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ORGANISM AND ENVIRONMENT AS ILLUSTRATED BY THE PHYSIOLOGY OF BREATHING

BY

JOHN SCOTT HALDANE, M.D., LL.D., F.R.S.

Fellow of New College, Oxford

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THE SILLIMAN FOUNDATION

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

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

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

PREFACE

Yale University did me the great honour of inviting me to deliver the Silliman Lectures for 1915. Owing to the war I was unable to give the lectures in the appointed year; and I must first of all thank the University for permitting me to postpone them till the present time.

The subject of the full lectures, as they will, I hope, before long appear in book form under the imprint of the Yale University Press, is the Physiology of Breathing. Much of the material contained in them is, however, of a technical character, hardly suited for public lectures. With the approval of the President, I have therefore delivered the following four public lectures confined to points of more general interest, the nature of which is indicated by the title.

JOHN SCOTT HALDANE.

New Haven, October, 1916.

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I

THE REGULATION OF BREATHING

Animal physiology deals with the activities observed in living animals, including men; but under certain limitations. It deals in the first place with all the activities which are unconscious, such as digestion, circulation of the blood, secretion, or the growth and maintenance of the tissues. It deals, also, with the unconscious element in conscious action. I may, for instance, breathe consciously, or move my pen in writing, or hear the noise which it makes; but of the details involved in any of these acts I have no direct consciousness. They are only revealed by experimental physiology. Physiology deals, also, with the sensations, impulses, and instincts of all kinds which appear in consciousness; but does not deal with the meaning and conscious control which are attached to them. It does not deal with this meaning and conscious control for the very good reason that the facts relating to them cannot be combined with the other material of physiology into a homogeneous system of scientific knowledge. If, however, the meaning and conscious control attached to sensation and instinct are disregarded, the latter can be treated as a part of physiology, and are so treated by physiologists.

When the activities included as physiological are

regarded as a whole, it is evident that in the case of any given organism they are co-ordinated in such a way that the life of the organism tends to maintain itself as a whole, or at any rate to fulfil its characteristic life-history. This applies not less to the reactions between the organism and its environment than to those between the parts of the organism. In the inorganic world as ordinarily observed and interpreted we find no such co-ordinated maintenance. How are we to understand its presence in the organic world? This is of course a very old question; but I wish to reconsider it in these lectures in the light, more particularly, of the very rapid advances which have been made during the last few years in the physiology of breathing.

We are familiar with two opposing theories as to the nature of the co-ordination. One of these is that known as vitalism, which assumes that within the living body there is constantly at work a special influence, the so-called "vital principle," which guides the blind physical and chemical reactions which would otherwise play havoc with the organism. The other is that the body is a very complex and delicate mechanism, so arranged as to bring about the co-ordination. According to one school this mechanism is the result of natural selection, though according to another its origin must be sought in special creation. I hope to be able to convince you that neither the vitalistic nor the mechanistic theory of the relation between organism and environment is tenable, and

that we must look to a more thorough and direct interpretation.[1]

Breathing is a form of physiological activity which goes on whether we are conscious of it or not. Only by a great effort can we suspend it for 30 or 40 seconds, and any hindrance to breathing is violently resisted. Although in the seventeenth century Mayow came very near to discovering the chemical changes in air during breathing, it was not till the latter half of the eighteenth century that these changes were understood. Black found that what we now call carbon dioxide is given off in breathing, and Priestley found that what we now call oxygen disappears as such. Lavoisier put these and many other facts together, and showed that just as in ordinary combustion of carbonaceous material, so in connection with respiration, oxygen combines with carbon and hydrogen to form carbon dioxide and water, and to liberate heat. Hence breathing is a process in which the essential factors are the conveyance of oxygen into the body, and the removal from it of carbon dioxide. Breathing can thus be compared to the supply of air to a fire and the carrying off by the air of the products of combustion.

Subsequent investigation showed that the oxidation

[1] It has been suggested to me that if a convenient label is needed for the doctrine upheld in these lectures the word "organicism" might be employed. This word was formerly used in connection with the somewhat similar teaching of such men as Bichat, von Baer, and Claude Bernard. Cf. G. Delage, L'Hérédité, Paris, 1903, p. 435.

process does not occur to any appreciable extent in the lungs, but in the living tissues of the body generally. Oxygen is taken up by the blood in the lungs, and thence carried by the circulation to every part of the body, the blood yielding its oxygen to the tissues in passing. Similarly the carbon dioxide formed is carried by the blood from the tissues to the lungs, where it is given off to the air breathed.

But another still more important point, often entirely missed in popular accounts of physiology, has appeared clearly. Within wide limits the oxidation process is practically independent of the abundance in supply of either oxygen or food material to the body. The amount of oxygen in the air breathed, or carried by the blood to the tissues, may be increased greatly without increasing the rate of oxidation; and even after long starvation the consumption of oxygen per unit of body weight remains about the same. The oxidation process is thus evidently very closely regulated. In the burning of a fire there is no such regulation unless it is artificially brought about. Although increase in the breathing does not cause increase in the rate of oxidation, yet it is evident that increase in breathing and in the rate of circulation accompanies increase in the rate of oxidation, as for instance during muscular exertion. Here again we have regulation coming in, but this time it is regulation of the air supply.

To account for the regulation the vitalistic theory presupposes the activity of the "vital principle" as a regulating agent which controls the consumption of

oxygen and regulates the air-supply, thus playing the part of a stoker who regulates the supply of both fuel and air to a furnace. On the mechanistic theory the regulation is automatic, and due to the working of a mechanism connected with the fire. The latter theory is of course the orthodox one at present. It is not, however, these theories which I wish to discuss in these lectures, but the character of the facts which each of the two theories is an attempt to explain. When the true character of these facts is realised it seems to me that the old and ever recurring controversy between mechanists and vitalists disappears.

It has been known for more than a century that breathing is dependent on the integrity of a very small area of the brain in the medulla oblongata. When this area, known as the respiratory centre, is destroyed all signs of co-ordinated breathing efforts disappear. Severance of the nervous connections between this centre and the various respiratory muscles paralyses these muscles; but so long as any connections are left respiratory efforts continue, and do so after severance of the connections between the centre and the higher parts of the brain. The action of this centre came to be regarded as automatic, inspiratory and expiratory impulses being alternately discharged from the centre down the motor or efferent nerves leading to the inspiratory or expiratory muscles, but no afferent impulses being required to liberate these rhythmic discharges. It was also found about the same time that any interference with the supply of properly aerated blood to the centre causes greatly increased activity

of the centre. A further very significant fact, observed originally by Hook in the seventeenth century, but forgotten and rediscovered by Rosenthal in 1875, is that if the blood in the lungs is over-aerated by artificial ventilation, the breathing stops for a time, the condition known as apnoea being established. It seemed, therefore, that just as increased breathing, or hyperpnoea, is due to defective aeration of the blood, so apnoea is due to excessive aeration. This interpretation of apnoea was soon challenged, as we shall see, but was firmly established by an ingenious experiment of Fredericq. He crossed the circulation of two animals, so that the blood coming from the lungs of the first animal passed to the respiratory centre of the second, and vice versa. It was then found that when excessive artificial ventilation was applied to the lungs of the first animal the second became apnoeic, or vice versa; while great hyperpnoea in the first animal was produced by the stoppage of the breathing in the second.

When aeration of the blood is defective in the lungs two changes in the arterial blood occur. On the one hand its content in oxygen becomes less, and on the other hand it becomes more highly charged with carbon dioxide. Blood which is not aerated with oxygen has a dark purple tint, contrasting with the bright scarlet of fully aerated blood. This difference in colour is due to the fact that haemoglobin, the substance which gives blood its colour and is contained in the red blood corpuscles, is the substance which carries nearly the whole of the oxygen, and

changes colour from a dark purple to bright scarlet when it takes up oxygen. The oxygen is taken up in the form of a weak chemical combination, the compound having the property of being stable only in presence of a certain concentration of free oxygen, and dissociating rapidly as the concentration of oxygen falls. The function fulfilled by haemoglobin as a carrier of oxygen from the lungs to the tissues is thus readily intelligible, as well as the difference in colour between arterial and venous blood. Substances in the blood combine to form similar readily dissociable compounds with carbon dioxide, but no change in colour is associated with this process.

Both deficiency of oxygen and excess of carbon dioxide in the air were found to produce increase in the breathing, and till recently the respective parts played by oxygen and carbon dioxide in regulating the breathing were by no means clear, and opinions on the subject were divided. I was myself led to investigate the whole subject through observations on the effects of air vitiated by respiration or by the gases met with in coal-mines and other confined spaces.

When air highly vitiated by respiration or combustion of carbonaceous material is breathed the amount of air inspired or expired is increased. The increase is due to the carbon dioxide in the air; for when this is removed there is no increase unless the deficiency of oxygen is extreme. The effect produced on the breathing by carbon dioxide in the inspired air increases out of proportion to increase in the percentage of the carbon dioxide. This fact suggested that in ordinary

breathing the ventilation of the lungs is such as to keep the percentage of carbon dioxide approximately constant in the air which is in close contact with the blood in the small airspaces or alveoli inside the lungs. If this is so, it is clear that the nearer the percentage of carbon dioxide (CO_2) in the inspired air approaches that in the lung alveoli the greater will be the quantity of air which must be breathed in order to keep the lung air normal in composition.

The matter was investigated a few years ago by Mr. Priestley and myself. We found that a sample of the alveolar air could easily be obtained by catching the last parts of a deep breath expired through a tube, and that for any individual under normal conditions, the percentage of CO_2 in this air remains practically constant during rest. On the other hand the percentage of oxygen in the inspired and alveolar air could be varied within wide limits without affecting either the amount of air breathed or the percentage of CO_2 in the alveolar air. It was only when the oxygen percentage fell very low that the breathing was increased. The percentage of CO_2 in the alveolar air is not quite the same in different individuals, but the average is 5.6 per cent for adult men.

When air containing different percentages of CO_2 was breathed it was found that the volume of air breathed was increased to such an extent as to keep the percentage of CO_2 in the alveolar air as nearly normal as possible. Nevertheless there was always a very slight increase in the alveolar CO_2 percentage with each increase in the breathing. For an increase

of 100 per cent in the ventilation of the lungs over the normal resting ventilation there was an increase of about 0.2 per cent in the CO_2 percentage in the alveolar air. Very accurate methods of sampling and gas analysis were of course needed in order to detect these differences. When the percentage of CO_2 in the inspired air reaches about the normal percentage in the alveolar air there is extreme panting. With higher percentages a point is soon reached where the CO_2 begins to produce abnormal effects, culminating in loss of consciousness. The breathing then quiets down to a large extent, and this quieting down of the breathing, as observed in animals, led formerly to a misinterpretation of the effects of CO_2 on the breathing.

If the breathing is by voluntary effort forced for a time, so as to reduce the percentage of CO_2 in the alveolar air, a period of apnoea results. This effect depends entirely on the reduction of the percentage of CO_2 in the alveolar air, for if the inspired air contains about 5 per cent of CO_2 it is impossible to produce apnoea by forced breathing, since under these conditions it is impossible to reduce the alveolar CO_2 percentage below normal. Careful observations by Douglas and myself showed that it is only necessary to reduce the alveolar CO_2 percentage by 0.2 per cent in order to produce apnoea. It thus appears that a rise of about 0.2 per cent in the alveolar CO_2 percentage is sufficient to double the breathing, while a fall of 0.2 per cent produces cessation of breathing.

We are now in a position to understand, up to a certain point, how the breathing is regulated. The

quantity of CO_2 brought to the lungs by the blood is constantly varying in accordance with varying states of bodily activity. For instance during the exertion of walking at a moderate rate the quantity of CO_2 brought to the lungs is three or four times what it is during rest. If the breathing did not increase correspondingly, the percentage of CO_2 in the alveolar air would rise, and loss of consciousness would result. But with the slightest rise in the alveolar CO_2 percentage the breathing begins to increase, and thus keeps down the alveolar CO_2. When, therefore, the production of CO_2 is three times what it is during rest, the breathing is also increased to nearly three times what it is during rest. The alveolar CO_2 percentage rises, it is true; but only by 0.4 per cent. This slight rise produces, as we have seen, an increase of 200 per cent in the breathing, so that the increase in breathing is almost proportional to the increase in the production of CO_2. Analysis of the alveolar air, and determination of the CO_2 produced and volume of air breathed during rest and work show that this explanation works out in practice, provided that no disturbing causes come in.

As the oxygen percentage in the alveolar air runs parallel with the CO_2 percentage, it is evident that regulation of the oxygen percentage is involved in regulation of the CO_2 percentage. The net result is that both the percentage of oxygen and that of CO_2 in the alveolar air are very constant, in spite of great changes in the amount of oxygen consumed and CO_2 given off by the body.

There is no doubt that it is through the blood that slight changes in the CO_2 percentage of the alveolar air affect the respiratory centre. The effects of these changes are equally rapid and marked when all the nervous connections between the lungs and the respiratory centre are severed.

To most persons it must come as a surprise that the breathing is so exactly regulated. Common observation shows us that the breathing is often more or less interrupted temporarily, and varies in frequency or depth at different times, as if the regulation were only rough. We also know that breathing is under voluntary control, and there is a popular idea that by special forms of training in breathing we can improve the aeration of the blood and the supply of oxygen to the body.

If samples of the alveolar air are taken it is found that they only give a constant percentage of CO_2 if the breathing is quite regular at the time, and they are taken at the same phase of the respiratory act—say at the end of inspiration or of expiration. Actually the percentage is varying distinctly from moment to moment round the average; and it is only the average that is constant. If, moreover, the percentage of CO_2 in the air inspired is suddenly increased, it takes some little time before the breathing increases to the new average. There is thus a considerable lag between changes in the alveolar CO_2 percentage and the response of the respiratory centre. This lag may be in either direction. If, for instance, the breathing is voluntarily held for a short time,

there follows excessive breathing; and if the alveolar air be then analysed it will be found that the CO_2 percentage has fallen below normal. The breathing is, as it were, making up for lost time.

This is easy to understand. Not only does it take an appreciable time for the blood to flow from the lungs to the respiratory centre, but both the blood and the lymph surrounding the tissue elements in the respiratory centre have a large capacity for absorbing CO_2. They saturate and desaturate somewhat slowly when brought into connection with varying concentrations of CO_2 in the alveolar air. Consequently the respiratory centre only responds gradually to these variations. Were it not so the breathing would be very jerky, and it would be difficult to interrupt it in speaking or singing or swallowing. Momentary variations in the alveolar CO_2 percentage have thus no appreciable influence on the breathing, and it is only the average that counts. But this average is regulated with an accuracy which is extraordinary.

It is evident that the average percentage of CO_2 in the alveolar air can be kept constant either by shallow and frequent or by deep and infrequent breathing. We can voluntarily set the breathing to very different frequencies, letting the depth take care of itself. For instance we can breathe three times or fifty times a minute. If, however, samples are taken of the alveolar air when once these different rates have been properly established, it is found that the average percentage of CO_2 is sensibly the same. Increased frequency is compensated for by diminished

depth, and vice versa. It is an entire mistake to judge of the amount of air breathed by the mere frequency of the breathing. With very rapid and shallow breathing only a little of the pure inspired air clears the air-passages and enters the lungs. The very rapid and shallow breathing of a dog in hot weather does not over-ventilate its lungs, and is only designed to promote evaporation from its tongue, and consequent cooling, since a dog sweats with its tongue, and not with its skin.

If the breathing is obstructed, so that considerable effort is needed to draw in and expel air, as in breathing through a partially closed tap, there is still no appreciable rise in the alveolar CO_2 percentage. The breathing is less frequent; but it is also deeper, and the fundamental regulation is practically undisturbed.

It was shown by Paul Bert that the physiological actions of CO_2 and various other gases depend upon the pressure which they exercise. This pressure depends on the number of molecules of the gas present in a given volume. For instance, 5 per cent of CO_2 present in dry air at the normal sea-level pressure of 760 millimetres of mercury has a pressure of $760 \times 5/100 = 38$ mm., and exercises the same pressure as 10 per cent of CO_2 in air at 380 mm. barometric pressure. It also contains the same number of molecules in a cubic centimetre. The air in the lung alveoli is saturated with aqueous vapour at the body temperature, and this vapour has a pressure of 47 mm., which must be allowed for in calculating from an analysis the pressure of CO_2 in alveolar air. As already seen the

average percentage of CO_2 in the alveolar air of adult men is 5.6. This is calculated for dry air. Allowing for the moisture present the pressure of CO_2 with normal barometric pressure is $(760—47) \times {}^{5.6}/_{100} = 39.9$, or, in round numbers, 40 mm.

On observing the alveolar CO_2 percentage at increased or moderately diminished atmospheric pressure we found, just as might be expected from Paul Bert's experiments, that it is the pressure, and not the percentage, of CO_2 which remains constant. The percentage is only constant if the barometric pressure remains the same. At five atmospheres' pressure the percentage of CO_2 in moist alveolar air during rest is only a fifth of what it is at normal pressure. At any one position on the earth's surface the changes in barometric pressure from day to day are so slight that the corresponding changes in the alveolar CO_2 percentage are not very noticeable; but with considerable changes in altitude, or in the case of workers in compressed air, these changes may of course be very great.

We thus reach the provisional conclusion that the breathing is so regulated as to keep the pressure or concentration of CO_2 in the alveolar air constant within narrow limits. The slightest increase in concentration of CO_2 causes an increase in the breathing which almost completely neutralises the increase in concentration. The slightest decrease in the concentration of alveolar CO_2 causes a compensating diminution in breathing. To put the matter somewhat differently, the respiratory centre reacts with

enormous delicacy towards the slightest changes, upwards or downwards, in the concentration of CO_2 in the alveolar air in contact with the arterial blood which supplies the centre.

It is of the highest significance that a slight change in the downwards direction is sufficient to suspend natural or involuntary breathing. CO_2 was formerly regarded as merely a "waste product," the getting rid of which as rapidly and completely as possible could only be a physiological advantage. It has turned out, however, that the presence of a certain concentration of CO_2 is essential to the continuance of breathing. This brings us at once into connection with a series of investigations independently initiated by Professor Yandell Henderson of Yale, and afterwards carried on side by side with the Oxford investigations. His work was at first concerned mainly with the effects of concentration of CO_2 on the circulation, and he found that undue removal of CO_2 from the blood has the most disastrous effects on the circulation, producing symptoms similar to those observed in the surgical condition known as "shock." He found that when CO_2 is removed from the body in undue quantity by excessive artificial ventilation of the lungs, the heart and circulation gradually fail, and death results. To this subject I will return later; but I am referring to it now in order to emphasise the point that the presence of CO_2 in a certain concentration in the arterial blood is just as necessary to life as, say, the presence of oxygen. An environment of CO_2 is apparently as essential as an environment of oxygen.

The effects in man of undue deficiency or undue excess of CO_2 can easily be observed. By forced breathing we can greatly reduce the alveolar CO_2 percentage and also the quantity of CO_2 in the arterial blood. The effects of continued forced breathing are very marked. These are "swimming" of the head, abnormal sensations of "pins and needles," loss of sensibility, contractions of various groups of muscles, and gradual loss of consciousness. By breathing during rest air containing 6 per cent or more of CO_2, or a less percentage during exertion, we can observe the effects of undue excess of CO_2—headache, giddiness, and often rapid loss of consciousness. Breathing is so regulated as to avoid these and other ill effects of excess or deficiency of CO_2. In other words the maintenance of breathing is but one manifestation of the co-ordinated bodily activities of which the outcome is the maintenance of bodily activity and structure as a whole. Breathing is a manifestation of life and therefore possesses its characteristic features.

It is evident that the mechanistic school of physiologists can point to the new facts with regard to the regulation of breathing as a confirmation of their principles. For the respiratory centre may be regarded as a mechanism which reacts in a very sensitive manner to slight changes in the concentration of CO_2. There is thus no mystery about the regulation of breathing—no need to invoke the presence of factors which are not physical or chemical. The respiratory centre is, in fact, typical of other bodily mechanisms. The delicacy of their reaction is due

to the delicacy of their mechanism, and not to the interference of some mysterious guiding influence such as the so-called "vital principle."

But the vitalists can equally find confirmation in the new facts. They can lay stress on the extreme delicacy of the regulation, and the fact that in man this delicate regulation is maintained, day after day, and year after year, in spite of all kinds of changes in the external environment, and in spite of the metabolic changes constantly occurring in all living tissues. These facts preclude the hypothesis that the respiratory centre is a permanent structure so stable that it is unaffected by changes in environment. The regulation, if it be a mechanism, is utterly mysterious from the physical and chemical standpoint, and necessitates the assumption that a special guiding influence is present, such as does not exist, so far as we know, in the inorganic world. The more delicate and definite the physiological regulations which the advance of experimental physiology is constantly discovering, the stronger the case for vitalism.

I have tried to put the case fairly on both sides; for both sides have always appealed to me strongly, and I have been utterly unable to accept the one-sided mechanistic arguments which have been put forward by many leading physiologists in recent times,[1] or the equally onesided vitalism of the vitalistic minority.

[1] As an example of these I may perhaps refer to Sir Edward Schäfer's Presidential address to the British Association in 1911.

Some of the immediate practical applications of the new knowledge with regard to the regulation of breathing are perhaps of sufficient interest to be mentioned shortly. The air of all sorts of confined spaces is apt to be vitiated by the presence of CO_2; and along with the excess of CO_2 there is usually a deficiency of oxygen, since the vitiation is due to processes of oxidation, in which oxygen is used up in proportion as CO_2 is formed. In the air of ordinary rooms CO_2 is formed and oxygen used up by respiration and by the burning of illuminants. The natural ventilation of an ordinary room is, however, so considerable that it is very seldom that the percentage of CO_2 in the air exceeds 0.5 per cent. What effects will the gaseous impurity in such air have? Clearly none that are appreciable. The breathing will be very slightly deeper, so as to keep the alveolar CO_2 percentage constant; but the increase in breathing will be less than a tenth, and such an increase is totally unappreciable subjectively. The slightly increased breathing will also keep the oxygen percentage in the alveolar air from falling, so that the diminished oxygen percentage in the air will be of no account. We must thus seek elsewhere than in the gaseous impurities of the air of rooms for the causes of the discomfort felt in crowded rooms.

In mines and other underground spaces the proportion of CO_2 often goes much higher, and may reach about 3 per cent in places where a light will still burn. With 3 per cent of CO_2 in the air the breathing is doubled. This effect becomes just noticeable during

rest; but during any exertion the effect is not merely noticeable, but very trying. During moderate work in pure air the breathing is three or four times what it is during rest; but when air containing 3 per cent of CO_2 is breathed the increase is to 6 or 8 times the amount of air breathed during rest in pure air. Panting is thus very severe, and hinders all hard work. Constant employment on hard work such as mining in air of this composition is apt to produce in the lungs the condition known as emphysema, and thus to cause premature disablement. The ventilation of a mine ought, therefore, to be at least sufficient to prevent the CO_2 percentage from exceeding about 1 per cent, where no other gaseous impurities than CO_2 are to be found.

One of the most interesting examples of the effects of CO_2 is that which occurs in diving with the ordinary diver's equipment. The diver is supplied with air by a pipe through which air is pumped down to him. The air passes into his helmet, and escapes into the water by a valve situated at the side of the helmet. The deeper he goes the greater is of course the pressure at which this air must be supplied; and the composition of the air which he breathes in the helmet will of course depend on the amount of air supplied to him and on the rate at which he vitiates this air. During work, for instance, he may produce four or five times as much CO_2 as during rest, so that he will need correspondingly more air during work.

Supposing that the diver is working at a depth of 22 fathoms, or 132 feet, the air supplied to him will

have a total barometric pressure of five atmospheres. If, now, the rate of supply, as measured by the strokes of the pump, is such as would keep the percentage of CO_2 in the air of the helmet at not more than 2 per cent during work, this quantity of air would suffice to keep him comfortable if he were at or near the surface. But if the same quantity of air is supplied to him at 22 fathoms, or five atmospheres' pressure, the effect of 2 per cent of CO_2 will, as we have seen, be the same as that of $5 \times 2 = 10$ per cent of CO_2 at surface. Hence if the diver exerts himself he will not merely pant excessively, but rapidly lose consciousness. It used to be a common occurrence for divers to lose consciousness in this way; and the fact that British naval divers were so commonly unable to do any work at considerable depths led to an investigation of the whole subject in the light of the new knowledge available, and to the laying down of regulations which now make work quite easy at the greatest depths required. The air supply to a diver ought evidently to be increased in direct proportion to the increase in the atmospheric pressure at which he works.

A diver is in no danger from want of oxygen, since the pressure of oxygen in his helmet and in his alveolar air is always far higher than in pure air at surface. It is almost always from oxygen want that a man dies who is asphyxiated by vitiated air in mines; but a diver may die from CO_2 poisoning in the presence of abundance of oxygen.

I must now turn to another line of investigation in relation to the regulation of breathing. In 1868

Hering and Breuer discovered that if expiration is prevented by blocking the outlet of air at the end of an inspiration, particularly if the lungs are well distended, rhythmic breathing efforts are interrupted. There is a long pause, during which there is nothing but expiratory effort; and only after this long pause is there an effort at inspiration. Similarly if inspiration is blocked at the end of expiration there is a long interval in which only inspiratory effort is observed. The rhythmic activity of the respiratory centre is interrupted in either case.

They also discovered that if the vagus nerves, which proceed from the medulla oblongata in the brain, and supply branches to the lungs, are cut, these effects are no longer produced. Rhythmic inspiratory and expiratory efforts continue, quite regardless of whether the lungs are inflated or deflated. Clearly, therefore, impulses proceeding up the vagus nerves from the lungs are concerned in the regulation of breathing. When these nerves are cut or frozen across the breathing immediately becomes less frequent, but deeper, and acquires a well-marked dragging character.

Hering and Breuer interpreted their observations as signifying that with the vagus nerves intact distention of the lungs excites the nerve-endings with the result that impulses which stop or inhibit inspiration, and excite expiration, pass up the nerves. On deflation of the lungs to a certain point during expiration a corresponding process occurs which inhibits expiration and excites inspiration. Thus the disten-

tion of the lungs during inspiration is the immediate cause of expiration, and the deflation on expiration is the immediate cause of inspiration. Subsequent investigation by various other observers confirmed in the main these conclusions. The regulation of breathing thus appeared to be an automatic process dependent, so long as the vagus nerves are intact, on the effects of alternate distention and deflation of the lungs. Until recently, also, many observers concluded from their experiments that apnoea is the summed effect of frequently repeated over-distention of the lungs, and has nothing to do with chemical changes in the blood. The majority believed that there is both a "chemical" and a "vagus" apnoea. The continued inspiratory or expiratory effort which accompanies continuous deflation or inflation of the lungs cannot properly be called apnoea, however.

I have already referred to the evidence showing that there is certainly no such thing as an apnoea due to the mere summed effects of repeated distention of the lungs, such as occurs in panting. The apnoea which follows forced breathing or excessive artificial ventilation of the lungs is due to reduction in the amount of CO_2 in the alveolar air and arterial blood, and to no other cause. Were it the case that repeated unusual distention of the lungs tends to cause apnoea we should have a physiological arrangement exactly suited to defeat the whole physiological end of increased breathing. It seems extraordinary that the extreme improbability of this should not have weighed more heavily with the authors of the "vagus" theory of apnoea.

The theory that the breathing is regulated merely by the effects of alternate distention and collapse of the lungs is also quite plainly absurd in view of what is now known about the part played by the carbon dioxide pressure in the alveolar air and arterial blood. The observations of Hering and Breuer and of others who have made experiments along the same lines are none the less significant, however. Mr. Mavrogorato and I have found that the main facts, apart from the effects of section of the vagus nerves, can best be observed and analysed in man. The subject breathes through a wide bored tap which can be opened or closed at any moment; the nose is clipped; and a pressure-gauge is connected between the mouth and the tap so as to show the inspiratory or expiratory pressure.

When the tap is closed at the end of inspiration it will be noticed on the gauge that there is expiratory pressure, slight at first, but afterwards increasing more and more rapidly, till at last, after an interval occupying the time of several normal respirations, there is a sudden inspiratory effort. The natural tendency of the respiratory centre to discharge alternate inspiratory and expiratory impulses thus breaks through the prolonged expiratory effort. Similarly, if the tap is closed at the end of inspiration there is a prolonged and increasing expiratory effort. If, now, apnoea is produced by forced breathing before the experiment, there is inspiratory or expiratory pressure as before; but it is a very long time before this pressure begins to increase. On the other hand if air containing CO_2

has been breathed before, so that the breathing is naturally increased, the inspiratory or expiratory pressure mounts up very rapidly, and is soon broken by an inspiratory effort. If the tap is closed midway in inspiration, long-continued inspiratory pressure, gradually increasing, is shown on the gauge, just as if the interruption had been at the end of expiration; and similarly there is long-continued expiratory pressure if expiration has been interrupted midway.

If we put together the human observations and the results obtained in animals with the vagus nerves intact and divided, it appears that the effect of distention of the lungs is to stop inspiratory and initiate expiratory discharge of the respiratory centre, while deflation of the lungs stops expiratory and initiates inspiratory discharge. Both inspiratory and expiratory discharges continue until they are again stopped by distention or deflation. The result is that the discharges from the centre are directly co-ordinated with actual inflation or deflation of the lungs. This is brought about through the vagus nerves. The degree of energy of the inspiratory or expiratory discharges depends, however, on the action of CO_2 in the blood upon the centre.

The degree of inflation or deflation necessary to inhibit inspiration or expiration and initiate expiration or inspiration depends quite clearly also on the chemical stimuli acting on the centre through the blood: for the breathing is far deeper when the pressure of CO_2 in the alveolar air and arterial blood is higher. We can thus understand how it is that when the fre-

quency of breathing is varied voluntarily or involuntarily, the depth naturally adjusts itself in such a way that the average alveolar CO_2 pressure remains sensibly constant: for the least lowering of alveolar CO_2 pressure enables the Hering-Breuer inhibitory effect to become effective within narrower limits of inflation and deflation, while the least raising of alveolar CO_2 pressure has the opposite effect. We can also explain a very interesting phenomenon recently discovered independently by Yandell Henderson in America and Liljestrand, Wollin and Nilsson in Sweden. When artificial respiration is performed on a conscious subject by Schäfer's or any of the other usual methods, air enters and leaves the chest in just about the normal amount, although the subject carefully refrains from himself making any breathing efforts. If the rate of artificial respiration is increased there is no increase in the air entering the chest per minute: for the breaths become shallower. If, finally, apnoea is produced by previous forced breathing, and artificial respiration is then applied, hardly any air enters the chest. The Hering-Breuer inhibition comes into play with the slightest inflation or deflation of the lungs, and the breathing is, as it were, jammed.

When the vagi are cut, an animal can still regulate its breathing so as to keep the alveolar CO_2 pressure constant; for the depth of the drawn-out respirations depends on the alveolar CO_2 pressure. But, as might be expected, the regulation breaks down easily under any strain, as was recently shown by Scott. The

breaths cannot follow quickly enough the requirements which are easily met by an animal with intact vagi.

In the regulation of breathing we have thus a striking instance of the co-ordination between the actions of two different nervous stimuli. The influence of the peripheral stimuli acting through the vagus nerves is dependent upon the action of the central stimuli, and vice versa. This interdependence is characteristic of the effects of nervous stimuli and indeed of all physiological stimuli. As an outcome of the interdependence in the present case, the breathing organs work as a whole, the discharges from the respiratory centre being correlated with the actual movements of the lungs.

Even after the vagi and nearly all other nervous connections to the respiratory centre are severed, alternate inspiratory and expiratory discharges from the centre continue in their proper order. The inspiratory discharge seems during its continuance to inhibit expiratory discharge, and vice versa. Here, also, we see the co-ordination which is inherent in all physiological activity, and which manifests itself even in the behaviour of an isolated heart or strip of muscle, but far more strikingly in the case of the nervous system, even after great mutilation, or in the case of the chemical activities of any living part of the body.

II

THE READJUSTMENTS OF REGULATION IN ACCLIMATISATION AND DISEASE

We have seen that under ordinary conditions the regulation of breathing is dependent on very small variations in the degree to which the arterial blood leaving the lungs is saturated with CO_2, and that a normal CO_2 pressure of about 40 mm. is maintained in the alveolar air of the lungs during rest. Nevertheless this normal pressure may become altered. Thus if the oxygen percentage or pressure in the lung air becomes very low in consequence of great deficiency in the oxygen percentage of the air breathed, or from the barometric pressure being very low, as at great altitudes, the breathing is increased and the alveolar CO_2 pressure falls. A similar fall occurs after mineral acids have been taken, or in diseases in which abnormal quantities of acid are discharged into the blood, or after severe muscular exertion. To understand how the breathing is affected under these various conditions, and on what the normal conditions of breathing ultimately depend, it is necessary to consider the blood, and particularly the gases contained in it.

When a liquid is brought into intimate contact with a gas the liquid takes up the gas in solution until a point is reached at which equilibrium or saturation occurs. At this point as many molecules of gas are being given off from the liquid as enter it, and the

pressure of the gas leaving the liquid is thus equal to the gas pressure outside. If, as in the lungs, a mixture of gases is in contact with the liquid, the pressure of each of the gases in the liquid becomes, if no interference to their passage inwards or outwards occurs, equal to the pressure of the corresponding gas in the gas-mixture. This holds good even if the liquid contains substances which form well-defined compounds with the gas; but in the latter case the amount of gas which the liquid has to take up before equilibrium occurs may be very large. If no such chemical combinations occur the volume of gas taken up by the liquid is in ordinary cases directly proportional to the pressure of the gas.

As we have already seen, the red corpuscles of the blood contain a coloured albuminous substance, haemoglobin, which enters into chemical combination with oxygen. The compound, oxyhaemoglobin, has the remarkable property of dissociating freely as the pressure of oxygen in the surrounding liquid falls, and re-forming as it rises. The oxyhaemoglobin thus acts as a reservoir of oxygen, enabling the blood to take up or give off far more oxygen with varying pressures of oxygen than water would take up or give off, and thus to act as a very efficient carrier of oxygen from the lungs, where the oxygen pressure is high, to the capillary vessels of the body tissues, where it is low in consequence of the constant consumption of oxygen. Human blood saturated in the lungs is capable of giving off about 18 cc. of oxygen per 100 cc. of blood, whereas water would only give off about 0.3 cc.

To understand the oxygen supply to the body, and the connection between oxygen supply and breathing, it is evidently necessary to understand the circumstances under which oxygen is taken up or given off by the haemoglobin of the blood. These circumstances can

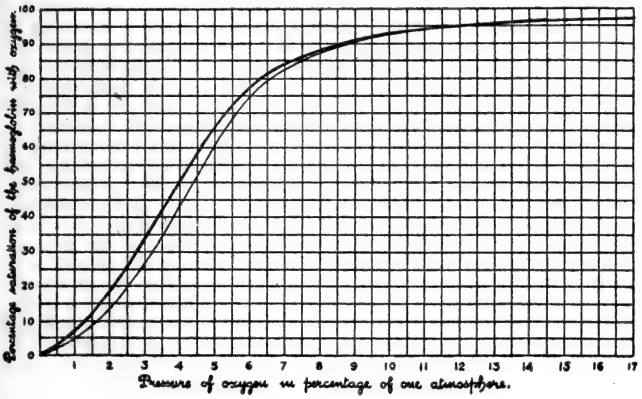

FIG. 1. Thick line—dissociation curve of oxyhaemoglobin in blood in the presence of 40 mm. pressure of CO_2. Thin line—the dissociation curve of oxyhaemoglobin in blood within the body.

be investigated outside the body, provided that we are able to reproduce outside the body the conditions which obtain within it. Until recently, failure to appreciate the importance of this led to great error.

The dissociation of oxyhaemoglobin with fall in the pressure of oxygen can best be represented graphically by a curve; and Figure 1 represents the law of dis-

sociation of human oxyhaemoglobin under the conditions so far known to exist in circulating human blood, including the rise of CO_2 pressure as the blood passes the capillaries. It will be seen that the curve has a very peculiar shape, with a double bend, which is of great physiological significance. At the steep part of the curve oxygen will evidently come off freely with a comparatively slight fall in oxygen pressure. The haemoglobin is thus admirably adapted for maintaining the oxygen pressure approximately constant within the pressures corresponding to the steep part as the blood passes through the capillary vessels of the body. So far as we know the circulation is never, under normal conditions, so slow that the oxygen pressure in the body capillaries falls below the steep part of the curve, and is seldom so rapid as to bring the oxygen pressure above the steep part. The oxygen pressure in the alveolar air is normally about 100 mm., or 13 per cent of an atmosphere, which corresponds to the flat upper part of the curve.

The general form of the dissociation curve of the oxyhaemoglobin in blood was discovered a few years ago by Bohr of Copenhagen. He and his pupils also found that the curve is much affected, not only by temperature, but by the pressure of CO_2 in the blood. In the absence of CO_2 the curve (as represented in the figure) shifts to the left, so that oxygen is given off much less readily. For a specified amount of oxygen to be given off in the absence of the CO_2 normally present in circulating blood, the pressure of oxygen would require to be lowered to about half the pressure

otherwise needed. Excess of CO_2, on the other hand, facilitates the dissociation, so that the giving off of CO_2 to the blood in the body capillaries helps to make the curve steeper and so facilitates the oxygen supply to the tissues.

The curve is not at all of the shape which would be expected on purely chemical grounds from what is known of other substances which dissociate in a similar manner. It was discovered by Barcroft and his pupils that the inorganic salts present along with the haemoglobin in the red corpuscles determine this peculiar form. When the haemoglobin is freed from these salts its dissociation curve has the form which would have been expected on chemical grounds—namely, that of a rectangular hyperbola. With this form of curve the oxyhaemoglobin would be wholly unsuited for performing the work which it actually performs in the body. The action of the salts is almost certainly connected with their power of causing the haemoglobin molecules to become aggregated into groups. Barcroft also found that it is in virtue of its action as an acid when in solution that CO_2 affects the dissociation curve. Alkalies shift the curve to the left, while acids shift it to the right; and the changing position of the curve is an extraordinarily delicate index of small changes in the reaction of the blood.

Both the plasma and the corpuscles of blood contain substances which enter into chemical combination with CO_2; and these combinations dissociate with fall in the pressure of CO_2, and re-form with rise, just as oxyhaemoglobin dissociates and re-forms. The whole

of the combined CO_2 can be removed from blood by exposing it to a vacuum, just as the whole of the loosely combined oxygen can be removed. A strong acid does not liberate any more. This is a very remarkable fact; for we cannot remove the CO_2 from a sodium carbonate solution by means of a vacuum, and sodium is certainly combined with CO_2 in blood. Blood contains an excess of alkali which is not combined with any strong acid, and must be in part combined with CO_2. The explanation lies in the fact that haemoglobin and other albuminous substances present in the blood are capable of acting as very weak acids and so partially preventing the CO_2 from combining with the available alkali. When the pressure of CO_2, and therefore its "mass influence" is reduced, more and more of it is driven out of combination, until with the CO_2 pressure at zero none is left.

From 100 volumes of human arterial blood about 50 volumes of CO_2 as gas are given off to a vacuum, and average venous blood contains only about 4 volumes more. The relations between pressure of CO_2 and the volume of CO_2 absorbed by human blood were recently investigated by Christiansen, Douglas and myself, and Figure 2 represents the results graphically. We found that blood takes up considerably more CO_2 at a given pressure of the gas when the oxyhaemoglobin is dissociated than when it is present as oxyhaemoglobin. The oxyhaemoglobin thus acts as if it were a more acid substance than dissociated or reduced haemoglobin. The relation between pressure of CO_2 and its absorption by the blood in the living body is

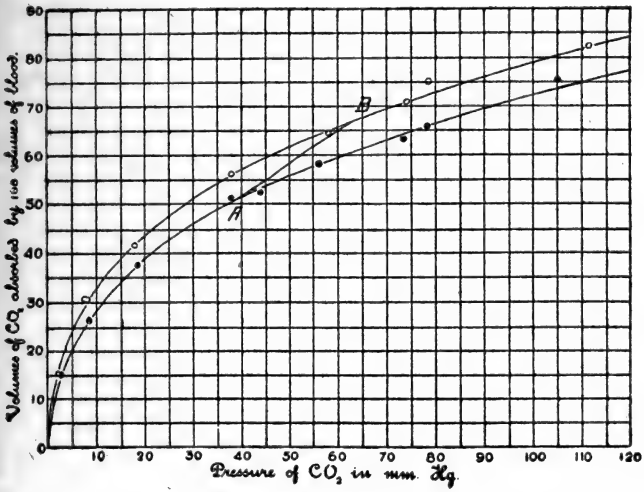

FIG. 2. Lower curve—absorption of CO_2 by blood in presence of air and CO_2. Upper curve—absorption of CO_2 by blood in presence of hydrogen and CO_2. The line A-B represents the absorption of CO_2 within the body.

therefore represented by the thick line starting at 40 mm. which is the pressure of CO_2 in arterial blood. This line rises steeply, so that far more CO_2 can be taken up by the blood with a given rise of CO_2 pressure than would be the case if oxyhaemoglobin and reduced haemoglobin had the same effect on the absorption of CO_2. It follows also that when the venous blood reaches the lungs and suddenly becomes oxygenated, the pressure of CO_2 in the blood suddenly rises. In this way much more CO_2 is given off than would otherwise be the case considering the existing

pressure of 40 mm. in the alveolar air. In other words the oxygenation of the venous blood in the lungs helps to turn out the CO_2—a fact long ago suspected by Ludwig, but of which the only evidence that could be obtained was negative until new and rapid methods of blood-gas analysis were introduced by Barcroft and myself.

As regards the carriage of both oxygen and CO_2 it is thus the case that the blood is of such a nature that the pressures of these gases in the blood leaving the tissues may vary but little in spite of the varying amounts of gas carried. With respect to oxygen, a glance at the dissociation curve of oxyhaemoglobin shows that it matters but little to the saturation of the blood with oxygen whether the oxygen pressure in the alveolar air is a little higher or a little lower. With respect to CO_2, however, variations in the alveolar CO_2 pressure will make a distinct difference to the CO_2 pressure in the blood leaving the tissues, so that it is intelligible that what governs the breathing is normally the CO_2 pressure, and not the oxygen pressure in the arterial blood.

A further point about the curves for both oxygen and CO_2 is that for any one individual they are extraordinarily constant from day to day and month to month. Under normal conditions no difference can be detected in them, just as with the gas pressures in the alveolar air. The significance of this constancy is unmistakable; and to a mechanist who pointed out that the taking up and giving off of gases by the blood is a purely chemical and physical matter, a vitalist

might well retort by asking what regulates all the complex conditions concerned in the process—the formation and marshalling of haemoglobin and salts in the corpuscles, and the astoundingly delicate balance of the various substances which are concerned in the carriage of CO_2.

Nevertheless the regulation of both the breathing and the carriage of gas by the blood can be disturbed, either temporarily or for long periods; and it is only by studying these disturbances that we can get further insight into the regulation. It has already been mentioned that when mineral acids are administered the breathing increases, so that the alveolar CO_2 pressure necessarily falls, while the amount of CO_2 in the arterial blood may be diminished in acid poisoning to a small fraction of what it normally is. The administration of alkalies has a similar effect in the opposite direction. Slighter effects of a similar kind can be brought about, at least temporarily, by mere changes in diet. In diabetes a condition sometimes occurs in which a great excess of organic acid is formed in the body; and this also is accompanied by great increase in the breathing and fall in the alveolar CO_2 percentage. A temporary effect in the same direction follows exposure to want of oxygen, or excessive muscular exertion. It was known that exposure to great want of oxygen leads to the production of lactic acid in the body, and that excessive muscular exertion must have the same effect, since the amount of work done excludes the possibility of the circulation being able to supply the muscles with the oxygen

required to keep up the work. These considerations led me to the conclusion that it is probably in virtue of its acidity that dissolved CO_2 (H_2CO_3 or carbonic acid) affects the respiratory centre, and that other acids will therefore have a similar effect, and will thus help CO_2 to excite the centre. This theory explains why less CO_2 in the alveolar air is sufficient to excite breathing under the various conditions just referred to.

At the time, however, there was no means available of accurately measuring the slight alkalinity of the blood. The old method of adding standard acid till an indicator changed colour was not only very rough, but also fallacious in principle. The blood is only very slightly alkaline, yet quite a large quantity of acid can be added to it before it becomes acid. It is full of so-called "buffer substances," which are capable of combining with acids or alkalies, but are not themselves very definitely acid or alkaline. Thus the amount of acid which has to be added to blood to change its reaction is a measure of the buffer substances rather than of the alkalinity of the blood. According to modern ideas the acidity or alkalinity of a solution depends on the relative concentrations in it of hydrogen and hydroxyl "ions." This concentration can be measured directly by the electrometric method, but the difficulties in applying the method to blood were very great.

In 1912, however, Hasselbalch of Copenhagen succeeded in obtaining reliable results; and he and Lundsgaard published curves showing graphically the rela-

tions between hydrogen ion concentrations and CO_2 pressure in blood. A difference in CO_2 pressure which would be sufficient to double the breathing, or to cause apnoea, produced a difference in hydrogen ion concentration which was just measurable by the method, so the method is very rough as compared with the delicacy of discrimination by the respiratory centre. By varying the diet from alkaline to acid-producing Hasselbalch succeeded in producing a variation of several millimetres in the alveolar CO_2 pressure. He then found that with the blood saturated with CO_2 at the *existing* alveolar CO_2 pressure the hydrogen ion concentration as measured was sensibly the same on either diet; whereas if the blood was saturated in both cases at the same CO_2 pressure the hydrogen ion concentration was markedly different on the two diets. The difference in alveolar CO_2 pressure was thus just sufficient to keep the hydrogen ion concentration, in so far as it could be measured by the electrometric method, constant in the two samples of blood, although there was presumably a slight difference as indicated by the difference in the breathing. Other similar experiments had a similar result, and there seems now to be no doubt that it is true that what the respiratory centre responds to is hydrogen ion concentration, and not mere CO_2 pressure.

The delicacy of the response of the respiratory centre to change in the reaction of the blood is very extraordinary; but what is still more marvellous is the fact that in spite of this delicacy the alveolar CO_2 pressure is so steady during rest. The respiratory

centre is responsible for neutralising, by getting rid of excess of CO_2, the changes in hydrogen ion concentration which would occur in the blood if the excess of CO_2 were not got rid of; but its action in regulating the breathing does not explain why, apart from the disturbing influence of CO_2, the reaction of the blood remains so marvellously constant, as shown by the constancy during rest of the alveolar CO_2 pressure. Acid-forming and alkali-forming substances are constantly being taken into the body in more or less irregular quantities. For instance the sulphur in albuminous food is oxidised to form sulphuric acid, and the phosphorus to form phosphoric acid; while on the other hand the organic acids contained as salts in vegetable foods are oxidised to CO_2 and thus introduce alkaline carbonates into the body. Acid or alkaline secretions, such as the gastric or pancreatic juice, are also being formed at intervals. Yet the reaction of the blood hardly varies even when tested by such an exquisitely sensitive indicator as the respiratory centre, while no other indicator shows any variation.

It is thus evident that to understand the physiology of breathing we must consider the regulation of the blood alkalinity. Two means are already known by which the blood-reaction is regulated. One of these is by regulation of the formation of ammonia in the body. It was discovered by Schmiedeberg of Strassburg and his pupils that when mineral acids are administered to dogs or to men the amount of ammonia salts eliminated in the urine increases greatly, at the

expense of the normal elimination of urea. Urea $CO(NH_2)_2$ is a nitrogenous body of neutral reactions in the form of which by far the greater part of the combined nitrogen passing through the body is eliminated. In acid poisoning the combined nitrogen goes more and more into the form of ammonia (NH_3), which, in virtue of its alkaline reaction when in solution, combines with acids and thus neutralises them. Even under average normal conditions in man the quantity of ammonia eliminated in the urine is about sufficient to neutralise the large quantity of sulphuric acid formed by the oxidation of the sulphur of albuminous substances; and with an alkaline diet this ammonia practically disappears from the urine. In the Strassburg laboratory it was also discovered that ammonia salts are converted into urea in the liver. We have now every reason to believe that ammonia is formed in large quantities in the intestine by the breaking down under ferment action of albuminous compounds. This ammonia is carried straight to the liver by the portal circulation, and there converted under ordinary conditions almost entirely into urea. But the liver appears to leave unconverted any ammonia needed to regulate the reaction of the blood, and the minutest deviations in reaction serve to regulate this process. Hence in the ratio between ammonia and total combined nitrogen in the urine we have a valuable index of any tendency towards acidity or alkalinity of the blood, though the composition of the alveolar air is a still more direct index.

Another known means of regulation is by the kid-

neys. Human urine is usually acid in reaction, though it is separated from the alkaline liquid, the blood. As shown clearly by L. J. Henderson of Harvard, the urine, like the blood, contains "buffer" substances, so that the slight acidity of the urine is an index of the separation of much acid from the blood. But the reaction of the urine, and therefore the separation of acid by the kidneys, varies from hour to hour, and depends on whether the diet is more or less acid forming or alkali forming. In herbivorous animals, which live on an alkali-forming diet, the reaction of the urine is normally alkaline; and in man the urine also becomes alkaline when alkalies are administered. It seems evident, therefore, that the kidneys, as well as the liver, are constantly regulating the alkalinity of the blood, and doing so with an accuracy which no means of direct physical or chemical measurement enables us to measure, but which is shown by the great constancy of the alveolar CO_2 percentage. Nevertheless, we can be quite certain that it is in response to the stimulus of very slightly altered reaction in the blood that the regulating activity of the liver and kidneys comes into play: for by such means as acid poisoning we can make the stimulus so strong that direct measurements can detect it.

It has been rightly pointed out by L. J. Henderson that the blood, and the body as a whole, are so full of so-called buffer substances that a considerable amount of acid or alkali might be added without any measurable disturbance of the blood alkalinity being produced. This is certainly true, and very important, but the

disturbances which physiology has to deal with are far more minute than those which are appreciable by chemical methods, so that exact regulation of the reaction of the blood is indispensable.

We have seen above that the composition of the blood is so regulated that not only is its reaction practically constant, but the volume of CO_2 taken up by a given volume of blood at a given pressure of CO_2 remains also the same under ordinary normal conditions. It is easy, however, to disturb this regulation temporarily. One means of doing so is by violent muscular exertion. Douglas and I found that a few minutes after violent exertion the volume of CO_2 taken up by a given volume of human arterial blood was reduced to about half. An hour later, however, the blood was again normal. The reduction was probably due to excessive discharge of lactic acid into the blood: for not only was the resting alveolar CO_2 pressure diminished, but Ryffel succeeded in showing that after similar violent exertion the proportion of lactic acid in the blood and urine is greatly increased. Ryffel showed also that this excess disappears in about an hour, which is the same time, as we had observed, that the alveolar CO_2 pressure requires to rise again to normal after a violent exertion. It is clear, however, that the capacity of the blood for taking up CO_2 cannot depend merely on its reaction, and must depend on the presence in regulated amount of all the various substances including albuminous substances, which enter into chemical reaction when CO_2 is present. Their amount must therefore be regulated—probably by the

endothelial cells which line the capillary blood-vessels. Here, then, we have another delicate regulation connected with breathing.

We must now turn to the respiratory regulation of oxygen supply. Normally, as we have seen, it is the CO_2 pressure in the blood, and ultimately the reaction of the blood, which seems to regulate the breathing. Under normal conditions there is always a sufficient reserve of oxygen in the alveolar air to saturate the haemoglobin of the blood to about the full normal extent, even if, from any cause, the oxygen percentage falls distinctly below normal. We can thus understand how it is that even if the oxygen percentage in the air breathed is reduced from 20.9 per cent, as in pure air, to as little as 14 or 15 per cent, which instantly extinguishes any ordinary flame, the breathing is not sensibly affected at the time, and the alveolar CO_2 percentage is undisturbed although the alveolar oxygen percentage has fallen from 14 to 7 or 8. When, however, there is a further reduction in the oxygen percentage the breathing begins to increase, and the alveolar CO_2 pressure consequently falls. The face and lips also begin to have a bluish or lead-coloured tinge, showing that the blood is not properly oxygenated in the lungs; and if such air is breathed for a considerable time headache and nausea come on. If there is only 6 or 8 per cent of oxygen in the air breathed intense panting is at once produced, accompanied by rapidly increasing dizziness, mental failure, and other alarming symptoms, as well as marked blueness or leaden colour of the face.

On studying more closely the effects of breathing air very deficient in oxygen we found that the alveolar CO_2 pressure still regulates the breathing; but the regulation is, as it were, set at a lower level. The great panting produced at first by want of oxygen is due to the fact that owing to the large reserve of CO_2 in the blood and lymph the alveolar CO_2 cannot be set at once to the new level without evident panting. When once the reserve of CO_2 has been got rid of, the breathing diminishes, while the blueness and other symptoms increase. If the oxygen percentage or pressure in the air is only diminished gradually there is no evident panting, although there is still some increase in the breathing, as shown by the lower alveolar CO_2 pressure. The formidable symptoms come on without the warning given by panting. Nevertheless apnoea can still be produced easily enough by forced breathing sufficient to reduce the alveolar CO_2 pressure further, even though the face is blue all the time, and consciousness fails before there is any desire to breathe. It was through attending too exclusively to want of oxygen as a cause of the "venosity" of the blood that so many mistakes were made by physiologists as to the causes of apnoea, and the general physiology of breathing.

The action of gradually developing want of oxygen is very insidious, until dangerous effects develop with dramatic suddenness. These effects have been repeatedly observed by balloonists, as well as in mines. Nothing illustrates the effects better than the experiences of the well-known meteorologist Glaisher and his

assistant Coxwell in a famous ascent from Wolverhampton in 1862. The balloon gradually reached a height of 26,000 feet, at which the oxygen pressure in the air was reduced to two fifths of the normal. Glaisher then first noticed that he could not read his instruments properly. Shortly afterwards his legs were paralysed, and then his arms, though he could still move his head. Then his sight failed entirely, and afterwards his hearing, and he became unconscious. Coxwell meanwhile endeavoured to pull the rope of the valve, but found that not only his legs, but also his arms were paralysed. He succeeded, however, in seizing the rope with his teeth, thus opening the valve. As the balloon descended Glaisher, about seven minutes after he lost consciousness, began to hear Coxwell's voice again, and then to see him, after which he quickly recovered. The balloon had probably reached a height of about 30,000 feet.

In another famous high ascent from Paris the three observers, Tissandier, Sivel and Crocé-Spinelli, were provided under Paul Bert's direction with bags of oxygen to breathe from if they felt any ill effects. Though the oxygen would have saved them they were all paralysed before they realised their danger; and only Tissandier survived. The balloon, as shown by a self-registering barometer, had reached a barometric pressure of 263 millimetres, corresponding to a height of 30,000 feet, so that the pressure was reduced to nearly a third of the normal.

The insidious effects of want of oxygen are perhaps still more strikingly illustrated in the case of

carbon monoxide poisoning. This gas (CO) is the poisonous constituent of ordinary lighting gas; and poisoning with it is extremely common in America on account of the high percentage of carbon monoxide in the carburetted water gas used extensively as a substitute for the old-fashioned coal gas still supplied in England. I discovered about twenty years ago that CO poisoning is also the cause of nearly all the deaths in great colliery explosions and fires, and a source of extreme danger to rescuers.

Claude Bernard found that CO enters into combination with haemoglobin, just as oxygen does, but forms a far more stable compound. In presence, therefore, of sufficient CO the oxygen-carrying power of the haemoglobin is suspended, and death must result from want of oxygen. It was supposed that CO has also a direct poisonous action on the nervous system. That this is not so I succeeded in showing by placing animals in compressed oxygen before giving them CO. In the compressed oxygen sufficient oxygen goes into ordinary physical solution in the blood to enable the animal to dispense with oxyhaemoglobin as an oxygen carrier; and the animal remains unharmed although its blood and tissues are saturated with CO. Animals which do not employ haemoglobin as an oxygen carrier live for weeks quite comfortably in an artificial air composed of 80 per cent of CO and 20 per cent of oxygen. CO is not oxidised in the living body, and apart from its one fatal property of combining with haemoglobin it is a physiologically indifferent gas.

In CO poisoning there is usually only a small percentage of CO in the air, and as the haemoglobin of the blood has a large capacity for CO it takes a considerable time for enough CO to accumulate in the blood to cause dangerous symptoms. These symptoms, however, come on in exactly the same insidious manner as those from oxygen want arising in any other way. The headache, nausea, etc., of CO poisoning are the same as those of mountain sickness, and the more remote nervous, cardiac, and other after-symptoms of CO poisoning or serious oxygen want produced in any other way are due to damage resulting from oxygen want, and to no other cause. The oxygen want produces not merely temporary functional effects, but structural changes in the cells of nervous and other tissues.

As CO in small but extremely dangerous proportions in air cannot be detected by smell or by a lamp, I introduced, as a test for it, the use of a small warm-blooded animal, such as a mouse or canary. A small animal has an enormously greater respiratory exchange and circulation rate than a man; and in consequence its blood becomes saturated with CO far more quickly. By watching the animal a miner can tell in good time whether he is in a dangerous atmosphere, though in the long run the animal is not more sensitive to CO than the man. The provision of small animals for testing purposes at mines in Great Britain was made obligatory by recent legislation.

Yandell Henderson discovered that after excessive artificial respiration on animals the breathing does

not return. The animal dies of want of oxygen, or failure of the circulation, without making any effort to breathe. Hence if we reduce the CO_2 pressure of the blood low enough no amount of oxygen want will excite the respiratory centre. Oxygen want is thus not by itself an adequate stimulus to the respiratory centre; but it helps the action of CO_2, or if we like to put it otherwise, causes the respiratory centre to react in presence of a degree of blood alkalinity which would be too high to excite it under normal conditions.

Although a slight, or even a considerable, deficiency in the oxygen pressure of the air breathed produces no immediate effect on the breathing, yet a long-continued deficiency has a very distinct effect; and the study of the effects of a long-continued deficiency has furnished, I think, one of the most interesting chapters in recent physiology. To observe the effects of long-continued deficiency it is only necessary to go to places at high altitudes, where the barometric pressure is low, but where men nevertheless live under perfectly healthy conditions. The Anglo-American expedition to Pike's Peak in 1911 had for its object the careful study of these effects.

On going to a very high altitude the breathing is increased at once, and the alveolar CO_2 pressure falls correspondingly; but if the altitude is only very moderate there is at first no effect on the breathing, just as happens when air containing a moderately reduced percentage of oxygen is breathed in the laboratory for a short time. After some days, however, it will

be found that the alveolar CO_2 pressure has fallen, which shows that the breathing is deeper. This fall reaches a certain amount, depending on the altitude, and then ceases. On the subject's return to sea level the alveolar CO_2 pressure does not at once return to normal again, but may take many days, or even some weeks, to do so. Figure 3 shows graphically the aver-

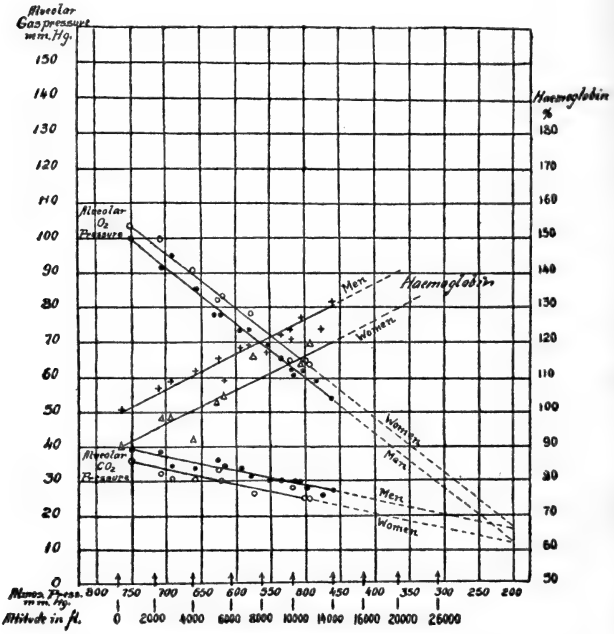

FIG. 3. Alveolar pressures of oxygen and CO_2 and percentages of haemoglobin in the blood of persons acclimatised to altitudes from sea level to 14,000 feet,—barometric pressures from 760 to 450 mm. of mercury.

age results of measurements of alveolar CO_2 pressure made by Miss Fitz Gerald, in connection with the Pike's Peak Expedition, on persons residing permanently at different altitudes. It will be seen that the alveolar CO_2 pressure diminishes regularly with altitude, starting from sea level. That this diminution is a response to the diminished alveolar oxygen pressure there can be no doubt. If the barometric pressure is kept steady, and the oxygen pressure is diminished by lowering the percentage of oxygen, the results are precisely the same, so far as can be judged by the available observations; and, as was first clearly pointed out by Paul Bert, practically all the physiological disturbances produced by low barometric pressures, or high altitudes, are due to lowering of the oxygen pressure.

From Figure 3 it is pretty evident that if the oxygen pressure is raised above the normal value at sea level, the alveolar CO_2 pressure will rise still higher. That this is actually the case has recently been shown by Hasselbalch and Lindhard, who have confirmed in a steel chamber many of the Pike's Peak results, and have added further observations of their own. It appears from their results that the alveolar CO_2 pressure does not rise much higher after the normal oxygen alveolar oxygen percentage has been exceeded; but the fact that there is a rise is of great interest, as showing that even the "normal" alveolar CO_2 pressure depends on the existing alveolar oxygen pressure.

What is the significance of the fall in alveolar CO_2 pressure at low barometric pressures? It might be

thought that the teleological significance at any rate is clear enough, since lowering of alveolar CO_2 pressure means raising of the oxygen pressure, thus compensating to some extent for any want of oxygen caused by the lowered oxygen pressure. But there may be no evident signs of want of oxygen, and lowering of alveolar CO_2 pressure is in itself a very disturbing influence, as has already been shown. When we first observed the persistent lowering of alveolar CO_2 pressure in connection with shorter experiments in a steel chamber we thought that lactic acid must have been formed in consequence of oxygen want, and that the persistence of the lowered alveolar CO_2 pressure after the experiment was due to lactic acid remaining in the body. But further observations by Boycott and Ryffel failed to confirm this theory; and the persistence observed after longer observations in the chamber, and stays in the Alps, was far too great to justify the lactic acid theory. As already mentioned the excess of lactic acid produced by muscular work disappears from the blood within about an hour.

Barcroft meanwhile found on the Peak of Teneriffe that the dissociation curve of the oxyhaemoglobin in human blood was displaced to the right if the determination is made in presence of 40 mm. pressure of CO_2 (that of the alveolar air at sea level), but was normal if made in presence of the existing lowered alveolar CO_2 pressure. From this it could be concluded that there is no appreciable change in the reaction of the arterial blood within the body at the higher altitude. The lowered alveolar CO_2 pressure

just compensated sensibly for diminished alkalinity of the blood. This we confirmed on Pike's Peak at a higher altitude.

As a result of the whole of the Pike's Peak and previous experiments we came to the conclusion that the point of alkalinity to which the kidneys, etc., regulate the blood is altered in the direction of slightly diminished alkalinity, so that, assuming the reaction of the respiratory centre to alkalinity to be steady, the alveolar CO_2 pressure has to be kept lower in order to preserve the balance. The very slight diminution of alkalinity required to account for the increased breathing is so small as to be at present beyond the range of measurement, as already explained. Hasselbalch and Lindhard have more recently published the results of electrometric measurements of the arterial blood alkalinity which show a sensibly unaltered reaction after acclimatisation to lowered barometric pressure in a steel chamber, with the alveolar CO_2 pressure much reduced.

It thus appears that the regulation of the alkalinity of the blood by the kidneys and liver is dependent on the oxygen pressure of the air. The change in environment has altered the setting of the regulator. This is a very striking example of the intimate connection between internal physiological regulation and external environment; but we have now to consider other instances.

It has long been known that the percentage of haemoglobin and relative number of red corpuscles increases at high altitudes. Figure 3 represents the

results of Miss Fitz Gerald's observations on the haemoglobin percentages in persons permanently living at different altitudes. These observations were all made by the colorimetric method of determination which I introduced a few years ago, and with a carefully standardised instrument. It will be seen that just as the alveolar CO_2 rises with fall in the barometric pressure, so the haemoglobin percentage rises. It appears also that in an atmosphere with a higher oxygen pressure than air at sea level a decrease in the haemoglobin percentage below what is termed "normal" would occur. Here also, then, the setting of the regulation of haemoglobin percentage is altered by change in environment.

Using the carbon monoxide method of Lorrain Smith and myself, we found that on going to a high altitude not only the percentage amount, but also the total amount of haemoglobin in the blood is increased. The total volume of the blood seems to diminish at first, thus raising the concentration of haemoglobin; but after a few days the volume of the blood increases above normal. The regulation of total haemoglobin, concentration of haemoglobin, and blood volume are thus all dependent on the oxygen pressure of the air breathed.

I now come to what was the most striking result of the expedition. In the lungs the blood is separated from the alveolar air by an extremely thin membrane consisting of the "protoplasm" of flattened epithelial cells. Do these cells play any active part in the gaseous exchange between the air and the blood? Or does

the gas simply pass through them by ordinary diffusion? This question has been debated ever since a suggestion that they may play some active part was made by Ludwig forty or fifty years ago.

By means of an apparatus known as the aerotonometer, Pflüger and his pupils compared the pressure of CO_2 in the blood with that in alveolar air, and found it to be about the same. The aerotonometer was then improved by Bohr of Copenhagen, an old pupil of Ludwig. His results seemed to show that sometimes there is a lower pressure of CO_2, and a higher pressure of oxygen in the arterial blood than in the lung air, in which case an active secretion of oxygen inwards, and of CO_2 outwards, must be assumed. Fredericq then got results in favour of the simple diffusion theory. Last of all Krogh of Copenhagen improved the aerotonometer still further, and obtained results which again favoured the diffusion theory.

Meanwhile Lorrain Smith and I attacked the problem by a new method, which was suggested to me by the study of CO poisoning, and which eliminated certain sources of very serious error in the aerotonometer method of measuring the arterial oxygen pressure. When blood is saturated with a mixture containing both oxygen and CO the haemoglobin combines partly with CO and partly with oxygen in perfectly definite proportions depending on the relative pressures of the two gases, although in consequence of the far greater affinity of CO for haemoglobin the pressure of oxygen must be about 300 times greater than the

pressure of CO if the haemoglobin of human blood at body temperature is to be divided equally between the two gases. Clearly, therefore, if the pressure of CO is known, and also the percentage saturation of the blood after equilibrium has occurred, the pressure of oxygen can be calculated very exactly. We therefore breathed an exactly known small percentage of CO until the blood ceased to take up any more CO. We then determined the percentage saturation of the haemoglobin with CO, and the pressure of CO in the alveolar air. From these data we calculated the pressure of oxygen in the blood leaving the lungs. CO, as already mentioned, is, apart from its action on haemoglobin, a physiologically indifferent gas like nitrogen or hydrogen. It is not oxidised in the body, and it appears to pass freely by simple diffusion, like nitrogen or hydrogen. We could therefore assume that it diffuses freely into the blood and finally reaches a pressure which is the same in the blood of the lungs as in the alveolar air.

In the human experiments we reached the apparently unmistakable result that the oxygen pressure in the blood leaving the lungs is considerably higher than in the alveolar air, and that there is therefore active secretion inwards. Experiments with animals showed, further, that when the percentage of CO was increased so as to produce symptoms of oxygen want the evidence of active secretion became much more striking.

On repeating the human experiments at a later date we could not get the same results. Douglas and I then

improved the method further, and found that both in animals and in ourselves we got results wholly consistent with the diffusion theory, provided that the percentage of CO was kept very low. If sufficient CO was given to produce symptoms of oxygen want we got active secretion. We also got active secretion if oxygen want was produced in a group of muscles by fatiguing work. Nevertheless the human experiments gave on the whole a much less striking result than the former ones, and we could not at the time see any reason for this.

The apparent acclimatisation to oxygen want in mountaineers or persons living at high altitudes then attracted our attention, and in conjunction with Yandell Henderson the Pike's Peak Expedition (in which he, Douglas, Schneider and I participated, while Miss Fitz Gerald made observations at neighboring mining camps and towns) was planned. When we reached the summit of Pike's Peak (14,100 feet) we were all more or less blue in the lips, as were other newcomers. We then suffered in various degrees for two or three days from mountain sickness, after which the blueness entirely disappeared, although our alveolar oxygen pressures remained nearly the same as while the blueness was present, and our haemoglobin percentages had not as yet risen appreciably. After this we made a number of determinations of the arterial oxygen pressure, and each one without exception showed a considerably higher pressure of oxygen in the arterial blood than in the alveolar air. On the other hand, when we breathed during the experiment air rich in oxygen, so

as to bring the alveolar oxygen to about the normal at sea level, the difference between arterial and alveolar oxygen pressure almost disappeared. We then determined the arterial oxygen pressure in a newcomer who was still blue, but did not become mountain-sick till some hours later. It was very little above the alveolar oxygen pressure; but three days later when he was acclimatised and well, his arterial oxygen pressure was as high as our own. The mean result was that on Pike's Peak, after acclimatisation, the arterial oxygen pressure was during rest only about 13 mm. lower than at sea level, but was 35 mm. higher than the alveolar oxygen pressure. The complete absence of any blueness after acclimatisation was thus easily intelligible. The lungs were actively secreting oxygen into the blood, even during rest. Nevertheless the blueness reappeared temporarily during prolonged muscular exertions, as in a long climb. The lung epithelium could thus apparently be fatigued by the extra work thrown upon it.

As already seen, the lung epithelium is at all times capable of actively secreting oxygen inwards if the requisite stimulus arising from oxygen want in the tissues is present. But at high altitudes this capacity is greatly increased, and secretion goes on continuously after acclimatisation. The stimulus, moreover, is essentially the same stimulus as produces the changes in the regulation of blood alkalinity and in the haemoglobin of the blood. The stimulus is want of oxygen in some form; but how does the want of oxygen act? The haemoglobin of the arterial blood must, after

acclimatisation, be practically as fully saturated as usual; and considering the increase in the haemoglobin percentage the amount of oxygen in the arterial blood must be greater than normal. The oxygen consumption during rest was the same on Pike's Peak as at sea level, and the circulation rate, so far as our tests could determine it, was about the same.[1] Hence the oxygen pressure in the capillaries of the body would be somewhat higher than usual, and our unusually rosy color seemed to confirm this.

The most probable explanation as to how oxygen want produces these effects is that there is some substance which normally undergoes almost complete oxidation in the lungs at each round of the circulation. At high altitudes it escapes past the lungs in abnormal quantity in consequence of the lowered oxygen pressure, and probably also of the longer time required by the blood in the lungs to reach its full oxygen pressure. There are many facts pointing to the assumption that such a substance exists and that its presence in the blood is the source of various phenomena accompanying oxygen want.

The increase in the capacity of the lung epithelium to secrete oxygen is comparable to the increased efficiency produced in almost any organ by increased use. This increased capacity suggests the probable explanation of why in the original human experiments of Lorrain Smith and myself we obtained much more

[1] By more accurate tests Krogh and Lindhard have recently shown definitely that there is no alteration in the circulation rate after acclimatisation in a steel chamber.

striking results than in the later experiments of Douglas and myself. The earlier experiments were very long ones, and we were frequently exposing ourselves to oxygen want for many hours at a time. We had probably thus both become more or less acclimatised, so that our lung epithelium reacted very promptly to the slight oxygen want produced by the CO. In no other way can I explain the fact that we were able to breathe with complete impunity percentages of carbon monoxide which in subsequent isolated experiments were found to produce severe symptoms. The same criticism applies to my own early experiments as to the effects of definite percentages of CO. I was breathing CO every day often for hours, and doubtless had become highly acclimatised to want of oxygen, so that I underestimated the effects of CO on ordinary unacclimatised persons.

The part played by the lung epithelium in acclimatisation to want of oxygen makes it possible to understand how mountaineers have succeeded in reaching such great heights as they have. In his recent explorations in the Himalayas the Duke of the Abruzzi reached the height of 24,600 feet, the barometric pressure being only 312 mm. An unacclimatised person at this pressure is rapidly disabled completely; but the Duke's party did not suffer at all from mountain sickness or other serious physiological inconvenience. Dr. Filippi, a member of the expedition, in his account of it expresses the opinion that there is no such thing as mountain sickness due to rarefaction of the air. He was entirely deceived by the influence of acclimatisa-

tion, just as I was in the case of CO poisoning. On rereading Glaisher's account of his balloon experiences I was much interested to see that though he did not clearly understand the cause of mountain sickness he was quite convinced that repeated ascents produced acclimatisation. I have recently found that the effects of acclimatisation can easily be observed at ordinary atmospheric pressure in a closed chamber in which the oxygen percentage has been greatly reduced. An acclimatised person remains of a normal colour, and has no unpleasant symptoms, while an unacclimatised person soon becomes blue in the face, and may faint.

In acclimatisation to high altitudes there are evidently three factors—the increased activity of the lung epithelium in absorbing oxygen, the increased breathing, and the increased percentage of haemoglobin. Of these the last raises the oxygen pressure in the capillaries of the body, the second diminishes the fall in alveolar oxygen pressure, and the first raises the arterial oxygen pressure much above the alveolar oxygen pressure, whereas at sea level the arterial oxygen pressure is no higher, as a rule, than the alveolar oxygen pressure. The teleological significance of these changes seems clear, and a vitalist would naturally point to this as evidence of the interference of the vital principle. But we must analyse the facts further.

III

REGULATION OF THE ENVIRONMENT, INTERNAL AND EXTERNAL

We must now attempt to analyse the meaning of the fact that the pressure of oxygen may be, and at high altitudes always is, higher in the arterial blood than in the alveolar air. The layer separating the blood from the alveolar air in the lungs appears under the microscope as an extremely thin layer of moist albuminous material made up of flattened cells. In such a layer gases are soluble, just as they are in water; and it seems natural that the membrane should take up a gas in contact with it till it is saturated, and give it off on the other side if the gas pressure is lower there. During rest at sea level this is in fact what happens with oxygen, as well as with every other gas which has been tested. The gas passes so readily that complete equilibrium between the gas pressure in the alveolar air and that in the blood has occurred before the blood leaves the lungs; and the gas pressure in the arterial blood is thus equal to that in the alveolar air. For CO_2 and nitrogen this has been shown by the aerotonometer and other methods: for oxygen it has been shown by the carbon monoxide method, the aerotonometer method being unreliable for oxygen.

But at high altitudes the moist albuminous material

suddenly reminds us that it is alive: for it begins to do something which at once recalls living things when it delivers oxygen at a higher pressure than that at which it receives it. The passage of oxygen molecules is accelerated in the inward direction, and this acceleration applies to them alone, and not to other molecules, so it is selective. It does not occur in a non-living membrane, and its presence is evidently dependent, firstly upon the peculiarities of the living membrane, and secondly upon the presence of a special stimulus acting on the membrane. We know, also, that the specific peculiarities of living tissues depend upon the maintenance of their external environment. Hence we can say that the acceleration depends, not only upon the factors just mentioned, but upon the integrity of the general environment of the membrane—in more familiar words, upon its nutrition, temperature, etc., and upon the regulated removal of so-called waste products.

Active secretion of oxygen is not a new phenomenon in physiology. It is now over a century since the famous physicist Biot made the discovery that the gas in the swim bladder of deep sea fishes is nearly pure oxygen. The pressure of oxygen in sea water is only about a fifth of an atmosphere, and is doubtless less than a tenth of an atmosphere in the blood circulating outside the walls of the swim bladder. Yet inside the swim bladder the oxygen pressure in the case of deep sea fishes may be 100 atmospheres or more. It was shown in 1877 by Moreau that fishes secrete just sufficient oxygen into their swim bladders to bring

their specific gravity equal to that of the water at whatever depth they may be, or even to counterbalance the effects of a float or weight attached to them. I have in my library Ludwig's copies of Moreau's papers. They are an interesting clue to what was passing through his mind in suggestions he made as to the possibility of oxygen secretion in the lungs. It was discovered by Bohr that the oxygen secretion in the swim bladder is, like salivary secretion, under nervous control; and Dreser found that oxygen secretion can be excited by pilocarpin, a drug which also excites secretion in other glands.

The cells in the wall of the swim bladder which secrete the oxygen are columnar, and arranged like the cells of many other secreting glands, whereas the lung epithelium is extremely thin. Nevertheless the elementary structure of the lung is glandular, just as in the case of the swim bladder; and both lung and swim bladder are developed as outgrowths of about the same part of the alimentary canal. Before the lungs expand at birth the lung epithelial cells are cubical, and similar to those of other secreting glands. That the secreting cells should be thicker in the swim bladder is natural considering the enormously greater pressure against which the cells have to secrete.

The pressure difference against which oxygen can be secreted in the lungs is evidently quite limited. This is shown by measurements of the oxygen pressures in the blood in CO poisoning, when the stimulus to secretion is pushed up to what is presumably a maximum. If there were no limit the secretion of oxygen would

afford complete protection, similar to that produced, as already described, when the oxygen pressure of the arterial blood is greatly raised by placing the animal in compressed oxygen. The pressure difference against which oxygen can be secreted in the lungs is also dependent on the pressure of oxygen in the alveolar air. When this becomes very low the pressure difference is diminished; and the flow of oxygen may be actually reversed if the alveolar oxygen pressure is low enough. A similar reversal seems to occur in the case of the swim bladder; and sometimes the air in the swim bladder seems to be utilized as a store of oxygen, drawn upon when the blood is insufficiently oxygenated by the gills. Possibly the active secretion current is reversed in direction.

Let us now compare the secretion of oxygen with that of other substances by other secreting glands. In the case of the kidney, various salts and crystalloid substances, particularly urea, are actively secreted by the gland cells, so that their concentration in the urine is far greater than in the blood. For instance there is usually about ten or fifteen times as much urea in a given volume of urine as in the same volume of blood, and when the kidneys secrete sugar there may be twenty or thirty times as much sugar in the urine as in the blood. Here then we have other cases of the flow of one kind of molecules being accelerated in one direction. In the kidney secretion we also see that the acceleration may be in either direction, and that it depends upon the molecular concentrations in the liquids on the two sides of the secreting

cells. We cannot by any means force up indefinitely the concentration of a substance in the urine; and if the concentration in the blood of a constituent of urine falls below a certain point, the secretion of that constituent ceases. If, for instance, the concentration of sodium chloride in the blood falls below normal, sodium chloride disappears at once from the urine, though it is still abundant in the blood. Sugar is not secreted at all by the kidneys unless its concentration in the blood exceeds the normal. In both these cases the acceleration is in the opposite direction to secretion, so that the passage of these substances is actively prevented.

The secretory action of the kidneys is strikingly dependent in other ways on the environment of the secreting cells. Their activity is easily abolished by want of oxygen, for instance, or by minute doses of various poisons, and may be increased by the administration of various drugs.

When we look at other cases of secretion we find that often enough some one or other of the substances secreted is not present as such in the blood, but is formed in the secreting cells. Instances of this are the formation and secretion of hippuric acid in the kidney, of urea, bile acids and pigments in the liver, or of casein and milk-sugar in the milk glands. The constituents or precursors of these substances are taken up from the blood, and their combination or decomposition takes place in the secreting cell. The resulting substances are then accelerated outwards from the secreting cell to the duct, while their precur-

sors are accelerated inwards from the blood into the cell.

The step from secretion to the processes which we commonly designate as cell nutrition or cell respiration is only a short one. The microscopic study of secreting cells shows that the substances secreted, or their immediate precursors, are often stored up for some time until the moment for their discharge comes. This storage is comparable to ordinary growth. In his famous book on Secreting Glands, published in 1830, Johannes Müller expressed the opinion that secretion and growth are merely different aspects of one kind of activity; the sole difference being that in secretion the product is removed, while in growth it remains. Müller was a vitalist, and his ideas on secretion were for the time swept away by the whirlwind of mechanistic speculation which passed over physiology about the middle of the last century; but in the main he was right. We now know that even in ordinary nutrition nothing remains still and inactive. Living structure is really alive and full of molecular activity: it is the expression of the directions and velocities which this activity takes. Substances are constantly being taken up from and given off to the environment; and even when these substances do not seem to be used up in adult nutrition, as for instance in the case of inorganic salts, there is a constant molecular interchange between the cell and its environment. This is proved by the fact that, as was first shown in particular by Sidney Ringer, the tissues are

extremely sensitive to the slightest changes in the concentrations of inorganic salts in their environment.

Cell-secretion, cell-respiration, and cell-nutrition are clearly only different aspects of the same whirl of molecular activity. Where secretion or nutrition seems to be stationary, there is in reality only a balance between ingoing and outcoming molecular streams. Instances of this occur when the kidney is not secreting chlorides, or when no oxygen is passing into or out of the swim bladder, or when all external activity is latent, as in a dry seed. The apparent stand-still is similar to that in a blood corpuscle in a test tube of blood half saturated with oxygen, when the stream of oxygen molecules entering the corpuscle is balanced by the stream leaving it. The unstable oxyhaemoglobin molecules in the blood corpuscle are constantly losing oxygen molecules and as constantly regaining others, so that the half saturation of the blood corpuscle with oxygen represents the average of the gains and losses of the haemoglobin molecules. This we can understand. But what conception can we form of the molecular streaming in the living cell and the strange co-ordination which the different molecular streams exhibit? I have tried to indicate how this problem, which will be followed up in the next lecture, rises directly out of the fact of oxygen secretion. But meanwhile we must follow further various other facts relating to respiration.

The evidence existing at present is strongly against the theory of active secretion of CO_2 outwards by the lung epithelium. Krogh's experiments gave very defi-

nite results on this point. In any case we should hardly expect to meet with active secretion of CO_2, considering that the breathing is regulated by the CO_2 pressure in the arterial blood, and that the oxygen supply to the lungs is dependent on this regulation. During very excessive muscular work it seems to be the oxygen supply to the body that first begins to fail. This is indicated by the fact that in very hard work the alveolar CO_2 percentage begins to fall, and may even become lower than during rest.

The delicate and exactly regulated organization by which CO_2 is removed from the blood in the lungs, and oxygen supplied, would quite clearly be of little service to the body if there were not also a regulation of the circulation of blood so as to keep the removal of CO_2 from the body tissues and their supply of oxygen correspondingly steady. We must now, therefore, consider what is known as to the circulatory regulation. Knowledge on this subject is unfortunately still very fragmentary, mainly because physiologists have failed to appreciate the delicacy of organic regulation, or have even lost sight of it altogether when investigating various matters of detail.

The blood brings to the tissues the various substances required for their normal life, and removes from them substances which are then carried to other tissues or to secretory organs. It is also a carrier of heat. The carriage of oxygen and CO_2 is thus only one of its many functions. Hence we must not expect that the circulation will be solely regulated with reference to the carriage of these gases. Bernard noticed

that during active secretion of saliva by a salivary gland the venous blood issuing from the gland was of a bright red colour, owing to quickening of the circulation; and Barcroft found that owing to the quantity of liquid and CO_2 abstracted from the blood during salivary secretion the absolute quantity of oxygen in a given volume of the venous blood may be greater, while that of CO_2 may be less, than in the arterial blood. As one constituent or another assumes greater or less importance in the exchange between blood and tissues we must expect the circulation to vary accordingly, and there is no doubt that it does so vary. The gaseous exchange is, however, everywhere of such immediate importance that we may be sure that the circulation is to a large extent regulated with reference to the gaseous exchange.

The flow of blood through any part of the body depends partly on the difference in blood pressure between arteries and veins, and partly on the resistance to the flow of blood from the arteries through the capillaries to the veins. Now the difference between the pressures in the main arteries and veins at any given body level is nearly constant. This is so because, if we neglect such part of the pressure as is accounted for by the mere height above or below the heart, the pressure in the larger arteries is high, and nearly constant, while that in the veins is so low as to be insignificant in comparison with the arterial pressure. Hence it is through variations in the resistance that variations in the rate of flow are brought about. But variations in the resistance depend almost entirely, so far as we

know, on variations in the calibre of the small arteries, caused by variations in the degree of contraction of the circular muscular coat with which they are provided. It was discovered by Bernard that the muscular coat is under the control of the nervous system through the vaso-motor nerves supplying the arteries. It is apparently, therefore, by these nerves that the rate of blood flow is controlled, though it may be that there is also some non-nervous means of control, due to the direct local action of chemical stimuli.

But how are the vaso-motor nerves themselves excited? It is known that there is a centre in the medulla oblongata in connection with afferent nerves by the excitation of which a widespread reflex augmentation or inhibition of the impulses which are constantly passing from the centre to the arteries is brought about. When this centre is destroyed or its connections severed there is also a great general fall in arterial blood pressure owing to dilatation of the arterioles. But the action of this centre does not explain the local regulation of blood flow in different organs in accordance with local requirements. That such local regulation occurs is known from observations of the local blood flow; it is known, also, that there are subordinate nerve centres controlling local blood supply, the response of these centres being to afferent impulses passing to the centres along locally distributed nerve-fibres. The afferent nerve-endings are apparently excited by excessive accumulation of products of metabolism or by deficiency of the substances used up. It may be that the products of

metabolism act directly on the walls of the small arteries, but it is somewhat difficult to imagine how this could be brought about.

Be this as it may, there is no doubt that in some way the blood flow through different parts of the body is regulated in accordance with the requirements of each part, so that during extra activity in any part there is a correspondingly greater blood flow. Measurements of the circulation through various organs have been recently carried out, in particular by Barcroft and his associates, in connection with simultaneous measurements of the oxygen consumption in these organs. The general parallelism between increased oxygen consumption and increased rate of circulation is evident from these measurements.

To measure the circulation rate of the body as a whole by direct means is impossible without operative procedures which hopelessly disturb the physiological conditions. Indirect methods have, however, been introduced recently. One of these is to measure in the lungs by a rapid method the gas pressures of the whole venous blood entering the lungs. From the gas pressures the gas contents can be calculated, as already seen, and a comparison of the venous with the arterial gas contents gives a direct measure of the ratio between oxygen consumption or CO_2 production and blood flow. If the amount of oxygen being taken up and CO_2 given off at the time is known, the blood flow itself can also be calculated. Using this method in man both Dr. Boothby of Boston and I have found that the blood flow increases proportion-

ately with the consumption of oxygen or production of CO_2. Accordingly the differences in gas contents between arterial and venous blood vary far less than does the rate of metabolism. To judge from observations on myself, the venous gas pressures are practically constant during rest. The differences in gas pressures between the two kinds of blood differ only slightly with great differences in the consumption of oxygen. The gross regulation of the circulation is of such a nature as to keep the venous gas pressures nearly steady, while regulation of breathing keeps the arterial gas pressures nearly steady. Hence although the pressure of oxygen is lower, and that of CO_2 higher, in the venous than in the arterial blood, yet in each case the pressure is relatively steady. How the peculiar forms of the dissociation curves of oxyhaemoglobin and of the compounds which CO_2 forms in the circulating blood contribute toward this result has been explained in the previous lecture.

The rate of the total circulation depends of course on the amount of blood pumped round by the heart; and it might seem at first as if the heart were the prime regulator of the circulation. This mistake has, in fact, been made by many physiologists through failure to look at physiological knowledge as a whole. Under normal conditions the heart simply maintains the pressure in the large arteries by pumping more, or less, blood according to the rate at which the blood-vessels allow blood to escape. It is thus the state of contraction of the blood-vessels in the various parts of the body that governs the rate of circulation.

The heart itself could not act as the prime regulator of the general circulation rate without producing great variations in the arterial blood pressure, so as to drive the blood at varying rates through the resistance of the arterioles. These great variations do not normally exist, as is easily shown by measurements of the blood pressure. Nor would primary regulation of the blood flow by the heart be of much use, since any regulation brought about in this way would apply to all parts of the body alike, whereas the increased or diminished requirements for blood are purely local, according as one part or another of the body is in a state of greater or less functional activity.

The heart is known to be provided with two sets of nerve fibres through which its action is controlled, and which reach it as branches of the vagus and the sympathetic nerves. The vagus fibres, when excited, exercise an inhibitory action, reducing both the frequency and the strength of the heart beats. The very significant discovery of this inhibitory action was made known by the brothers Weber in 1845. Excitation of the sympathetic fibres, discovered by von Bezold in 1862, increases the frequency and strength of the heart beat.

The inhibitory influence of the vagus fibres is at once increased reflexly if the blood pressure in the aorta (the great artery leaving the heart) rises, and diminished if it falls. As an additional preventive to excessive arterial blood pressure there is a further nervous connection through which excessive rise of blood pressure causes reflex dilation of the arteries

of the intestinal area, so that the pressure is relieved. The accelerator or augmentor nerve fibres are, according to recent investigations by Bainbridge, brought reflexly into action by rise in the pressure in the great veins opening into the heart.

It is clear also that the amount of blood pumped by the heart must depend on the supply of venous blood, and there is experimental evidence, first brought by Yandell Henderson, that fall in venous blood pressure may actually limit the heart's output of blood, so that the frequency of the heart beats is no measure of the rate of circulation, just as the frequency of breathing is no measure of the amount of air breathed. In this connection the state of contraction or relaxation of the walls of the veins is a factor of great importance. Yandell Henderson's observations, part of which are not yet published, though communicated to me verbally, seem to indicate that contraction of the peripheral veins dams back blood in the capillaries. Less blood passes on to the great veins and the pressure in them becomes insufficient for the adequate filling of the heart.

The immediate causes of contraction of the walls of the veins are not yet exactly known; but the observations of Yandell Henderson on the influence of the pressure of CO_2 on the circulation are extremely significant. When the body is greatly impoverished in CO_2 by excessive artificial respiration the circulation fails, apparently from an inadequate supply of blood to the heart. The simplest explanation of the facts seems to be that the tonic contraction of the walls of

the veins is dependent inversely on the pressure of CO_2 in the blood. Accordingly deprivation of CO_2 leads to contraction of veins, with resulting congestion of capillaries and a decrease in the volume of the blood in active circulation equalling that induced by haemorrhage. On the other hand, any condition, such as muscular work, which is accompanied by increased pressure of CO_2 and diminished oxygen pressure in the blood leads to dilation of the veins, and consequent increased rapidity in return of blood to the heart, with increase of venous blood pressure. What part, if any, the nervous system plays in this process, or what other substances beside CO_2 are of influence, there are as yet no data to enable us to decide. From the circulatory phenomena in asphyxia due to breathing air deprived of oxygen (when there seems to be a great increase of both arterial and venous blood pressure) we may, however, infer that want of oxygen is one such factor.

The state of tonic contraction of the unstriped muscle such as is found in the walls of blood vessels depends, doubtless, on many other conditions besides nervous control. Recent investigation shows that one of the most interesting of these conditions is the supply to the blood of adrenalin, a specific product of the activity of the suprarenal glands. This discovery illustrates in a striking way the interdependence of different parts of the body—a subject to which I shall presently return.

When we review what is known as to the regulation of the circulation it is evident that it is not primarily

the heart, or the nervous system, which is the regulator, but the metabolic activity of the body as a whole. The blood circulates at such a rate as is sufficient to keep its composition approximately constant at any part of the body, and the rate of flow seems to be greater or less at any one part in proportion as the causes tending to disturb the composition of the blood are greater or less at the same part. Among the chief of these causes is consumption of oxygen and liberation of CO_2. Hence the circulation rate is to a large extent determined by the activity of the latter processes, and varies, just as the breathing varies, in such a way as to keep the gas pressures in each part of the body approximately constant.

This is not an isolated fact in physiology. Claude Bernard pointed out in 1878 in his *Leçons sur les phénomènes de la vie* that the blood is a fluid of remarkably constant composition, and practically provides a constant internal environment for the living cells of which the body of a compound organism is made up. He seems to have been led to this conclusion by his well-known studies on the sugar of the blood. While still under the influence of the old ideas of the blood as a very variable liquid he began his investigations under the expectation that the amount of sugar in the blood would vary in proportion to the sugar absorbed by the intestine, and would disappear when no sugar or other food was taken. To his astonishment, however, he found sugar still abundantly present in the blood during starvation, and that any increase which he could produce in the blood

sugar, by feeding with sugar or sugar-forming material, was slight. If sugar was introduced in very large quantities it was simply excreted in the urine. He then discovered the part played by the liver in regulating the concentration of sugar in the blood, and he soon saw that other conditions of life are similarly regulated. This led him to express the opinion that "all the vital mechanisms, varied as they are, have only one object, that of preserving constant the conditions of life in the internal environment."

Bernard's teaching has been to a large extent forgotten or obscured in masses of unconnected detail, but in reality has been strikingly confirmed by the progress of physiology since his time, and not merely in connection with the physiology of respiration. Let us look at some of the facts.

I will refer first to the regulation of the amount of water in the blood, since this is a subject which Dr. Priestley and I have quite recently been investigating. It is well known that when large quantities of water are drunk an increasing secretion of urine follows. This increased secretion is evidently the expression of what may be called metaphorically the effort of the body to rid itself of unnecessary water. We made a study of the water excretion by the kidneys on the same lines as we had followed in studying the regulation of breathing.

The increase in secretion of urine a short time after drinking a large quantity of water is very remarkable, the increase being usually to about twenty-fold or more, so that as much urine may be secreted in an hour

as is usually passed in twenty-four hours. The urine consists of nearly pure water, containing only what are relatively speaking traces of the ordinary urinary constituents. Now this fact in itself is very remarkable. The blood plasma contains a considerable amount of sodium chloride, and usually there is more sodium chloride in the urine than in the blood plasma; but in the urine secreted after water drinking there is hardly any sodium chloride. The sodium chloride is held back, while the water passes in large quantities.

What we wished, however, to investigate specially was the change in the blood to which the increased secretion was a response. One would naturally look for evidence of dilution of the blood by the water; and dilution would be shown by a diminution in the percentage of haemoglobin, since this can be measured with great accuracy and none of the haemoglobin is excreted or destroyed. There was, however, no diminution in the haemoglobin percentage during the period of most rapid excretion of the urine. Evidently the blood was not diluted, in spite of the fact that sometimes a volume of liquid exceeding that of the whole of the blood had been carried by the blood from the intestines to the kidneys in the course of a few hours.

Dr. Priestley then determined the electric conductivity of the blood serum, as this gives a very sensitive measure of the concentration of salts in the blood. The result was that there was a very slight but constant diminution of the conductivity during the extra secretion. This proved that though the blood

was not diluted as a whole there was a very slight diminution in the proportion of salts to water. Some of the salts had presumably passed from the blood into the water contained in the intestine, with the result of decreasing very slightly the percentage of salts in the blood. The enormous extra secretion of water was the response of the kidney to this very slight change. At the end of the extra secretion the conductivity had returned to normal.

When, instead of pure water, a dilute solution of sodium chloride in water was drunk, there was again an enormously increased secretion of urine. This was accompanied by an easily measurable dilution of the blood, and the slightly increased conductivity showed that not only water but also salt was in slight excess over the other constituents. Both water and salt pass out in the urine, though at first very little of the salt goes, indicating that the excretion of the extra water is a process independent of the excretion of the extra salt.

After prolonged sweating, so as to deprive the body of much water, the urine becomes very scanty and concentrated. But in this case the blood may not become measurably more concentrated, even though the body has lost by sweating a quantity of water nearly equal in weight to the whole of the blood.

The regulation of the proportion of water in the blood can thus be placed side by side as regards delicacy with the regulation of its reaction and components: its pressures of CO_2 and oxygen, its percentage of sugar, urea, salts, and albuminous substances. Had

we the means of determining the innumerable other substances present in blood we should doubtless discover a similar delicacy of regulation.

All parts of the body seem to participate in this regulation. We have already seen how this is so in the case of breathing, circulation, and the activities of the kidneys and liver. Recent investigations reveal the same thing in connection with such organs as the thyroid, suprarenal and pituitary glands. The regulation of the blood temperature in warm-blooded animals is one of the most striking instances. During muscular exertion the heat production in the body may be increased six or eight fold, but the temperature of the arterial blood is only increased by a quite insignificant amount, as increase in the skin circulation and in the evaporation of moisture from the body compensates for the increased production of heat; while if the external temperature is varied the effects on the body temperature are also compensated by changes in the skin circulation and evaporation, and by variations in the heat-production of the body. The regulation is through the central nervous system, and is exactly comparable to the respiratory regulation of the blood.

The phenomena observed after bleeding or transfusion of blood are of great interest in this connection, and have recently been studied in some detail by Boycott and Douglas, using the new method available for determining the total haemoglobin and total blood volume in the body during life. After bleeding the total blood volume in the body is very rapidly recov-

ered. The capillary walls seem to take up the liquid and solid material required, and this material is at the same time reconstituted so as to produce blood plasma of normal composition. But the regeneration of the lost red corpuscles is a much slower process, so that the new blood is at first very deficient in corpuscles, and several weeks may be needed for their complete regeneration. If, however, the bleeding is repeated at intervals the process of regeneration of corpuscles becomes faster and faster, so that frequent re-bleedings can be easily borne by the animal. Similarly, if blood is transfused from one animal to another the liquid part of the injected blood is rapidly eliminated, but not the red corpuscles. Hence for a considerable time the blood is abnormally rich in corpuscles. If, however, the transfusion is several times repeated the excess of corpuscles disappears more and more rapidly. The capacity of both the blood-forming and the blood-destroying process is thus increased by use. Young red corpuscles are known to be formed in the bone-marrow, while the products of destruction of red corpuscles are found in the liver and excreted in the bile. The capacity for formation or destruction of corpuscles is thus associated with the physiological activity of these parts of the body, but this activity is evidently regulated with great exactitude.

If we look, not merely at the internal, but also at the external activities of an organism Claude Bernard's generalisation seems still to hold. The co-ordinated activities of the senses and muscular system are mainly directed to the end of providing for nutrition. Behind

and controlling these activities are the instinctive excitatory or inhibitory impulses which we know as hunger, thirst, satiety, discomfort and comfort. These impulses may be regarded as expressions of the many-sided activities which are all directed towards keeping the internal and external environment constant.

On examining the forms which vitalism has taken we find that the vital principle has been commonly regarded as an influence which resists the tendencies of physical and chemical influences to produce disintegration of the body structure. The great chemist Liebig, for example, looked at the oxidation processes in the body from this point of view, and regarded the vital force as something protecting the structure of the body from becoming the prey of oxidation.

But let us examine the whole matter more closely. It is quite evident that the activities of the various parts of the body are not merely in the direction of maintaining the internal environment constant, but also in the direction of disturbing it. The muscles by their activity may be engaged in obtaining nutriment for the body, but they are also consuming this nutriment wholesale. The kidneys are not merely removing superfluous or harmful material from the blood, but they, too, are consuming oxygen and other substances, and producing CO_2 and other metabolic products. This is also true even of the lungs and the respiratory centre, for the respiratory centre is violently excited by the products of its own oxidation if its blood supply is checked. Now when we examine those activities which tend to disturb the internal

environment we find that they are no less persistent than the activities which maintain its constancy. The muscles still continue to consume oxygen and form heat, even though they are for the time at rest, and though all loss of heat from them is prevented. The kidneys still absorb oxygen when they are not secreting. In a sense, too, they are still secreting, even when there is no external sign of secretion, for the absence of external secretion is only the expression of an equal balance between constant intake and constant output of material. When the muscles and sense-organs are not at work on the getting of food, or in other conservative processes, they seem to employ themselves otherwise—for instance in what we know as play.

No physiological facts are more significant than those relating to the persistence of the fundamental metabolic phenomena. In Liebig's time it was observed that the excretion of urea rises and falls with the amount of nitrogenous food consumed, although during starvation there is still a certain minimum excretion of urea. This was interpreted as signifying that all superfluous nitrogenous food simply falls a prey to oxygen, and is wasted. When, however, the facts were further investigated it was found that within wide limits the oxidation in the body does not increase or diminish with increase or diminution of the nitrogenous food consumed. Even after long starvation the oxygen consumption per unit of body weight is practically undiminished during rest. When more nitrogenous food is consumed in the body and oxidised to urea, less fat or carbohydrate is consumed.

Rubner showed that nitrogenous food, fat, and carbohydrate are substituted for one another as material for oxidation in exact proportion to the energy which they yield in the body. The sum of this energy per unit of body weight remains constant during rest, whether food is given or withheld. Even when loss of heat is prevented as far as possible, the oxidation processes in the body remain sensibly constant in spite of prolonged deprivation of food. The diminished oxidation of nitrogenous material during starvation depends simply on the fact that the body stores its energy-forming material mainly as fat, and consequently uses up mainly fat during starvation. When all the fat is exhausted there is again, before death from starvation, a great increase in the oxidation of nitrogenous material. This latter fact adds new emphasis to the persistence of the oxidation processes.

The internal environment which is maintained so constant is in reality the expression of a balance between activities which disturb and activities which restore it. When we speak of "the function" of an organ and regard this function as what it does to restore the internal environment we are thinking in terms of an imperfect and misleading conception of what that organ is, and what an organism is: for we are thinking of only one side of its activities to the exclusion of others which are just as important. To put this into philosophical language we are thinking abstractly, or regarding only a part of the reality we are dealing with. We can speak more correctly of

the function of a part of a machine: for this part does nothing else than fulfil its function, provided the machine is assumed to be perfect and stable. In a living organ however we are dealing with something of which the functions, if we speak of functions, are endless, since the activities are endless, constantly seeming to grow in number as we investigate further. Its true function, to the eye of a physiologist, is to maintain these endless activities in balance with the endless activities of other organs, and not merely to perform one specified action.

It is evident that the balancing of molecular activities on which the maintenance of the internal environment depends is centred in the bodies of the cells which make up the living tissues. The composition and volume of the blood are the outcome of their joint active or passive influences. We are thus brought back to the problems of cell-secretion, cell-respiration, cell-nutrition, cell-movement, cell-heat-production—problems which, as we have already seen, are only different aspects of one problem—that of what may be called cell-metabolism. Living cells are the nodal points of the molecular and ionic streams of which one outcome is the constant internal environment. The living cells are the seat of the molecular or ionic accelerations or retardations which manifest themselves in secretion, and of the main chemical changes which express themselves as metabolism in its varied outward forms. When we concentrate attention exclusively on some one detail of cell-metabolism we

necessarily lose sight of the co-ordination which expresses itself in the persistence or constancy of cell-structure and of the internal environment. But the co-ordination is plain when we look at the phenomena as a whole, and becomes more and more detailed the more we penetrate towards the living tissue elements.

The phenomena of breathing have turned out to be the outward expression of one side of the co-ordinated activities which we lump together under the name of metabolism. Our conception of breathing depends, therefore, on the ideas we can form of this metabolism.

At the conclusion of this lecture let us glance at what may be called physiological causation. All physiological activities seem to be in response to external or internal causes or "stimuli." Physiologists speak of a "stimulus" rather than a "cause," since the word "stimulus" expresses the fact that other external conditions determine the response besides the stimulus itself. The response depends, not merely on the strength of the stimulus, but on the "excitability" of the responding tissue. In other words the response may be partially or wholly inhibited or greatly increased by varying conditions in the environment of the tissue. The character or direction of the response may also depend on these conditions, or even on the strength of the stimulus itself.

As has been already shown, the respiratory centre normally responds with rhythmic inspiratory and expiratory responses to the stimulus of a very minute

diminution in the alkalinity of the blood. But the duration of the responses is modified by stimuli dependent on inflation or deflation of the lungs, while the extent of inflation or deflation which is effective in this direction depends on the strength of the primary chemical stimulus. The effect of this primary stimulus is also dependent on the supply of oxygen to the centre, and is increased if the oxygen supply is defective. If we prefer to put the matter in another way, deficiency of oxygen is itself a stimulus to the centre, but is dependent for its effect on the reaction of the blood, and is quite ineffective if the alkalinity increases slightly. Other substances, such as morphia, chloral, or chloroform, diminish the responses of the centre to a given diminution in blood alkalinity; and from the analogy of other tissues we may be quite sure that slight changes in the concentration of the salts and other substances in the blood, or changes in its temperature, must similarly affect the response of the centre in one direction or another. We can even imagine the respiratory centre responding, not, as normally, to changes in alkalinity, but to changes in the concentration of, say, calcium salts.

When we seek for the "cause" of a physiological reaction we are thus landed in a maze of contributory causes. We can wander in this maze for as long as we like, but there is no end to it. So far as it is possible to judge, those who seek in physiological phenomena for the same kind of causal explanations as can usually be assigned in connection with inorganic phe-

nomena have no prospect but to remain seeking indefinitely, unless they cut the knot by relapsing into vitalism.

But is there no scientific clue through this apparent maze? Does not the element of regulation which, as we have seen throughout, is the outstanding feature of biological phenomena, furnish the clue? In the next lecture this question will be discussed.

IV

ORGANIC REGULATION AS THE ESSENCE OF LIFE. INADEQUACY OF MECHANISTIC AND VITALISTIC CONCEPTIONS

In the previous lecture we saw that the internal environment is kept constant as the result of a continuous and extraordinarily delicate regulation of the balance between opposing activities. What general conception can we form of this balancing process?

An obvious possible interpretation is that each of the various organs concerned in the balancing process has such a physical and chemical structure that it reacts to a given small deviation in the internal environment so as to prevent further deviation in this direction. As the combined result of the reactions of all the organs the internal environment as a whole remains constant. It is evident, for instance, that the respiratory centre reacts to very small differences in the hydrogen ion concentration in the blood, in such a way as to prevent larger differences from occurring. The temperature-regulating centre reacts to small differences in the blood-temperature. The kidneys react in a similar way to very small differences in the concentrations of water, urea, and numerous other inor-

ganic or organic substances. The organs, such as the liver, or fat-containing tissues, in which material is stored, appear to behave similarly; and we have now every reason to believe that we should find the same regulating activity in every organ or part of the body if our methods of investigation were sufficiently delicate, and we knew the small differences to be detected. In every direction the progress of physiology and pathology is revealing the astounding delicacy and complication of the regulating processes.

Up to a certain point we can rest satisfied in the idea that the regulation of the internal medium depends upon the specific structures and corresponding reactions of the organs which bring about the regulation. But the more we learn about the delicacy and complexity of the regulating processes, the more definitely does a difficulty appear. It is not for nothing that the body regulates its internal environment so exactly. The investigations which reveal the exactitude of the regulation reveal equally its fundamental importance to the nutrition and normal working of every part of the body. The organs and tissues which regulate the internal environment are themselves centres of nutritional activity, dependent from moment to moment on their environment. They are constantly taking up and giving off material of many sorts, and their "structure" is nothing but the appearance taken by this flow of material through them. The fact has already been referred to that when the supply of oxygen to the tissues is seriously restricted the result is not merely a slowing down of activity, but actual

structural change. Similar structural change is known to result from many other slight alterations in the composition of the blood; and so far as the evidence goes, it points to the conclusion that the specific structure of every part of the body depends upon the specific composition of the blood, as well as on the influence of the adjacent tissues or external environment. The regulation by the tissues and organs of the internal environment is thus only their regulation of their own structure and activity.

A living organism has, in truth, but little resemblance to an ordinary machine. The individual parts of the latter are stable, within very wide limits of immediate environment, and in no way dependent on whether the machine is in action or at rest. This stability does not exist in the living organism. We find, it is true, that the living organism may react in a constant manner to a given change, just as a machine might do; but on investigation this turns out to be because the internal environment is at the time constant or "normal." Were it otherwise not even the superficial resemblance would hold. As we have seen, for example, in the case of the respiratory centre, this reasoning applies to nervous reactions just as much as to other physiological reactions.

It seems clear, therefore, that we cannot base our explanation of the constancy of the internal environment on the structure of the organs which regulate it, since closer examination shows that the "structure" of these organs is itself dependent on the constancy of the internal environment. We are only reasoning

in a circle when we attempt to explain the constancy of the internal environment by the specific characters of bodily structure. The fact is that both the internal environment and the "structure" of the body remain approximately constant; but of this fact no explanation has been reached.

The explanation cannot lie in the external environment, since this is far less constant than the internal environment, which it constantly tends to disturb. It is nevertheless the case that the external environment, in so far as it is in relation with the organism, exhibits constancy. The composition and amount of the food and drink in the alimentary canal approximate to a certain average; the partial pressures of oxygen and carbon dioxide in the air which is in contact with the body, in the lungs, remain also nearly constant under most conditions; the impressions transmitted inwards from without are similarly more or less constant on an average; and excesses of heat or cold are generally avoided. Just as the internal environment seems, at first sight, to be regulated by the organism, so also does the external environment, but to a far less intimate extent. In both external and internal environment, the regulation is the expression of a balancing of opposing processes of loss or gain of material or energy; and the processes involving loss are no less persistent on the whole than those involving gain.

It is mainly through the nervous system that the body is, in the higher organisms, in relation with the external environment. When we look broadly at the

activities of the nervous system, they are evidently of such a character that the external environment, is regulated just as is the internal environment. It is in virtue of these nervous activities that the stream of material and energy which is constantly entering and leaving the body is kept so nearly constant. Appetite and satiety, muscular activity and fatigue, external temperature and heat loss, external light or sound or other sensory stimuli and the responses to them, are balanced against one another through the nervous system. We cannot draw any complete line of separation between the regulation of the internal and that of the external environment; for evidently the one is complementary to, and indispensable to, the other. Regulation of the external environment is in fact only the outward extension of regulation of the internal environment, and the ultimate dependence on the external environment of the organs which regulate it is as evident as their more immediate dependence on the internal environment. Deficiency or excess in normal stimuli, normal nutrition, normal temperature and respiratory exchange, are as important to the nervous system as to other organs. The environment determines the nervous reactions, and the nervous reactions the environment, but the constancy or regulation which emerges is still unexplained. The conception of an organism as a mere labile structure which determines, and is at the same time determined by, its environment is unsatisfactory, for the reason that the specific persistence of life is left unaccounted for. The facts must be examined more closely.

We have seen that it is characteristic of an organism to react towards disturbing influences in such a way as to maintain approximate constancy in its structure, internal environment, and even external environment. If the disturbance is merely slight, temporary, and of normal occurrence, a simple and normal compensating reaction occurs, and everything seems afterwards to return again to its former state. But if the disturbance is abnormal, or continued, a significant fact emerges more and more clearly: for new and apparently original compensatory reactions arise, or an ordinary compensatory reaction is greatly strengthened, or supplemented. The new reaction is accompanied by corresponding structural change, which remains to a greater or less extent after the cause of disturbance has disappeared.

We are now in contact with facts of a sort which tend to lie in the background in connection with the customary laboratory physiology of the present time, but which spring into such prominence in common everyday observation, and particularly in connection with clinical medicine and surgery, as to make the physiology of ordinary text-books appear somewhat unreal. In the course of these lectures various facts of the class here referred to have been described. The Anglo-American expedition to Pike's Peak was undertaken with the express object of ascertaining to what extent, and in what manner, the body adapts itself to a continued diminished concentration of oxygen in the air breathed. The results showed that new adaptations, apart from those demonstrable during

short exposures, come into play during prolonged exposure to a diminished oxygen concentration. Another striking instance of the same class of fact is in connection with the effects, referred to in the previous lecture, of repeated bleeding or transfusion of blood, as observed by Boycott and Douglas. After repeated bleedings the animal replaces the lost blood with increasing rapidity. After repeated transfusions it gets rid of the excess with corresponding readiness. Presumably in the one case there is an increase in the amount or activity of the blood-forming tissues, and in the other an increase of the blood-destroying tissues.

We have only to look round, outside the limits of the present conventional physiology, in order to find innumerable instances of similar facts. Striking examples are afforded by the phenomena of immunity to attacks by micro-organisms, and to the action of poisons. Still more remarkable instances are those connected with the recovery of function or reproduction of tissue after injury or disease, or even complete loss of parts of the body. In the higher organisms reproduction of lost parts is a less prominent feature than in lower organisms, but indirect restoration of function is a fact of common observation, and is in some ways more significant and remarkable.

It thus appears that with disturbance of external or internal environment, or living structure, the reactions which occur are, whether immediate or gradual, of such a character that the organism adapts itself so as to maintain, not merely its existence as a structure, but

also its characteristic activities and relations to external environment. The life of the organism may be modified, it is true; but in the modification it retains all its essential characteristics, so that its identity is unmistakable. It persists actively, and not merely passively. Without active adaptation everything would tend to go from bad to worse, as in the case of an untended machine.

If the internal environment is interfered with, as by loss of material or the introduction of foreign or superfluous material, the occurrence of adaptive changes is evident. If the structural elements of the body are interfered with, as in local injuries or infective attacks, processes of repair soon manifest themselves at the damaged point: the leaky and paralysed blood-vessels become functionally competent again: exuded material is absorbed; and the altered and functionally abnormal tissue elements and nerve-endings return to a normal condition. We are gradually coming to realise how intensely delicate is the adjustment of immediate internal environment and organised structure involved in the existence of normal conditions, and the more we realise this the more significant appears the process of recovery or adaptation. Another point with regard to this process is that if injury has not gone too far the restored tissues have become more resistant. It is, for instance, a well-known fact that the blisters and other signs of local injury produced by unaccustomed hard use of the hands or feet are no longer produced after "hardening" by practice. The tissues have become adapted to the new conditions, and the adaptation is

no mere "functional" change, but is also "structural," as shown, for instance, by thickening of the epithelium.

When structural elements are destroyed or actually removed, the process of reproduction is limited in the higher organisms. We then observe the phenomenon of other parts with similar function taking on the special functions of the lost part. Gradual recovery owing to other parts performing missing functions is a matter of everyday experience in Medicine and Surgery; and though the evidence is to a large extent still indirect, we cannot doubt that in all such cases structural changes are associated with the functional adaptation. The phenomena of vicarious function are also quite clearly adaptive changes, i.e., changes of such a nature that the life of the organism maintains as a whole its identity.

When one regards the facts of memory from the purely physiological standpoint it is evident that memory is a phenomenon of the same nature as adaptation. An experience or effort which has been gone through leaves its mark in the body as increased power of reaction to a similar experience or performance of a similar effort, just as an attack of an infectious disease, or vaccination, leaves its mark in a power of quickly repelling a similar infection. Were it not so memory would be a useless incumbrance.

In this connection we may recall the facts relating to the effects of practice in the carrying out of any operation, such as writing, riding a bicycle, or playing a musical instrument. Here frequent repetition of what was at first a difficult and very imperfectly per-

formed operation leads to its being performed with ease and certainty, without there being any consciousness of the innumerable details of nervous and muscular adjustment which are involved.

Of all other analogous facts the most remarkable, in the higher organisms, are those relating to reproduction of the whole organism. None of the innumerable structures special to the adult organism are present in the developing ovum; but as if guided by stimuli which awaken memories of its parents and ancestors, it builds up the adult structures and activities by degrees, often reproducing even the finest nuances in the character of either parent. In a living organism the past lives on in the present, and the stored adaptations of the race live on from generation to generation, waking up into response when the appropriate stimulus comes, just as conscious memory is awakened.

Looking at all these facts we are inevitably forced to the conclusion that the life of an organism, including its relations to internal and external environment, is something of prime reality, since it persists actively and as a whole, and moreover tends to do so in more and more detail with enlarging experience, so that life is a true development. What persists is neither a mere definitely bounded physical structure nor the activity of such a structure. There is no sharp line of demarcation between a living organism and its environment. The persistence of the internal environment and its activities is, in fact, as evident as that of the more central parts of an organism; and a similar persistence, becoming less and less detailed, extends outwards into

the external environment. An organism and its environment are one, just as the parts and activities of the organism are one, in the sense that though we can distinguish them we cannot separate them unaltered, and consequently cannot understand or investigate one apart from the rest. It is literally true of life, and no mere metaphor, that the whole is in each of the parts, and each moment of the past in each moment of the present. Organic wholeness covers both space and time, and in the light of biological fact absolute space and time, and self-existent matter and energy, are but abstractions from, or partial aspects of, reality.

We are thus brought face to face with a conclusion which to the biologist is just as significant and fundamental, and just as true to the facts observed, as the conclusion that mass persists is to the physicist.

We saw previously that the structure of a living organism has no real resemblance in its behaviour to that of a machine, since the parts of a machine can be separated without alteration of their properties. All of these properties are also independent of whether the machine is in action or at rest. In the living organism, on the other hand, no such separation can be made, and the "structure" is only the appearance given by what seems at first to be a constant flow of specific material, beginning and ending in the environment. We have now seen that the apparent flow has a persistence and power of development of its own, which we cannot account for by mere constancy in the physical and chemical environment. What persists is not mere matter or energy: for the matter and energy which

seem to pass through an organism are constantly being replaced. Nor is it mere form: for the flowing material is intensely specific. Structure, composition and activity are inseparably blended together in life, and no phenomenon in the inorganic world seems to us to be similar to the phenomenon of life. The fundamental facts with regard to life do not fit into the conceptions by means of which we at present interpret inorganic phenomena. Life is something which the biologist as such must treat as a primary reality, and no mere artifact. It is with life, and not merely with physics or chemistry, or bio-physics or bio-chemistry, that these lectures have dealt. From the outset of my own scientific work I have been guided by the conception that it is with life, and not with what physics and chemistry are at present capable of interpreting, that physiology deals; and this conception has grown clearer in my mind as a scientific working hypothesis with advancing experience as a physiological worker.

What aims does this conception carry with it for physiological investigation? The ground hypothesis or conception is that each detail of organic structure, composition, and activity is a manifestation or expression of the life of the organism regarded as a separate and persistent whole. We have therefore to make use of this hypothesis as a tool for investigation, just as the physicist uses the conceptions of mass and energy, or the chemist the atomic theory. We assume, therefore, that it will be found on sufficient investigation that the scattered observations of living organisms with which preliminary sensory observations supply

us are capable of unification under our guiding hypothesis; and we proceed to investigate them further with this faith present to us. We notice, for instance, that animals breathe. The breathing is a manifestation of the animal's life, for any hindrance to breathing is violently resisted with the animal's whole available power. Further investigation shows us more definitely what breathing is, the essential element in breathing being the due supply of oxygen to the body, and removal of carbon dioxide. By more detailed investigations, such as I have endeavoured to describe in these lectures, we reach a further knowledge of how the phenomena of breathing are integral manifestations of the whole life of the organism, including its past history; and the aim remains before us of reaching similar knowledge of how the development, maintenance and functional efficiency of each structural element are regulated.

One of the earliest steps in this voyage of discovery is to find any detail of structure or activity that can be regarded as a "normal." We look for normal structure, normal chemical composition, and normal standards of activity. And we do so because we know that life maintains itself: that this maintenance expresses itself in normals for everything connected with life. In the inorganic world there appear to be no normals in this sense; and chance, not order, seems, to the present very limited vision of physical science, to reign supreme.

When we have found what appears to be a normal, such, for instance, as a normal concentration of carbon

dioxide in the alveolar air, we first test it under varying conditions so as to make sure of its relative stability, and then proceed to investigate its connection with and subordination to other normals. Thus we find that the normal concentration of carbon dioxide in the alveolar air is connected with or subordinate to the normal composition of the blood, the normal activity of the respiratory centre, heart, kidneys, and other organs, the normal composition and amount of the food and the normal concentration of oxygen in the air. Our general working hypothesis would have told in a general way that connections of this kind must exist; but special investigation could alone tell us how they exist and how one is directly subordinate to another. It is this kind of investigation that is experimental physiology. The normals of anatomy are not mere physical structure, nor are the normals of physiology mere averages: they are manifestations of the life of an organism regarded as a whole. We have seen, for instance, in the case of the alveolar carbon dioxide pressure, in the percentage of haemoglobin in the blood, in the structure of bone-marrow, how a subordinate normal alters as the organism adapts itself so as to preserve its more fundamental normals under new conditions. In pathological conditions we find remarkable alterations in subordinate normals, and these alterations are undoubtedly the expression, to a large extent, of adaptations to the altered conditions. Pathological phenomena are not mere chance effects of the environment on the organ-

ism. Pathology is a real science, and part of the science of biology.

Anatomy and physiology, but more particularly anatomy, have become hide-bound in the conception that living structure is simply physical structure; and in consequence of this anatomy has for the present the aspect of almost a dead science, in spite of the new life impulse from experimental embryology. The time has come for biology to liberate herself and step forth as a free and living experimental science, with a world before her to conquer by the help of clearer ideas of what life is, and how it can be investigated.

Biology is no inexact science, contented with rough pictorial approximations. The bane of physiology in the past has been inexact measurement and imperfect observation. The new physiology will be different. Its measurements and observations will be more exact, and, as has been shown in the previous lectures from actual instances, of a delicacy often far exceeding that of existing physical and chemical methods. But the observations and measurements will not be of phenomena which if isolated are mere illusions. The new physiology will not be content with causes, but will seek out the organisation of which "causes" are only the outward appearance.

For the reasons already given, organism and environment cannot be separated in considering life. But we seem to be able to reach a satisfactory interpretation of the physics and chemistry of the external, and even of the internal environment, when these states are looked at apart from their relations to

organic activity. The oxygen which passes into the lungs is just ordinary oxygen, driven inwards to the alveoli by an ordinary atmospheric pressure difference. The process is organically regulated, but the regulation appears to be something external to the oxygen, which still retains its usual properties. We can then trace its diffusion into the blood, its combination with haemoglobin, its carriage onwards by the pumping action of the heart, and its dissociation from the haemoglobin in the systemic capillaries. It has come under more intimate organic control in the blood, but we can still trace it as molecules of ordinary oxygen. When it reaches and is absorbed by the tissues in cell metabolism the organic control becomes far more intimate. It is caught up in a whirl in which its behaviour is from the physical and chemical standpoint utterly mysterious. We can imagine no form of chemical combination which will now explain the behaviour of the oxygen. The mental picture of oxygen atoms or molecules seems to fade away, and to be replaced by another picture in which organisation is not something external to organised material, but is absolutely identical with the material, so that both the material and its movements are nothing but manifestations of the organisation. It is life and not matter which we have before us.

We can endeavour to hold on to the physical and chemical picture, and to seek for substances in the living structure which combine with, or enter into other physical or chemical relations with the oxygen. But a little consideration shows that even if we find

such instances, their presence and formation is organically determined by something beyond; and of this something we can form no physical or chemical picture. We also realise more clearly that in following the physical and chemical picture of the oxygen from the outset we have only done so by ignoring the organic control which, though present, seems less intimate. We have ignored, or put aside for the time, the regulated maintenance of breathing, the maintenance of the delicate normal structure of the lungs and of other parts connected with breathing, the regulation of the circulation and of the composition of the blood, and the maintenance of endless other things in which organic regulation manifests itself. But when we reach the living tissues we can ignore the organic regulation no longer: for we can see nothing clearly except an evident manifestation of the most intimate organic regulation. The physical and chemical picture is entirely obliterated by the picture of organism.

We may reflect that although we cannot at present trace the combinations into which oxygen enters in the living tissues, yet the oxygen atoms are there in some form. We can demonstrate their presence by elementary analysis, and we can separate chemical compounds, such as proteins, which contain oxygen. It can therefore be only a matter of further investigation to discover how the oxygen and other atoms combine in the living tissues and how these compounds react with one another to bring about the phenomena of life. This reflection brings us very close to a fundamental question. Physics and chemistry have brought us not

one step nearer to a physico-chemical conception of the characteristic phenomena of life, though they have been indispensable in elucidating these phenomena—in enabling us to formulate with increasing sharpness and detail the preponderant and omnipresent rôle of organisation in connection with biological phenomena. The more clearly we consider the matter the more clearly does it appear that this failure is not merely due to lack of ordinary physical and chemical data of the kind already familiar to us. No such data that we can remotely conceive would help us: no advance, for instance, in our knowledge of the chemical constitution and physical properties of protein compounds. We can reach no other conclusion than that it is the very conceptions of matter and energy, of physical and chemical structure and its changes, that are at fault, and that we are in the presence of phenomena where these conceptions, so successfully applied in our interpretation of the inorganic world, fail us.

What reasons have we for assuming, as we are apt to assume, that our physical and chemical conceptions or mental pictures of the surrounding universe correspond with reality? The reason is that they do actually enable us to predict much of our experience of the inorganic world, and up to a certain point have proved eminently reliable. Nevertheless they leave an enormous blank in our knowledge: for they assume a world of various kinds of matter and various forms of energy, variously distributed; but as to why this variety and distribution exist they leave us in ignorance. From the very nature of the ordinary conceptions of

matter and energy as independent entities this ignorance is unavoidable. Clear enough indications exist, however, that the progress of pure physical and chemical investigation is pointing towards truer and more adequate conceptions. The discoveries of the periodic law and of the transmutations of chemical elements in connection with radio-activity indicate an underlying connection between different forms of matter. With Faraday's discovery that in electrolytic dissociation the ions have each a definite electrical charge, and the more recent discoveries of the energy locked up in atoms, and liberated as radio-activity in their decomposition, an underlying connection between matter and the energy associated with it has become no less apparent. Thus even if we look only at the evidence afforded by the investigation of the inorganic world it seems clear enough that our present conceptions are only working hypotheses:—the pictures which our own generation has formed of it; but only imperfect pictures not adequately representing reality.

In the organic world we meet with something in the face of which these working hypotheses are far more definitely inadequate; and the very existence of biology is a direct challenge to them. We can nevertheless see how they can, up to a certain point, be used successfully in interpreting biological phenomena. For we can take the structure of the living body, not as living structure, but as something given and independent of its environment; and having once made this fundamentally false assumption we can proceed with the investigation of the supposed physical structure

in the same way as the physicist or chemist would proceed. This method yields much provisional information for further investigation and more correct interpretation, through which real physiology advances; and the mere possession of the provisional information is itself of great value. By showing that the living body could in certain respects be regarded as a heat-producing machine Lavoisier made a great step forwards, though he did not realise that the heat-production is organically regulated. For an animal in normal environment the hypothesis that there is a constant relation between intake of energy in the form of free oxygen and food-material, and output of energy as heat and in other forms, has stood the test of the most rigorous experiments. The fundamental observations of Regnault and Reiset, Pflüger, Rubner, and others have, however, shown that both intake and output of energy are strictly regulated, like other physiological activities; and what is implied in this organic regulation has already been discussed. The preliminary comparison of the organism to an energy-transforming machine has been of great value in certain directions, but has misled, and still continues to mislead, physiologists in others. The real source of the misunderstanding has been the assumption that physical and chemical working hypotheses are more than working hypotheses of limited profitable application, and accurately correspond to reality itself.

This assumption has given rise to the mechanistic theory of life as a necessary corollary, as well as to all that is vaguely designated as "materialism." But

though the assumption is false it must be borne in mind that working hypotheses applicable to the available sense data are indispensable to the advance of knowledge and practice. With limited data crude and simple working hypotheses, sufficient to cover the data without further complication, are alone of practical use; and both knowledge and practice, in dealing with isolated and imperfect data, naturally proceed on crude hypotheses. Where we can as yet see no organic determination in isolated observations relating to life the best available description of them is in mechanistic terms such as we apply to the inorganic world. Such descriptions supply an indispensable basis for more adequate description and interpretation; but to give a general application to the crude working hypotheses on which these descriptions are based implies a disregard of the wider biological observations which indicate that further investigation would reveal organic determination. This disregard is a very marked feature in current text-books of physiology. Each part of physiology, and even each subdivision of a part, is apt to be treated in isolation from the rest, with the necessary consequence that not only is no place left for the facts relating to organic determination, but the isolated details are very imperfectly described, as has been illustrated again and again in the course of these lectures.

The real reason of this defect is that physiologists have been endeavouring to fit their descriptions to the imperfect current working hypotheses of physics and

chemistry—an attempt which, in view of the facts of physiology can only end in certain failure. They assume as self-evident, for instance, that what they are dealing with is "living matter." In reality these two words contradict one another. What we interpret as being in the sense ordinarily current, "matter," cannot be also interpreted as living.

Why has physiology failed to free herself from this misunderstanding? The fact of organic regulation has been evident enough from early times, and, except in more or less recent text-books, has received prominent attention from physiological writers. Various causes have, I think, contributed, and I should like now to refer to one which is specially prominent.

The physiologists who laid most stress on organic regulation adopted the theory known as Vitalism—a theory which, though unorthodox, is still very much alive, and of which the eminent experimental embryologist, Hans Driesch, is probably the best-known living representative. The vitalistic theory is that although matter and energy are, whether outside or inside of the body, just what current physical and chemical conceptions describe them as, yet in the living body they are guided by what older physiologists called the "vital spirit," "vital force," or "vital principle," and what Driesch[1] calls "entelechy." As is well known, Driesch discovered the fact that if the constituent cells of an embryo in its earliest stages of development are dis-

[1] The clearest and shortest exposition of Driesch's argument is, I think, contained in his recent book, *The Problem of Individuality,* London, 1914.

arranged, or separated entirely from one another, a complete embryo may still develop, even from a single cell. He argues from this and other facts of analogous character, (1) that any mechanistic explanation of life is unthinkable, and (2) that we must assume the interference of a guiding influence, "entelechy," which directs the material present, so that it develops in the right way.

Driesch's destructive criticism of the mechanistic theory is particularly searching and cogent, and it seems to me that both he and the older vitalists have been justified up to the hilt in refusing to accept this theory. In the previous part of this lecture I have endeavoured to express the vitalistic criticism in a still more general form than it has assumed in the writings of the vitalists. To me the mechanistic theory of life appears impossible, not merely in connection with the facts of heredity and embryology, but at every point in biology.

To the vitalistic theory itself, however, there are insuperable objections. Experience shows us that where an organism reacts in any way it is always in response to some stimulus, whether this stimulus originates from without or within. The stimulus of fertilisation normally initiates the segmentation of an ovum, and from all analogy we must conclude that the differential stimuli arising from neighbouring cells or other parts determine the subsequent differential behaviour of each cell in the segmented ovum. On separating the cells these differential stimuli are removed, and each cell naturally starts again from the beginning.

Perhaps the case of the respiratory centre or of the kidney illustrates as well as anything else the objections to vitalism. We have seen with what marvellous exactitude the respiratory centre regulates the hydrogen ion concentration of the blood, but also that the response of the centre is nevertheless dependent on, and proportional to, an increase, however small, in the hydrogen ion concentration of the blood. If our methods of measurement had been less exact, if, for instance, we had employed rougher methods of gas analysis in investigating the alveolar air, or if we had been compelled to rely simply on the methods, delicate as they seem to a chemist, which are at present available for measuring hydrogen ion concentration, it might have seemed as if the respiratory centre acted without a stimulus, guided by an outside agency, just as a locomotive is guided by the driver, who shuts off or turns on steam according to requirements, and thus keeps his train up to time in spite of various accidental hindrances. Vitalism is a theory of this kind: it ignores the participation of the environment in the regulation, and consequently does not correspond to the observed facts, and is thus of little use as a working hypothesis in actual investigation. Its only real merit is that it serves as a means of expressing facts relating to organic regulation, and the defects of mechanistic theories. These facts are registered by referring them to the vital principle or entelechy.

The further physiology seems to advance in the direction of mechanistic explanations the more obviously it is driven into vitalism. For advance in

mechanistic explanation implies the assumption of more and more definite and complex physical and chemical structure in the body, and the development and maintenance of this structure has then to be accounted for, with a resulting relapse into vitalism, whether acknowledged or only implied. The helpless struggling in this direction of the mechanistic school which still represents modern orthodox physiology will be a marvel to future generations. It is in vain that the mechanistic theorists endeavour to exorcise what du Bois-Reymond called the "spectre of vitalism." This spectre is nothing but the shadow cast by the mechanistic theory itself—a shadow which has only become, and could only become, deeper the longer the mechanistic theory has lasted.

Both the mechanistic and the vitalistic schools have survived up to the present day, but we can understand that actual investigators have preferred to avoid vitalism so far as they could, as the vitalistic hypothesis seemed to set a limit to experimental investigation, and they rightly and instinctively felt that there is no such limit. So long as vitalism seemed the only alternative to mechanistic interpretations, they were driven towards the latter. In the din of controversy between vitalists and mechanists there was, however, a complete failure to go to the root of the matter, and enquire into the validity of the assumptions as to physical reality which were accepted by both sides.

In considering the facts of physiology we have hitherto looked at them from the standpoint of the individual organism only. But we know that in all

but the lower forms of animal and vegetable life the body is made up of cells and cell-territories, and that each cell is a centre of life. The life of the body as a whole is maintained by co-operation amongst the constituent cells. In the course of the common life the individual cells are constantly perishing and being reproduced, but the continuity or persistence of the common life is as evident throughout these changes as throughout the nutritive processes in which the chemical molecules passing through the body are constantly being replaced.

Not only do the constituent cells reproduce themselves and perish, but so does the whole organism itself; and its death is evidently just as much a normal phenomenon as is the death of any of its constituent cells. Death has sometimes been compared to the wearing out of a machine, but such a comparison throws no light on death, since the body is not a machine. Besides death and reproduction, there are many other biological phenomena which show us that life is not merely the life of individual organisms, but the life of a society of organisms. It is the life of a family, and beyond that the life of a species; or if we endeavour to push the biological analysis still further, the life of the universe itself, though such a life must remain outside the limits of clear mental vision until we can connect biological with physical and chemical conceptions.

The distinctively biological conception which I have endeavoured to formulate more definitely in these lectures enables us to interpret what are ordinarily re-

garded as biological phenomena. But the higher organisms, at any rate, are also centres of knowledge and volition. It is unmeaning to treat consciousness as a mere accompaniment of life, or to ignore the differences between blind organic activity, and rational behaviour. Conscious personality is far more than mere organism, and the conception of life is just as inadequate in connection with personality as the conceptions of matter and energy in connection with life.

It is not the time and place to recapitulate the reasoning which leads to this conclusion; but we may, perhaps, ask why, if the reasoning is correct, there is still a place for human physiology as distinguished from psychology. The practical reason is that although a man is a person and not a mere organism, we cannot trace personality throughout all, or nearly all, of what we observe in a man. To interpret the details as best we can, we have to fall back on the conception of life in the biological sense, just as in details of what we observe in connection with living organisms we have to fall back on ordinary physical and chemical interpretations. Though we know that these interpretations on a lower plane of knowledge can only be provisional, yet we should be very helpless in practical life without them. Their practical value is unmistakable, and we cannot dispense with them. On this view the conflicts between materialism and spiritualism, realism and idealism, science and philosophy, are only apparent.

In establishing the Silliman Lectures, the Founders, although they left complete freedom to lecturers to

treat their subjects as they thought fit, expressed the wish that the courses should have reference to "the presence of God in the natural and moral world." It is with hesitation that I venture to refer to this wish: for I know that in some ways my own conclusions are probably different from those of many who have thought very deeply on this subject.

In the preceding lectures I have endeavoured to describe the results of investigations on the physiology of breathing, and at the same time to show that these and other investigations lead to a biological conception of life which cannot be reconciled with the mechanistic conceptions handed down to us from the latter half of the last century. I have also argued that in virtue of this biological conception we must claim for biology an independent position as a science dealing with the manifestations of an order immanent in the natural world. This order is of a far more intimate character than the order hitherto disclosed by study of what we at present call the inorganic world.

To some men it has seemed that the facts of organic life furnish evidence of the existence of an external creator. The writings of Paley, for example, have popularised this view. If, as Paley tacitly assumed, organisms were machines there would be some basis for this argument: for the formation of the body cannot be explained as a physical and chemical process. The hypothesis that the body is formed in each individual by an act of miraculous creation would at any rate serve to stop a gap in our knowledge, though a God who did nothing but create machines would be

a mere Juggernaut. We have seen, however, that organisms are not machines, and with the machine theory the argument, such as it was, for special creation disappears. Biology leads us to the conception, not of an external Creator, but of an order immanent in the natural world. This order is, however, conceived as blind and unconscious, and cannot, so conceived, be identified with what we have learnt to understand as God.

It is not from the data of biology, and still more clearly not from those of the physical sciences, that we derive our conception of God, but from the facts of knowing and consciously doing which we observe in ourselves and our fellow men as conscious personalities. In knowledge the mind extends itself over our whole universe, so that what exists for us exists as known, however imperfectly, and as a sphere of our activities, however imperfect these activities may be. But we find that neither knowledge nor conscious activity in general is the mere knowledge or activity of individual men. Just as the behaviour of the cells in a compound organism is unintelligible if they are considered one by one, apart from their relations to the whole organism, so the acquisition of knowledge and conscious activity in general, are unintelligible from the point of view of the individual man. We can endeavour to picture to ourselves a man who would be entirely self-centred—who would be a God to himself; but the attempt ends in failure. It is the perception that in us as conscious personalities a Reality

manifests itself which entirely transcends our individual personalities, that constitutes our knowledge of God. In the world of duty and knowledge, not in the natural world as such, we find the God whom our fathers have worshipped, and in whose strength they have been of good courage, and faced trouble, danger and death. God is near to us, and not far away.

The facts of biology lead to the conclusion that the physical and chemical interpretation of the world is fundamentally imperfect, however useful it may be. The biological interpretation is itself similarly imperfect in view of the facts relating to conscious personality. But when we regard the natural world, as it seems to me we ought and must, not as something completely interpreted in the light of existing theory, but as an imperfect interpretation which is the expression of countless centuries of human effort, the natural world becomes part of the world of duty and knowledge. Natural science and its applications are the rough-hewing in the spiritual world, and the fundamental conceptions of each of the natural sciences are the tools, fashioned by human endeavour, with which this rough-hewing is done. Scientific results are in themselves only incomplete and abstract presentations of reality, just as the stones are not part of the building till they are dressed and fitted into place. Other workers do their part in the building, but without the rough-hewing their efforts would be in vain. Biology, for instance, is absolutely dependent on the preliminary work of the physical sciences, just as other more concrete sciences are dependent on biology. The claim

is often made, either explicitly or implicitly, and in our own times particularly on behalf of the mathematical and physical sciences, that scientific results represent complete and "objective" reality. This claim cannot be justified.

We learn to know God, not by any process of abstract reasoning or external revelation, but by practically realising in our own everyday lives, and those of our fellow men, that we are not mere individuals but one with a higher Reality. In losing our individual lives we find our true life, and in no part of human activity is this losing of the individual self more clearly realised than in scientific work. When, but only when, we see that the natural world appears to us as it does through the devoted scientific work which has fashioned its present appearance, we have found God in the natural world. The life of such a man as Charles Darwin is in truth a standing proof of the existence of God.

I think the Founders of the Silliman Lectures must have felt this when they left complete liberty to each lecturer to treat his subject just as seemed best for his immediate purpose, and without reference to theology.

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