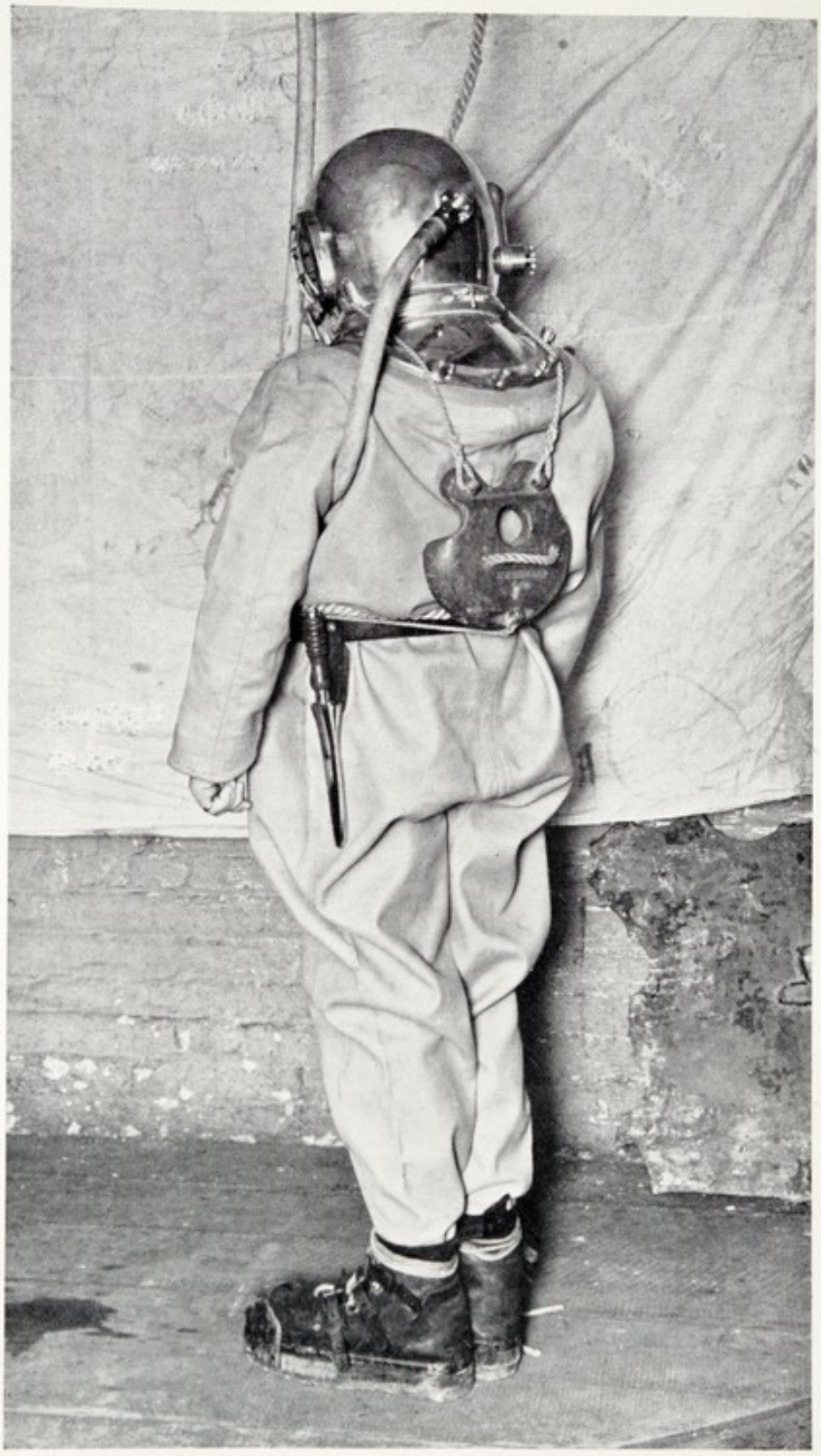


FIG. 92. Diving-dress, back view, showing attachment of air-pipe.

XI

EFFECTS OF HIGH ATMOSPHERIC PRESSURES

WE have seen in Chapter X that the foundations of our scientific knowledge of the physiological effects of low atmospheric pressures were laid broad and firm by the investigations of Paul Bert, which were collected together in his book, already so often referred to, *La Pression barométrique* (1878). This book also contains the observations of Paul Bert on the effects of high atmospheric pressures, which he was the first to interpret clearly. Paul Bert's conclusions remain valid up to the present day, though they have been amplified and extended by later work.

Very high atmospheric pressures are met with in deep diving, in engineering work under water or in waterlogged strata, and in escapes from submarines. It is therefore of great importance that the physiological effects of high atmospheric pressures should be clearly understood.

Apart from laboratory experiments on animals, the highest atmospheric pressures (up to about 10 atmospheres absolute) 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, one of the founders 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 watertight to a stout waterproof dress covering the whole body except the hands, which project through close-fitting elastic cuffs (Figs. 91 and 92). 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 wires and connected to an air-pump at the surface. The air supplied by this pump escapes through an adjustable spring valve at the side of the helmet (Fig. 93). The effect of this arrangement is that the pressure of air in the helmet is at least equal to, and can, by varying the resistance of the outlet valve, be made greater than, the water-pressure at the level of this valve. For every 34 feet of fresh water (or 33 feet or 10 metres of sea-water) the pressure increases by one atmosphere, i.e. nearly 15 lb. 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 his abdomen; and at a greater depth blood would 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.

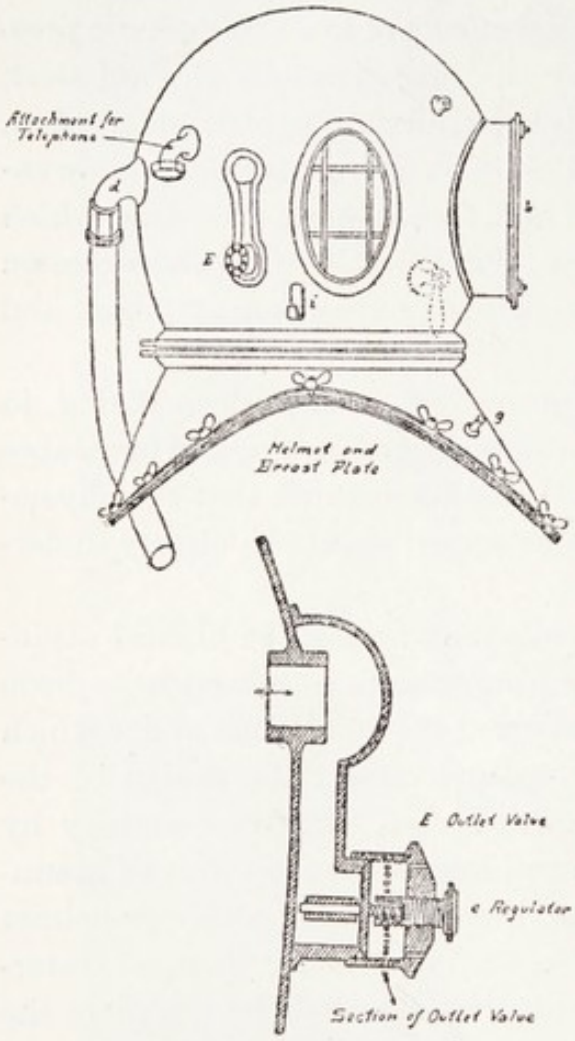


FIG. 93. Helmet and section of outlet valve.

In order to enable the diver to sink and stand firmly on the bottom, the dress is weighted with 40 lb. leaden weights back and front, as shown in the figures, with 16 lb. of lead on each boot—about 112 lb. 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 attached 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. As he sinks till the surface of the water reaches his helmet, the water seems to grip him all round. If the escape valve is fully open he feels by this time that his breathing is somewhat laboured. The reason of this is that the pressure in his lungs is that of the water at the outlet valve, 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 he must during exertion, his breathing is apt to become fatigued for the reasons and in the

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FIG. 94. Diver in ordinary dress blown up. His head is down and his arms outstretched.

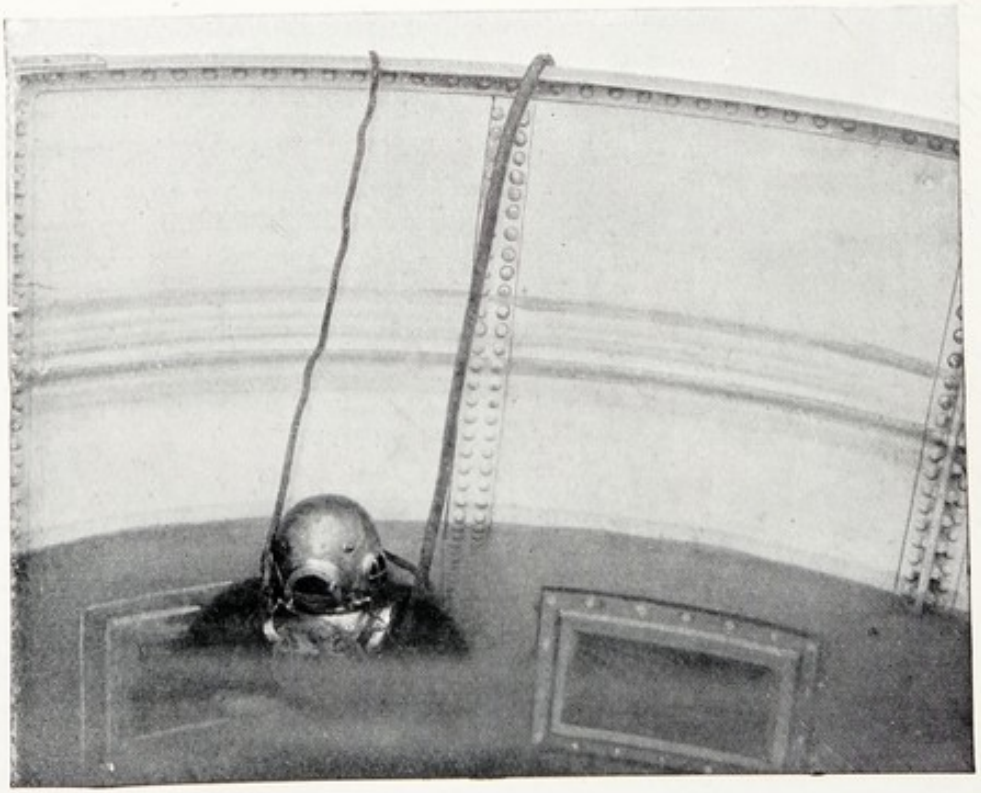


FIG. 95. Diver in laced-up dress purposely blown up. His head is up and his arms free.

manner described in Chapter V. With another foot of adverse pressure respiratory fatigue comes on very rapidly. Therefore one of the first things which a diver has to learn is to avoid the adverse pressure by so regulating the spring on the outlet valve that the breathing is always easy. The spring, of course, regulates at the same time the amount of air in the dress, and therefore the buoyancy of the diver. A practised 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 bottom, it may easily happen that the air gets into the legs of his dress. The result of this accident is that his head goes down, so that the excess air cannot escape readily. Under such conditions the diver is blown helpless to the surface with his arms fixed in an outstretched position (see Fig. 94). If his air-pipe is caught by some obstruction under water, he will be 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 in being blown up; and to avoid this danger an arrangement for lacing up the legs of the dress was introduced, though it is seldom used. Its effectiveness is shown by Figs, 94 and 95.

In the Denayrouze apparatus, formerly extensively used on the Continent, the air is pumped into a steel reservoir on the diver's back. By means of a reducing valve air is supplied from the reservoir according to his requirements. The arrangement is a beautiful piece of mechanism, but is an encumbrance and 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.

In recent years, for diving to very great depths, as in the salvage of the gold from the *Egypt*, a form of apparatus quite different in principle has been introduced. This apparatus consists of a strong and rigid casing of metal, which may have articulated limbs, in which the diver is wholly enclosed. He is therefore protected from the external pressure and consequently breathes air at normal atmospheric pressure. He can himself do almost no work, but he can direct operations carried out from the surface. At best, operations

of this kind are very slow, and they would often be quite ineffective, so that the ordinary method is much better if it is practicable.

For engineering work in preparing foundations, etc., under water, a diving-bell is sometimes employed. This is a heavy metal box open below, and supplied with compressed air through a pipe (Fig. 96). It is lowered to the bottom with the workmen sitting in it, and the pressure of the air is so regulated that water cannot enter the bell, and the men can work dry on the bottom. The diving-bell in its original crude 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 waterlogged strata near the surface, is a further development of the diving-bell. It is now largely used for sinking the foundations of the piers of bridges, etc., through soft ground on the bottom of a river or the sea. The caisson (Fig. 97) is the bottom section of the steel pier and resembles the diving-bell except for the fact that it communicates with the surface through a tube occupying the centre 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 obtained through an air-lock on the surface. The men enter the air-lock through a door which they then close. They then let the air-pressure rise till they can open the door into the central tube; in coming out the reverse process is used.

In tunnelling 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 waterlogged London clay, and under the Hudson and East rivers at New York, have been constructed by this means. In the sinking of colliery shafts through waterlogged strata the freezing or cementation processes are now generally used, since, except in strata fairly near the surface, the water pressures are too high for the compressed-air process.

Men working under the conditions described are of course subject

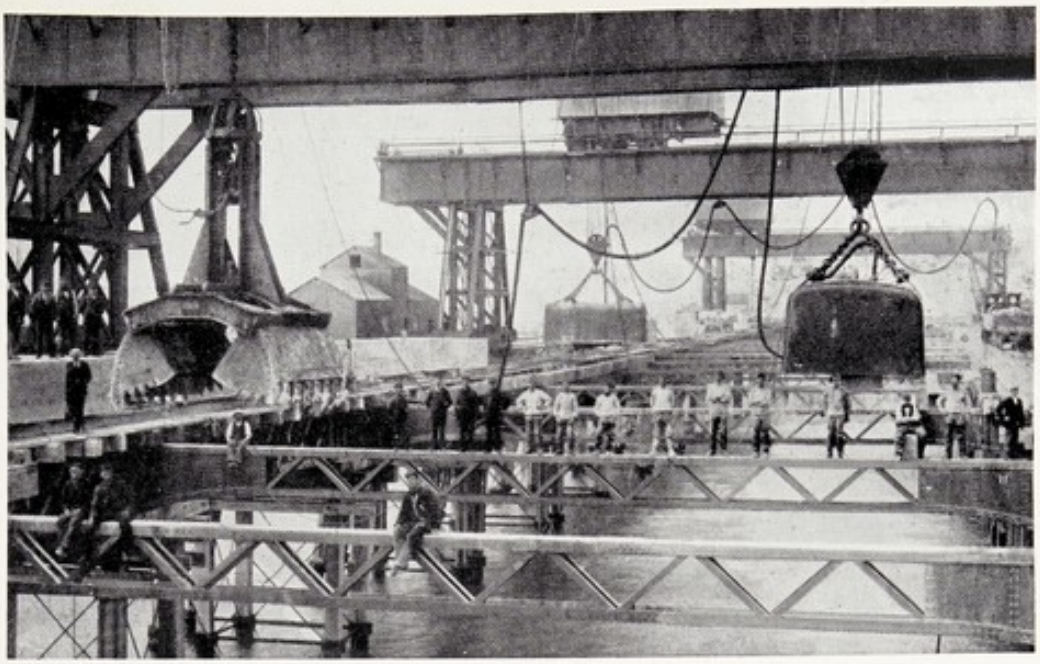


FIG. 96. Diving-bell in use at National Harbour Works, Dover. Each bell measures 17×10 feet by $6\frac{1}{2}$ feet high, and weighs about 35 tons.

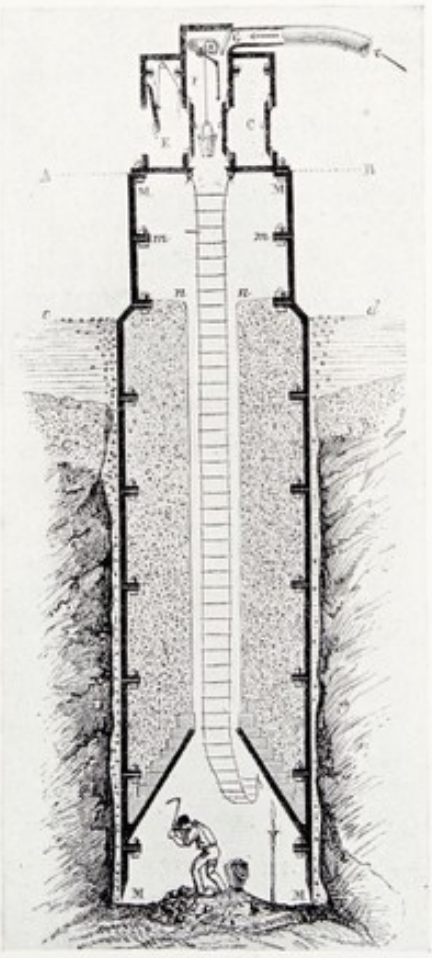


FIG. 97. Diagram showing use of caisson in making the foundations of a bridge. (After Foley.)

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to the various physiological disturbances which 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. When this occurs it is due to unbalanced pressure on the membrana tympani, owing to the fact that the Eustachian tube is not freely open so as to allow equalization of the air pressure of 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 practised diver goes quite easily within two minutes to a pressure of 7 atmospheres or more, while one who is not accustomed to compressed air may have a long struggle to open up his Eustachian tubes before he can reach an extra pressure of half an atmosphere. It also happens occasionally that there is similar 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 the pressure of 6 or 7 atmospheres and is breathing pure air is perfectly comfortable if he has escaped ear and sinus trouble. His voice is, however, altered by the compressed air for purely physical reasons, 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 might 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. This idea, however, was totally fallacious and indeed ridiculous, since pressure is transmitted instantly, equally, and undiminished in all directions through liquids, and in this respect the tissues of the body, except bone, behave as liquids. As will be seen below, many divers have lost their lives owing to well-meant injunctions to descend and ascend slowly. As regards other conceivably possible effects of a few

atmospheres of mechanical pressure, it should be remembered that the internal pressure of water has been calculated as being thousands of atmospheres. Since the tissues are mainly 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 the easily avoidable effects on the ears and sinuses mentioned above), not to the mechanical pressure, but to the increased partial pressure of the gases in the air breathed. If the air breathed is pure, the only gases which come into consideration in this connexion are nitrogen and oxygen; but if the air is rendered impure by respiration, as is commonly the case in diving, carbon dioxide must also be taken into account. The case of this gas may be considered first, though Paul Bert did not himself allude to it in connexion with the work in compressed air, as he was not practically familiar with diving.

Owing to the difficulties frequently experienced by divers attempting to work at depths of more than 12 fathoms a committee was appointed by the British Admiralty to investigate the whole subject of the difficulties and dangers associated with deep diving (Haldane and others, 1907). It appeared that men who attempted to make any serious exertion when at depths of more than 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, they were frequently found to contain 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 of 3 per cent. of CO_2 at 11 fathoms, or a total pressure of 3 atmospheres, is equal to that of $3 \times 3 = 9$ per cent. at normal atmospheric pressure; so it was no wonder that the divers became unconscious. The pumps were often found to be leaking badly past the pistons, as many of them were old, and no tests for this leakage were then employed. Even 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 the 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 the surface on account of the higher oxygen-pressure, as explained on p. 233.

By far the most serious danger to divers and other workers in compressed air is, however, of quite a different character. From the earliest days of diving and working in compressed air it had been observed that soon after returning to atmospheric pressure the men frequently became ill and sometimes died or became paralysed. 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 his return to the surface; soon he became unconscious and his pulse disappeared, and in a short time he was dead. In other cases his legs became paralysed, 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 'caisson disease'—a somewhat misleading name, which is much better replaced by 'compressed-air illness'.

Paul Bert investigated in animals the nature of compressed-air illness 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 locally 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 is evident. At the high pressure

the blood in the lungs is exposed to greatly increased partial pressure of nitrogen and oxygen, although, as shown in Chapter II, there is no increased pressure of CO_2. Since, 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 from 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 pressure 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 nitrogen, 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. Fig. 98 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. It was found that fat in particular is apt to be very full of bubbles and thus become spongy. It had been found by Vernon (1907), in connexion with another investigation, that gases are much more soluble in oils than in water. In connexion with the diving 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. The tendency of fatty substances to act as a special reservoir of dissolved nitrogen is thus intelligible; and Boycott and Damant (1908) afterwards showed that fat animals, other conditions being the same, are considerably more liable to symptoms of compressed-air illness than spare animals. Not only ordinary fat, but the myelin sheaths of nerve-fibres, 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

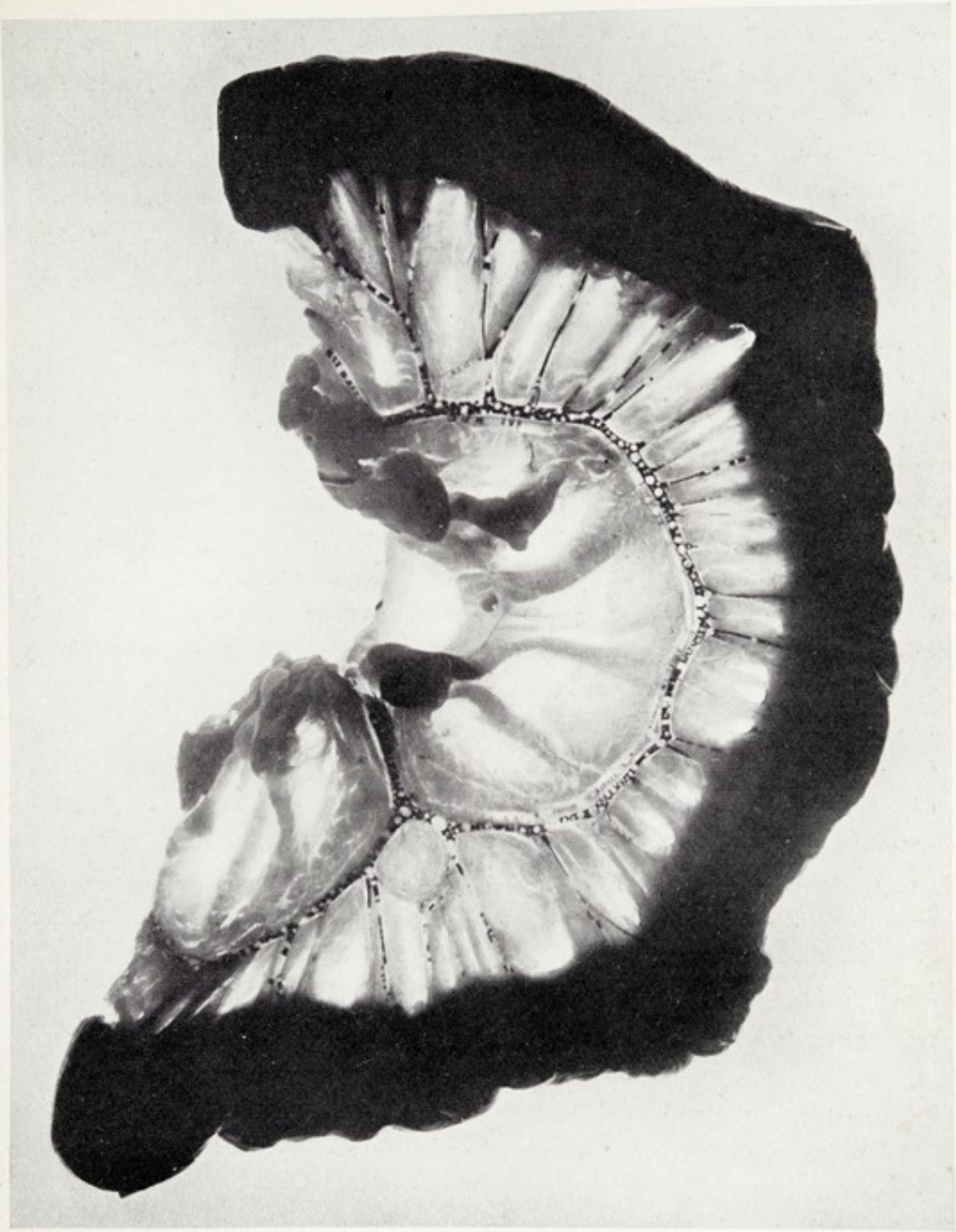
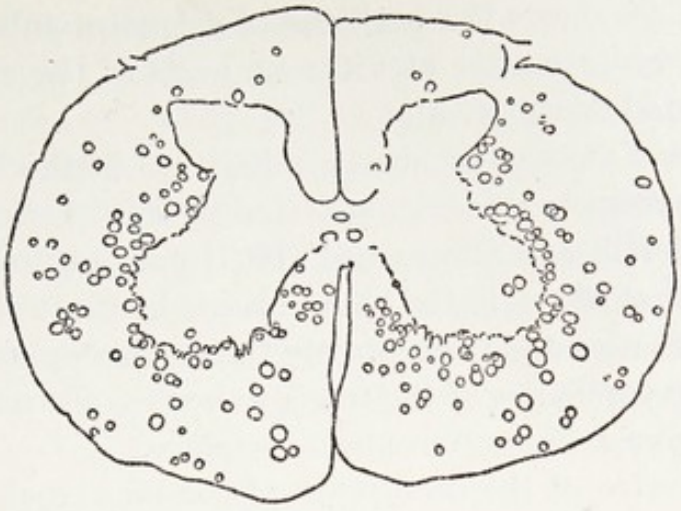
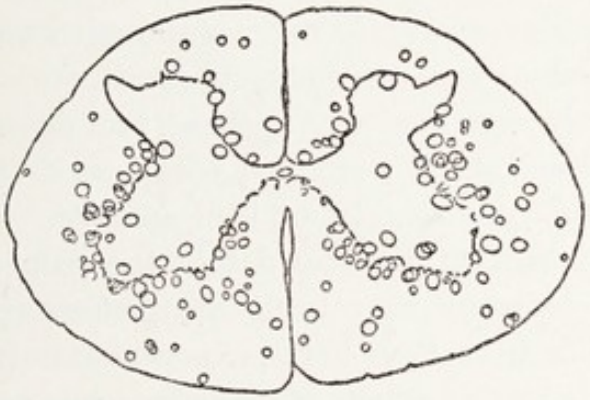


FIG. 98. Portion of goat's mesentery showing bubbles in blood-vessels caused by rapid decompression in $1\frac{1}{2}$ minutes from 100 lb. pressure, after $1\frac{1}{2}$ hours' exposure at this pressure.

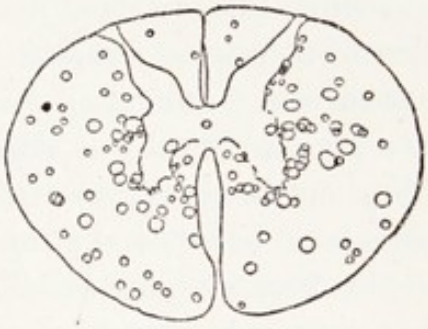
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6th cervical



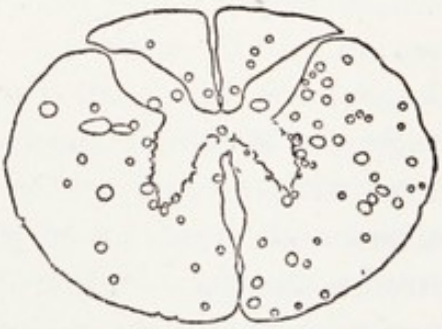
4th lumbar



11th dorsal



2nd cervical



3rd dorsal

FIG. 99. 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 lb. 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.)

'bends'. Fig. 99 shows the positions of a large number of bubbles found in the white matter at different parts of the spinal cord in goats after rapid decompression.

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 (1907) not only confirmed this, but showed that there is the same excess in the urine. Hill and Macleod (1903) 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.

As a preventive of the occurrence of compressed-air illness Paul Bert recommended slow and gradual decompression; but his experiments in this direction were not very successful, as he had not 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 compressed-air illness remained common if the extra pressure used was above approximately 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 experiments. 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 connexion 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 roughly 1·5 atmospheres, and in extensive deep diving operations. Figs. 100 and 101 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 at first disappointing, and from causes which will be made evident below. There is, however, important scope for oxygen administration during decompression, or 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 compressed-air illness, 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 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 impracticable on account of changes of tide 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 $1\frac{1}{4}$ 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 $2\frac{1}{4}$ 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 Haldane thought it 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 Boycott, Damant, and Haldane (1908) at the Lister Institute, London, in a large steel chamber which was given for the purpose by the late Dr. Ludwig Mond (see Figs. 102 and 103). They 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 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 behaviour and the manner in which they held the affected limb (Fig. 104). 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 they 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 became the routine practice of divers, and is not known to have ever resulted in harm, if the excess pressure did not exceed about 6 atmospheres.

They 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 (1854), who were the first to give a medical account of the symptoms of compressed-air illness. 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



FIG. 104. 'Bends' of foreleg in a goat.

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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 till 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 grey matter, on the other hand, has a very free blood-supply and no extra capacity for storing nitrogen. Other tissues, 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, Boycott, Damant, and Haldane estimated that the whole body of a man weighing 70 kilos will take up about 1 litre 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 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 saturation, 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 10 minutes, and that saturation would be practically complete in an hour. The progress of the saturation would follow the logarithmic curve shown in Fig. 105, but it would be an entire mistake, which in fact has led again and again to fatal results, to imagine that this rate of saturation and desaturation could be applied to the body as a whole. This mistake has even been made in recent years in spite of all the

warnings given in the papers just referred to. 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

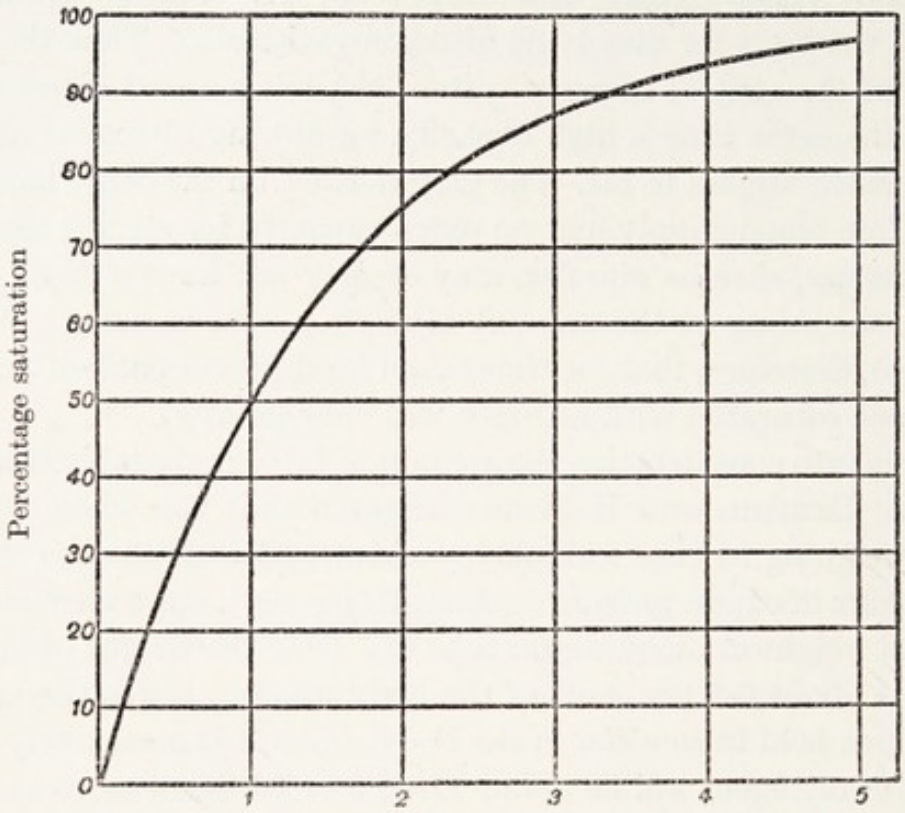


FIG. 105. Curve showing the progress of saturation of any part of the body with nitrogen after any given rise of pressure. The percentage saturation can be read off on the curve, provided the duration of exposure to the pressure, and the time required to produce half saturation of the part in question, are both known. Thus a part which half saturates in one hour would, as shown on the curve, be 30 per cent. saturated in ½ hour, or 94 per cent. saturated in 4 hours.

experiments on animals, that liability to compressed-air illness increases with duration of exposure. Boycott, Damant, and Haldane found that in goats the liability increased up to about 3 hours' exposure, but did not increase farther 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 they calculated from the goat experiments, taking into account the greater rate of circulation in the goat on account of its much smaller weight (p. 407), that in man the liability would increase up to about 5 hours' exposure. They had therefore to allow for those parts of the body which would become half

saturated in about $1\frac{1}{4}$ hours, but for nothing slower than this. Recent experiments by Argyll Campbell and Sir Leonard Hill (1933) indicate a still slower rate of saturation in certain fatty tissues, but probably this gives rise to no symptoms.

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

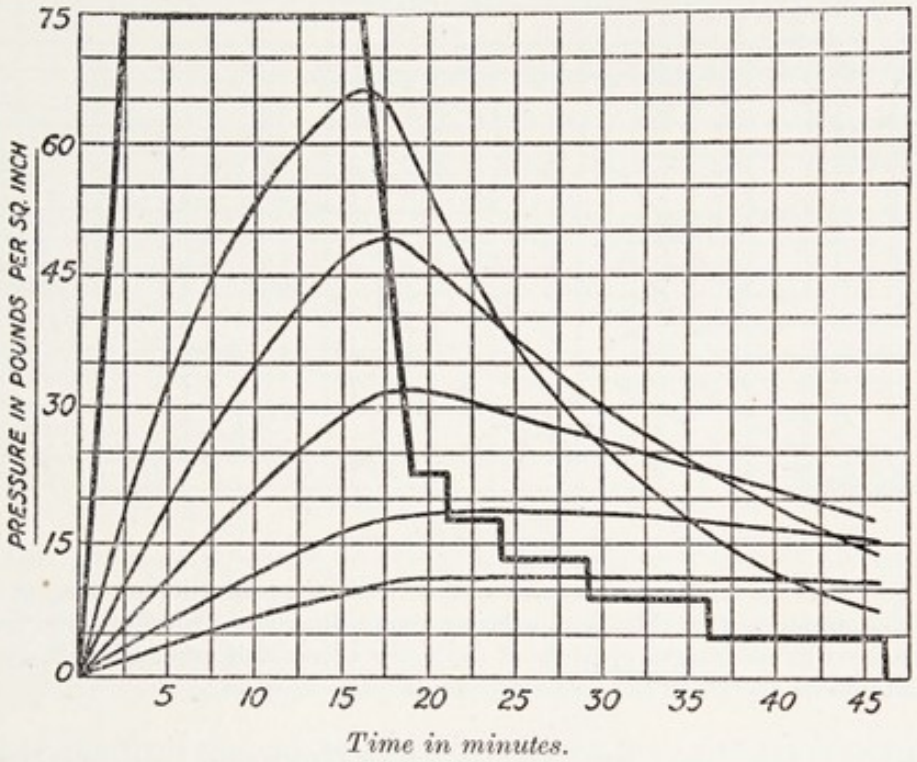


FIG. 106. Diving to 168 feet by new method: Diver 14 minutes on the bottom and 46 minutes under water. The curves from above downward represent, respectively, the variations in saturation of parts of the body which half saturate in 5, 10, 20, 40, and 75 minutes; the thick line representing the air-pressure.

after the initial reduction of total pressure to half 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 10 feet of ascent.

Fig. 106 represents what is happening during a dive to 28 fathoms, with the stay on the bottom limited to 14 minutes, and 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 $17\frac{1}{2}$ pounds per square inch (or 1·17 atmospheres) of excess air-pressure. This leaves a margin of safety. Fig. 107 shows what happened by the old method, with the same time on the bottom. It will be

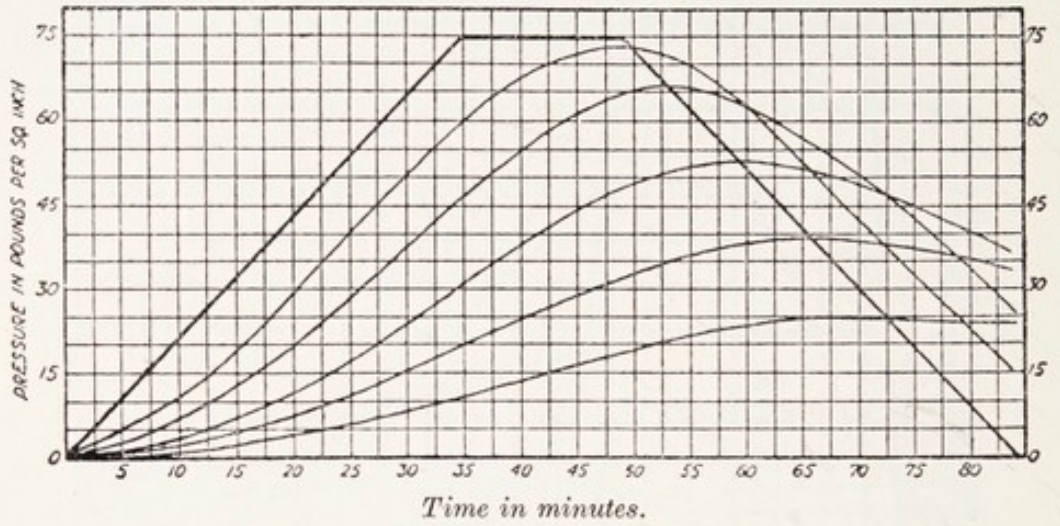


FIG. 107. Diving to 168 feet by old method: Diver 14 minutes on the bottom and 84 minutes under water. The curves from above downward represent, respectively, the variations in saturation of parts of the body which half saturate in 5, 10, 20, 40, and 75 minutes; the thick line representing the air-pressure.

seen that (1) the dive took twice as long a time, and (2) when the diver reached surface the maximum supersaturation was 36 lb. (2·4 atmospheres), so that he would run a most dangerous risk. It is evident from the figure that the slow descent and most of the slow ascent were simply adding to the danger. These figures show also in a clear way the advantages of cutting down the duration of stay on the bottom. It appears from Fig. 106 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. Fig. 108 shows, for instance, that it would take nearly 5 hours by the stage method, and 10 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, or 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 twenty-five years ago

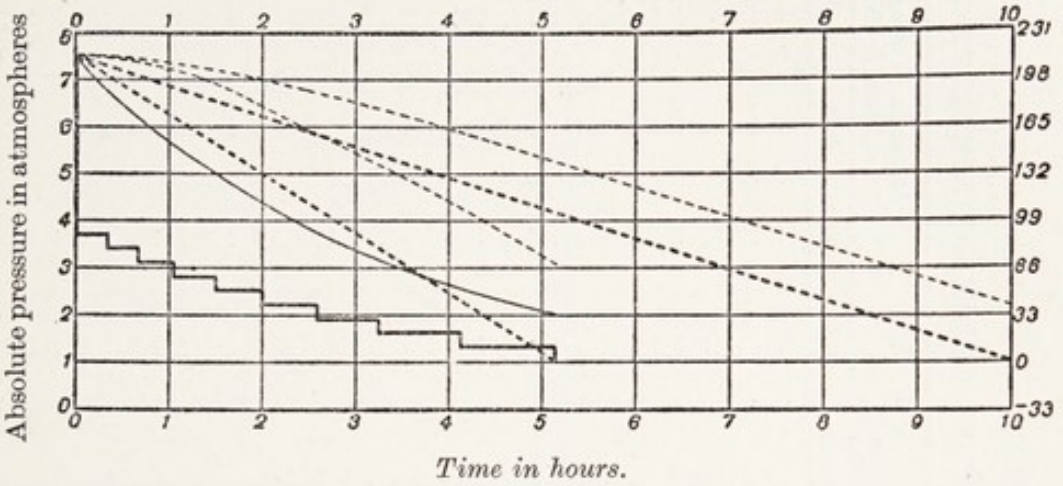


FIG. 108. Theoretical ascents of a diver after a prolonged stay at 213 feet of sea-water. Stage decompression in 309 minutes compared with uniform decompressions in 309 minutes and in 10 hours. Continuous lines = stage decompression; interrupted lines = uniform decompression. Thick lines = air-pressure; thin lines = saturation with atmospheric nitrogen in parts of the body which half saturate in 75 minutes.

of the method of decompression embodied in these 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 was 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. Haldane calculated the tables with great care on the theoretical lines borne out by the experiments and

TABLE I

STOPPAGES DURING THE ASCENT OF A DIVER AFTER ORDINARY LIMITS OF TIME FROM SURFACE

Depth		Pressure	*Time from surface to beginning of ascent*	*Approximate time to first stop*	*Stoppages in minutes at different depths*[1]						*Total time for ascent in mins.*
Feet	*Fathoms*	*Pounds per square inch*			*60 ft.*	*50 ft.*	*40 ft.*	*30 ft.*	*20 ft.*	*10 ft.*	
0–36	0–6	0–16	No limit	1	..	..	..	..	..	..	0–1
36–42	6–7	16–18½	Over 3 hours	1	..	..	..	..	..	5	6
42–48	7–8	18½–21	Up to 1 hour	..	..	..	..	..	..	..	1½
			1–3 hours	1½	..	..	..	..	..	5	6½
			Over 3 hours	1½	..	..	..	..	..	10	11½
48–54	8–9	21–24	Up to ½ hour	..	..	..	..	..	..	..	2
			½–1½ hours	2	..	..	..	..	..	5	7
			1½–3 hours	2	..	..	..	..	..	10	12
			Over 3 hours	2	..	..	..	..	..	20	22
54–60	9–10	24–26½	Up to 20 mins.	..	..	..	..	..	..	..	2
			20–45 mins.	2	..	..	..	..	..	5	7
			¾–1½ hours	2	..	..	..	..	..	10	12
			1½–3 hours	2	..	..	..	..	5	15	22
			Over 3 hours	2	..	..	..	..	10	20	32
60–66	10–11	26½–29½	Up to ¼ hour	2	..	..	..	..	..	..	2
			¼–½ hour	2	..	..	..	..	..	5	7
			½–1 hour	2	..	..	..	..	3	10	15
			1–2 hours	2	..	..	..	..	5	15	22
			2–3 hours	2	..	..	..	..	10	20	32
66–72	11–12	29½–32	Up to ¼ hour	2	..	..	..	..	..	2	4
			¼–½ hour	2	..	..	..	..	3	5	10
			½–1 hour	2	..	..	..	..	5	12	19
			1–2 hours	2	..	..	..	..	10	20	32
72–78	12–13	32–34½	Up to 20 mins.	2	..	..	..	..	..	5	7
			20–45 minutes	2	..	..	..	..	5	10	17
			¾–1½ hours	2	..	..	..	..	10	20	32
78–84	13–14	34½–37	Up to 20 mins.	2	..	..	..	..	..	5	7
			20–45 mins.	2	..	..	..	..	5	15	22
			¾–1¼ hours	2	..	..	..	..	10	20	32
84–90	14–15	37–40	Up to 10 mins.	2	..	..	..	..	..	3	5
			10–20 mins.	2	..	..	..	..	3	5	10
			20–40 mins.	2	..	..	..	..	5	15	22
			40–60 mins.	2	..	..	..	3	10	15	30

90–96	15–16	40–42½	Up to 10 mins.	3	..	..	..	..	..	3	6
			10–20 mins.	2	..	..	..	..	3	5	10
			20–35 mins.	2	..	..	..	..	5	15	22
			35–55 mins.	2	..	..	..	3	10	15	30
96–108	16–18	42½–48	Up to 15 mins.	3	..	..	..	..	3	5	11
			15–30 mins.	3	..	..	..	3	7	10	23
			30–40 mins.	3	..	..	..	5	10	15	33
108–120	18–20	48–53½	Up to 15 mins.	3	..	..	..	2	3	7	15
			15–25 mins.	3	..	..	..	5	5	10	23
			25–35 mins.	3	..	..	..	5	10	15	33
120–132	20–22	53½–59	Up to 15 mins.	3	..	..	..	2	5	7	17
			15–30 mins.	3	..	..	..	5	10	15	33
132–144	22–24	59–64½	Up to 12 mins.	3	..	..	..	3	5	5	16
			12–25 mins.	3	..	..	2	5	10	12	32
144–156	24–26	64½–70	Up to 10 mins.	3	..	..	..	3	5	5	16
			10–20 mins.	3	..	..	2	5	10	12	32
156–168	26–28	70–75	Up to 10 mins.	3	..	..	2	3	5	5	18
			10–16 mins.	3	..	2	3	5	7	10	30
168–180	28–30	75–80½	Up to 9 mins.	3	..	..	2	3	5	5	18
			9–14 mins.	3	..	2	3	5	7	10	30
180–192	30–32	80½–86	Up to 13 mins.	3	..	2	3	5	7	10	30
192–204	32–34	86–91½	Up to 12 mins.	3	2	2	3	5	7	10	32

[1] During each stoppage the diver should continue to move his arms and legs.

TABLE II

STOPPAGES DURING THE ASCENT OF A DIVER AFTER DELAY BEYOND THE ORDINARY LIMITS OF TIME FROM SURFACE

Depth		Pressure — Pounds per square inch	Time from surface to beginning of ascent	Approximate time to first stop	Stoppages in minutes at different depths								Total time for ascent in mins.
Feet	Fathoms				80 ft.	70 ft.	60 ft.	50 ft.	40 ft.	30 ft.	20 ft.	10 ft.	
60–66	10–11	26½–29½	Over 3 hours	2	..	..	..	..	..	..	10	30	42
66–72	11–12	29½–32	2–3 hours	2	..	..	..	..	..	..	10	30	42
			Over 3 hours	2	..	..	..	..	..	..	20	30	52
72–78	12–13	32–34½	1½–2½ hours	2	..	..	..	..	..	..	20	25	47
			Over 2½ hours	2	..	..	..	..	..	..	30	30	62
78–84	13–14	34½–37	1¼–2 hours	2	..	..	..	..	..	..	15	30	47
			2–3 hours	2	..	..	..	..	..	5	30	30	67
			Over 3 hours	2	..	..	..	..	..	10	30	35	77
84–90	14–15	37–40	1–1½ hours	2	..	..	..	..	..	5	15	25	47
			1½–2½ hours	2	..	..	..	..	..	5	30	35	72
			Over 2½ hours	2	..	..	..	..	..	20	35	35	92
90–96	15–16	40–42½	1–1½ hours	2	..	..	..	..	..	5	15	30	52
			1½–2½ hours	2	..	..	..	..	..	10	30	35	77
			Over 2½ hours	2	..	..	..	..	..	30	35	35	102
96–108	16–18	42½–48	40–60 minutes	2	..	..	..	..	..	10	15	20	47
			1–2 hours	2	..	..	..	..	5	15	25	35	82
			Over 2 hours	2	..	..	..	..	15	30	35	40	122
108–120	18–20	48–53½	35–60 minutes	2	..	..	..	..	5	10	15	25	57
			1–2 hours	2	..	..	..	..	10	20	30	35	97
			Over 2 hours	2	..	..	..	..	30	35	35	40	142
120–132	20–22	53½–59	½–¾ hours	3	..	..	..	..	5	10	15	20	53
			¾–1½ hours	3	..	..	..	5	10	20	30	30	98
			Over 1½ hours	3	..	..	..	15	30	35	40	40	163
132–144	22–24	59–64½	25–45 minutes	3	..	..	..	3	5	10	15	25	61
			¾–1½ hours	3	..	..	..	10	10	20	30	35	108
			Over 1½ hours	3	..	..	..	30	30	35	40	40	178

144–156	24–26	64½–70	20–35 minutes	3	..	..	..	3	5	10	15	20	56
			35–60 minutes	3	..	..	..	7	10	15	30	30	95
			Over 1 hour	3	..	..	20	25	30	35	40	40	193
156–168	26–28	70–75	16–30 minutes	3	..	..	..	3	5	10	15	20	56
			½–1 hour	3	..	..	3	10	10	15	30	30	101
			Over 1 hour	3	..	5	25	25	30	35	40	40	203
168–182	28–30	75–80½	14–20 minutes	3	..	..	..	3	3	7	10	15	41
			20–30 minutes	3	..	..	2	2	3	10	15	25	60
			½–1 hour	3	..	3	3	7	10	20	30	35	111
			Over 1 hour	3	..	15	25	30	30	35	40	40	218
182–194	30–32	80½–86	13–20 minutes	3	..	..	..	3	3	7	15	15	46
			20–30 minutes	3	..	..	3	3	5	10	15	25	64
			½–1 hour	3	..	3	5	10	12	20	30	35	118
			Over 1 hour	3	5	20	25	30	30	35	40	40	228
194–206	32–34	86–91½	12–20 minutes	3	..	..	3	3	5	7	10	20	51
			20–30 minutes	3	..	3	3	3	5	10	20	20	67
			½–1 hour	3	3	3	5	10	15	20	30	35	124
			Over 1 hour	3	15	20	25	30	30	35	40	40	238

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, and before symptoms have time to develop, 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 XII, 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 vapour. As the bubble is at atmospheric pressure and the total gas-pressure in the surrounding tissues is only about $75+18{\cdot}5 = 93{\cdot}5$ 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 lb. per square inch). The operations were successful, and these remarkable dives are described in a paper by Assistant-Surgeon French, U.S.N. (1916), who was one of the medical officers in immediate charge.

Eleven dives were made to depths of from 270 to 306 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 3 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 stupefied by the prolonged action of the high pressure of oxygen. At 40 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 lb. in $3\frac{1}{2}$ minutes, which ruptured both the eardrums of one of the doctors. As 75 lb. pressure was reached the patient suddenly recovered and sat up, feeling all right again. He was then gradually decompressed to 20 lb., in about $1\frac{1}{2}$ 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 lb. were made, but 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 conditions of apparently the most desperate character. It would have taken over 4 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.

The decompression tables quoted above stop at 34 fathoms, and until recently ordinary diving work at even this depth was hardly practicable, since the time on the bottom had to be so much cut down in order to avoid a very lengthy and trying decompression. This state of matters has, however, been remedied through the introduction by Sir Robert Davis (Director and Proprietor of Siebe, Gorman & Co.) of the decompression chamber which goes by his name. This is a cylindrical steel chamber big enough to hold two men, and provided with a trap door in the bottom through which a diver can enter when the chamber is lowered into the water, the chamber itself being kept full of air and properly ventilated by compressed air conveyed through a pipe (Figs. 109, 110, 111 and 112).

The chamber, with an attendant inside it, is lowered to a depth corresponding to an early stage of the diver's stage decompression. On coming up to this stage he enters the chamber, which is then closed, and his further stages are completed within it in comfort, the chamber being meanwhile hauled up on deck. In order to hasten the decompression he is given oxygen to breathe as soon as the pressure is low enough to make this safe.

An Admiralty Committee was recently appointed to test the use of the Davis decompression chamber up to a depth of 50 fathoms (90 metres) and an extension of time on the bottom to half an hour. Numerous experiments were carried out for the Committee on goats in steel chambers at Messrs. Siebe, Gorman & Company's works, and afterwards on men, under the direct supervision of Captain Damant; and a long series of trials in deep water in Loch Fyne. Tables embodying the practical results of these experiments are given in the new Diving Manual published by this firm.

Two important new conclusions were drawn. The first was that where the average saturation of tissues which half-saturate in 5, 10, 20, and 40 minutes exceeds about 6 atmospheres it is no longer quite safe to reduce the absolute pressure in the ratio of 2 to 1, but 1·75 to 1 is safe. The second was that the effect of breathing oxygen in hastening safe decompression is a good deal less than that calculated from the increased proportion of nitrogen leaving the lungs at each round of the circulation. Other things being equal, breathing oxygen instead of air during the decompression stages would halve the time required to make these stages safe, and provided the total time was the same it would not matter whether the pressure was reduced or not during the time occupied in breathing oxygen. It was found, however, that the effects on goats were extremely bad if the pressure of oxygen was not reduced during the decompression. To make the decompression quite safe it was not only necessary to reduce the pressure by stages in the ordinary way, but also to increase by at least 15 per cent. the time which had been calculated as safe if 'other things were equal'. The reason for this appears to be as follows. When oxygen at high pressure is breathed the rate of blood-circulation is diminished as explained at p. 390. By this means the brain and other parts of the body, with the exception of the lungs, are protected against the poisonous effects of a high oxygen-pressure; but the consequence is that nitrogen is washed out of the body more slowly than would otherwise be the case. With decompression in the Davis decompression chamber the breathing of oxygen began at a depth of about 60 feet, corresponding to an oxygen-pressure of nearly 3 atmospheres, as experiments on men had shown that this is safe. At this oxygen-pressure the slowing of the circulation would be very considerable, and, as we have seen, is quite measurable even at an oxygen-pressure of one atmosphere. In spite of this disadvantage, however, the gain in time by breathing oxygen in the decompression chamber is a large one, though presumably much less while the oxygen-pressure remains very high than when it is lower.

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 far 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 was 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 the use of stage decompression has not been possible 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 are enjoined to keep their arms and legs moving as much as possible during the stoppages at each stage, or in the decompression chamber when it is used. Bornstein (1910 *b*) 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 accidental cases of sudden decompression. Thus a diver, who is blown up 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 re-solution at once. With any delay, however, the bubbles become

larger and therefore 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 (Japp, 1912). 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 $2\frac{1}{4}$ 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 lb. at the face and 7·5 lb. in the rest of the tunnel. The total atmospheric pressure is thus 50 lb. at the face and 22·5 lb. 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 of different undertakings, seems to afford the best means of solving the difficulties with air-locks; but existing state regulations might need modification to enable the improvement to be introduced. In any case there is now no justification for imperilling 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.

In connexion with compressed-air illness some very interesting

observations have recently been made by Laurie, of the *Discovery* Expedition (1933 *a*, *b*), while investigating the biology of whales at South Georgia. The whales live largely on lower animals which exist at great depths, and thus have to make long and very deep dives to obtain their food. As they come up very rapidly they might be expected to be liable to the most dangerous forms of compressed-air illness. Laurie found, however, that the blood of whales which had been killed contained an unusually low proportion of free nitrogen. On following the matter up further he found that if this blood were saturated with air the free nitrogen which was at first present diminished rapidly; and he traced the effect to an aerobic bacterium which was present in the blood of all the whales, and which had the power of fixing nitrogen, just like the bacteria in the root-nodules of leguminous plants. It appeared that this organism is quite harmless to the whales, but keeps the proportion of free nitrogen in their blood and tissues low, so that the pressure, even during a deep dive, never becomes sufficiently high to produce bubbles on decompression. If confirmed, this would seem to be a most remarkable example of an advantageous symbiosis, but later work has led Laurie to doubt whether the active agent is actually a bacterium.

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 3 or 4 atmospheres, very remarkable tonic convulsions may be 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 even below 1 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 3 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 3 atmospheres of oxygen the blood will only take up about 7 volumes per cent. 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 XII, 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 3 atmospheres. As was shown in Chapter VIII, 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 2 atmospheres pressure. We can therefore easily understand why so high an oxygen-pressure as 3 or 4 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 and those of Claude Bernard 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 wonderful internal environment the constancy of which protects them from so many variations in the external environment, yet the cells lining the air-passages and

lungs are exposed directly to the high oxygen. It was discovered by Lorrain Smith (1899) 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 the American diver referred to above was exposed for 3 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 it was found by Boycott, Damant, and Haldane that out of seven goats one died in 3 hours from pneumonia, while the others were also affected, but recovered on decompression. At an oxygen-pressure corresponding to 50 fathoms they could not detect in themselves any subjective symptoms during short exposures at rest; but quite probably such symptoms might appear after longer exposure or during exertion; and the behaviour, described above, of the experienced American diver seems suggestive of this.

The experiments of the present Admiralty Committee have shown that men sitting in a steel chamber at a pressure as high as 3 atmospheres of oxygen experienced no abnormal symptoms; but in some of the diving trials with men at work on the bottom at even less than 2 atmospheres of oxygen-pressure, somewhat abnormal behaviour, and particularly loss of memory, were occasionally observed, and were strongly suggestive of an effect on the brain similar to that already described as caused by too low an oxygen-pressure.

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 probable that both the lungs and the rest of the body are capable of acquiring some degree of acclimatization or immunity to the effects of a high pressure of oxygen. Some of the observations of the present Admiralty Committee seem to point in this direction, and more definite evidence is furnished by the experiments mentioned below on rats.

The histological changes in the lungs of rats exposed for long periods to oxygen at 635 mm. Hg partial pressure (= 83·6 per cent. at 760 mm.) have been investigated by Smith, Bennett, Heim, Thomson, and Drinker (1932 *a*, *b*). They found that in rats under one month old there were no clinical signs. In older animals the severity of the reaction and the mortality rate increased in proportion to age. Only a few of the animals died from acute poisoning. The majority recovered and survived several months. The rats were more resistant to a second exposure. The changes in the lungs were hyperplasia and hypertrophy of the alveolar cells, which are normally more numerous in young animals than in old, perivascular oedema and thickening and hyaline change of the walls of the arteries. These changes began in the smallest vessels, but eventually larger arteries were similarly affected.

There is one further effect of high pressures which has acquired considerable practical importance in consequence of the introduction of submarine escape apparatus. The apparatus used in the British Navy was invented by Sir R. Davis and took the place of an earlier apparatus also invented by him. It is shown in Fig. 113, and its description is as follows: a rubber breathing and buoyancy bag contains a CO_2 absorber which is connected by means of a flexible tube (E) to a mouthpiece (F). An oxygen cylinder (B), provided with a control valve (C), is connected by a tube to the breathing bag. The opening of the cylinder-valve admits oxygen to the breathing bag and charges it to a pressure equal to that of the surrounding water, whatever the depth. The wearer is thus able to breathe in a normal manner through the mouth-piece, the nose being closed by clip G. The breathing bag is provided with an automatic non-return air release

valve (K), which allows air to escape from the bag as the external pressure decreases during ascent to the surface. It is most important on adjusting the apparatus to wash out all the nitrogen contained in the lungs and apparatus. If this precaution is not taken the wearer will have no warning of his danger if the oxygen supply becomes exhausted. Further, since the pressure in the bag automatically adjusts itself to the external pressure by means of the release valve, it is of vital importance that the wearer should continue to breathe freely through the mouth-piece throughout the ascent. If he does this the pressure in his lungs is also, of course, kept continuously in equilibrium with the decreasing external pressure. Should he, however, fail to breathe freely through the mouth-piece the intrapulmonary pressure will remain high, and a considerable pressure difference may be set up between the interior of the lungs and the surface of the body. The consequences of this are serious and will be considered below. It may also be remarked that the Hering-Breuer reflex gives no protection at all against distension of this kind.

Similar forms of apparatus are now used in other navies such as the Momsen 'lung' used in the U.S. Navy, and indeed these appliances now form part of the normal equipment of submarines and have proved their value as life savers.

The Davis apparatus was used in the case of the *Poseidon* disaster in 1932. Owing to the use of the apparatus several members of the crew managed to reach the surface. One of them, however, was dead when picked up or died shortly afterwards. A post-mortem examination showed the presence of air-bubbles in some of the blood-vessels and the conclusion was reached that the man had died of compressed-air illness. Other accidents have occurred during courses of instruction in the use of submarine escape apparatus carried out in the U.S. Navy, some of them being fatal. One such fatal accident, reported by Polack and Adams (1932), occurred on May 22nd, 1931, at San Diego in California. The man who was killed made a practice escape from a depth of 15 feet, reaching the surface in 2 or 3 seconds. He had only been submerged for a short time. On reaching the surface he closed the shut-off valve of his apparatus as instructed and swam to the ladder. On reaching it, however, he could not grasp it and fell back. He was quickly pulled out, breathed a few times, and died. Post-mortem examination showed numerous minute haemorrhages scattered throughout both lungs, minute tears in the parietal pleura,

small subarachnoid haemorrhages and definite dilatation of the right ventricle. In another fatal case in America the course of events was very similar and the conclusion was reached, as in the case of the *Poseidon* disaster, that the victim had died of caisson disease. There are, however, difficulties in accepting this explanation. Thus with one exception, all the ten American accidents mentioned by Polack and Adams occurred in practice escapes from less than 30 feet and after short exposures to the increased pressure. It is well known, however, that experience has shown that stage decompression is not necessary during ascent from any depth less than 7 fathoms.

In seeking some other explanation it is important to recall that certain features are common to all these accidents. In every case there was very rapid ascent and an interval after reaching the surface before the onset of any symptoms. If the victims did not breathe freely during the ascent, the intrapulmonary pressure, as stated above, could not fall along with the external pressure. Now some experiments of Chillingworth and Hopkins (1920) showed that increase of intrapulmonary pressure in dogs caused the systemic arterial pressure to fall almost to zero while the venous pressure rose greatly. At the same time the carotid pulse failed while the heart continued to beat. These facts were taken to indicate the existence of a mechanical block in the vessels of the lungs. This interpretation of the submarine escape accidents cannot, however, account, among other things, for the delay in the onset of the symptoms. Moreover, it would seem that any mechanical block in the circulation should have been relieved immediately the man reached the surface and breathed.

In view of these considerations Polack and Adams, as reported in the paper mentioned above, carried out experiments on dogs to test the hypothesis that rise of intrapulmonary pressure causes heart failure in consequence of abnormal resistance to the circulation. They found that 80 mm. Hg intrapulmonary pressure sustained for 10 seconds stopped the circulation through the lungs sufficiently to cause a great fall of systemic arterial pressure and simultaneously corresponding rise of venous pressure. Thus in one experiment the systemic arterial pressure was originally 156 mm. Hg. On raising the intrapulmonary pressure to 80 mm. the systemic arterial pressure fell to 28 mm. Hg and the venous pressure rose to 120 mm. water. On releasing the intratracheal pressure the systemic arterial pressure gradually returned to 128 mm. Hg, reaching this level within one minute.

Now these experiments prove conclusively that the explanation of the submarine escape accidents is not to be found in failure of the right ventricle brought about by the effect of high intrapulmonary pressure in causing resistance to the circulation. The rise of venous pressure proved that the right ventricle received very little blood during the continuance of the high intrapulmonary pressure because, clearly, the veins entering the heart were occluded when the intrapulmonary pressure rose. It is obvious therefore that high intrapulmonary pressure does not cause heart failure in consequence of an abnormal strain thrown on the right ventricle owing to excessive resistance to the outflow of blood from it, because there was little or no blood entering the ventricle to be pumped onwards.

Another explanation had therefore to be sought. Now Ewald and Kobert (1883) found that a rise of 35 mm. Hg was enough to distend lungs removed from the body and to cause an escape of air through what they called the normal stomata of the alveolar wall into the pulmonary capillaries. In the living animal a pressure of 50 to 90 mm. Hg produced the same effect. Katz (1909) also found that when rabbits were exposed to an intrapulmonary pressure of 40 mm. Hg air found its way into the abdominal cavity. Rode and Kronecker (Kronecker 1909) found also that even a slight intrapulmonary pressure (16 inches of water) in rabbits led to air passing into the abdominal cavity. They concluded that the air was not forced through the alveolar walls into the pleural cavity but passed through the walls of the smaller bronchioles into the loose connective tissue surrounding the bronchioles, bronchi, and trachea. Thence they supposed the air to pass into the tubular sheath of connective tissue surrounding the oesophagus and so to the abdomen and all over the body. It has now become clear that ordinary leakage of air from the lungs does not explain the submarine escape accidents. Joannides (1931) found that an intrapulmonary pressure of 60 to 100 mm. Hg caused air embolism, as well as emphysema, pneumothorax, and pneumoperitoneum. These experiments explain the fact that in acute bronchitis and whooping-cough emphysema of the neck and arms is sometimes observed. Probably pneumothorax and pneumoperitoneum would also be found in such cases if it were looked for.

In the light of these observations Polack and Adams carried out further experiments on dogs. They recorded the femoral blood-pressure, the pressure in the internal jugular vein and the intrapulmonary

pressure. They also tied into the carotid a special cannula filled with normal saline which was so arranged as to act as a trap for any air-bubbles which might occur in the blood in the carotid artery. On raising the intrapulmonary pressure to 60 mm. Hg for 10 seconds they observed the typical fall of arterial pressure and rise of venous pressure previously described. No air-bubbles appeared in the carotid trap. On raising the intrapulmonary pressure to 80 mm. Hg for 10 seconds the same effects were observed on the arterial and venous blood-pressures, but in addition numerous air-bubbles appeared in the carotid trap a few moments after the release of the intrapulmonary pressure. When the intrapulmonary pressure was kept at 100 mm. Hg for 10 seconds still more air appeared in the carotid trap, and the animal ceased to breathe though the heart continued to beat for 2 minutes.

In this case they found *post mortem* that there was extensive interstitial emphysema in the mediastinum, extending from the neck to the diaphragm. There was also much emphysema around the blood-vessels in the lungs. Haemorrhagic areas were seen in the areolar tissue about these vessels and extending into the lung substance. Similar areas were found on the surfaces of the lungs. On microscopic examination they found throughout the lung (*a*) perivascular haemorrhages, (*b*) collapse of the pulmonary veins, (*c*) interstitial emphysema, and (*d*) alveolar emphysema with rupture of alveoli. Air emboli were found in the coronary and mesenteric arteries, and surface vessels of the brain. There was air in both ventricles—as much as 77 c.c. in one case.

As the result of numerous experiments they found that intrapulmonary pressures of 90 mm. Hg or more caused immediate traumatic air embolism with serious injury, while pressures of 80 mm. Hg and less caused no permanent damage. They repeated these experiments on animals whose chests were bandaged to prevent expansion of the lungs. They found that under these circumstances increased intrapulmonary pressure does not cause air embolism. Hence the possibility of performing Valsalva's experiment without harm.

They had evidently found a full explanation of the submarine-escape accidents.

When a man comes up rapidly from a depth of even as little as 15 feet with his mouth closed and without breathing his excess of intrapulmonary pressure over external pressure rises accordingly to

a high figure. As soon as this excess exceeds about 80 mm. Hg there is stretching and tearing of many alveoli and their contained capillaries, with the result that air is forced into these vessels as long as the excess intrapulmonary pressure is maintained. This air reaches the heart through the pulmonary vessels *after* the release of the intrapulmonary pressure. Here it is broken up into numerous fine bubbles which may fill the heart with foam, so stopping the circulation and causing death from anoxaemia and asphyxia. Some of the bubbles may, however, pass through the heart into the general circulation, causing air emboli.

These findings thus account completely for all the facts of submarine escape accidents. In the first place they account for the finding of air emboli, though the exposure to high pressure has not been great enough nor of long enough duration to cause compressed-air illness. They also account for the fact that in the accidents there has always been an appreciable interval between the time of reaching the surface and the onset of symptoms. This period is accounted for by the time taken for the air emboli to travel from the heart to a vital area.

The distribution of the bubbles and the consequent lesions is much affected by the position of the body—a point of some importance with reference to prophylaxis and treatment.

It follows from these observations that submarine escape accidents of this kind would be entirely prevented by strict observations of the following points:

(1) All men being trained in the use of the escape apparatus must become thoroughly familiar with the problem of breathing while wearing the apparatus under water *before* they ever make an attempt to practise an escape.

(2) Continuous and free breathing *must* go on during the ascent.

XII

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 connexion 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 important part in determining the amount of breathing required to keep the composition of the arterial blood constant, and are thus intimately connected 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 (1910 *a*) was the first to show, excessive breathing brings about failure of the circulation. Further observations were made by Henderson and Haggard (1918 *b*, *c*). Thus we cannot at all fully understand how the breathing is regulated, and the significance of variations in it, 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 paralysed 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 express this more definitely 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 tends to 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 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 aerated, 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 connexion 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 brought about by the activity of the gland.

We can form a general idea as to what changes in the gaseous composition of the blood determine the circulation-rate through the tissues if we compare 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 on p. 43, 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 Fig. 19 (assuming that the haemoglobin of arterial blood is 95 per cent. saturated) and the thick line in the corresponding curve for CO_2 (Fig. 16) 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, but under the influence of anaesthetics and severe operative procedure, 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, made under conditions which cause the minimum of interference with normal physiological processes, 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.

Attempts which have been made to measure the circulation-rate in animals directly are, therefore, only of historical interest. Such were the measurements carried out by means of Ludwig's 'Stromuhr' and improved forms of it which were devised. The same statement applies to determination of the rate of circulation of some substance injected into the blood (Hering, 1829).

The difficulty as regards human experiments has 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. On the other hand, various formulae have been suggested with the object of deducing the rate of blood-flow from observations of the blood-pressure, pulse-rate, velocity of the pulse wave and other factors. These formulae are, however, of very small value since they include so many factors which cannot be determined with accuracy. Valuable information of a rough kind was obtained by Zuntz and Hagemann (1898) 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, a method which had been suggested in principle by Fick (1870). These experiments seemed to show clearly that the 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.

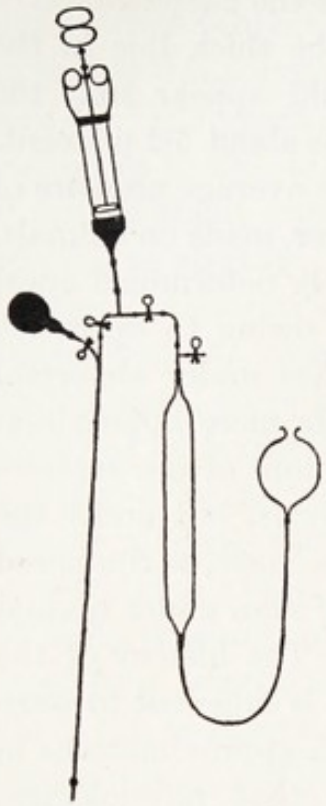


FIG. 114. Lung-catheter as used by Loewy and von Schrötter. The lung-catheter consists of a central inner tube open at the lower end, and an outer tube ending below in a distensible bulb which can be blown up by the rubber bag when the end of the catheter is placed in position in a bronchus. By means of the syringe and glass sampling-tube a sample of gas from beyond the bulb can be collected over mercury free of air.

Other very interesting experiments were made on man by Loewy and von Schrötter (1905). They succeeded in introducing a modified Pflüger lung catheter (Fig. 114) into a branch bronchus or one of the two main bronchi in man. The supply of fresh 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 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 the normal 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 Haldane (p. 56) 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. If, as indicated by the venous oxygen-pressure, the blood had lost about 25 per cent. of its normal charge of oxygen in passing round the body, the venous oxygen-pressure corresponded to about 60 per cent. saturation of the haemoglobin with oxygen, and this is about 25 per cent. less than the saturation of the arterial blood. 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 in both arterioles and veins would be below normal. The results of these experiments seem to possess high significance, as showing that during rest the blood loses only a small proportion of its oxygen in the course of its circulation.

Of recent years one of the earliest attempts to measure the circulation rate in man was made by Yandell Henderson (1905), and he

applied his method during the Pike's Peak Expedition. It depends on his observation that, if a man is laid on a plank and suspended from a height, the inertial recoil of the whole body at each beat of the heart can easily be recorded and amplified. From these records it was possible to calculate the mass of blood ejected at each heart-beat. The method, though rough, served to indicate that on Pike's Peak after acclimatization the rate of blood-flow remained practically normal in spite of the considerable altitude.

Apart from this work of Yandell Henderson, measurements of the circulation-rate have been dependent on some application of the principle applied by Zuntz and Hagemann or some modification of it, or by means of the use of an indifferent gas. We may first consider the latter method.

It was suggested by Bornstein (1910*a*) that the circulation-rate can be calculated from the absorption of a physiologically indifferent gas which enters the blood simply by diffusion, and the coefficient of solubility of which in blood is known. Bornstein himself used nitrogen as the indifferent gas, but it has been shown that it is far from being suitable for the purpose.

Markoff, Müller, and Zuntz (1911–2) suggested that nitrous oxide would prove to be much more suitable, and Yandell Henderson tried to determine the circulation-rate by means of N_2O during the Pike's Peak Expedition, but without success.

About the same time Krogh and Lindhard (1912) worked out in detail the nitrous-oxide method and made extensive use of it. This method gives absolute and not merely relative results. The principle of the method is that the lungs are filled 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 a few 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. The percentages of nitrous oxide in the two samples are determined, and also the total volume of gas in the lungs (this involves a determination of the volume of the residual air). It is then possible to calculate how much nitrous oxide has been absorbed in the interval between the two alveolar samples. Then knowing the solubility of nitrous oxide in blood and assuming that the blood leaving the lungs is fully saturated with nitrous oxide to the existing partial pressure of the gas, one can calculate from the loss

of nitrous oxide from the air in the lungs 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 returning to the lungs continues to be free of nitrous oxide.

In their original paper Krogh and Lindhard described two methods of carrying out the experiment, which they called respectively the residual method and the equilibrium method.

The residual method is carried out as follows:

A suitable gas mixture, containing 10 to 25 per cent. N_2O and 20 to 25 per cent. O_2, is prepared, and a small recording spirometer is filled with about 4·5 litres of this mixture. The respiratory exchange of the subject at rest is first determined. He then makes a maximal expiration to air and at once makes a deep inspiration from the spirometer. The breath is then held for 5 to 15 seconds. This is the introductory period, during which it is assumed that the lung tissue becomes saturated with N_2O. An expiration of at least one litre is then made into the spirometer and a sample of alveolar air is taken. The breath is then held during the actual experimental period, i.e. for 6 to 25 seconds, and a large, sharp expiration is made, and a second alveolar sample is taken. The residual air in the lungs is then determined separately by inspiring a known volume of hydrogen and determining how much it is diluted.

The equilibrium method is carried out rather differently:

The initial expiration is of normal depth, not maximal. Then three respirations of from 1 to 2 litres are taken, inspiring from the spirometer and expiring into it again. At the end of the last expiration an alveolar sample is taken. The breath is then held as before for the experimental period and a final maximal expiration is made and the second alveolar sample is taken.

The equilibrium method has been generally used by Lindhard and subsequent workers to the exclusion of the residual method.

Henderson and Haggard (1925) returned to the principle of using inhalation of a foreign gas for measurement of the circulation rate. After careful consideration of the principles involved and after trying various gases which seemed *a priori* to be suitable for the purpose they came to the conclusion that the vapour of ethyl iodide had particular advantages. These advantages they considered to be as follows: (1) minute amounts of ethyl-iodide vapour in air can be determined accurately by means of iodine pentoxide. (2) The

co-efficient of distribution of ethyl iodide between air and blood at body-temperature is about 2·0, a conveniently low value. (3) Ethyl iodide is decomposed in the tissues of the body almost completely, so that the amount returning in the venous blood to the lungs is negligible, Hence the circulation-rate is given by a relatively simple formula. Henderson and Haggard worked out the details of the method, including a method of obtaining the necessary samples of 'alveolar air', which they considered simplified the procedure.

The ethyl-iodide method was at first widely accepted, but it was not long before other workers pointed out serious sources of error. H. Barcroft (1927) pointed out that the automatic sampling method of Henderson and Haggard did not give true samples of the alveolar air. Moore, Hamilton, and Kinsman (1926) and Davies and Gilchrist (1926–7) showed that the ethyl iodide is not completely destroyed in the body but returns to the lungs. Starr and Gamble (1926–7) and Wright and Kremer (1927–8) found that the coefficient of distribution of ethyl iodide between air and normal blood is three or four times as great as stated by Henderson and Haggard. Starr and Gamble also found that the iodine-pentoxide method is not reliable for the determination of ethyl iodide. Another source of error which has been pointed out is loss of ethyl iodide owing to its ready absorption by water and india-rubber (Davies and Gilchrist, 1926–7). It appears therefore that the ethyl-iodide method, which at first seemed to be so promising, cannot be relied upon to give accurate results.

Marshall and Grollman (1928) attempted to use ethylene, but later gave up the use of this gas owing to the difficulties arising from apparent variations in its solubility in the blood of different individuals. Grollman (1929) then introduced the use of acetylene. He found that, though acetylene as commonly obtained is contaminated with toxic impurities, it can be breathed with perfect safety if it is carefully purified. He determined the amount of acetylene in the samples by the method of Treadwell and Tauber (1919), which he found to be satisfactory. It should be noted, however, that precautions have to be taken to avoid error due to the solubility of acetylene in the liquid used for the absorption of CO_2.

Grollman's method of determining the circulation-rate by means of acetylene is as follows: the subject expires through his mouth, his nose being closed by a clip, so as to empty the lungs as completely as possible. This expiration is made through a wide-bored three-way

tap connected on the one hand to a rubber bag of about 2,800 c.c. capacity, and opening on the other hand to air. The rubber bag is filled with a mixture of air and acetylene (8 to 12 per cent.). Immediately the preliminary expiration is completed the subject holds his breath for an instant while the experimenter turns the tap as quickly as possible. The subject then takes a deep inspiration, emptying the bag completely. He then expires into the bag and again inspires and repeats this procedure, taking at least six full inspirations from the bag in all. The inspirations and expirations should be deep enough to empty and fill the bag completely but without excessive effort. As soon as these preliminary inspirations and expirations have insured complete admixture of the contents of the bag and the air in the lungs a sample of the mixture is withdrawn by means of a vacuous sampling tube. Five to eight seconds later, a second sample is collected. The second sample must be obtained within 23 seconds of the beginning of the rebreathing procedure so as to ensure that no acetylene returns to the right side of the heart, and the subject continues rebreathing during the whole of this time. The subject then breathes air quietly for about 15 minutes so as to allow of the removal of all acetylene from the body. A bag full of expired air, for the determination of the metabolism, is then collected in the ordinary way. The two samples are then analysed and the percentages of acetylene, oxygen, and nitrogen in them are determined. The rate of absorption of oxygen per minute is also determined by measurement and analysis of the expired air collected. The calculation of the circulation-rate from the data so obtained is somewhat complicated. Full details of it are given by Baumann and Grollman (1931).

Meanwhile, it had appeared to be probable that the nitrous-oxide method as used by Krogh and Lindhard in their original experiments was subject to certain serious sources of error, and, in order to get a more direct and accurate insight into the blood-flow through the lungs, Christiansen, Douglas, and Haldane (1914) introduced a new method which was rendered possible by their determination of the CO_2 dissociation curve of normal human blood and was based on the principle suggested by Fick. They determined the CO_2-pressure of the venous blood after oxygenation but without its losing any CO_2. As they had already discovered (p. 52), this pressure is higher by an easily calculated amount than that of the unoxygenated venous blood. Mixtures of air containing about the required percentage of

CO_2 were prepared. A deep breath of one of these mixtures was taken in immediately after a maximal expiration. After two seconds part of the air in the lungs (about $1\frac{1}{2}$ litres) was expired, so as to obtain a sample of alveolar air. The rest of the breath was held for 5 seconds and a second sample of alveolar air was then taken. If these two samples gave practically the same percentage of CO_2, it was evident that the CO_2 in the alveolar air was 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. They were in effect using the whole of both lungs as an aerotonometer. For any particular person it was easy by means of two or more experiments with slightly different mixtures to find the mixture which gave equilibrium. With the help of Fig. 16 (p. 57) the CO_2-content and the true value of the venous CO_2-pressure could easily be calculated. It was simple also to calculate how much CO_2 the blood had taken up in passing round the body when the normal alveolar CO_2-pressure was known. 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 Fig. 16 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.

The investigation was continued by Douglas and Haldane, who had found meanwhile, as was also clearly pointed out by Sonne (1918–19), that it is quite impossible by taking merely a single breath to produce an even mixture in the lung alveoli as regards any constituent of which the percentage differs materially from that previously present in the alveolar air. Thus with a single deep breath we cannot get an

even mixture on inhaling a mixture containing a foreign gas such as nitrous oxide or hydrogen, or a mixture containing much less oxygen than the pre-existing alveolar air, though we can easily get an even mixture as regards CO_2 by the method just described.

As they wished to determine, not merely the CO_2-pressure of oxygenated venous blood, but also the oxygen-pressure under various conditions and the CO_2-pressure of venous blood before oxygenation, they proceeded to make experiments in such a way as to avoid this source of error. The work, however, had to be interrupted owing to the outbreak of war and the absence of Douglas on active service. But, with the help of Mavrogordato, Haldane continued the experiments and communicated a number of results to the Physiological Society in 1915, which demonstrated very clearly the fallacies which might arise from incomplete mixture of a single deep breath in the lungs, as well as the real venous oxygen-pressures during normal breathing, after forced breathing, etc.

After the War the subject was again taken up by Douglas and Haldane (1922), and the method they finally adopted, when it was desired to determine the venous oxygen-pressure as well as the circulation-rate, was as follows: the approximate composition of the gas mixture required to give equilibrium with the venous gas-pressures, was first obtained from a pilot experiment. A mixture of this composition was then prepared in a Douglas bag with the help of two or more gas-meters. Two other bags were filled respectively with mixtures, one containing about 0·5 per cent. more CO_2 and less oxygen, and the other 0·5 per cent. less CO_2 and more oxygen than the mixture in the first bag.

In making an experiment a maximal expiration was first made, followed instantly by a deep inspiration from one of the bags, another maximal expiration to air and inspiration from the bag, and a final deep expiration to air and inspiration from the bag. The last inspiration was held for two seconds, and then a sample of alveolar air was taken at the end of a sharp expiration of about 1,600 c.c. The depth of this expiration was regulated by attaching to the end of the respiratory tube the adjustable 'concertina' (p. 209). The concertina was detached from the rest of the apparatus figured by Haldane, Meakins, and Priestley, inverted and set so as to hold just 1,600 c.c. As soon as the first sample was taken the concertina was released, and after 5 seconds a second alveolar sample was taken with a maximal

expiration, so that about 3,500 c.c. in all had been expired into the concertina. After a short period of rest to restore approximately basal conditions this procedure was repeated successively with the gas mixtures in the other two bags.

If the gas mixtures in the bags were chosen correctly and the experiment was successful, the true venous CO_2- and oxygen-pressures were 'straddled' and could be calculated from the rise or fall of the CO_2- and oxygen-pressures in the successive alveolar samples.

Just before or just after the experiment, and with the subject remaining under exactly the same conditions, the metabolism was determined with all the usual precautions by the Douglas-bag method. Samples of alveolar air for the determination of arterial CO_2-pressure were taken as nearly as possible at the same time and under the same conditions as the samples for the venous gas-pressures. The experiments were always made some hours after a meal, to avoid changes in alveolar CO_2-pressure consequent on secretion of the digestive juices (p. 116).

The venous CO_2-pressure determined in the way just described is the CO_2-pressure of unoxygenated venous blood, and account must be taken of this fact in reading off from the dissociation curves the corresponding venous CO_2-content. The true (unoxygenated) CO_2-pressure provided a check on the oxygen-pressure of the venous blood. A series of results are given in the table on p. 375.

Consideration of this table shows how striking is the agreement in individual determinations of the excess of venous over arterial CO_2-pressure or of arterial over venous oxygen-pressure, even on different days. Different individuals gave very distinctly different results, but the same individual under the same physiological conditions gave very consistent results.

It is evident also from the figures of the table that the mean difference in CO_2-pressure between arterial blood and venous blood was 14·7 mm., as compared with a difference of 9·9 mm. when the venous blood was in its natural state before oxygenation. In order to be able to compare these figures for the blood in the living body with the figures of Christiansen, Douglas, and Haldane (1914) for defibrinated blood outside the body, it is essential to take into account the respiratory quotient prevailing during an experiment. Fig. 15 is constructed from the same data as Fig. 16 taken from Christiansen, Douglas, and Haldane, but allowing for the fact that arterial blood is only about

Barometer mm. Hg	Mixture in bag		First alveolar sample		Second alveolar sample		Approximate venous gas-pressure				Alveolar CO_2 % during expt.	Excess of venous over arterial CO_2-pressure	Respiratory exchange per min. in c.c. at S.T.P.		Respiratory quotient	Pulse-rate per min.
	CO_2 %	O_2 %	CO_2 %	O_2 %	CO_2 %	O_2 %	CO_2		O_2				O_2	CO_2		
	6·95	5·23	6·63	6·49	6·68	6·12	..		..		5·53	..	..	..	..	84
(Pilot expt.)	,,	,,	6·51	6·61	6·72	6·09	..		..		..	..	..	..	..	..
749	7·11	3·96	6·91	4·76	6·91	4·88	6·91 7·04	6·98 (49·0 mm.)	5·00 4·58	4·79 (33·6 mm.)	5·62 (39·4 mm.)	1·36 (9·6 mm.)	640	572	0·894	75
	,,	,,	6·90	4·84	6·97	4·71										
	7·00	*c.* 19·5	6·99	..	7·25	..	7·51	7·58 (53·2 mm.)		..	5·69 (39·9 mm.)	1·89 (13·3 mm.)	623	502	0·805	81
	7·87	,,	7·46	..	7·52	..	7·58			..						
	8·35	,,	7·80	..	7·72	..	7·64			..						
750	7·32	3·95	7·04	4·70	6·95	4·78	6·86 6·75	6·83 (48·0 mm.)	4·86 4·94	4·90 (34·5 mm.	5·33 (37·5 mm.)	1·50 (10·5 mm.)	608	530	0·871	76
	,,	,,	6·89	5·16	6·82	5·05										
	,,	,,	6·74	5·92	6·81	5·76	6·88			?[1]						
	7·42	*c.* 19·4	7·30	..	7·47	..	7·64	7·68 (54·0 mm.)		..	5·69 (40·0 mm.)	1·99 (14·0 mm.)	655	553	0·845	77
	7·72	,,	7·41	..	7·51	..	7·61			..						
	8·41	,,	7·92	..	7·86	..	7·80			..						
754	7·55	,,	7·31	..	7·48	..	7·65	7·75 (54·8 mm.)		..	5·37 (38·0 mm.)	2·38 (16·8 mm.)	637	586	0·921	81
	7·89	,,	7·35	..	7·56	..	7·77			..						
	8·36	,,	7·78	..	7·81	..	7·84			..						
	7·13	3·79	6·87	4·72	6·75	4·69	6·63	6·65 (47·0 mm.)	4·66 4·95 4·91 5·20	4·93 (34·8 mm.)	5·29 (37·4 mm.)	1·36 (9·6 mm.)	615	536	0·872	80
	,,	,,	6·92	4·69	6·77	4·82	6·62									
	,,	,,	6·85	4·93	6·75	4·92	6·65									
	,,	,,	6·80	5·22	6·75	5·21	6·70									
	Mean values for oxygenated venous blood						7·67	(54·0 mm.)		..	5·58 (39·3 mm.)	2·09 (14·7 mm.)	638	547	0·857	80
	Mean values for unoxygenated venous blood						6·82	(48·0 mm.)	4·87	(34·8 mm.)	5·41 (38·1 mm.)	1·41 (9·9 mm.)	621	546	0·879	77

[1] As the high percentage of oxygen in the first alveolar sample indicated very imperfect washing out of the deep alveoli, the venous oxygen-pressure could not be calculated.

95 per cent. saturated with oxygen in the body. This allowance has the effect of raising slightly the level of the curve for oxygenated venous blood. This figure as explained on p. 56 shows graphically the relations between CO_2-pressures in oxygenated and unoxygenated venous blood with varying respiratory quotients. It is obvious that variation in the respiratory quotient has a great effect on these relations.

The circulation-rate is obtained as follows: the mean values given in the table on p. 375 show that the excess CO_2-pressure of unoxygenated venous blood over arterial blood was 9·9 mm. From Fig. 15 it appears that the gain of CO_2 by the venous blood corresponding to this figure was 62 c.c. per litre, but the production of CO_2 per minute was 546 c.c., hence the circulation-rate calculated from the CO_2 results was 546 divided by 62 = 8·8 litres per minute. A corresponding calculation from the oxygen data indicates that the venous blood had lost 72·9 c.c. of oxygen per litre, and since the consumption of oxygen was 621 c.c. per minute the circulation-rate was 621 divided by 72·9 = 8·5 litres per minute.

Additional results obtained with Douglas as subject are given in the tables which follow.

Various modifications of the original method of Douglas and Haldane have since been introduced, for instance, by Henderson and Prince (1917), Meakins and Davies (1921–2), and several others, but it seems

DOUGLAS

Weight 66 kilos.; haemoglobin percentage about 92 (Haldane scale).

	No. of determinations of venous gas-pressure	*CO_2-pressure of mixed venous blood in mm. Hg*		*O_2-pressure of mixed venous blood in mm. Hg*		*Alveolar CO_2-pressure in mm. Hg*	*Excess of venous over arterial CO_2-pressure in mm. Hg*	
		Oxygenated	*Unoxygenated*	*Observed*	*Calculated*		*Oxygenated*	*Unoxygenated*
Lying down after fasting for 15 hours	8	(45·8)	44·0	46·1	47·1	40·6	(5·2)	3·4
Sitting upright on chair	5	(46·9)	44·8	46·0	44·8	40·1	(6·8)	4·7
Sitting upright on chair after fasting for 6 hours	14	45·8	(43·7)	..	47·5	40·2	5·6	(3·5)
Ergometer, 103 kg.m. per min.	9	(52·5)	48·0	34·8	35·7	38·1	(14·4)	9·9
	9	54·0	(49·0)	..	35·3	39·3	14·7	(9·7)
Ergometer, 264 kg.m. per min.	24	57·2	(51·5)	..	32·7	41·1	16·1	(10·4)
Ergometer, 512 kg.m. per min.	11	62·6	(54·8)	..	28·1	41·0	21·6	(13·8)
Ergometer, 752 kg.m. per min.	12	65·3	(56·8)	..	26·2	41·5	23·8	(15·3)

DOUGLAS

	Respiratory exchange in c.c per min. at S.T.P.		*Resp. quotient*	*Pulse-rate per min.*	*Blood-flow per min. in litres*		*Output of heart per beat in c.c.*	*Percentage utilization of arterial oxygen*	
	O_2	CO_2			*From* CO_2	*From* O_2		*From* CO_2	*From* O_2
Lying down after fasting for 15 hours . .	233	180	0·77	53	7·5	6·8	135	19·0	20·9
Sitting upright on chair.	295	248	0·84	66	8·0	8·4	124	22·5	21·4
Sitting upright on chair after fasting for 6 hours	256	200	0·78	59	8·0	..	135	19·5	..
Ergometer, 103 kg.m. per min. . . .	621	546	0·88	77	8·8	8·5	112	43·1	44·5
	638	547	0·86	80	8·8	..	110	44·0	..
Ergometer, 264 kg.m. per min. . . .	891	744	0·835	88	10·9	..	124	49·6	..
Ergometer, 512 kg.m. per min. . . .	1,390	1,215	0.875	114	13·8	..	121	61·3	..
Ergometer, 752 kg.m. per min. . . .	1,974	1,775	0·90	137	18·7	..	136	64·2	..
Ergometer, 870 kg.m. per min. . . .	2,415	2,370	0·98	170	..	..	..	..	..

doubtful if any of these modifications are an improvement on the original method, and indeed some of them definitely introduce new sources of error.

The results obtained by these various methods are not, at first sight, easy to reconcile and interpret.

In their original paper Krogh and Lindhard (1912) found that the resting circulation-rate was about 3 to 8 litres per minute. Other workers using the same method have generally obtained a value of 3 to 4 litres (Lindhard, 1915; Boothby, 1915; Newburgh and Means, 1915; Liljestrand and Stenström, 1925; Christensen, 1932). The method has, however, been subjected to much criticism as regards the results obtained during rest. It seems to be probable that the rate of flow of blood through the lungs may be very appreciably diminished during the period while the breath is held, since during this period venous blood which had been pumped out of the large veins by the preceding deep inspirations will be accumulating in them again. Moreover, it is difficult to be certain that perfect mixture of the spirometer air and alveolar air is attained during the three preliminary respirations, and any failure to obtain homogeneous mixture, combined with the fact that the alveolar samples are obtained by partial expirations, will tend to give too low results for the circulation-rate. The method was criticized by Sonne (1918–19) and Douglas and Haldane (1922) on the score of incomplete mixture of the alveolar and spirometer gases, but Krogh and Lindhard (1917) and Christensen (1931*a*) have argued that if the later directions of Krogh and

Lindhard are followed carefully, there is no danger of error from this cause. This conclusion, however, can hardly be reconciled with either the results of Douglas and Haldane or those of Lundsgaard and Schierbeck (1923).

There are other drawbacks to the use of the method. The procedure is difficult to carry out, and Christensen (1931 *a*) has found it to fail owing to difficulties encountered in performing the analyses after combustion of the nitrous oxide. Krogh and Lindhard themselves pointed out that their method was only reliable with subjects who had a normal vital capacity.

The acetylene method (Grollman, 1929) has been found by Grollman (1932) and others (Christensen, 1932) to give results with resting subjects which are in close agreement with those obtained by the nitrous-oxide method, namely, a circulation rate of about 4 litres per minute. Moreover, Grollman (1930) found that in successive determinations on one subject extending over $3\frac{1}{4}$ hours the figures obtained for the circulation-rate only varied between 3·9 and 4·2 litres per minute. He also found that observations made by means of this method over a period of 2 years on the same subject under strictly basal conditions gave results which varied between 3·64 and 4·16 litres per minute, indicating that the cardiac output remains very constant from day to day.

Grollman (1932) discussed the assumptions which underlie the method, which are (1) that samples taken for analysis must represent a homogeneous gas mixture, the acetylene and oxygen-pressures of which are in equilibrium with the blood leaving the lungs; (2) that the blood takes up acetylene strictly in accordance with the physico-chemical laws of solution of gases in liquids; and (3) that, since acetylene is not destroyed in the body, the whole rebreathing of the acetylene mixture must be completed in less time than corresponds to a single circuit of the blood.

He concluded that he and his colleagues have shown that these assumptions are fully justified, and that the method is reliable. Moreover, Christensen (1932) calculated that even if blood returns to the lungs before the second sample is taken, the greatest error so caused cannot exceed 12 per cent., because of the rapid passage of acetylene from the blood to the tissues. This contention seems to us to be correct.

Grollman (1931) and Grollman, Proger, and Dennig (1931) found

that it is impossible to complete the procedure of rebreathing within the time occupied by a single circuit of the blood, if the cardiac output exceeds 10 litres per minute. They therefore came to the conclusion that the method is not applicable in its simple form when, owing to muscular exercise, the heart expels blood at a greater rate than this. Christensen (1931 *b*), however, carried out 325 circulation-rate experiments on 3 women and 4 men before and during work on an ergometer. The work varied from 480 to 1,680 kg.m. per minute and the oxygen consumption from 0·220 to 3·940 litres per minute. The corresponding cardiac outputs varied from 4·0 to 37·2 litres per minute and the stroke volumes from 50 to 209 c.c.

Christensen concluded that the acetylene method is very suitable for work experiments, and that the results are in close agreement with those given by the nitrous-oxide method.

Grollman (1932) found that the method was applicable in many pathological cases, and controlled it by comparing the alveolar-air analyses with analysis of the gases of the arterial blood obtained by puncture of an artery.

It seems to be clear that the results given by the acetylene method agree closely with those of the nitrous-oxide method both at rest and during work, but it has the great advantage of being much easier to carry out.

Douglas and Haldane (1922) measured the venous gas-pressures—oxygen and CO_2—in several adult men under conditions which varied from complete rest while fasting to hard muscular work, and deduced the circulation-rate and output of the heart per beat as described on p. 376.

They found that during rest from 5 to 8 litres of blood passed through the lungs per minute in different men, and that during the hardest work performed in their experiments the estimated flow amounted to about 24 litres per minute.

It is evident that the nitrous-oxide method, the acetylene method, and the method of Douglas and Haldane all give concordant results for the circulation-rate during work. During rest, however, the values obtained by Douglas and Haldane's method were definitely greater than those obtained by the nitrous-oxide and acetylene methods, which, however, are in agreement with one another. The reason for this discrepancy is not clear and hitherto no direct comparison, carried out on the same subject, has been made between the last two

methods on the one hand and that of Douglas and Haldane on the other.

There is no question that the systolic discharge of the heart may, at least under abnormal conditions, vary enormously. This is very clearly shown by the experiments of Patterson and Starling (1914) with a 'heart-lung preparation'—i.e. a preparation in which the only circulation is 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 change in the pulse-rate. It does not follow, however, that there are corresponding variations in systolic discharge in normal men and animals with organic regulation of the circulation intact and not absent as it is in the case of the heart-lung preparation.

Yandell Henderson (1906) had previously used quite a different method on animals. He worked with dogs, and, after removing the pericardium, placed a recording plethysmograph round the heart. By this method he found that the volume of blood discharged per heart-beat was approximately the same, whether the heart was beating faster or slower. Thus, within wide limits, the volume of blood discharged per minute in his experiments seemed to depend almost entirely on the pulse-rate. He concluded, that under normal conditions the heart is, practically speaking, always filled adequately 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 (p. 405).

If we apply Henderson's conclusions to man it is evident that they cannot be reconciled with those of Krogh and Lindhard (1912), whose results indicated that the systolic output may be trebled during muscular work. These observers found that during rest the amount of blood circulating through the lungs of adult men varies from about 2·8 to 5 litres per minute, and that the arterial blood loses about 30 to 60 per cent. of its available oxygen on an average in its passage through the tissues during rest, while during considerable muscular work the loss is about 50 to 70 per cent.

The following table, derived from the figures recorded in their paper, gives the calculated volumes of blood passing through the lungs and the calculated percentage losses in its available oxygen as it passes round the tissues.

Subject	*Work in kg.m. per minute*	*Calculated blood-flow—Litres 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)[1]	45
A. K.	0	2·95	47
,,	446	16·0	47
,,	524	17·6	51

[1] Uncorrected value for blood-flow during the experiment.

It will be seen from this table that, allowing for the fact that the haemoglobin of normal arterial blood is only about 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 much as six times as great as during rest. Since it was estimated that 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 that which occurs in the depth of breathing during muscular work.

Lindhard (1915) also found a considerable increase in the systolic output during work, e.g. from 88 to 208 c.c. Boothby (1915) and Newburgh and Means (1915) found that with increasing metabolism the output per beat increased at first quite rapidly and then more slowly. Christensen (1931 *b*), using the acetylene method, found that the systolic output increased considerably during work (about 3 to $3\frac{1}{2}$ times). He also found that the highest pulse frequency and smallest systolic output at rest occurred in the case of subjects who were completely untrained. Training resulted in an increase in the stroke volume, both at rest and at work. This Christensen attributed to hypertrophy of the heart. Grollman (1932) concluded that there is no simple relationship between changes in pulse-rate and cardiac output.

The experiments of Douglas and Haldane (1922) indicated that, in many subjects, the output of blood per beat is no greater during moderate or even hard work than during rest, and amounts to about 120 c.c. per beat for a man of average build and weight. In other subjects, however, the output per beat is much less at rest, and

increases considerably during work, the greatest change observed being from 67 c.c. per beat at rest to 152 c.c. when the subject was working at the rate of 705 kg.m. per minute. Bock, Vancaulaert, Dill, Fölling, and Hurxthal (1928), using a slight modification of Douglas and Haldane's method, also found considerable individual differences in the response of the stroke volume to muscular work.

It seems fairly clear that Henderson's conclusions are not valid for man, and that the systolic output of the healthy human heart may vary considerably according to the conditions.

Another matter which calls for consideration is the degree of utilization of the available oxygen of the arterial blood. The values found by Krogh and Lindhard are not very far from those obtained in the horse by Zuntz and Hagemann (1898), but do not agree at all well with those of Loewy and von Schrötter (1905) 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.

On Henderson's theory, too, 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 the discharge of CO_2 per litre of the blood.

Lindhard (1915) found that the utilization increased more or less with the degree of work and reached, indeed, in one case 80 per cent. Boothby (1915) found that the utilization increased rapidly at first with increasing work and thereafter more slowly. Newburgh and Means (1915) only found a slight increase in utilization (on one subject) during work. Nevertheless, these authors all concluded that the circulation-rate increased in direct proportion to the increase in metabolism; a statement which is not compatible with increased utilization of the arterial oxygen during work. Christensen (1931 *b*) found that the utilization usually increased with the work, but not always. When the work approached the limit of the subject's capacity the utilization tended to diminish again after its initial rise. Training led to better utilization. His results, which are given in the table below (p. 383), indicate that the circulation-rate does not increase in anything like direct proportion to the metabolism, though he finds that the relation is linear on the average.

Subject	*kg.m./min.*	*O_2 absorbed litre/min.*	*Min.-Vol. litres*	*Pulse frequency*	*Output per beat*
E. L. L.	Rest	0·220	4·4	64	69
	600	1·600	16·8	176	95
	840	2·100	19·4	187	104
B. L.	Rest	0·270	4·6	69	68
	480	1·430	16·6	121	137
	720	1·970	19·7	151	134
M. T.	Rest	0·240	4·6	77	60
	600	1·570	14·5	131	111
	720	1·790	17·4	145	120
	840	2·050	19·0	159	120
	960	2·450	23·8	168	142
M. P.	Rest	0·240	4·1	78	50
	720	2·240	25·1	156	161
M. N.	Rest	0·250	4·2	70	60
	720	1·930	16·5	148	140
	960	2·220	20·6	140	147
	1200	2·830	23·0	174	132
	1440	3·260	26·9	170	149
	1680	3·940	37·2	179	208
H. E. N.	Rest	0·275	4·4	73	60
	720	1·930	20·5	116	177
	960	2·400	21·8	132	165
	1200	2·960	25·1	147	171
	1440	3·410	28·7	165	174
	1680	3·790	28·9	167	173
O. B.	Rest	0·300	4·6	65	71
	720	2·120	19·1	131	146
	1200	2·980	23·65	160	149
	1440	3·390	29·2	166	176
	1680	3·790	35·10	168	209
Arm-work	940	2·880	25·3	161	157

First four subjects in poor training; last three in good training.

The results of Douglas and Haldane showed that considerable individual differences exist in the resting circulation-rate in man. On the other hand, they showed that there is very little variation in the resting venous gas-pressures of the same individual at different times. In fact the venous 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. From these results it would seem that the general circulation-rate does not at first increase in anything like direct proportion to increased metabolism, this conclusion being borne out, though less strikingly, by the results obtained by the nitrous-oxide and acetylene methods as well as by that of Douglas and Haldane. The latter observers found that with moderate exertion (about a third of the maximum possible) on a Martin's ergometer, the difference between arterial and venous CO_2-pressure became about $2\frac{1}{2}$ times as great as usual, so that the venous blood could not be more than about 45 per cent. saturated with oxygen. As the severity of the work is increased, however, there comes a time when the limit of percentage utilization of the oxygen is reached, and thereafter the circulation-rate varies much more directly in proportion to the general metabolism.

Henderson and Prince (1914) determined in a number of persons the oxygen consumption per beat of the heart, or what they call for brevity the 'oxygen pulse'. This value is obtained by simply dividing the oxygen consumption per minute by the pulse-rate.

Fig. 115 shows graphically a fairly typical example of their results. It will be seen that with the low oxygen consumption per minute the oxygen consumption per beat is low, but increasing rapidly up to a maximum as the oxygen consumption increases owing to muscular exertion. When, however, this maximum is reached, further increases of the oxygen consumption per minute cause no increase in the oxygen consumption per beat. Interpreting these data in the light of the results just discussed it appears that the increased oxygen consumption per beat is due partly to increased output of blood per beat and partly to increased utilization of the charge of oxygen in the arterial blood. When, however, increased stroke volume and increased utilization reach their physiological limits, further increase in the oxygen

consumption per minute can only be obtained by increase in the rate of heart-beat.

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

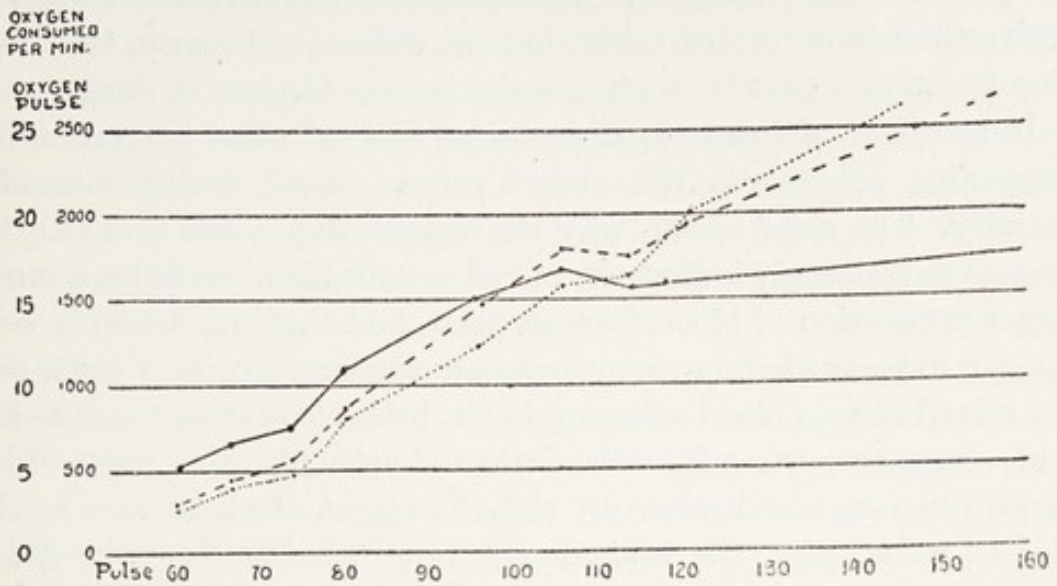


FIG. 115. Subject Y. H., weight 75 kilos.; haemoglobin 107. In this diagram the broken line expresses the oxygen consumption per minute, the dotted line the CO_2 elimination, and the solid line the oxygen pulse. During the short periods of vigorous exertion and rapid heart-rates, the CO_2 elimination 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.

evidence from a series of experiments by Leonard Hill and Nabarro (1895) 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. 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 oxygen*
		Artery	*Vein*	*Difference*	
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 $3\frac{1}{2}$ 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 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 grey 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 held voluntarily 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 Haldane 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 unaerated 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, since it can only add slightly to the oxygen charge of the arterial part of the mixed blood leaving the heart.

It is evident from the facts just referred to that the relative increase in blood-flow through the lungs during exertion is much less than the relative increase in air breathed. At first sight, therefore, it might seem that the regulation of the circulation differs fundamentally from the regulation of the 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 regulated delicately 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' (Yandell Henderson, 1908; 1909 *a*, *b*; 1910 *a*, *b*, *c*, *d*; Henderson and Harvey, 1918). 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 removal of an excessive quantity of CO_2 from the body by forced 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 connexions between respiration and circulation. On these and other observations (p. 405) he also based the theory that an immediate cause of shock may be excessive respiratory activity.

The blood-gas changes caused by excessive artificial respiration were first investigated by Ewald (1873) in connexion with apnoea. 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 oxygen as well as CO_2 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 abnormally low oxygen-pressure must, other things being

equal, be produced by forced breathing. Ewald's analyses show, however, that there is something more to cause this low oxygen-pressure 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 oxygen want in the tissues. But the diminution in the proportion of oxyhaemoglobin 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 (1911).

Douglas and Haldane (1922) reported observations on the effect on the circulation-rate of excessive removal of CO_2 from the body by forced breathing. The experiments were difficult to carry out because of the very low venous oxygen-pressure during the apnoea after forced breathing, and consequent mental state of the subject. He had to be watched very closely to see that he 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. Nevertheless, though it was necessary to use a gas mixture containing only about 3·7 per cent. of oxygen and 4·8 per cent. of CO_2, it was found possible to get some reliable results. These showed that, though there is a considerable fall, after forced breathing for about 3 minutes, in the CO_2-content of the mixed venous blood, there is, relatively speaking, an even greater fall in the oxygen content.

In one experiment a mixture of 3·67 per cent. O_2 and 4·85 per cent. CO_2 was inhaled during the period after forced breathing. Four deep

breaths of the mixture were taken, the last being held. The first alveolar sample contained 4·71 per cent. CO_2 and 4·30 per cent. O_2, the second 4·68 per cent. CO_2 and 4·31 per cent. O_2. The venous gas-pressures were therefore: CO_2 33·25 mm., O_2 30·9 mm. Hg. The mean of eight concordant experiments gave venous pressures of 34·0 mm. Hg CO_2 and 31·9 mm. O_2.

During forced breathing, such as was used in these experiments, the arterial CO_2-pressure is reduced to about 14 mm. Hg, i.e. by about 65 per cent. This, taking into account the effects of deoxygenation, corresponds to a rise in pH of about 0·5. The venous CO_2-pressure was only reduced from 45 to 34 mm. or by about 25 per cent. This corresponds to a rise of pH of about 0·1.

The oxygen-pressure—31·9 mm.—of the venous blood would, with the existing lowered CO_2-pressure, correspond to a saturation of the haemoglobin of about 55 per cent. But in consequence of the forced breathing the arterial haemoglobin would be about 100 per cent. saturated. The blood, therefore, had lost about 45 per cent. of its combined oxygen during its passage round the body, and, allowing for the extra amount of dissolved O_2 in the arterial blood, this would mean a loss of about 47 per cent. in the total charge of O_2. This indicates considerable slowing of the circulation, since under normal conditions during rest the blood loses far less of its charge of oxygen.

Hence the slowing of the circulation caused by the removal of CO_2 by forced breathing prevents the alkalosis in the venous blood and tissues from increasing by more than about one-fifth as much as in the arterial blood. Thus the body is effectively protected by the slowing of the circulation and to a lesser extent by the shift of the dissociation curve of HbO_2 from excessive rise of pH. This protection, however, is only attained at the expense of incurring considerable oxygen want. Effective as this slowing of the circulation is in protecting the body against violent disturbance of hydrogen-ion pressure brought about by excessive ventilation, conditions do occur, as shown on p. 405, in which it is inadequate.

Douglas and Haldane also reported 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 the arterial and venous CO_2-pressure of Haldane; 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 breathing had increased five times or more, but the circulation had apparently not increased at all. The pulse, etc., were also hardly affected.

A similar result was obtained by Liljestrand (1918), who used the nitrous-oxide method of Krogh and Lindhard. It must be remembered that, while inhalation of, say, 5 per cent. of CO_2 increases the respiration and causes a rise in arterial CO_2-pressure, it also brings about a rise in the arterial oxygen-pressure. The first-mentioned effects both tend to increase the circulation-rate, but the last acts in the opposite direction. This is evident from the results of Dautrebande and Haldane, which are referred to below. 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 (Yandell Henderson and Harvey, 1918), who first noted the signs of increased circulation-rate on Haldane, while the latter was nearly overcome by accumulation of CO_2 in a mine rescue apparatus, without any deficiency of oxygen. 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 XI) would have a similar effect.

That this effect is actually produced in man is indicated by the results of experiments by Dautrebande and Haldane (1921). They found that when pure oxygen is 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 2 atmospheres pressure has a rapid poisonous action on the lungs and other living tissues directly exposed to it (see Chapter XI), there are no evident cerebral symptoms until oxygen at much higher pressures is breathed.

The conclusion that a high oxygen-pressure slows the circulation

is borne out by the observations of Tinel (1927), who found that in several patients who had been trephined the exposed grey matter became paler when pure oxygen was breathed. Changes in the blood-flow through the medulla oblongata of anaesthetized and decerebrate cats were studied by means of a thermopile method by Schmidt and Pierson (1934). They could discover no vasomotor nerve control over the vessels of the medulla, but found that both excess of CO_2 and lack of oxygen caused dilatation, though anoxaemia was effective only when it was intense. Excessive ventilation of the lungs was followed, definitely and regularly, by contraction of the vessels.

The most striking experiments indicating a great slowing of the circulation when oxygen at very high pressure is breathed by an animal are those of Argyll Campbell (1929–30 *b*). He found that in an animal breathing oxygen at about 5 atmospheres pressure the pressure of CO_2 in the tissues, as indicated by that in injected gas left in contact with them, rises to as much as 28 per cent. of an atmosphere (214 mm. Hg), so that it is hardly possible to say whether the animal is being poisoned most by the oxygen or by its own CO_2. Argyll Campbell was inclined to attribute the rise in CO_2-pressure to the effect of abnormal oxygenation on the dissociation of CO_2 from the blood, as observed by Christiansen, Douglas, and Haldane; but any effect of this nature would be quite inadequate to account for the observed facts.

The effect of a high pressure of oxygen in slowing the circulation has already been referred to in connexion with the use of oxygen in stage decompression of divers (p. 351).

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 adrenaline, 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 centre, 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 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. It is probable also that blood escapes from abdominal organs into the general circulation. Henderson, Haggard, and Coburn (1920) 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 flushings 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 distension of large veins, though the colour is now red and not blue. The increased pressure in the great veins causes the distension 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 made inefficient by the anoxaemia, there would probably be no over-distension. As Knowlton and Starling (1912) found, oedema of the lungs and over-distension 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. 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 the 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 investigated by a quite different method by Henderson, Prince, and Haggard (1918). 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 (Fig. 116), thus obtaining a measure of the venous 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

oxygen-want due to forced breathing becomes so intense as to affect the heart-muscle seriously that the arterial blood-pressure falls.

Putting all the 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

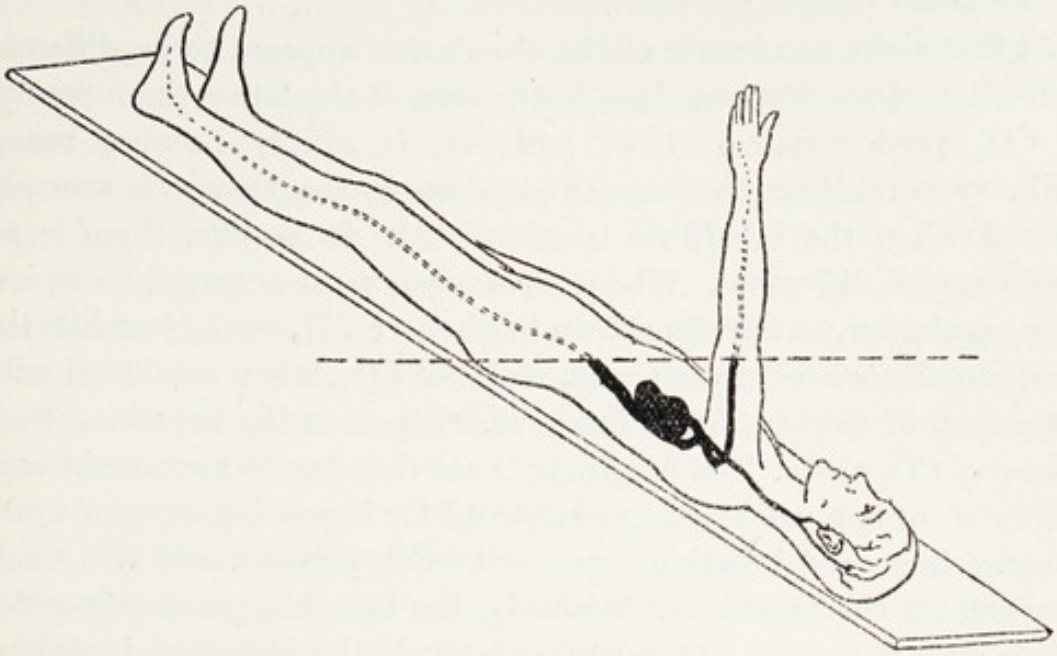


FIG. 116. Measurement of venous blood-pressure by placing subject in a head-down position.

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 great increase in blood-flow through the muscles, with a corresponding increase in venous blood-pressure, as Henderson and Haggard (1918 *d*) found with the apparatus shown in Fig. 116.

The correspondence between blood-flow and amount of work done by a muscle appears clearly in data obtained by Markwalder and Starling (1913–14) for the coronary circulation with varying work of the heart in a heart-lung preparation. 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 varies within wide limits in proportion to the work done. The changes 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 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 under ordinary conditions the oxygen-pressure in the tissues is scarcely altered when the breathing is stimulated. In reality, there is no fundamental difference. Whenever oxygen want occurs the respiratory regulation, as already shown in Chapter VII, works just like the local circulatory regulation, and excess of CO_2, when combined with deficiency of oxygen, has a far greater effect on the breathing than excess of CO_2 alone. The breathing is not then free to increase in such a way as to compensate approximately for increasing oxygen want, 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 of 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 X.

When once the fundamental fact is grasped that the flow of blood throughout the body is, in general, correlated with the gas-pressures in the capillaries, the whole physiology of the circulation appears in a new light. It is not the heart nor the bulbar nervous centres 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 vasomotor 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, therefore, that it is not the immediate function of the heart 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 judgements. It is difficult to pick a way through all these details, but some salient points concerning the immediate control of the heart's action must now be referred to.

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 centres specially connected with the circulation, but the metabolic activities

of the tissues. At bottom the regulation of circulation is a chemical regulation, just as in the case of breathing.

The frequency and strength of the heart-beats 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 (p. 131), so that the inhibition tends to prevent an excessive rise of arterial pressure and consequent fatigue of the heart or over-dissention 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 heart-beats 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 shown by Bainbridge (1915–16), who found that, even if the accelerator nerves are cut, increase in venous pressure causes marked quickening of the heart-beats provided that the vagi are still intact. Part, at any rate, of this effect is due to inhibition of the tonic inhibitory action of efferent vagus fibres. 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 heart-beat are well known and very evident.

There is no necessary connexion between rate of heart-beat and circulation-rate. This has been shown by various experiments, but most strikingly by the experiments of Starling and his pupils (p. 380) on the bodies of animals in which an artificial circulation through the heart and lungs alone had been established, the physiological connexions with the central nervous system and rest of the body being cut off. In such a 'heart-lung preparation' the rate of heart-beat 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 wide limits by simply varying the rate at which blood is supplied to the right side of the heart. Thus Patterson and

Starling (1914) found that with a pulse-rate which was steady at 144 the circulation-rate in a heart-lung preparation from the dog could be varied from 215 to 2,000 c.c. per minute by simply regulating the supply of blood to the right side of the heart.

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 connexion 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 heart-rate is relatively limited —much more so than might be inferred from study of a heart-lung preparation. In fact Henderson's view, referred to above, that the output of the heart during systole is usually pretty constant under normal conditions seems to be, roughly speaking, correct.

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 centre in the medulla from which vasoconstrictor impulses radiate, and subsidiary vasomotor centres in the spinal cord. Another and much more direct means of regulating the distribution of blood was discovered by Krogh (1918–19, 1929). He 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 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 (1879–80), 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 the exchange enormously, 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-fibres. 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, indicating capillary dilatation.

Probably it is the stimulus of the presence in excess of certain metabolic products, particularly carbonic acid, and the deficiency of other substances, 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 an experiment of Meakins and Davies (1920). 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 either tends to fall too much to secure an adequate supply of blood to the brain and other important parts, or else to rise too high.

There appears to be an elaborate nervous defence 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 carotid sinus nerves and the 'depressor' branch from the cardiac vagus. Excitation of the depressor fibres causes inhibition of the vasomotor centre 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 centre and consequent rise in blood-pressure. An important normal stimulus to pressor action of the vasomotor centre is quite evidently the reflex nervous effect described by Lovén (1866). This reflex seems to be admirably adapted to effect efficient co-ordination of the circulation as a whole with variations in activity of different organs. In muscular work, for

instance, there is, as explained on p. 398, a very great increase in the flow of blood through the active muscles, brought about by local dilatation of the arterioles and capillaries caused by local excess of CO_2 and lack of O_2. At the same time afferent impulses are initiated in the muscles which stimulate the vasomotor centres and cause general constriction of vessels in other parts of the body and consequent rise of general arterial blood-pressure.

In asphyxia, on the other hand, the action of the heart is impaired by want of O_2 with the result that blood accumulates in the veins, which become engorged. At the same time, as shown clearly by Mathison (1910–11, 1911), the want of O_2 and excess of CO_2 in the arterial blood cause strong stimulation of the vasomotor centres, with consequent rise of arterial blood-pressure.

We may compare the action of the bulbar centres controlling blood-pressure and heart-rate with that of the respiratory centre in its linked responses to direct chemical and peripheral nervous stimuli; but data are not yet available for pursuing the comparison in detail.

From this general survey of the experimental evidence relating to regulation of circulation, it will be seen that the main 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 oxygen and carbonic acid. Various other factors participate and are, in the long run, very important, but not in the same immediate and striking manner.

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 we 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 (1910), and found to be normal except in cases confined to bed with serious symptoms. 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. (French, Pembrey, and Ryffel, 1909–10), though the CO_2-pressure in the mixed blood leaving the heart may be above normal.

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 of 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 colour 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 X); and this will tend to diminish the real anoxaemia, though without diminishing the cyanosis. Unless the breathing became shallower no material relief could be looked for owing to active secretion of oxygen inwards by the lung epithelium, as this would increase only slightly the oxygen in the 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, either to 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 were 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 or 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 VIII). 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 possibly only an expression of fatigue produced by the over-frequent heart-beats.

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 VIII. This seems to be the explanation of the orthopnea 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 centre is complicating defects of circulation.

A very interesting investigation demonstrating a relation between

vascular disturbances in the lungs and the Hering-Breuer reflex was published by J. S. Dunn (1919–20), who was working at the time in conjunction with Barcroft. He produced multiple embolism of pulmonary arterioles by intravenous injection of starch granules. When only a moderate degree of embolism was produced (so as not to cause immediate death) he observed 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, 1919–20) 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 V) 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 quite a new light on the intense and exhausting dyspnoea caused by pulmonary embolism, and seen also in cardiac cases where similar dyspnoeic attacks sometimes occur, often accompanied by periodic breathing. The very striking effects of morphia in relieving these attacks completely were recorded by Claude Wilson (1923), and are probably due to the morphia removing the hyper-excitability of the vagus nerve-endings.

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 centre, 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 connexion 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 centre, 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 counterbalancing 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 centre, 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 very ineffective, since the injected liquid leaks out from the vessels quickly. Bayliss (1918) therefore introduced his well-known gum-saline solution for use in cases of loss of blood and similar conditions. The gum does not leak out at all readily from the vessels, and in virtue of the osmotic deficiency 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 p. 412. Nevertheless, since increase of knowledge about iso-agglutination has made transfusion of blood a safe procedure its use has become much more frequent and is, in suitable cases, undoubtedly the most effective form of treatment.

The conditions known as 'wound-shock', 'surgical shock', 'anaesthetic 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 coloured, and the breathing often shallow and 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 combated 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 'alkali reserve' of the blood decreases greatly, as Henderson and Haggard showed (Chapter IV). Nevertheless, the anoxaemia and alkalosis cannot be overcome. The circulation-rate steadily diminishes; the heart, probably in consequence of anoxaemia, begins to fail, apart altogether from its inadequate supply of venous blood, and finally fails entirely. If, however, the forced breathing is stopped before cardiac failure has occurred, death may occur from prolonged apnoea and consequent acute asphyxia, as mentioned on p. 185. 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 produced 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 might sometimes be produced in a patient; and it seems possible that in this way the condition generally known as shock is sometimes produced or intensified.

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 (Medical Research Committee, 1919), and Dale and Laidlaw (1918–19) have shown that similar symptoms are caused by the action of histamine produced by tissue disintegration. In 'histamine shock' the venous return to the heart is inadequate, just as in acapnial shock, and blood appears to stagnate in dilated capillaries. The effect of this in causing imperfect filling of the rest of the vascular system and consequent failure of the circulation is intensified owing to the fact that the dilated capillaries are abnormally permeable (Krogh, 1929). There is therefore considerable passage of fluid from the vessels to the tissue spaces, and the blood becomes concentrated and its volume is diminished. These effects are very noticeable in cases of extensive burns. In these cases also the onset of 'shock' is commonly delayed—'secondary shock'—and is attributable to absorption of toxic products from the injured tissues (Report of Committee on Treatment of Burns in Colliery Explosions, 1933). Dale and Laidlaw regarded the dilatation of capillaries as a primary action of the poison. The respiratory centre 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 centre 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 centre, 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 centre 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 acapnial shock. These investigations throw much light on the fatal accidents of anaesthesia.

In connexion 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 5 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 gramme of body-weight is enormously greater than in a large 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 (1909–10), 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 between the different parts of animals, including the blood, do not depend on differences in size of the animals. Blood-volume measurements on small animals were made by Chisholm (1911) and Boycott (1912). Figure 117 shows the results of Boycott (obtained by the modified Welcker method) in rabbits of different sizes. It will be seen that there is little 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 small 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, but not fatal, 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 centre. This is probably due to diminished circulation-rate and consequent fall in oxygen-pressure and increase of CO_2-pressure in the medulla, although the pressor reaction is limited in the manner already explained. The blood-

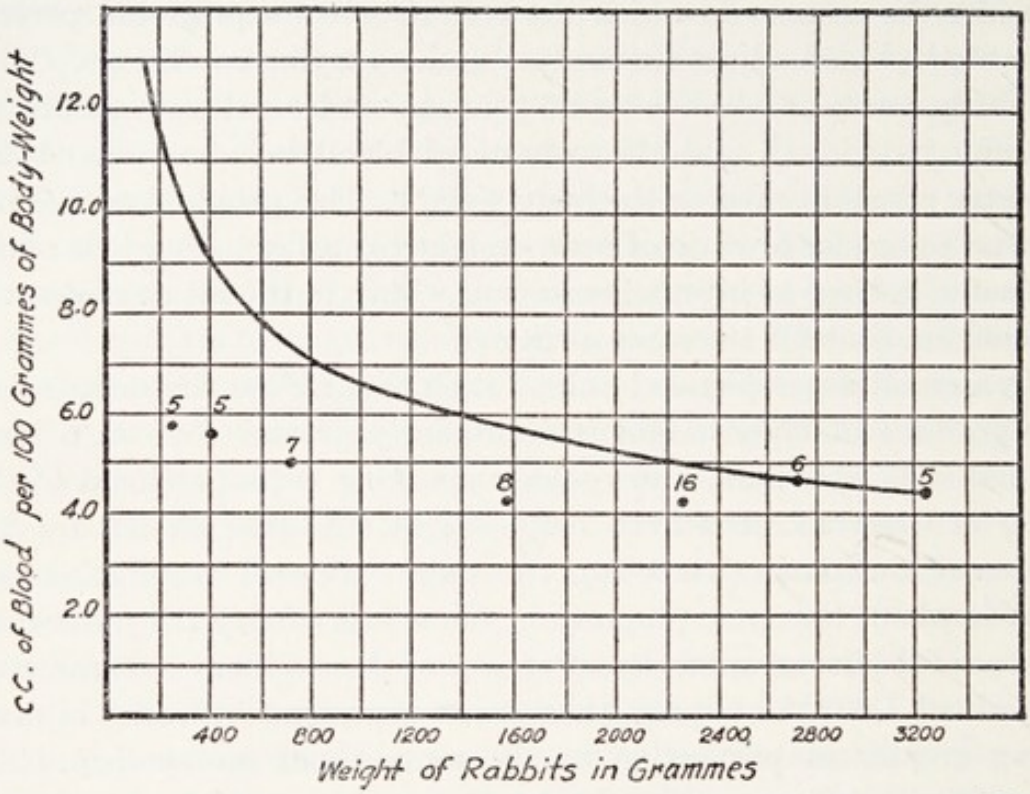


FIG. 117. Blood-volumes of rabbits in c.c. of blood per 100 grammes of body-weight (Boycott). The curve shows what the blood-volumes would be if they varied in the proportion of body-surface to body-weight. The dots show average results of actual determinations by the modified Welcker method. The numbers indicate the number of determinations for each group of observations.

volume is soon 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 (1909) with the help of the carbon-monoxide method of determining the blood-volume in living animals. They found that on repeated 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 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 altitudes 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 X). In different individuals the rise varies considerably. Thus in persons who had been living for some weeks on the summit of Pike's Peak it was found that the haemoglobin percentage varied from 113 to 153 per cent. of the normal. The rapidity with which the change occurs also varies greatly in different individuals. Figure 118 shows the rate at which the change occurred and disappeared in one of the members of the Pike's Peak Expedition, and Fig. 119 shows the far faster rate of increase in haemoglobin in Mr. Richards, a mining engineer who kindly made a careful series of observations on himself on going to a mine in Bolivia at a height of 15,000 feet. Figure 118 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 increases, 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 Fig. 119, the increase is mainly brought about at first by disappearance of plasma owing to a pressor reaction of the vasomotor centre, with consequent increased

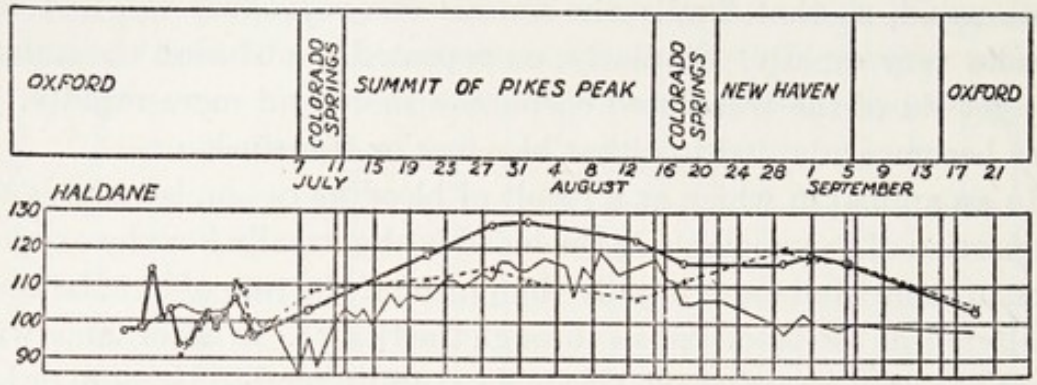


FIG. 118. Ordinates represent percentages of the average haemoglobin percentages obtained before ascending the Peak (Oxford and Colorado Springs) on the particular subject. Continuous thick line = total oxygen capacity or total amount of haemoglobin. Continuous thin line = percentage of haemoglobin. Interrupted line = blood-volume. The values in Oxford before the start of the expedition are plotted without relation to time.

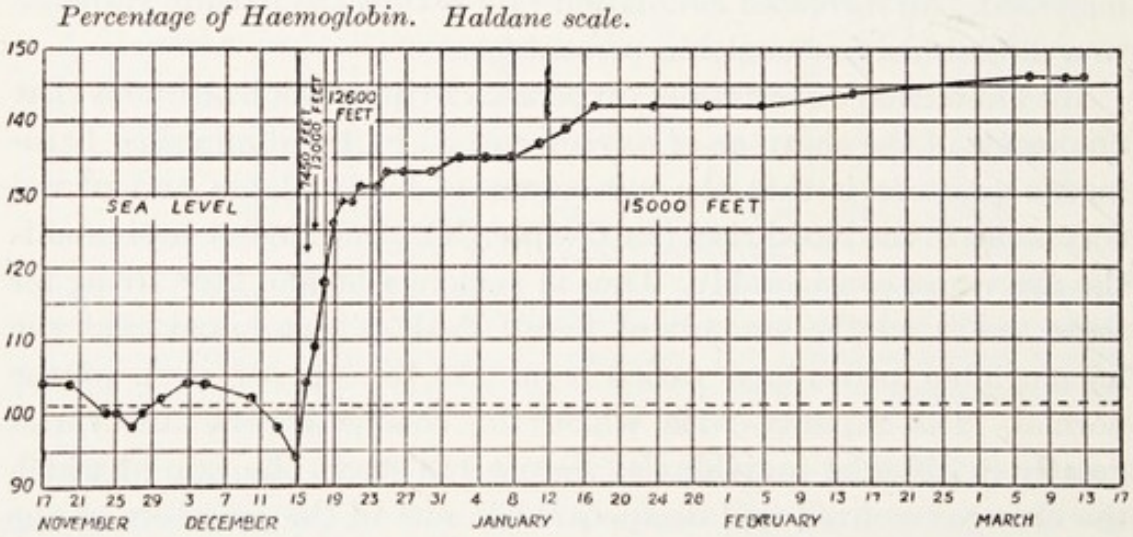


FIG. 119. Rise of haemoglobin percentage on going gradually to a height of 15,000 feet and staying there. The interrupted line represents the mean percentage of haemoglobin at sea-level.

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 probably due to a pressor reaction. Gregg, Lutz, and Schneider (1919–20) 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.

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, Loewy, Müller, Caspari (1906). 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 (1906–7) showed, 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 to them by Dr. Parkes Weber (1911), Douglas and Haldane found that the haemoglobin percentage was increased 80 per cent.; the blood-volume 100 per cent.; and the total haemoglobin 260 per cent.; and they found similar increases in another case. Lorrain Smith and McKisack (1902) had already found a considerable increase in a non-congenital heart case with chronic cyanosis.

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 Haldane found it greatly increased. Boycott and Douglas (1908) examined three other cases with a similar result. In the most marked of these 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 anoxia of the tissues, to which the increased haemoglobin percentage is a natural response.

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 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 vasometer centre is perhaps shown most strikingly by the effects on the blood of section of the spinal cord below the vasomotor centre in the medulla. Cohnstein and Zuntz (1888) 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. 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 (1900) with the help of the carbon-monoxide method as stated on p. 247 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. Boycott and Haldane (1903) found the same condition in the 'anaemia' of ankylostomiasis. Miss FitzGerald (1910) found 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. These facts suggest that the apparent anaemia is due to some cause leading to abnormal dilatation 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 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 connexion between breathing and circulation is already very evident, many points in the connexion 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.

XIII

AIR OF ABNORMAL COMPOSITION

IN the present chapter we propose to describe the mode of occurrence and physiological effects of the more commonly occurring gaseous and other impurities in air. The number of noxious gases, vapours, 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, 0·03 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 0·94 per cent. consists of argon. Careful analyses have indicated that over all the earth's surface, including the tops of high mountains, the proportions are the same, though they may be expected to vary appreciably in the stratosphere. Very minute traces are also present of hydrogen and various rare gases. Ordinary atmospheric air, contains, however, aqueous vapour in varying proportions; and about 1 per cent. is on an average present in a climate such as that of Great Britain, more being present in summer than in winter. In summer weather the percentage of CO_2 near the ground may be as low as 0·025 during the day, and as high as 0·035 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 0·05, nor does that of oxygen fall below 20·90, 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 may cease more or less; and then

the impurities in the air of a large and smoky town may become very appreciable. Russell (1884) found, for example, that in London the percentage of CO_2 might rise to 0·14 during a dense choking fog such as used to occur.

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, Haldane 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 0·01 per cent. of CO present in the air of a very dense 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 it persists even when the air is warmed and thereby rendered much clearer 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, limestone, and other materials.

Besides sulphuric acid the smoky air contains particles of black carbonaceous matter which greatly help to absorb the light, and also contain substances which have an unpleasant odour and more or less irritant effects 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 hardly ever present in sufficient concentration to be of any direct consequence in other ways to health. Their greatest importance

arises from their obstruction of light, and from the inconvenience and expense thus caused, 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. The 'pea soup' fogs which were so common in London fifty or sixty years ago are now seldom seen.

It is not within a town but in the outskirts that the densest, and sometimes the most irritating, fogs are met with. Within a town the warming of the houses warms the air in contact with them. This not only evaporates fog particles, but, what is much more important, produces wholesale convection currents which keep the air below much purer. As the warmed air ascends it cools by adiabatic expansion, and therefore reforms the fog above; while the downcoming air warms by adiabatic compression besides being warmed by the houses, so that the air at ground-level tends to be quite clear. We thus get the familiar London 'overhead' fogs, during which daylight is almost completely obstructed, but the air below is clear, so that when lights are turned on there is no difficulty with traffic. In the outskirts of a town, and in the open country, the convection currents are absent if the ground is cooler than the air. Hence visibility becomes very bad though there is plenty of diffused daylight.

The convection currents protect a town against any heavy concentration of the impurities present in the air during a fog, and it is easy to calculate that but for them the air in a large town would soon become dangerous during the wind stagnation in foggy weather (Haldane, 1931). The only really dangerous effects of fogs have been experienced in the outskirts of a town, in places where factories, electrical generating stations, etc., are surrounded by open country. The best-known example of this was the disastrous fog near Liège in 1930, when a number of men and numerous animals were killed, the symptoms being those of bronchitis, which was found to be caused by nothing more than the irritating constituents of ordinary smoke. In Liège itself no bad effects from the same fog were observed.

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 constant 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 of 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 unless it is removed by purification. 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 oxygen or CO_2.

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 connexion 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 comes into play as the air becomes warmer, or heat production in the body is greatly increased by muscular exertion.

Evaporation from the skin is partly due to simple diffusion of water through it, and partly to sweating. As the surrounding temperature rises the loss of water by simple diffusion increases very rapidly, apparently in correspondence with increased circulation. In proportion therefore, as loss by conduction and radiation fall off in warm air, loss by evaporation of diffused water increases; and it is only when this means of cooling becomes insufficient that sweating begins to play the major part (Hancock, Whitehouse, and Haldane, 1929–30).

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 Haldane has 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 centre 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, although 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-passages. 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 a standard as possible 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 0·02 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 sweating. 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 Haldane (1905) showed experimentally, this temperature is reached when the wet-bulb temperature reaches a certain point. Thus in perfectly 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 did not matter in still air whether the temperature was 88° with the air saturated, or 133° with the air very dry, provided that the wet-bulb temperature was 88°, though in the latter case there was much more

evaporation, and more sweating was needed. When the wet-bulb temperature was above 88° the rate of rise of body-temperature, other things being equal, was dependent on the excess of wet-bulb temperature (Haldane, 1914–5).

When even moderate muscular work was being done the critical wet-bulb temperature was, even with almost no clothing, at 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, and the less the amount of clothing.

In the climate of Great Britain the wet-bulb 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.

Actual rise of body-temperature may be due, not to excessive moisture in the air, but to failure of the sweat glands to supply the water needed; and this is apt to occur in persons not acclimatized to heat or in bad muscular training. In a wind at considerably above body-temperature, even though the wet-bulb temperature is only moderate, this occurs very readily, since the amount of heat which requires to be got rid of may be very large.

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, Sir Leonard Hill devised the 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 bulb is covered with an

absorbent jacket which can be moistened with water. By the rate at which the alcohol 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 make some reference to the subject.

The air of occupied rooms is liable to be contaminated by escapes of gas used for lighting or heating; and under certain circumstances fatal or very serious accidents from this cause may occur, and the gas may be used very easily for purposes of suicide or even murder. The 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 Haldane was a member reported on the influence of the use of water-gas in connexion with poisoning by lighting-gas, and he investigated the conditions under which poisoning may occur in bedrooms (Haldane, 1899).

It might be supposed that the sense of smell would always give warning of an escape of 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, roof, 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 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 favourable to ventilation, the gas can never accumulate to more than a very limited concentration in the air of a room.

Another complication in connexion 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. Haldane 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 diffusible 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 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, it was 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 room 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, Haldane 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 connexion 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 has turned out to be round about 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 of nearly equal parts of hydrogen and CO. This gives a very hot, though small, flame, and although the flame by itself is 'blue' and practically non-luminous, 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 'carburetted' by the addition of cheap oil in a chamber where the oil is 'cracked' by means of heat. The product is known as carburetted water-gas, and is very largely used to supplement 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 carburetted water-gas, the committee referred to above found that with carburetted water-gas poisoning was far commoner than with gas made by distillation of coal, as in English towns supplied with coal-gas only. Apart from actual danger from gas poisoning, there was also the constant anxiety as to the supposed risk. 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 carburetted 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 still more 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 carburetted 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 may be more or less odourless. 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.

Although a garage can hardly be regarded as an occupied room, so many fatal accidents from CO-poisoning occur in garages that the matter requires mention here. It cannot be too widely known that if a petrol-engine is set running in a garage without the doors being widely open, the air will be dangerously poisonous within a few minutes, since the exhaust gas is intensely poisonous from the presence of CO, and is large in amount.

Air of Mines. The air of mines is liable to be contaminated by various gases known to British miners as blackdamp, firedamp, afterdamp, and smoke. Of these, blackdamp is the commonest and most universally present; firedamp is hardly found, except in connexion with coal or oil; afterdamp occurs only after explosions; whitedamp in connexion with spontaneous heating of coal, when the gas often looks white from condensed moisture; and smoke in connexion with fires or blasting.

Blackdamp 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 blackdamp is heavier than air, it was formerly identified with CO_2. Its true

composition was first ascertained by Haldane and Atkinson (1894–5). 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 blackdamp may be formed by several different oxidation processes, among which oxidation of coal, timber, and 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 blackdamp 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 micro-organisms. 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: otherwise the blackdamp is simply nitrogen.

Blackdamp of one sort or another is found in practically all mines, though in coal-mines where there is much firedamp its presence can often be detected only by analysis, on account of the predominance of firedamp. Occasionally there is so little CO_2 present in blackdamp that it is lighter than air; or it may be lighter than air owing to admixed firedamp. Haldane found that the blackdamp formed simply in the oxidation of dry coal at ordinary temperatures contains small percentages of CO (Haldane and Meachem, 1898) and very little CO_2; but blackdamp as ordinarily found in considerable concentrations in coal-mines is free from CO, and contains usually about 12 to 15 per cent. of CO_2, and is thus a good deal heavier than air.

The difference between blackdamp as formed from air-dried coal in the laboratory or underground and blackdamp as it issues in a concentrated form underground, was found to be due to the coal being wet. With wet coal far more of the oxygen which disappears is converted into CO_2, and the whole of the CO formed at first is oxidized to CO_2 (Haldane and Makgill, 1933). The formation of some CO during an oxidation process is by no means confined to the oxidation of coal.

In consequence of the oxidation which is always occurring in air-dried coal, a very small proportion of CO is always present in the return air of a colliery; and since the ratio of CO formed to oxygen

which disappears increases rapidly as the temperature of the coal rises, this ratio can be used to detect any serious heating of coal, or to negative a suspected case of such heating (Ivon Graham, 1920–21).

The action of blackdamp on lamps and candles is of much practical importance, particularly as a miner trusts to his lamp to warn him of the presence of blackdamp or firedamp. 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 blackdamp 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 (Haldane and Llewellyn, 1912–13). With a fall of about 3 to 3·5 per cent. in the oxygen an oil or candle flame is extinguished. Aqueous vapour or CO_2 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. In pure air a candle is not extinguished till the barometric pressure falls to a tenth (3 inches of mercury). As the pressure falls the flame becomes blue from below upward, and goes out shortly after it has become blue and non-luminous right up to the top (observation by Gorman Davis and Haldane).

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 blackdamp added to air depends within wide limits on the percentage of CO_2 in the blackdamp, 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 pressure 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 blackdamp unless he does so suddenly, as in descending a shaft or steep incline.

In former times miners often worked in air containing so much blackdamp 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 good deal of the emphysema from which old miners used to suffer was due to this cause (Haldane, 1916).

The ordinary *firedamp* of coal-mines is, practically speaking, pure methane (CH_4). In a very 'fiery' seam as much as 5,400 cubic feet of methane may be given off per ton of coal extracted (T. D. Jones, 1932). The methane is adsorbed in the coal (Ivon Graham, 1916–17), and may have 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 large quantities of CO_2 are adsorbed in coal and may come off either without or with firedamp. When so much CO_2 comes off along with firedamp as to make the latter heavier than air the mixture is known as 'bottom gas', since, although it is inflammable, it lies along the bottom of a roadway (Haldane, 1933). Dangerous sudden outbursts of CO_2 are unknown in British and American coal-fields, but have been met with in the Gard district in France and in Silesia. 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 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 or hydrogen 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, as well as in sewers and other underground spaces.

When about 5·4 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. of methane the mixture ceases to be inflammable. This fact limits considerably the direct dangers from explosions of firedamp.

The presence of non-explosive proportions of firedamp in air can easily be detected by the appearance of a 'cap' on the flame of a lamp. The cap is a pale, non-luminous 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 120 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 firedamp 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 firedamp and blackdamp.

As regards its physiological properties, firedamp 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 VII and VIII. In actual practice the danger from asphyxiation by firedamp is considerably greater than from blackdamp, since

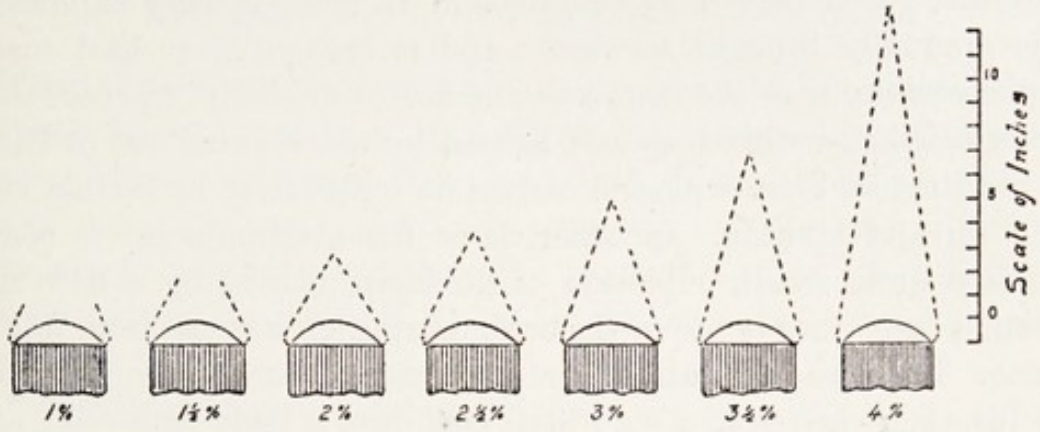


FIG. 120. Diagram showing outlines of caps visible on an oil flame with different percentage of methane.

a man going with an electric lamp or no lamp into air progressively vitiated by firedamp 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 centre.

Afterdamp. Afterdamp is the gas produced as the result of an explosion, and has been known for long to be specially dangerous. Haldane (1896 *a*) made an inquiry into the causes of death in colliery explosions, 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.

Colliery explosions were formerly attributed simply to explosions of firedamp. About fifty years ago it was first clearly pointed out by Galloway that this explanation is unsatisfactory, and that the spread of an explosion must be due to coal-dust. Further evidence of the prominent part played by coal-dust in all great colliery explosions was gradually brought forward ; and it became clear that many explosions occur in the complete absence of firedamp, 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 firedamp, caused by a defective lamp, a spontaneous fire in the coal, or 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 travelled about a hundred yards, were strikingly shown in experiments made with pure coal-dust at Altofts Colliery under Sir William Garforth's direction (Record of British Coal-dust Experiments, 1910). On account of their danger in a populous neighbourhood these experiments were transferred to Eskmeals on the Cumberland coast, and subsequently to Buxton. They showed that when an equal weight of shale-dust or other similar material was present along with the coal-dust the mixture could only burn with difficulty and under specially favourable conditions, though with many kinds of coal a still higher percentage of incombustible dust was needed to make conduction of flame entirely impossible.

Sir William Garforth's plan of stone-dusting all the roads in collieries with shale-dust or other non-combustible dust, so that at every point there is more than half as much shale-dust as coal-dust, has now been adopted generally in Great Britain for many years ; and the only serious recent explosions have been in mines where this precaution was not adopted, or the explosion occurred where stone-dusting was used ineffectively. 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 pure afterdamp were

analysed by Wheeler (Record of British Coal-dust Experiments, 1910). The following is a typical example:

Carbon dioxide	11·9
Carbon monoxide	8·6
Hydrogen	2·9
Methane	3·1
Nitrogen	73·5

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 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 VII, 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, Haldane (1895 *b*) introduced the plan of making use of a small warm-blooded animal such as a mouse or small bird. 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 a considerable time to affect a man will affect the bird or mouse very quickly. This test has now come into very general use, and was, for instance, largely used during the War by the tunnelling 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 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 may be 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 smouldering fires left by the explosion.

When air in a mine is for any reason not safe to breathe, self-contained breathing apparatus is now frequently employed. It is beyond the scope of this book to describe these appliances in detail, 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 nose-clip. 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 litres per minute. This is as much as a man uses during fairly 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 litres are coming in. If less than about 2 litres 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.

Another, and much simpler, apparatus was recently introduced in the United States, and is most useful in cases where the continued burning of an oil safety-lamp shows that there is plenty of oxygen in the air. The apparatus is so arranged that the inspired air is passed over a catalyst which oxidizes CO to CO_2, and thus renders the air harmless.

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.

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 becomes red hot or bursts into flame if enough 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 whitedamp. The higher the temperature of coal which is slowly oxidizing, the greater the proportion of CO in the residual gas. The effects of whitedamp 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 travelled some distance in

a mine, the particles have subsided and the smoke has become more or less odourless and transparent gas. Many very serious accidents, involving sometimes the loss of as many as 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 smouldering 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 gun-cotton, 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 reddish-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. Haldane has found that exposure to the fumes from as little as 0·05 per cent. of nitric oxide in air may be fatal to an animal. This subject has been referred to more fully on p. 225 in connexion with poisonous gas used in war.

Poisoning with CO under various circumstances 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 Schafer'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 in view of the properties of CO haemoglobin. Henderson and Haggard (1920*c*, 1920–1) have 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 centre, the breathing is apt to remain for some time inadequate. 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. In addition, the CO_2, by lowering the pH of the blood, increases the circulation-rate and thus acts at once in relieving the want of oxygen (Haldane, 1924). A mixture of oxygen with 7 per cent. of CO_2 is now used with great effect for reviving purposes.

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 is acute dilatation of the heart; pneumonia is also a frequent sequela; 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 connexion 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 consideration. To this subject Haldane has given very close attention, and a full general discussion of it will be found in the First Report of the Committee on Control of Underground Temperature (1920).

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 'miner's phthisis' among certain classes of miners led Haldane and others 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, so long as their lungs are otherwise healthy. 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, and necessitate the strictest precautions. 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?

It is in the production of phthisis (pulmonary tuberculosis) and bronchitis that the continued inhalation of a harmful variety of dust shows its effects most clearly. The table, on p. 441, compiled from the statistics of the Registrar-General's Decennial Supplement, 1927, 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 probably on the whole the dustier occupation. It will be seen, however, that among the coal-miners there is not only very little phthisis, but considerably less than the average for all other occupations. Among tin-miners, on the other hand, there is a great excess of phthisis; and detailed investigation has shown clearly that it is to the nature of the dust inhaled that this excess is solely due (Haldane, Martin, and Thomas, 1904).

In the early days of the British pottery industry it was found that breathing the pulverized flint (which is pure silica) largely used in the industry produces a very fatal form of lung disease, afterwards shown to be pulmonary tuberculosis; and great precautions are now taken against inhaling this dust. In one industry after another it has been found that breathing dust with a high percentage of free or uncombined silica gives rise likewise to phthisis, and the disease is now generally known as silicosis, though it was formerly known under various names, such as 'potter's rot' at Stoke, 'grinder's rot' at Sheffield, 'stonemason's complaint' at Edinburgh, 'miner's complaint' in Cornwall, or 'machine disease' at the Rand mines. Where it occurs in mines it is still often called 'miner's phthisis'. The common factor in its causation is the inhalation of fine dust containing a high percentage of free silica. On the other hand, when the percentage of free silica is low, even when a great deal of dust is breathed, the disease is not produced. Coal-miners, for instance, breathe a great deal of dust of shale, etc., containing only about 30 per cent. of free silica, but are, as shown in the table, and always have been since statistics were available, singularly free from phthisis. In earlier times, when phthisis was much more prevalent in Great Britain than now, their relative freedom from phthisis was still more striking than at present. Coal-miners, and men working in other sorts of mines where the percentage of free silica in the dust is low, but the air very dusty, must breathe far more free silica than in mines where, as on the Rand, silicosis is still produced in spite of such scrupulous precautions by wetting and other means that dust is never visible underground.

Thirty years ago it looked as if silicosis could be entirely prevented by keeping the drill-holes, grindstones, and everything else wet. The presence of visible dust was prevented and the danger was much diminished, but the disease still remained formidable; and by means

of the 'konimeter', invented in its original form by Sir Robert Kotzé, it was shown that very fine dust escaped through the water.

The importance of extremely fine and ordinarily invisible silica dust was strikingly shown by the death statistics of flint-knappers. These are men, of whom a few remain in Norfolk still carrying on the very ancient and skilled occupation of shaping flints for various purposes. Close inspection shows that at each chip a very little smoke-like dust is formed, but there is no visible dust in the air of the small sheds where the men work. At Haldane's request the conditions were reported on by Dr. E. L. Collis, then of the Home Office, to the Royal Commission on Metalliferous Mines and Quarries, and his account (Appendix J of the Report of the Commission, 1914) embodied mortality statistics prepared by the Registrar-General's Department. It was found that over a period of twenty-five years about 80 per cent. of the deaths of flint-knappers were due to phthisis, their mortality from phthisis being about 50 times that for other persons in the same agricultural neighbourhood, and 25 times that for all males above 15 in England and Wales.

On examining the table on p. 441 it will be seen that a high phthisis mortality accompanies all the occupations in which men are exposed to dust, like that of powdered flint, hard sandstone, the Cornish lodes, which contain a high percentage of free silica, or the millstone grit of grindstones. It will be seen that slate-miners and quarriers show a high phthisis mortality; but this is confined to men working in the sheds, which have hitherto not usually been clean and would thus be likely to cause tuberculous infection. The age-distribution of the deaths is suggestive of infection, and slate does not contain very much free silica. It seems possible that the apparent rather high phthisis death-rate among limestone workers is due to some workers in sandstone or chert being included among them.

In this table and in that on p. 448 death-rates calculated from less than a total of three deaths are enclosed in brackets.

No less instructive than the occupations showing a high phthisis rate are those which, in spite of dust-inhalation, show a low rate. Among the latter come quarriers of igneous rock (not granite), including many men employed in dressing and crushing the stone. This group consists of the men employed at the Leicestershire and Carnarvonshire quarries on the very hard stone used for roadway purposes, etc. This stone contains only a low percentage of free silica.

DEATHS FROM PHTHISIS PER 1,000 LIVING IN EACH AGE-PERIOD, ENGLAND AND WALES, 1921–3

Age-periods:	*15–20*	*20–25*	*25–35*	*35–45*	*45–55*	*55–65*	*65–70*	*Over 70*
All occupied and retired civilian males	0·7	1·4	1·3	1·6	1·7	1·5	1·4	0·6
All coal-miners	0·6	1·0	0·9	1·2	1·2	1·3	1·1	0·6
Tin and copper miners, underground workers	[0·0]	1·2	9·6	20·0	25·3	41·9	9·7	10·7
Sandstone miners and quarriers	[0·0]	1·2	1·1	2·8	5·2	4·3	3·2	[0·0]
Miners and quarriers of igneous rock, not granite	[0·0]	[0·9]	[0·0]	[0·9]	0·5	[2·9]	[0·0]	[3·0]
Limestone miners and quarriers	[0·9]	1·8	0·6	1·3	1·9	2·4	0·0	[2·3]
Slate miners and quarriers	[0·0]	[0·5]	1·9	1·9	3·1	4·9	7·3	[0·9]
Sandstone masons, cutters, and dressers	3·5	[0·0]	[0·7]	4·7	10·8	10·8	8·9	0·8
Limestone masons, cutters, and dressers	[0·0]	1·0	1·5	3·2	4·6	1·9	[0·9]	[0·5]
Slate masons, cutters, and dressers	[0·0]	[1·2]	4·1	4·5	6·2	10·5	10·1	[5·5]
Cement makers, lime burners, etc.	[0·0]	0·6	1·0	1·2	1·4	0·8	1·3	[0·0]
Potter's, millworkers and slipmakers	1·3	3·1	1·7	4·1	6·2	6·5	3·6	[0·0]
Metal-grinders	0·6	1·4	2·4	5·5	11·5	12·5	7·6	3·8
Coal-boat loaders	[3·3]	[3·0]	0·8	1·6	1·4	1·4	[0·0]	[1·7]
Stevedores	[0·0]	2·9	2·1	3·8	4·2	4·0	[0·0]	[0·0]
Other dock-labourers	1·3	1·9	1·6	3·4	3·9	3·6	2·8	3·3
Cotton-strippers and grinders and card-room jobbers	1·3	[0·5]	[0·2]	[0·7]	1·8	3·5	[2·8]	[6·0]

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 tends to be 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 of fact, reach the alveoli. Arnold (1885) 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. In connexion with the use of shale-dust for preventing colliery explosions, Beattie (1912) 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. The subject was followed further under Haldane's general direction by Mavrogordato (1918), Carleton (1924), and Haynes (1926) in investigations undertaken for the Medical Research Council and Safety in Mines Board. 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 is inhaled, these cells, when they are fully loaded, detach themselves and wander 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 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 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 and men in certain other dusty occupations from phthisis is connected with their capacity for dealing with inhaled dust particles (Haldane, 1917–18).

Figs. 121, 122, 123, and 124 (after Haynes, 1931) illustrate the manner in which all of the fine dust-particles, of whatever kind or shape, are taken up by the phagocytic dust-cells of the alveolar wall, and how these living cells tend to cast loose when they are fully charged, either into the alveolar cavities and thence up the bronchial tubes, or into the lymphatics. It appears that, if the free silica in these cells is sufficiently concentrated, the cells themselves and what is around them become injured and injure neighbouring cells, while if the free silica is much less concentrated the cells can function normally. One special form in which the injury from free silica shows itself is in greatly increased liability to tuberculous infection. It seems, however, that certain forms of dust, such as china-clay, may

fail to stimulate normally the casting-off process, though without producing liability to tuberculous infection.

At the end of a few months the lungs of a guinea-pig which have

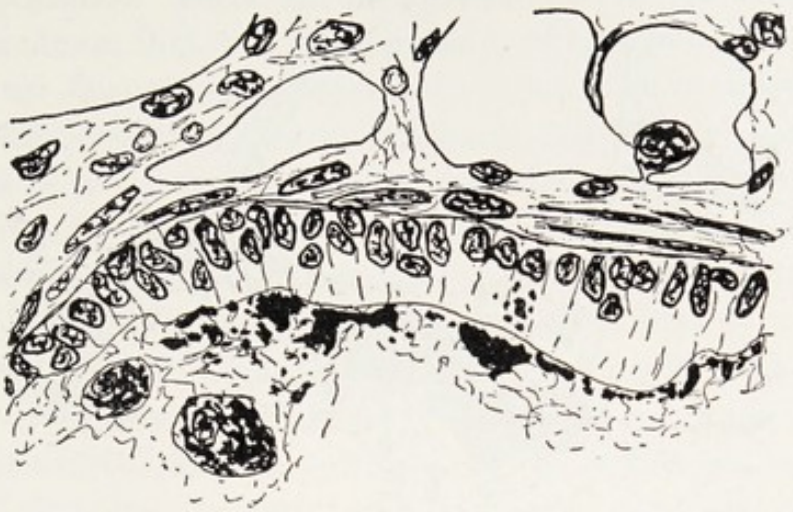


FIG. 121. Animal killed immediately after a single 2-hour exposure to shale-dust. Dust-cells and free cells in a bronchus. Dust particles within a ciliated columnar epithelial cell. Sessile dust-cell about to detach.



FIG. 122. Animal killed immediately after a single 2-hour exposure to shale-dust. Heavily loaded dust-cells free in alveolus, detaching and attached to alveolar wall.

been heavily charged with coal-dust or shale-dust by experimental inhalations are again free from dust. On the other hand, this is not the case when the dust inhaled is quartz. Much of the quartz remains *in situ*, though within dust-collecting cells. Part is, however, carried onwards to lymphatic glands. The quartz does not bring about the same wandering process as the coal-dust or shale-dust does.

Haldane was for long inclined to attribute the difference to some positive quality in the diluent dust; but Gye and Kettle (1922) and later Kettle alone (1934), published experiments which pointed

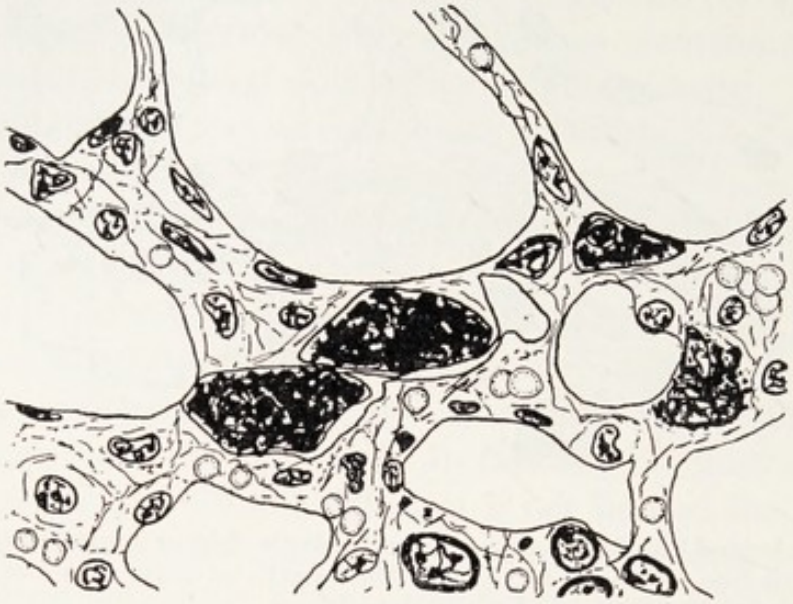


FIG. 123. Animal killed immediately after a single 2-hour exposure to shale-dust. Two very heavily loaded cells filling an alveolus.

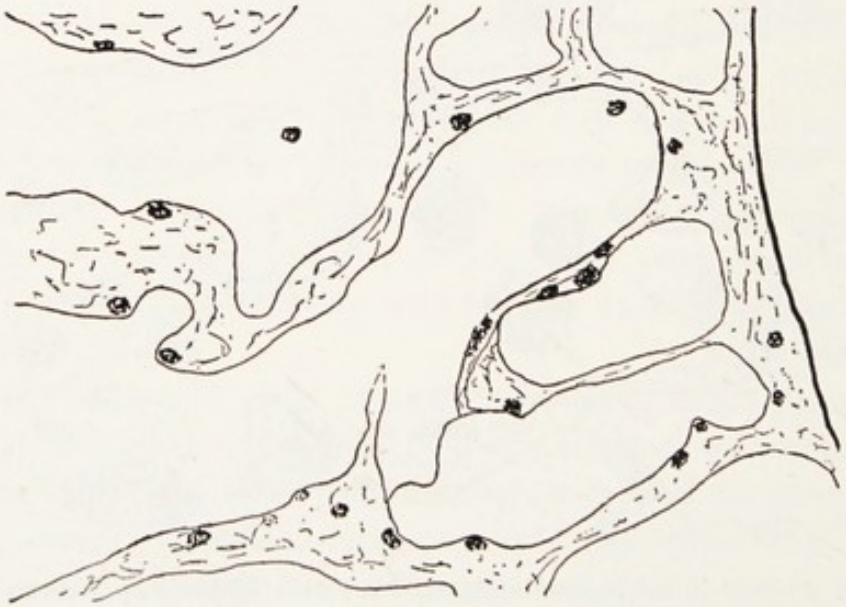


FIG. 124. Animal killed 4½ hours after a single 2-hour exposure to shale-dust. Low-power view of juxtapleural alveoli (unstained) showing amount and distribution of the dust.

clearly to detrimental effects of dissolved silica, and more particularly to these effects showing themselves in defencelessness of tissues against tuberculous infection. The direct detrimental effects were confirmed by Haynes, who also failed to get any indication of positive

effects of diluent dust in stimulating the dust-clearing process. It thus appears that Gye and Kettle were correct in inferring that it is a positive chemical action of the free silica, and its solubility, which are of importance. There are no grounds for an opinion that was formerly common that it is the angularity of quartz-dust that makes it dangerous. Quartz, and particularly in the form of extremely fine particles, dissolves gradually in dilute alkaline liquids, and must be slowly soluble in the slightly alkaline medium within the living body. This accounts for its detrimental action, and also for the fact that on post-mortem examination of the mineral residue of lung from a case of silicosis a high proportion of free silica is not found.

The presence of the scattered fibrosis which accompanies silicosis can be detected at a very early stage by careful X-ray investigation, and this method has been perfected in the examination of Rand miners. Unfortunately, however, the disease, even if underground work is stopped, usually goes forward to fully developed phthisis, with a fatal end. It has not been stopped early enough. On the other hand, evidence is accumulating that scattered fibrosis, due to inhalation of considerable amounts of a dust which does not lead to tuberculous infection, often gives the same X-ray picture as early silicosis, and is of very little significance unless it becomes extreme.

The X-ray investigations carried out for the King Edward VII Welsh National Memorial Fund (Report for year ending 1929), showed that such pictures are extremely common among elderly colliers who are perfectly well, have never worked in siliceous rock, and show no tendency towards phthisis. The experiments of Haynes have also shown that practically any kind of insoluble dust, including coal and calcium carbonate, will, when breathed in great excess, produce fibrosis. A picture which, in the case of a Rand miner, means silicosis, has thus no such significance where a highly siliceous dust is not breathed.

Apart from this there are, at least in some coalfields, a number of cases of non-tuberculous fibrosis in which fibrosis is extreme, with corresponding disablement, and parts of the lungs are blocked with dust which corresponds chemically to the composition of the coal-dust and shale-dust breathed. The evidence so far available points towards the conclusion that in these cases chronic or recurring bronchitis has, by paralysing the normal process of dust-removal, led to the dust-accumulation and corresponding fibrosis. Among

the causes leading to this bronchitis are undue exposure to cold in returning to surface, fumes from blasting, and latent pulmonary tuberculosis. There is at present an unfortunate tendency to trust solely to X-ray examination in the diagnosis of silicosis, and to designate as silicosis all forms of industrial fibrosis, thus causing much alarm, and diverting attention from effective preventive measures in preventing either real silicosis or serious dust fibrosis.

Some very interesting results bearing on silicosis have been obtained recently by workers at the Banting Institute, Ontario. They have shown that when quartz dust is introduced into the body in any way silica appears at once in the urine, presumably as soluble silica hydrate or silicate, and that the proportion of silica in the urine may be enormously greater than in the blood, so that silica is evidently excreted very actively by the kidneys (King and Dolan, 1934). This shows clearly that quartz goes into solution in the body. Evidence is also brought forward that silica in solution is carried in the lung lymphatics, and is often present in large amounts in silicotic nodules and elsewhere when particles of silica cannot be seen microscopically. Free silica can thus be removed from the lungs and elsewhere in a soluble form by the kidneys, and in this way we can account for the low proportion of free silica found at death in cases of undoubted silicosis (Irwin, 1934). The arrest of silicosis in other cases becomes also intelligible.

A further very significant discovery was that, if chronic bronchitis is produced in an animal exposed to quartz dust, typical silicotic nodules develop rapidly, whereas without the bronchitis (and consequent paralysis of dust excretion) it is practically impossible to obtain more than a diffuse fibrosis during the life-time of the animal (Robson, Irwin, and King, 1934).

Shale-dust contains about 25 to 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 about as much quartz, but also produce a harmless dust. In fact nearly all the dust ordinarily met with is of the harmless variety, and Mavrogordato's investigation indicated that quartz-dust becomes relatively harmless when it is well mixed with other dust of the harmless variety. The lung-cells clear out the quartz when they are clearing out the other dust.

Although bronchitis is not silicosis, yet a high bronchitis mortality

may be associated with silicosis, as well as with inhalation of various sorts of dust. In order to judge of the significance of a high bronchitis death-rate, we must take account of the fact that liability to bronchitis in the late years of life depends very largely on the amount of muscular exertion which an occupation implies. As has frequently been found (p. 382) from measurements of the circulation-rate in man, the increase in breathing during muscular exertion is far more marked than the increase in heart-action. It is therefore only to be expected that in an occupation involving much muscular exertion the lungs will tend to fail, owing to emphysema and associated bronchitis and fibrosis, more than the heart and other organs. As is shown very clearly in the last Registrar-General's Supplement, mortality from bronchitis in the later years of life (there being almost none before forty-five, except in childhood) varies enormously with 'social class' and occupation. Roughly speaking, the chance of death from bronchitis in old age is about seven times as great among the class of more or less unskilled workers, who work mainly with their legs and arms, as among the so-called upper and middle classes, whose occupation involves but little hard muscular work. There is no marked difference for disease of the circulatory system, kidneys, or digestive system, and not very much for pneumonia. These facts are brought out in a striking diagram at p. xiv of the last Decennial Supplement. Coal-mining is an occupation involving much hard muscular work. Hence it is only to be expected that in late life the bronchitis mortality in it should be high, as is actually the case, and has been for many decades. There is no general statistical evidence pointing clearly to dust in the coal-mining industry as an important cause of bronchitis.

Nevertheless, there is clear evidence that in certain occupations involving exposure to dust-inhalation the bronchitis mortality is increased by the inhalation to a far greater extent than could be accounted for as a result of muscular exertion. It is only at the ages of forty-five and upwards that bronchitis mortality becomes serious. The next table gives the bronchitis mortality at over forty-five in various occupations associated with exposure to dust, or involving much muscular exertion.

It is evident from the table that dust from nearly pure silica and certain other kinds of siliceous stone, as well as from such material as raw cotton, is a very serious cause of bronchitis. On the other hand, the mixed lime and silicate-dust to which cement workers are so much

exposed seems to do no harm; and allowing for the fact that the work of a coal-miner implies hard muscular work, it does not appear that inhalation of coal-dust or shale-dust contributes materially to the bronchitis mortality among coal-miners or coal-boat loaders. It seems probable, therefore, that even if no dust-inhalation accompanied coal-mining, the bronchitis mortality would still be almost as high in old age, apart from cases in which chronic bronchitis has itself led to excessive accumulation of dust in the lungs.

DEATHS FROM BRONCHITIS PER 1,000 LIVING IN EACH AGE-PERIOD, ENGLAND AND WALES, 1921–3

Age-periods:	*45–55*	*55–65*	*65–70*	*Over 70*
All occupied and retired civilian males	0·6	1·9	5·1	17·7
Social class I (upper and middle)	0·2	0·5	1·3	7·0
Social class V (unskilled workers)	1·1	3·1	7·7	24·1
All coal-miners	0·6	3·4	9·6	29·9
Tin and copper mines, underground workers	3·0	11·7	33·8	64·5
Cotton strippers and grinders and card-room jobbers	2·9	12·5	25·6	78·8
Cement workers, lime burners, etc.	0·2	0·8	6·3	15·7
Potter's millworkers and slipmakers	2·0	13·3	16·7	33·9
Metal grinders	2·2	6·1	21·3	28·7
Sandstone masons, cutters, and dressers	1·2	12·4	24·1	29·2
Limestone masons, cutters, and dressers	0·6	3·1	4·3	25·0
Slate masons, cutters, and dressers	[0·0]	[0·9]	[0·0]	21·9
Coal-boat loaders and dischargers	0·8	5·0	12·9	29·8
Stevedores	[0·3]	5·9	12·3	35·9
Other dock-labourers	1·6	4·5	9·9	31·3
Building-trade labourers	0·9	2·9	6·7	31·7

The figures suggest that where, as in the case of tin-miners, cotton-strippers, sandstone workers, etc., the bronchitis death-rate is excessive, this is due to irritation caused by angular or fibrous dust sticking in the air-passages. The very low bronchitis death-rate of slate-workers adds to the suspicion that their high phthisis-rate may be due to infection in the sheds.

It may be well to mention here a theory which has recently been put forward very prominently by Dr. W. R. Jones, a skilled mineralogist (1934). His theory is that silicosis is caused, not by free or soluble silica, but by the widely distributed mineral named sericite, which is a silicate of alumina and potash. He has found that this substance is present in the ash of the lungs of men who have died of silicosis, and that sericite, or at any rate silicates, may be as abundantly present as free silica, or more abundantly. Part of his argu-

ment is based on the fact that silicosis is a most formidable disease in the Rand mines, where sericite forms the chief cementing material in the quartz pebbles of the reef, while silicosis is practically absent in the Mysore gold-mines, where the reef contains little or no sericite, but an even higher percentage of free silica than in the Rand mines. This seems at first sight a striking coincidence; but it had already been pointed out by Haldane that the dust in the Mysore mines consists largely of dust from a basic 'country rock' containing no free silica. Analyses of samples of this dust by Mr. A. Shaw showed that it contained not more than 30 per cent. of free silica—no more than in harmless shale-dust—while the Rand dust contains about 70 per cent. of free silica, an extremely dangerous proportion. Another part of his argument consists of amazing and totally mistaken statements to the effect that dust of undiluted free silica can be breathed with immunity from silicosis. Yet another part of his argument is based on the fact that a very large number of cases have been diagnosed recently as 'silicosis' among South Wales colliers who have never worked in highly siliceous stone. As regards these cases, there is no evidence that they are silicosis in the ordinary sense of a condition which ends in phthisis. If they were, the death-rate from phthisis among ordinary Welsh colliers would not be, as it is, considerably below that of other occupied persons, just as among coal-miners elsewhere.

In the cases in question great accumulations of coal-dust, together with shale-dust, are present in the lungs; and it appears that this is due to the normal process of dust-elimination being interfered with by bronchitis. These cases are therefore primarily cases of bronchitis, and there seems to be good evidence that they are far more frequent under conditions where miners are exposed for some time to great cold during their return to the surface on trolleys.

In connexion with the sericite theory Robson, Irwin, and King (1934) investigated the influence of sericite when dust consisting mainly of sericite was breathed by animals which, as described above, had been sensitized by the simultaneous inhalation of a very dilute irritant gas. The sericite produced no silicotic fibrosis, whereas pure quartz did. What was perhaps equally significant was the absence of this fibrosis in spite of the presence of a good deal of quartz in the sericite dust. There would seem, therefore, to be good reason for believing that sufficient dilution with sericite would render quartz dust harmless.

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 even in a shallow well is sometimes dangerously polluted. Haldane (1895–6) investigated this subject, visiting various wells where men had been asphyxiated, in order to see what had happened. He found plenty of foul air, and that its composition was similar to that of blackdamp, 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 blackdamp or chokedamp 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 brim-full 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 Haldane lent him an aneroid barometer and thus convinced him that the outbursts of gas were due to natural and not supernatural causes. By always carrying a lighted candle or lamp with him, a well-sinker can guard most effectually against the danger from blackdamp; 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 blackdamp it would be lighter than air, and thus likely to escape unnoticed.

An interesting case which came under Haldane's notice later may be mentioned in this connexion. 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 analysed for CO_2, but no noticeable excess was found. On analysis Haldane 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 (Blount, 1906). 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 blackdamp contained 99·6 per cent. of nitrogen and 0·4 per cent. of CO_2.

When all the oxygen is exhausted in a gas space underground, and organic matter is present, either methane or hydrogen may be formed by anaerobic fermentation, and may, apparently, accumulate in large volumes—for instance, in sand containing polluted water, with impervious clay above it. Under favourable conditions this gas may be driven out and form an explosive mixture with air (Haldane, 1932).

Air of 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 travelling 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 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 Haldane was a member, and he made numerous analyses of the air (1897). 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 0·06; 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.

The ventilation of tunnels for motor traffic presents a still more serious problem than that of ventilation for steam traffic. This is on account, essentially, of the large amount of CO given off in the exhaust-gas of motor vehicles driven by petrol. A very valuable investigation was made into this problem in connexion with the Holland Tunnels under the Hudson River at New York (Report of U.S. Bureau of Mines, 1927). It appeared that on an average about 6 per cent. of CO is given off in the exhaust-gas from a motor vehicle. The total amount of CO given off at any particular time in the tunnel depends, of course, on the number of vehicles in the tunnel, and their average sizes, but the data collected made it possible to estimate the amount with a maximum number of vehicles passing; and the maximum ventilation required in the Holland Tunnels was calculated accordingly. The original calculation was for ventilation which would keep the

percentage of CO below 0·04 per cent., which would prevent any symptoms from appearing in persons passing through the tunnels; but subsequent experience showed that in order to keep the tunnels free from appreciable smoke or smell a higher standard of purity had to be maintained.

In each of the pair of Holland Tunnels there are two lines of vehicles running in the same direction, and there is a ventilating duct above and below. Air is driven into the lower duct by fans on the surface, and distributed evenly into the roadway by graduated openings. Similarly, air is exhausted evenly into the upper duct, which is connected with exhaust fans on the surface. The percentages of CO in the air at different parts of the tunnels are continuously and automatically indicated by the very delicate apparatus designed originally by Dr. Katz of the Bureau of Mines; and this enables the ventilation to be cut down in correspondence with diminution of traffic, thus saving much expense. The scheme has worked excellently.

The Mersey Tunnel connecting Liverpool with Birkenhead, and quite recently opened, is the largest of its kind, the existence of rock beneath the bed of the river making a large tunnel possible. In the main tunnel, which is about two miles long, there is provision for four lines of vehicles, two each way, and there is a smaller branch tunnel on each side. There are three ventilating stations on each bank, and the ventilation, which can be increased to over three million cubic feet per minute, is designed to keep the CO-percentage below 0·02 at any point, as shown by Katz indicators. The air is driven in through ducts below the roadway, and distributed evenly, as in the Holland Tunnels; but there is no overhead outlet duct, the air simply passing along the rest of the tunnel itself to the shafts which contain the exhaust fans. This plan was adopted as it was shown experimentally that in the event of a sudden fire resulting from the bursting of a petrol tank in a collision, the smoke would pass out more readily and harmlessly without the upper duct, while the air would ordinarily be equally pure at all parts with either method.

Air of Sewers. The air of sewers is perhaps mainly of interest in connexion with the time-honoured belief that 'sewer gas' spreads infection. Some of Haldane's earliest scientific work was concerned with the air commonly present in sewers, and was started by the late

Professor Carnelley and Haldane (1887) 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 is gained to the sewer. The air is saturated with moisture, and may be somewhat warm, as 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, Haldane found only about 0·2 per cent. of CO_2. On determining the number of bacteria in the air Carnelley and Haldane found that fewer were present in the sewer 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. Haldane investigated (1896 *b*) one case of this kind where five men lost their lives at a manhole—the last four in brave attempts at rescue. All the symptoms described, including irritation of the eyes, were those of H_2S poisoning; and though the air was not poisonous when Haldane 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 Haldane has several times smelt it in sewers. In one case which he investigated two men were killed by CO poisoning from lighting-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 he was 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 does ashore. 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 by an Admiralty Committee of which Haldane 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 per minute, without any unpleasant draught affecting 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 vapour 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. It may be pointed out, however, that in so far as these substances produce effects which interfere with respiratory processes, either directly or through their nervous after-effects, they have been discussed in Chapters V, VII, and VIII.

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