Monographs on Physiology

THE PHYSIOLOGY OF MUSCULAR EXERCISE

F. A. BAINBRIDGE

MONOGRAPHS ON PHYSIOLOGY

EDITED BY

ERNEST H. STARLING, M.D., D.Sc., F.R.S., F.R.C.P.

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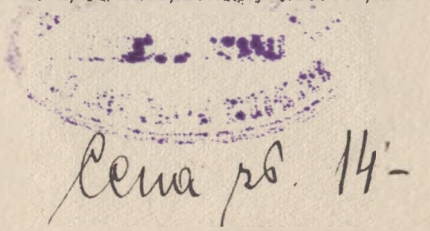

THE PHYSIOLOGY OF MUSCULAR EXERCISE

BY THE LATE

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"The strength of the British Empire lies in the strength of character of the individual Englishman, taken all alone by himself. And that strength I am persuaded is perennially nourished and kept up by nothing so much as by the national worship, in which all classes meet, of athletic outdoor life and sport."

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EDITOR'S PREFACE.

In no science is the advance at any one time general. Some sections of the line are pushed forward while other parts may remain for years with little movement, until in their turn they are enabled to progress in consequence of the support afforded by the advance of the adjacent sections. The increasing number of series of monographs in different sciences is a recognition of this fact, as well as of the concentration of interest which characterises this age of specialisation.

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ERNEST H. STARLING.

NOTE TO SECOND EDITION.

In revising the Monograph on Muscular Exercise written by the late Professor Bainbridge, I have been careful to preserve the general character of the work in its original form. The subject-matter of several sections has necessarily been expanded in order to include the results of recent research.

G. V. ANREP.

AUTHOR'S PREFACE TO THE FIRST EDITION.

RIGID investigation of the nature and significance of the processes taking place in the body during muscular exercise must, as a rule, be undertaken in the laboratory. It is, however, those in charge of patients, or responsible for the health and training of large groups of individuals, who are brought into direct contact with the problems presented by exercise, as carried out under the ordinary conditions of daily life. The fullest co-operation between the laboratory worker and the physician is of supreme importance for bringing about a clearer understanding and more effective practical application of the principles underlying the behaviour of the body during muscular exercise, since on a knowledge of these principles depends success or failure in the treatment of the unfit and in the building up of the sound man. In writing this monograph, therefore, I have attempted to present my subject in such a way as to promote a closer connection between the investigator in the laboratory and those directly concerned with the health and well-being of the community.

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CHAPTER I.

INTRODUCTORY.

MUSCULAR exercise is of such constant occurrence in daily life, and its more obvious effects are so familiar to every one, that the complexity of the processes underlying it is apt to be overlooked. Yet a knowledge of the changes taking place in the body during exercise, and of the adjustments involved in carrying it out efficiently, is of more than mere academic interest. It is essential, for example, that the clinician, who is called upon almost daily to decide whether, and to what extent, his patients should take exercise, should be acquainted with the effects which muscular activity produces upon the various organs of the body, and particularly with the significance of the circulatory and respiratory changes associated with it. Further, the elaborate investigations of industrial fatigue which have been carried out during the last few years leave no doubt that not only the efficiency of the worker as a member of the community, but also his health, and even his entire outlook upon life, are closely bound up with the conditions under which his manual labour is carried out. A fuller realisation and a more direct practical application, by employers and administrators, of the physiological principles which underlie the capacity of the body to perform muscular work, would undoubtedly greatly increase the output and improve the health of industrial workers.

Muscular exercise is the highest expression of the activities of the body considered merely as a machine, and almost all the resources of the body are mobilised in order to bring about the greatest efficiency of the neuro-muscular system. To a spectator its most conspicuous features are the wonderful co-ordination of the muscular movements and the immense power of the body to develop energy, particularly when these are displayed to perfection, as, for example, in the gracefulness of an expert dancer or

figure-skater, or in the power of a trained crew rowing in a boat-race. These are rendered possible by the concentration for the time being of the entire energies of the higher nervous centres upon the actual muscular movement, and the individual, who is engaged in such exercise, is usually conscious of little but the effort he is making, his whole attention being focussed upon the actual physical exertion.

The important part played by the central nervous system is also seen in the large accession of working power which occurs, when exercise is performed under the stimulating influence of emotional excitement, or, conversely, in the lessened efficiency of a man who is not interested in the work which he is carrying out. Since muscular exercise is as much a nervous as a muscular process, its beneficial effects are evident in the psychical as well as the physical life of the individual; and, as William James has said: "Even if the day ever dawns in which it will not be needed for fighting the old heavy battles against nature, it (muscular vigour) will still always be needed to furnish the background of sanity, serenity, and cheerfulness to life, to give moral elasticity to our disposition, to round off the wiry edge of our fretfulness, and make us good-humoured and easy of approach." Consequently, induced movements—useful though they may be—fall far short of voluntary exercise as a means of maintaining health and vigour.

Although the nervous system initiates and controls every movement of the body, the energy required for the carrying out of physical work is developed in the muscles themselves, and their power to transform potential into kinetic energy, which appears as work or heat, and to renew their store of energy is the central fact of muscular exercise. For a long time, physiologists were content to study the causes of this transformation of energy and the conditions which regulate the mechanical efficiency of the muscles. Their investigations, carried out for the most part on isolated muscle, yielded many valuable results, but the tendency to regard muscular exercise as almost exclusively a muscular act led to a narrow and imperfect conception of its true character. It has gradually become clear that the processes taking place in the muscles, important though they are, constitute only a fraction of the total activities of the body during exercise, and that muscular movement is a very

different thing from voluntary exercise. Although the setting free of energy, when a muscle contracts, is a non-oxidative process, oxygen is necessary for the restoration of its potential energy, and, in the absence of oxygen, mammalian muscle rapidly loses the power of contraction. Further, since the energy of muscular work is ultimately obtained from the oxidation of the food-stuffs, the enormous increase in the amount of energy developed in the muscles during exercise involves a corresponding rise in the intensity of their metabolic activities and in the extent to which they consume oxygen. Indeed, it is now well known that the amount of oxygen which a man consumes is a criterion of the degree of activity of his muscles during exercise.

A man, who is performing hard physical work, may use eight or ten times as much oxygen as during rest, and the burden of meeting this demand for oxygen falls upon the respiratory and circulatory systems, which, for this purpose, are indissolubly linked together. Every increase in the requirements of the body for oxygen is accompanied by adaptive changes in the circulation and the respiration, which enable oxygen to be transferred more rapidly from the lungs to the tissues; and the rapid, deep breathing, the powerfully beating heart, the high blood-pressure, and the frequent pulse, present in the man who is engaged in violent exercise, are just as much a part of the exercise, and just as vital to its effective performance, as the movements of the muscles themselves. Violent exercise taxes the resources of the circulatory and respiratory systems equally with those of the muscles; and, partly because it is called upon to maintain an adequate supply of oxygen to the brain as well as to the muscles, partly, perhaps, owing to the larger number and greater complexity of the adjustments required for this purpose, the heart, as a rule, reaches the limit of its powers earlier than the skeletal muscles, and its functional capacity determines a man's capability for exertion. It is clear, then, that, apart from the changes taking place in the muscles themselves, the activities of the rest of the body are largely directed during exercise to the provision of an adequate supply of oxygen for the muscles, the heart, and the brain; hence any picture of muscular exercise must include the whole range of these activities.

If the body is to work efficiently and to develop its physical

powers to their full extent, it is absolutely essential that the movements of the muscles on the one hand, and the activities of the circulatory and respiratory systems on the other hand, should be co-ordinated and integrated into a harmonious whole. Perfect co-ordination brings about the maximum of work with the minimum of effort. Incomplete co-ordination, on the contrary, inevitably spells inefficiency. An exaggerated response on the part of the respiratory and circulatory systems involves a useless expenditure of energy; a deficient response rapidly throws out of gear the controlling influence of the nervous system, cripples the energies of the skeletal muscles, and renders exercise ineffective or even impossible. In order to realise the completeness to which this co-ordination can attain, and the effects of even the slightest disturbance of the balance between the activities of the muscles and of the rest of the body, it is only necessary to watch a trained and an untrained man running in a race or engaged in some other form of exercise. In the former, every organ is working smoothly, and is contributing its proper share towards bringing about the perfect harmony of action which is requisite for efficient exercise. In the latter, the less perfect adjustment of the body is evident, both to the man himself and to others, in the greater sense of effort, in the clumsiness of movement, and in the more severe respiratory and circulatory distress.

Muscular exercise thus presents three problems. The first is the changes taking place in the skeletal muscles, whereby the transformation of energy, which constitutes muscular movement, is effected; the second is the nature of the adjustments occurring elsewhere in the body in order to provide the muscles with the oxygen and food-stuffs required for this purpose; and the third is the means by which these are interwoven and bound together to produce the fabric of muscular exercise. The attempt to answer the second and third of these questions is the main thesis of the following chapters, and the first question will only be considered in so far as it bears upon the general argument.

CHAPTER II.

THE SOURCES OF MUSCULAR ENERGY—THE MECHANICAL EFFICIENCY OF THE BODY—THE TEMPERATURE OF THE BODY DURING EXERCISE.

FROM a metabolic point of view the immense development of energy which takes place in the body during heavy work is the most striking feature of muscular exercise. Thus, Benedict and Cathcart (1913) found that, in one subject, the total production of energy, which varied from 1·09 to 1·27 calories per minute during absolute rest, reached from 10 to 14 calories per minute during heavy work. In one experiment, carried out on a bicycle ergometer, the subject—a professional cyclist—performed in a little over four hours an amount of work, which was equivalent to a cycle ride of 100 miles; throughout this period his production of energy averaged 9·75 calories per minute. This figure is probably not far short of the maximal production of energy of which the body is capable for a prolonged period of work, although a considerably larger output of energy per minute is possible during a brief spell of very severe work, such as running upstairs with a heavy load. Lupton calculates that in most extreme forms of exercise of a nature too severe to be prolonged more than about 10 seconds, there is a total liberation of energy of 1·00 calorie per second of exercise. This would give a figure of 60 calories per minute if the exercise could be prolonged.

The two questions which naturally spring from observations of this kind are, first, from what source do the muscles obtain the potential energy which they transform into kinetic energy, and, second, what fraction of the total energy produced in the active muscles is converted into effective, external work? Underlying these questions is a further problem, namely, what is the real nature of the processes of which a muscular contraction is the outward manifestation?

No detailed discussion of these questions is possible here, but it is necessary to refer briefly to two aspects of the metabolism

during exercise, namely, the sources of muscular energy and the mechanical efficiency of the body.

The Sources of Muscular Energy.

The belief that protein normally serves directly as a source of muscular energy has long been abandoned. The greater excretion of uric acid (Cathcart, Kennaway, and Leathes, 1908, Kennaway, 1908), and of creatinin (Leathes and Orr, 1912), in the urine after severe physical exertion represents merely a greater wear and tear of the muscle; and the trivial extent of the increase indicates that, as regards its chemical structure, the muscular machine is remarkably stable. The energy, which the muscular machine transforms into external work, must therefore be provided by the oxidation either of fat or carbohydrate or of both these substances.

The Respiratory Quotient.

The problem as to the nature of the material oxidised during muscular work was first seriously attacked by Chauveau (1896), who studied the effect of muscular exercise upon the respiratory quotient. He observed that the respiratory quotient rose considerably during exercise, although it tended to fall again if the exercise was prolonged. He regarded the initial rise in the respiratory quotient as evidence that carbohydrate is the sole source of muscular energy, and the subsequent fall of the quotient as indicating the conversion of fat into carbohydrate as a preliminary to its final oxidation. Chauveau's conclusions were vigorously controverted by Zuntz (1896), who found that the respiratory quotient was unaffected by exercise, whether the diet was rich in carbohydrate and poor in fat, or rich in fat and poor in carbohydrate; and his observations accord with those of Loewy (1908), of Katzenstein (1891), and of others. The following table is taken from Katzenstein, the observations being made on man :—

TABLE I.

	Oxygen Intake c.c. per Minute.	CO_2 Output c.c. per Minute.	Respiratory Quotient.
Rest	263·7	211·0	0·80
Walking on level ground .	763·0	614·2	0·80
Climbing	1252·2	1002·5	0·80

On the ground of these observations, Zuntz put forward the view that the muscles, whether resting or active, utilise fat and carbohydrate in the proportions in which they are presented to the muscles. Additional support for this view was found both in the fact that vigorous muscular work can be carried out by a starving man, whose store of carbohydrate has presumably almost disappeared, and also in observations, such as those of Atwater and Benedict (1903) and of Zuntz (1900), on the amount and efficiency of the work performed on a diet rich or poor in carbohydrate. Zuntz found in one experiment that the performance of 1 kilogrammetre of work involved the production of 9·3 calories of heat (above the resting value) on a carbohydrate diet, and of 10·3 calories on a diet consisting chiefly of fat; thus the work was carried out almost equally efficiently whatever the character of the diet.

This observation was confirmed by Atwater and Benedict who found, as the following figures show, that the total production of heat during the performance of a given amount of mechanical work was the same, whether the diet was rich or poor in carbohydrate :—

TABLE II.

	Fat Diet.	Carbohydrate Diet.
Mechanical work (calculated as heat) . .	550	543
Heat production	4555	4593
Total expenditure of energy . . .	5105	5136

These experiments do not prove conclusively that fat can be utilised as a source of muscular energy, since, at least in Atwater and Benedict's observations, sufficient carbohydrate was available in the body to provide the energy expended. They do appear to show, however, that if it is utilised, fat is oxidised directly and does not undergo a preliminary conversion into carbohydrate; if the latter change occurred, approximately 30 per cent. of the energy liberated by the oxidation of fat would not be available for mechanical work (Zuntz), and the mechanical efficiency would be lower on a fat than on a carbohydrate diet.

Zuntz' view that fat and carbohydrate can serve equally well as sources of muscular energy was for many years almost

universally accepted, the more so since it is in accordance with the common experience that work appears to be carried out equally efficiently in individuals whose diets are totally dissimilar as regards their content of fat and carbohydrate. Later evidence, however, has led many physiologists to consider that, provided it is available, carbohydrate is the main, and possibly the sole, source of muscular energy. In a recent study of muscular metabolism, Benedict and Cathcart (1913) have pointed out that it is unsafe to draw conclusions from isolated experiments on the respiratory quotient; and their own observations revealed a striking lack of uniformity between the results of individual experiments. An average of their results indicates, however, that muscular work produces a small but definite rise in the respiratory quotient, whether the diet is rich or poor in carbohydrate.

TABLE III.—EFFECT OF EXERCISE ON THE RESPIRATORY QUOTIENT. (BENEDICT AND CATHCART.)

Preceding Diet.	Date.	Lying Before Work.	During Work.	Lying After Work.
Carbohydrate—rich	Jan. 24	0·87	0·87	0·76
	,, 25	·80	·92	·78
	,, 26	·86	·83	·79
	Feb. 14	·87	·93	·78
	,, 15	·81	·95	·81
	,, 16	·87	·88	·76
Average		0·85	·90	·78
Carbohydrate—poor	Jan. 17	·77	·87	·73
	,, 18	·77	·74	·70
	,, 19	·77	·74	·71
	Feb. 7	·84	·91	·82
	,, 8	·81	·86	·76
	,, 9	·79	·82	·77
Average		·79	·82	·75

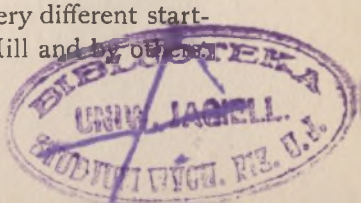
Krogh and Lindhard find that work is more economically performed on a carbohydrate diet than on a fat diet. When the work is severe the subjects are found to perform it with greater difficulty on fat than on carbohydrate, and become much more tired. The net expenditure of energy per calorie mechanical work varies from about 4·6 calories when fat alone is catabolised (R.Q. = 0·71) to about 4·1 calories, when carbohydrate alone is catabolised (R.Q. = 1·00). The waste of energy from fat is, therefore, 0·5 calorie, or 11 per cent. of the heat of combustion of

fat. On transition from rest to moderate work the respiratory quotient is generally altered. Krogh and Lindhard find that on an average the respiratory quotient is increased when the quotient is low, and diminished when it is high before the work. The fall at high quotients is greater (0·05) than the increase at low (0·03). At quotients between 0·8 and 0·9 the average change on the transition to work is very slight. On basis of these experiments Krogh and Lindhard suggest that both during rest and during work the proportion of fat to carbohydrate catabolised is a function of the available supplies of these substances, and that carbohydrate is formed from fat and stored when the quotient is below 0·8, while a corresponding transformation of carbohydrate to fat takes place when the quotient is above 0·9.

Severe and prolonged exercise depletes considerably the reserve of carbohydrate in the body, and if, as Zuntz supposed, the active muscles use fat and carbohydrate in the proportions presented to them, the rapid diminution of available carbohydrate should result in a gradual fall of the respiratory quotient during prolonged work. This did occur in some of Zuntz' experiments, but Benedict and Cathcart find, on the contrary, that the respiratory quotient actually rises more during heavy prolonged work than during light or moderate work. When the work is finished, however, the respiratory quotient usually falls below that observed previous to the performance of work (Table III.). Benedict and Cathcart explain this by supposing that the muscles, when resting after work, are again oxidising fat and carbohydrate in the proportions presented to them, and that, owing to the reduction of the store of carbohydrate in the body during the work, less carbohydrate is available after a period of severe work. The evidence presented by Benedict and Cathcart leads them to conclude that the metabolism of active muscle differs qualitatively as well as quantitatively from that of resting muscle, and that, whatever may be the character of the diet, the energy of muscular work is derived mainly from carbohydrate. But, as Benedict and Cathcart are careful to point out, it does not prove that carbohydrate is the sole source of muscular energy.

Experiments on Isolated Muscle.

The problem has been approached from a very different starting point by Fletcher and Hopkins, by A. V. Hill and by others.



Working with isolated frog's muscle, Fletcher and Hopkins (1902-1917) have shown that the chemical changes taking place during muscular contraction occur in two stages, of which the first is the formation of lactic acid, and the second is its removal. The production of lactic acid, which culminates in a muscular contraction, is a non-oxidative process and can take place in the absence of oxygen; its subsequent removal is an oxidative process and demands an adequate supply of oxygen. Fletcher and Hopkins consider that the appearance of lactic acid precedes, and is intimately bound up with, the mechanical shortening of the muscle, whereas its oxidation is effected after the contraction is over, and brings about the return of the muscle to its former resting condition. Their results have been confirmed and supplemented by A. V. Hill (1911-1913), who found that, in the absence of oxygen, the production of heat in an active muscle is limited to the period of contraction, whereas, in the presence of oxygen, the production of heat continues for some time after the contraction.

As the outcome of these investigations, the conclusion has been reached (A. V. Hill, Fletcher and Hopkins) that the process of muscular contraction consists essentially in the transformation of some form of potential energy into surface energy, and that this change gives rise to a condition of tensile stress within the muscle, which therefore tends to shorten and to perform work; if it is not allowed to shorten, the surface energy is dissipated as heat. But some difference of opinion exists as to the form in which its potential energy is stored in the muscle. A. V. Hill and Meyerhof hold (*a*) that, in the initial process of contraction, glycogen, or some product of glycogen, is changed explosively into lactic acid; (*b*) that in the recovery process the glycogen (or its product) is restored and the lactic acid removed; (*c*) that the recovery process consists of an oxidation (either of lactic acid or carbohydrate), of which part of the energy appears as heat, part is absorbed in restoring the muscle to its original condition of readiness for mechanical activity. A. V. Hill and Meyerhof find that only one-sixth of the lactic acid produced during contraction undergoes oxidative removal, the other five-sixths being once more built up into glycogen. The work of the Emden school seems to show that some hexose-diphosphate is a link in the chain by which glycogen and lactic acid are mutually transformed into one another. Fletcher and Hopkins consider that the potential energy resides

"in a particular condition of a physico-chemical system," and that a system of colloidal fibrils or longitudinal surfaces, such as is assumed to exist in muscle, possesses a potential of energy which may be discharged as work or heat when $H^{\bullet}$ ions are brought into relation with it. They believe that the formation of lactic acid from glucose, by setting free $H^{\bullet}$ ions, initiates the discharge of part of this energy in the form of a muscular contraction; the return of the colloidal system to its former resting condition, and the restoration of its potential energy, are effected at the expense of the energy furnished by the oxidation of lactic acid after the contraction is over.

There is every reason to believe that in muscle, as elsewhere in the body, lactic acid appears as an intermediate stage in the combustion of carbohydrate, and Parnas and Wagner (1914) have shown that the appearance of lactic acid coincides with a diminution of the carbohydrate content of isolated muscle. But, in muscle, to quote Fletcher and Hopkins, lactic acid has "its special rôle to play in connection with the muscle machinery. In the evolution of muscle it would appear that advantage, so to speak, has been taken of this acid phase in carbohydrate degradation, and that, by appropriate arrangement of the cell-elements, the lactic acid, before it leaves the tissue in its final combustion, is assigned the particular position in which it can induce those tension changes upon which all the wonders of animal movement depend."

The logical deduction, which springs from this conception of the nature of muscular contraction, is that the carbohydrate stored in the muscles, and elsewhere in the body, furnishes the main reservoir of energy upon which the muscles draw for the carrying out of work. This inference is supported by the observations of Winfield (1915), who has found that fat does not diminish in amount in excised frog's muscle, when this is made to contract in air or in an atmosphere of hydrogen. There is no clear evidence that, either in Winfield's experiments or in those of Fletcher and Hopkins, the store of carbohydrate in the muscles was exhausted, and these experiments do not exclude fat as a possible source of muscular energy. But they do suggest that, so long as carbohydrate is available, it alone is utilised to provide the energy of muscular work.

Experiments on the Heart.

Additional evidence bearing on the sources from which the energy of muscular work is derived has been furnished by Evans (1912, 1914) in his study of the metabolism of the heart; and this evidence gains in value from the fact that the muscle was provided with its normal blood-supply. Using the heart-lung preparation, in which the circulation of the blood is limited to the heart and lungs, Evans found, in confirmation of Rohde (1910), that the respiratory quotient of the isolated heart varies within the same limits, and under the same conditions, as that of the body generally. The isolated heart, therefore, is able to oxidise the same materials as those used by the body as a whole. He then calculated from the respiratory quotient of the heart that the energy expended by the heart was derived to a much greater extent from fat than from carbohydrate. Even after the addition of glucose to the circulating blood, only just over a third of the total energy of the heart was obtained from the oxidation of carbohydrate, although the respiratory quotient was distinctly raised by the addition of glucose.

TABLE IV. (EVANS.)

	Oxygen Consumed in c.c. per kgm. of Work.	Output of Carbonic Acid in c.c. per kgm. of Work.	Respiratory Quotient.
Exp. (1) Before adding glucose	14	10·1	0·723
After ,, ,,	18·5	14·7	0·785
Exp. (2) Before ,, ,,	15·2	12·1	0·795
After ,, ,,	17·3	14·3	0·826

In calculating the proportion of fat and carbohydrate used by the heart, Evans assumes that about 15 per cent. of the total energy of the heart is derived from protein, and that the oxidation of fat, carbohydrate, and protein is complete; but the necessity for making these assumptions does not affect the general accuracy of the results.

Unless it is assumed that the metabolism of cardiac muscle differs fundamentally from that of skeletal muscle, and of this there is no evidence, there appear to be three possible interpretations of these results. The first is that much of the carbohydrate used by the heart is derived from fat; although Chauveau believed

this to take place, the evidence against its occurrence is very strong. The second possibility is that, although fat is being oxidised in the heart-muscle, the energy derived from this process is utilised, not in the contractile process, but in some other way. The third possibility is that fat does actually serve as an important source of muscular energy. Evans' experiments do not furnish any decisive argument in favour of either of these two possibilities, since the effect of glucose upon the respiratory quotient might be accounted for on the assumption that the muscle avails itself of the larger supply of carbohydrate to use a greater proportion of carbohydrate as compared with fat.

It is possible, therefore, to maintain that the oxidation of fat observed in these experiments formed part of the basal metabolism of the heart, and that the energy required for the contractile act was obtained entirely at the expense of carbohydrate. But, in some of Evans' experiments, the respiratory quotient was so low that the energy derived from carbohydrate must have barely equalled that appearing as *external* work done by the heart; in these circumstances, fat must also have served as a source of energy. If, as these experiments seem to show, the energy derived from the oxidation of fat as part of the basal metabolism of the heart muscle can be diverted at any moment for utilisation in the contractile process, it seems rather arbitrary to assume that fat is not always being drawn upon for this purpose. At first sight, Winfield's observations would appear to preclude this inference, but Winfield worked with excised muscles, whereas, in Evans' experiments, the heart was receiving its normal blood-supply. It may be that, under the conditions of Winfield's experiments, the tension or "pressure head" of oxygen, though sufficient for the oxidation of carbohydrate, is inadequate for the combustion of fat, and that fat demands for its combustion an intensity, so to speak, of oxygen-supply which can be attained only when the normal circulation is present.

The fact that, on occasion, the heart can obtain practically the whole of its energy from fat, with no appreciable loss of efficiency or waste of energy, is readily intelligible on the assumption that the normal heart draws on fat to some extent for this purpose. This is the case in the isolated, diabetic heart in which, as Starling and Evans (1914) have shown, the

respiratory quotient is very low, its average value being 0·708. The work of these hearts, which was nearly equal to that of a normal heart, must have been effected almost entirely at the expense of fat (or of protein). This must also be the case during muscular exercise after prolonged starvation, when the carbohydrate store of the individual has been exhausted. Unfortunately direct evidence as to the effect of muscular work upon the respiratory quotient under these conditions is very scanty; and, since glycogen appears to be present in the body, even after prolonged starvation (Prausnitz), the possibility of carbohydrate being used in these circumstances must be taken into account.

Conclusion.

It seems clear from the evidence of Benedict and Cathcart on the respiratory quotient, and that of Fletcher and Hopkins on isolated muscle, that, when both fat and carbohydrate are available, the muscles display a marked preference for carbohydrate as a source of energy. At the same time there is good reason for believing that fat is also utilised for this purpose, although the extent to which this occurs is still uncertain.

The processes taking place during a muscular contraction are so intimately bound up with the momentary appearance of lactic acid and its subsequent oxidation that, at first sight, the conclusion just stated appears hardly compatible with Fletcher and Hopkins' conception of the nature of muscular contraction. But Bayliss has pointed out that it is not the production of lactic acid as such, but the appearance of hydrogen ions, which initiates the act of contraction, and there is no difficulty in believing that the production of hydrogen ions can occur at some stage in the combustion of fat.

In that case, the appearance of lactic acid during muscular contraction would cease to have any peculiar significance, and the preferential utilisation of carbohydrate by the muscles during exercise might be attributed to the readier mobilisation of carbohydrate, and perhaps to the more rapid disruption of glucose as compared with fat, rather than to any absolute necessity for the presence of lactic acid to bring about the act of contraction.

It should be remembered, however, that the work of Atwater and Benedict and of Krogh and Lindhard does not exclude a

possibility of fat being converted into carbohydrate as a preliminary stage.

The Mechanical Efficiency of the Body.

The proportion of the total expenditure of energy during muscular exercise, which appears as external work, represents the mechanical efficiency of the bodily machine.

The total production of energy in a given time may be determined by means of the Atwater-Benedict calorimeter, or by measuring the consumption of oxygen. Zuntz calculated that the absorption of 1 litre of oxygen represented the production in the body of from 4·6 to 5 calories according to the character of the material oxidised, the value varying directly with the respiratory quotient. This corresponds closely with the figure 1 gramme oxygen consumption = 3·4 calories which was obtained by Benedict and Joslin (1910), since 1 litre of oxygen weighs 1·43 grammes. If the external work done by the subject is measured, it, too, can be calculated in calories from the equation 1 calorie = 425 kilogrammetres; these data will give the mechanical efficiency of the body.

The efficiency (E) of the body is obtained from the equation $E = \frac{a \times 100}{b}$, where a = actual work measured and b = total expenditure of energy in a given time. This is termed the *gross* efficiency, and is often taken for a period of twenty-four hours. A knowledge of the gross efficiency is of great value, as Benedict and Cathcart point out, for determining the energy output of a body of labourers and artisans working under the ordinary conditions of life, and for ascertaining the nutritional requirements of bodies of men carrying out severe muscular work. But, since a considerable part of the day is spent in rest, during which time there is an expenditure of energy unaccompanied by external work, the gross efficiency does not fairly represent the true potentiality of the body for severe work. To determine the possible efficiency of the body, the energy required for the maintenance of the body, when the individual is at rest, should be deducted from the total expenditure of energy during the working period. When this correction is made, one obtains a value, called the *net* efficiency, from the formula $\frac{a \times 100}{b - c}$, in which a is the amount of work performed, b is the total expenditure of energy for the period during which the work was performed, and c is the expenditure of energy during a similar resting period. The following figures, taken from Benedict and Cathcart, show the maximum gross and net efficiencies in six individuals :—

Subject.	Gross Efficiency.	Net Efficiency.
1	19·4	23·1
2	17·8	20·4
3	18·6	21·6
4	19·8	22·7
5	18·2	20·8
6	21·2	25·2

The work done in these experiments was carried out on a bicycle ergometer. Benedict and Cathcart conclude that the average net efficiency of muscular work is about 21 per cent., and figures varying from 20 to 28 per cent. have been found by many other observers (Zuntz, Durig, Rubner, Macdonald). An interesting fact brought out by Zuntz is that the mechanical efficiency varies with the kind of work performed. It is greater, for example, for mountain climbing than for walking on the level.

The chief conditions which influence the net efficiency of muscular work are training, the speed with which the work is performed, and fatigue. The effects of training are shown by Zuntz' observation that, in subjects working on a bicycle ergometer, the efficiency varied from 20 per cent. in the untrained man to 25 per cent. in the trained subject. Further, Benedict and Cathcart found that, in a very highly trained man, not only was the average efficiency always greater than that of ordinary individuals, but that the maximum net efficiency at times reached 33 per cent., a figure which was never attained by the untrained person.

The speed at which work is carried out has a striking influence upon the efficiency of the individual. Macdonald (1914) has shown that there is an optimum rate of work at which the efficiency is greatest; and the same conclusion has been reached by Benedict and Cathcart, who found that, when a constant amount of work was performed at varying speeds, the optimum efficiency was reached at a very moderate speed, and that the efficiency fell off very rapidly when the speed was increased. In their experiments the subject pedalled a bicycle ergometer at varying rates. His optimum efficiency was obtained with a speed of seventy revolutions of the ergometer per minute, and the following table shows the effect of increasing the number of revolutions, the total amount of work done being constant:—

TABLE V.

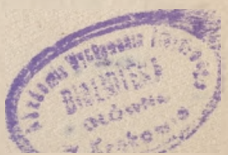
Revolutions per Minute.	Heat Equivalent of Work Done.	Net Efficiency.
(1) 71	1·57	24·5
(2) 108	1·58	15·6

Lupton also finds that the external work done in a muscular contraction is diminished by an amount depending upon the velocity of shortening. Rapid movement means large internal friction and large loss of energy as heat. In the muscle of a human arm a movement completed in one second wastes 26 per cent. of its energy in overcoming the frictional resistance of the muscle itself, a movement completed in half a second some 52 per cent. until, in a movement in about 0·26 second, no external work can be done at all.

A. V. Hill calculates that the efficiency of the initial stage of an isometric contraction of a frog's muscle is almost 100 per cent. But in presence of oxygen during relaxation there is a further evolution of heat equal to that set free during the initial stage. So that the maximum theoretical efficiency of a muscle in presence of oxygen would not be more than 50 per cent.

One of the chief advantages of training is improved co-ordination of the muscular movements, and the elimination of useless and ineffective movements, the result being that a given amount of work can be performed with a smaller expenditure of energy. It is clear, therefore, that the nervous system, which brings about these changes, is largely responsible for the higher mechanical efficiency of the trained man. Again, perfect co-ordination due to constant practice is probably the explanation of the fact that walking is performed more economically than almost any other form of exercise. On the contrary, exercise to which a man is unaccustomed is usually carried out very inefficiently.

The nervous system also plays an important part in determining the relation between the rate at which a man works and his mechanical efficiency. The bodily machine possesses a natural rhythm, which is set by the central nervous system, at which a man works most effectively and with the least fatigue; and the process known as 'getting into one's stride' probably involves the adjustment of the speed of work to the natural



rhythm of the individual. Doubtless this rhythm is susceptible to modification by training, and a man may, as a result of practice, attain his optimal efficiency at a higher rate of working than would otherwise be the case. But this can occur only to a limited extent; and the study of fatigue among industrial workers has made it clear that, in so far as it disturbs this rhythm, the process of 'speeding-up' of workers defeats its own end by lessening their mechanical efficiency and by inducing excessive fatigue. It must be remembered, however, that the worker is also inefficient if the rate of work is slower than the natural rhythm of the individual. It follows, then, that, from an industrial point of view, the most effective workers are those whose natural rhythm of work is most rapid, since they can perform more work in a given time without fatigue or loss of efficiency.

So far as the muscles are concerned, the optimum speed of work is that which allows the recovery process, that is to say, the restoration of potential energy, to keep pace with the expenditure of energy in the muscles and heart. If the speed at which work is performed is such that this balance is upset, the accumulation of waste products and the diminishing store of potential energy lessen efficiency by inducing fatigue. But, since the fatigue induced by exercise has its seat primarily, and often exclusively, in the central nervous system, the decline in efficiency, when work is performed at an excessive speed, is probably due quite as much to less effective co-ordination of movement as to changes in the muscles themselves.

There is indeed very little evidence that, under normal conditions, the metabolic conditions of the muscles alter sufficiently to exert any marked influence upon the mechanical efficiency of the body. Zuntz (1903) found that a dog, trained for walking on the level, performed a given amount of work more economically when walking on the level than when climbing. The dog was then trained to ascend an incline, the result being that, after two years, its mechanical efficiency was greater for climbing than for walking on the level. This experiment has been regarded as showing that individual muscles, when trained, work more efficiently than untrained muscles, but the result may equally well have been due to more complete co-ordination of movement as the outcome of training.

It is probable then, that, under the ordinary conditions of

life, the efficiency of the nervous system is the chief factor upon which depends the mechanical efficiency of the body, and that the extent to which training improves the efficiency of the individual is mainly determined by the reactive powers of his nervous system.

Another factor which influences the optimal speed of working is the amount of work which has to be carried out. Work at high speed can only be kept up for a short time, since the onset of fatigue rapidly lowers the efficiency of the body; and the trained worker learns to adjust the rate at which he works to the amount which he has to do. Every climber, for example, knows that the Swiss guide sets a pace which at the beginning of the day appears to him too slow and at the end of the day seems too fast, the truth being that the guide has learned by experience the pace which yields the optimum efficiency.

The Temperature of the Body During Exercise.

In addition to that appearing as external work, part of the energy expended by a man during muscular exercise is utilised by the heart, by the respiratory muscles, and in other ways. But, even taking this into account, a large fraction of the energy set free in the body during exercise is for practical purposes wasted, since it is degraded into heat and lost from the skin and lungs. The loss of heat, however, does not quite equal its production, and the temperature of the body rises until a balance is reached at a higher level.

The first reliable observations on the temperature during exercise were carried out by Pembrey and Nicol (1898), who pointed out that, in order to measure accurately the body temperature, it is necessary to take either the rectal temperature or that of the urine as it leaves the bladder; temperatures taken in the mouth are quite unreliable. Pembrey found that, during exercise, the temperature may reach 38·9° C. (102° F.); and a temperature of 40° C. or even 40·5° C. has been recorded by L. Hill (1910). Pembrey has also emphasised the important fact that the rise of temperature depends, not only on the severity of the exercise, but also on the rate at which heat is lost from the body. The loss of heat is modified by the temperature and humidity of the surrounding air, by the amount and nature of the clothing worn, and by the presence or absence of wi

The influence of some of these factors is indicated by the following figures (Pembrey), obtained from a number of soldiers who marched the same distance on a hot day and on a cold day :—

TABLE VI.

March of Seven Miles.	Average Increase in Pulse-rate per Minute.	Average Increase in Rectal Temperature.	External Temperature.	
			Dry Bulb.	Wet Bulb.
Hot day . . .	62	1·4° F.	79° F.	67·5° F.
Cold day . . .	14	0·8° F.	45° F.	38° F.

The influence of the temperature and humidity of the external air upon the loss of heat from the body, and, therefore, upon the temperature of the body during exercise, is very conspicuous in fat individuals. Owing to the dense covering of subcutaneous fat, the body loses heat less readily (Lusk), and the temperature rises to a greater extent, in fat, than in thin, subjects taking the same amount of exercise.

Among the comparatively few continuous records of the rectal temperature during severe exercise are those of Benedict and Cathcart (Fig. 1). The most striking features, which they observed, are the rapidity with which the temperature rises at the beginning of exercise and falls after its conclusion. The fall in temperature during the exercise in one experiment (Dec. 22) coincided with a diminution in the muscular work performed ; and it is very probable that, other conditions being constant, the rise of temperature during the exercise is proportional to the intensity of the muscular work.

The most important effect of the higher temperature is that it increases the total metabolism of the body, and, therefore, the consumption of oxygen. This effect may be very considerable. Linser and Schmid (1904) found that a rise of 3° C. in the temperature of the body led to an increase of 40 per cent. in the output of carbonic acid. The more active metabolism means more complete oxidation of waste products, the prevention of excessive accumulation of food-stuffs, and a general quickening of the vitality and functional power of every organ, which adds to the well-being and vigour of the whole body. It is of interest to note that it is the oxidation of fat and carbohydrate which is increased,

and not that of protein (Graham and Poulton), whereas, in fever, the breaking down of protein is abnormally large.

Its beneficial effects are perhaps best seen in the case of the muscles. Lagrange (1889) suggested that a rise of temperature increases the efficiency of the skeletal muscles, and that the advantages of a preliminary canter, or of warming up to work, for instance, are due to a rise of temperature in the active muscles.

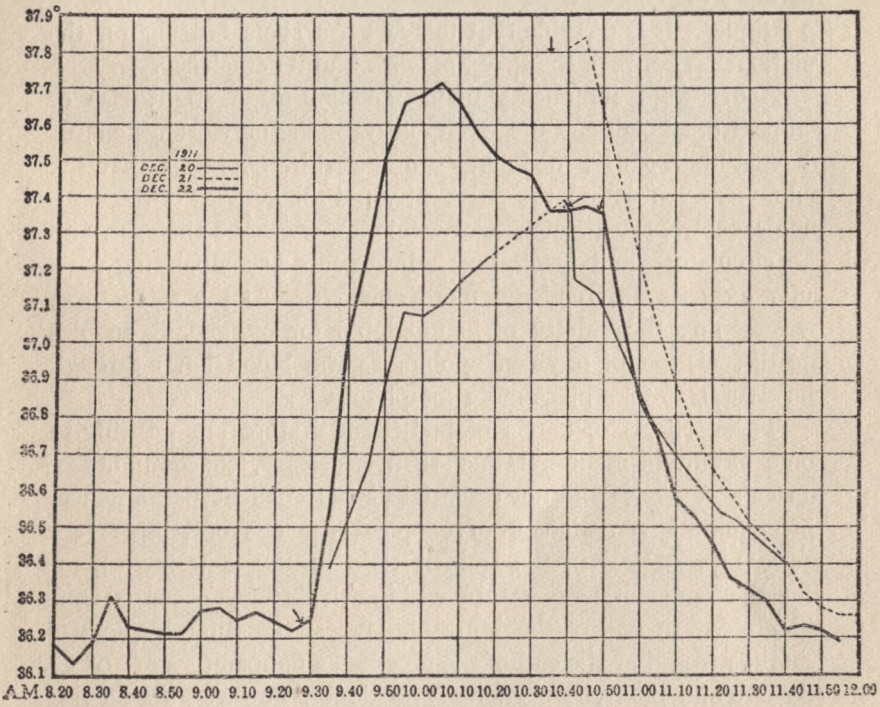


FIG. 1.—Continuous records of the rectal temperature obtained by thermal element during severe muscular work (Benedict and Cathcart). Arrows indicate beginning and end of exercise.

As Pembrey has observed, however, other factors have also to be taken into consideration, such as an increased blood-flow through the muscles, and adjustments of the heart and respiration. Bayliss (1915) has pointed out that the transformation of potential into kinetic energy in the first phase of muscular contraction has a negative temperature coefficient, since it depends upon the development of surface energy and is not an oxidative process, whereas the restoration of energy has a positive coefficient, which

is much larger than the negative coefficient of the physical change. The result is that a moderate rise of temperature will increase the oxidative removal of lactic acid and the restoration of potential energy to the muscles, while not appreciably lessening their power to transform potential into kinetic energy. In this way a rise of temperature during exercise is favourable to muscular work because, by preventing the accumulation of lactic acid, it increases the efficiency of the muscles and lessens their liability to fatigue. It is possible that this fact has some bearing on the relationship between the speed of work and its efficiency.

Apart from its effects upon metabolism, a slight rise of temperature heightens the excitability of the nervous system, or at least that of the medullary centres, with the result that the pulmonary ventilation, the pulse-rate, and the activity of the vasomotor centre, are greater than would otherwise be the case, and the circulatory and respiratory adjustments accompanying muscular exercise are rendered more effective. At the same time, by lessening the affinity of hæmoglobin for oxygen, it enables the dissociation of oxyhæmoglobin, as the blood flows through the tissues, to take place more completely.

These effects of a rise of body temperature are possibly to some extent incidental, rather than necessary, concomitants of muscular exercise and not essential for its efficient performance, since, for a given amount of exercise, the rise of temperature appears to be less in the trained than in the untrained man. But the range of temperature within which they occur is considerable. In one of the Marathon races, the runner who was least distressed at the end of the race had a temperature of 40° C. (Savage and Barasch). There is no doubt, however, that a rise of temperature beyond a certain point is actually harmful to the body, and more especially to the nervous and vascular systems. This point, though varying in different individuals, usually appears to be reached when the temperature rises above 38·9° C. or 39·5° C. Graham and Poulton, who raised their temperature by means of external moist heat, felt no discomfort until the rectal temperature rose to 38·9° C.; at this level restlessness, irritability, and dyspnœa appeared. The ill-effects become more marked as the temperature of the body rises until they culminate in the disorganisation of the bodily functions which constitutes heat-stroke.

Summary.

Under normal conditions protein does not serve as a source of energy during exercise, and the energy expended by the muscles must ultimately be derived from the oxidation of either fat or carbohydrate.

The rise of the respiratory quotient during exercise points to a preferential utilisation of carbohydrate by the muscles, but does not exclude the possibility that they may also obtain energy from the oxidation of fat.

In isolated muscle, the production and subsequent removal of lactic acid, which is an intermediate product of carbohydrate metabolism, are so intimately bound up with the process of muscular contraction that Fletcher and Hopkins regard carbohydrate as being normally the main source of muscular energy. This conclusion is supported by the observation that prolonged activity of isolated muscle diminishes its content of carbohydrate, but not of fat.

The general conclusion is reached that, when both fat and carbohydrate are available, the skeletal muscles display a preference for carbohydrate as a source of energy, but that fat is also utilised for this purpose.

The net efficiency of the bodily machine usually varies from 20 to 25 per cent. and may occasionally reach 33 per cent.

The chief conditions which affect the mechanical efficiency of the body are training, the speed with which work is performed, and fatigue.

The body possesses a natural rhythm which is set by the nervous system, and a man works most efficiently when his speed of working corresponds with this rhythm.

The extent to which the temperature of the body rises during exercise depends, partly on the severity of the exercise and partly upon the temperature and humidity of the atmosphere and other conditions.

The rise in temperature increases the metabolic activity of the body, and adds to the effectiveness of the circulatory and respiratory adjustments occurring during exercise. By these means it promotes the more efficient carrying out of muscular work.

CHAPTER III.

THE RESPIRATORY CHANGES DURING EXERCISE—THE REACTION OF THE BLOOD DURING EXERCISE.

THE evidence derived from the study of isolated muscles makes it clear that they normally contain a considerable store of potential energy, which can be transformed into work and heat in the absence of oxygen. For example, an excised frog's muscle, kept in nitrogen, can give a maximal contraction every five minutes for two hours and a half before showing signs of fatigue (Fletcher, 1902). But this process, at least in mammalian muscle, comes to an end comparatively quickly, unless the energy of the muscle is renewed as rapidly, or almost as rapidly, as it is used up; and this is normally effected by the oxidation of fat and carbohydrate. In health, an ample reserve of fat and carbohydrate is always present in the body, which can be and is drawn upon during muscular work. The disappearance of glycogen from the liver during exercise has been repeatedly demonstrated in animal experiments; and Benedict and Cathcart (1913) have recently calculated that in one of their subjects, during 262 minutes' work, 368 grammes of glycogen were oxidised.

The doctrine that the oxygen needed for these oxidations either is, or can be, stored up in the muscles in excess of their immediate needs has been finally disproved by Fletcher and Brown (1914), and, at any moment, the supply of oxygen available for the tissues barely exceeds the demand. Indeed, in this respect, the body lives practically from hand to mouth, and no hoarding up of oxygen appears to be possible. Muscular work at once increases the consumption of oxygen, the consumption of oxygen per minute varying almost directly with the work done in the same time (Fig. 2); and the relationship is so close that the oxygen-consumption of the body during exercise is now usually taken as a measure of its intensity (Benedict and Cathcart, 1913; Lindhard, 1915; Boothby, 1915).

The oxygen is used only in the recovery processes, but not during actual contraction of the muscle; it is possible therefore to take muscular exercise requiring far more oxygen than can conceivably be supplied through the circulation during exercise itself. The organism thus goes into a heavy 'oxygen debt.' Were it not for the fact that the body is able to meet its liabilities for

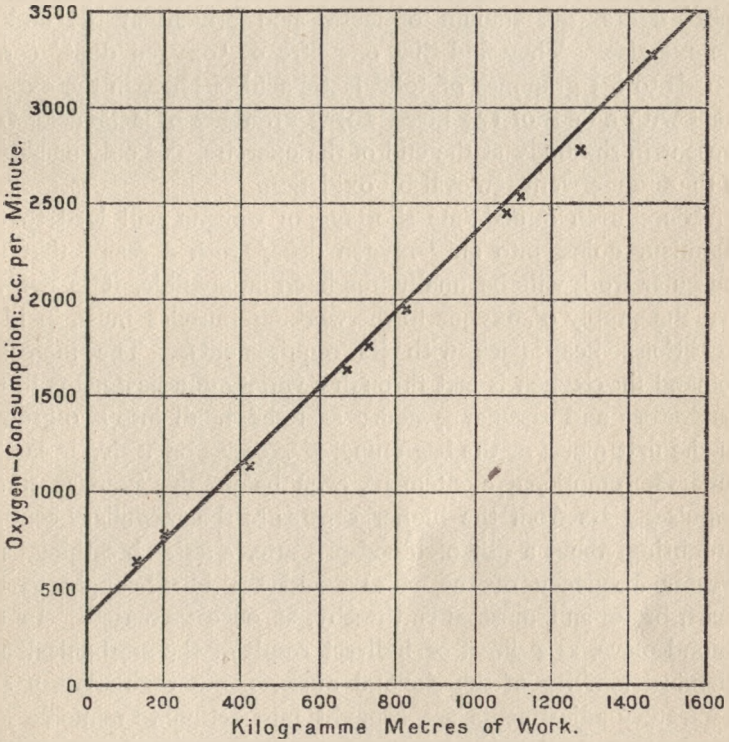


FIG. 2.—(Constructed from Lindhard's data.)

oxygen considerably in arrears, it would not be possible for man to make anything but the most moderate muscular work.

A. V. Hill and Lupton determine the 'oxygen debt' by measuring the amount of oxygen used after cessation of exercise, in recovery therefrom. The maximum figure for 'oxygen debt' they give is 13,250 c.c. of oxygen; this was observed after a violent gymnastic exercise for thirty seconds, involving rapid contraction of all the muscles and leading to exhaustion; this exercise was preceded by a rapid quarter-mile

run. The organism goes into an 'oxygen debt' in every case when the muscular exercise is such that the oxygen requirement exceeds the oxygen intake. Meyerhof has shown that the amount of oxygen consumed in the recovery phase of muscular contraction is sufficient to oxidise only one-sixth of the lactic acid produced, the rest of the lactic acid being restored in the form of glycogen. Hill and Lupton calculate on basis of the 'oxygen debt' figure, the amount of lactic acid present at the end of the exercise. They find that one litre of 'oxygen debt' corresponds to 8·1 grammes of total lactic acid. Thus, in the experiment with a debt of 13¼ litres, 107·2 grammes of lactic acid were present in the body at the end of the exercise, and only one-sixth of these underwent removal by oxidation.

Since even a moderate shortage of oxygen will lead to the organism going into an 'oxygen debt,' with a result that the muscular work will be finally rendered impossible, it is evident that the supply of oxygen to the working muscles must, in ideal conditions, keep pace with its requirements. The increased demand for oxygen is met through a variety of adjustments in the respiratory and vascular system; and these fall into two groups. In the first place, at the beginning of exercise or, if this is carried out under emotional excitement, even before the exercise starts, impulses pass from the higher centres to the medullary centres, and bring about a rise of blood-pressure, deeper breathing, and greater frequency of the pulse; and the blood-supply to the heart, brain, and muscles is, thereby, at once increased. In the second place, as a direct or indirect result of the mechanical and chemical activity of the skeletal muscles, other circulatory and respiratory adjustments are brought into action to reinforce and supplement the initial changes induced through the medullary centres. The nature of these processes, and the means by which they are correlated with the intensity of the muscular work, may now be considered in some detail.

The Respiratory Changes During Exercise.

The part played by the respiratory mechanism during exercise is twofold. On the one hand, it is called upon to provide in the lungs the additional oxygen required by the body; on the other hand, it serves as a delicate mechanism for regulating the reaction of the blood, and for preventing the acids pro-

duced in the active muscles from causing any gross change in the reaction of the blood.

The amount of oxygen which can pass into the blood is determined primarily by the total ventilation of the lungs; and the closeness of the relationship between the pulmonary ventilation and the amount of work performed (as measured by the oxygen-consumption of the body) has recently been brought out by Means and Newburgh (1915), by Krogh and Lindhard (1917),

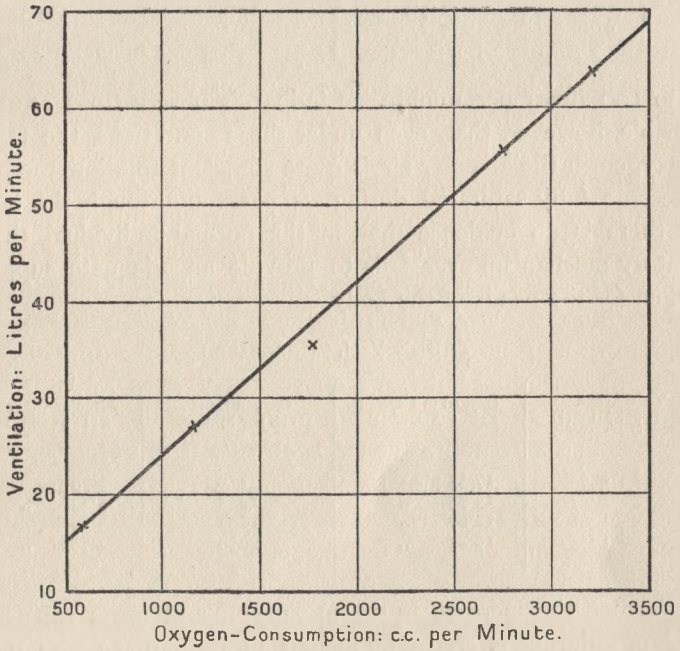


FIG. 3.—Relation between consumption of oxygen and pulmonary ventilation (constructed from Lindhard's data).

and by Boothby (1915), who find that the ventilation of the lungs is approximately a linear function of the oxygen-consumption of the body (Fig. 3 and Table VII.).

The accuracy of the adjustment between the amount of oxygen used by the tissues, and that supplied by the lungs, is equally clearly shown by the trivial alteration in the percentage of oxygen in the alveolar air, however violent the exercise may be. During heavy muscular work the consumption of oxygen may reach 3 litres per minute, and the pulmonary ventilation may be

TABLE VII. (BOOTHBY.)

	Oxygen-Consumption.		Total Pulmonary Ventilation.	
	c.c. per Min.	Percentage Increase, 175 c.c. = 100.	Litres per Minute.	Percentage Increase, 5·5 = 100.
Rest	175	100	5·5	100
	185	105·7	6·7	121·8
Work	320	182	9·8	178
	448	256	12·8	233
	559	320	15·5	282
	608	347·4	16·8	305·5
	912	521	24·1	438

50 to 100 litres per minute. Lindhard's observations render it probable, however, that, even under these conditions, the tension of oxygen in the alveolar air is quite sufficient to allow the blood to become fully saturated during its passage through the lungs; and there is no evidence that, in the normal individual, the respiratory mechanism ever fails to provide an adequate supply of oxygen for the needs of the body.

TABLE VIII. (LINDHARD.)

Ventilation. Litres per Minute.	Oxygen in Expired Air.	Oxygen Cons., c.c. per Minute.	Alveolar CO_2 at 0° and 760 mm. Hg.
14·2	17·55 per cent.	410	3·75 per cent.
32·9	15·74 ,,	1441	5·43 ,,
46·8	16·07 ,,	1893	5·30 ,,
68·2	16·87 ,,	2250	4·78 ,,

Further, the increase in the expansion and mean capacity of the lungs during exercise, by increasing the surface area of the alveoli (M. Krogh, 1915), permits oxygen to diffuse more readily from the alveolar air into the blood than during rest. In this respect, the conditions are more favourable to the passage of oxygen into the blood during exercise than during rest.

The Regulation of Respiration During Exercise.

It may be concluded that, when a man performs muscular work, the activity of his respiratory centre, and therefore the supply of oxygen in the lungs, varies directly with the severity of the work; and the question at once arises what is the nature of the mechanism by which this correlation is effected? Before

attempting to answer this question, it is necessary to consider the conditions which bring about greater pulmonary ventilation during exercise. It is generally admitted that the normal stimulus to the respiratory centre is the chemical composition of the blood. The response of the centre to this stimulus depends, however, not only on the magnitude of the stimulus, but also on the sensitiveness of the centre; and it will be convenient in the first instance to discuss separately these two factors.

The Stimulus to the Respiratory Centre.

The work of Miescher (1885) and of Haldane and Priestley (1905) led them to believe that the normal stimulus to the respiratory centre was the tension of carbonic acid in the arterial blood. A little later, Haldane and Boycott (1908) suggested that the actual stimulus to the respiratory centre is not the tension of carbonic acid but the $H^{\bullet}$ ion concentration of the arterial blood. This has been confirmed by the more recent work of Winterstein (1911) and of Hasselbalch (1912). The latter showed that, by altering the diet, the tension of carbonic acid can be varied, although the reaction of the blood remains constant; and he concluded that the pulmonary ventilation is so adjusted as to maintain the $H^{\bullet}$ ion concentration of the blood constant. According to this view, which has been generally accepted, carbonic acid excites the respiratory centre merely because it acts as an acid when in solution, and the activity of the respiratory centre depends entirely upon the $H^{\bullet}$ ion concentration of the blood. It follows that, provided the sensitiveness of the respiratory centre remains constant, the pulmonary ventilation will vary with, and will furnish an index of, the $H^{\bullet}$ ion concentration of the blood.

Every watery solution contains both $H^{\bullet}$ ions and (OH') ions, and in a perfectly neutral solution, such as pure water, the concentration of the two ions is equal, each of them having a concentration of 1×10^{-7} at 25° C. In an acid solution, the $H^{\bullet}$ ions are in excess of the (OH') ions, the converse being the case in an alkaline solution. Since the product of the $H^{\bullet}$ and (OH') ions in any solution is always the same, namely 1×10^{-14}, the reaction of the solution can be found by determining the concentration of the $H^{\bullet}$ ions. If this is greater than 1×10^{-7}, the solution is acid, whereas if it is less than 1×10^{-7}, the solution is alkaline. The $H^{\bullet}$ ion concentration of a solution, often represented by the abbreviation C_H, is therefore a measure of its acidity; it may also be expressed as its negative exponent, this being termed its P_H value. Thus the negative exponent of 3×10^{-8} is 7·52, and a solution whose C_H is 3×10^{-8} is said to have a P_H value of 7·52. It should be noted that the more acid the solution the *smaller* is its P_H value.

Evidence has recently been brought forward, however, by Hooker, Wilson, and Connett (1917), and by R. W. Scott (1918), that this conclusion is not altogether correct, and that carbonic acid may act as a specific stimulus to respiration independently of its acid properties when in solution. Hooker and his co-workers found that the respiratory centre is excited to a greater degree by blood possessing a high tension of carbonic acid than by blood in which its tension is low, the $H^{\cdot}$ ion concentration of the blood being the same in each case. Scott has shown that, under certain conditions, the respiratory activity does not run parallel with the reaction of the blood but varies with the tension of carbonic acid. It is possible that these results occur only under special conditions, and it has yet to be proved that they hold good in the normal animal. There is, moreover, some doubt as to whether the method adopted by Scott for measuring the $H^{\cdot}$ ion concentration of the blood is reliable.

The Sensitiveness of the Centre.

The sensitiveness of the respiratory centre is probably constant (Haldane) in the resting individual, although Lindhard has brought forward some evidence for the existence of slight seasonal variations. Krogh and Lindhard (1913) have proved, however, that the greater pulmonary ventilation, which occurs at the outset of exercise, can only be the result of increased excitability of the respiratory centre; and they have given grounds for believing that it is brought about by the passage of impulses from the higher centres to the respiratory centre, simultaneously with the outflow of impulses to the skeletal muscles.

Whether this change persists throughout the whole period of exercise is still a matter of discussion. But the activity of the vaso-motor and vagus centres, as well as that of the respiratory centre, is modified at the beginning of exercise by impulses from the higher centres; and, since such impulses almost certainly continue to act upon the vaso-motor centre throughout the period of exercise, it is reasonable to believe that this is the case also as regards the respiratory centre, and that during exercise this centre is always more excitable than during rest. Again, the observations of Haldane (1905) make it clear that a rise of body-temperature heightens the excitability of the respiratory centre;

the rise of temperature during exercise must therefore enhance the responsiveness of the respiratory centre to increased $H^{\bullet}$ ion concentration of the blood.

The hyperpnœa or dyspnœa occurring during muscular exercise has, therefore, a twofold origin. On the one hand, the greater production of acid in the active muscles tends to increase the $H^{\bullet}$ ion concentration of the blood, and Boothby has brought forward some indirect evidence that the change in the reaction of the blood is proportional to the severity of the work done. On the other hand, the excitability of the centre is heightened in the manner just described, and this change also is probably proportional to the amount of muscular work, since both the rise of body-temperature and the outflow of impulses from the higher centres to the respiratory centre will usually be greater during heavy work. Hence the correlation between the pulmonary ventilation and the severity of muscular work appears to depend partly upon the fact that the $H^{\bullet}$ ion concentration of the blood varies with the activity of the muscles, and partly upon the correspondence between the intensity of the impulses sent out from the higher centres to the muscles and to the respiratory centre respectively. This relationship is obviously liable to be disturbed either by excessive production of acid in the active muscles, or by exaggeration of the excitability of the respiratory centre, a result which may follow upon an inadequate oxygen-supply. The extreme hyperpnœa, which may be brought on by comparatively slight exertion in cases of 'soldier's heart,' for example, represents a disturbance of the normal relationship which is possibly caused by one or other of these means.

A further consequence which follows upon the above line of argument is that, owing to the greater excitability of the respiratory centre, a comparatively trivial change in the reaction of the blood is needed in order to bring about a large increase in pulmonary ventilation. This conclusion is of significance, since the increased $H^{\bullet}$ ion concentration of the blood during exercise has been credited with modifying the activity, not only of the respiratory centre, but of other centres and organs. It seems desirable, therefore, to refer to the factors which regulate the reaction of the blood, and to the extent to which this alters during exercise.

The Reaction of the Blood.

It is well known that the addition of fixed acid to blood or blood-plasma produces a much smaller change in its reaction than if the same amount of acid were added to pure water. The difference depends upon the fact that blood, or plasma, contains substances which react with the acid to form compounds dissociating to a very slight extent and, therefore, setting free very few H ions. In virtue of their action in stabilising the reaction of the blood, and in preventing any gross change in its reaction when acid is added to it, these substances have been termed 'buffer' substances. This buffer action was formerly attributed (Moore and Wilson, 1906) to the proteins in the plasma, but L. J. Henderson (1908) has shown that the power of protein to react with weak acids or alkalies does not come into play, except to a very limited extent, so long as the $H^{\bullet}$ ion concentration of the blood is within the limits compatible with life. The only buffer substance of practical importance present in blood-plasma is sodium bicarbonate. When a fixed acid is added to blood, it reacts with sodium bicarbonate, setting free carbonic acid, but, owing to the very slight dissociation of H_2CO_3, the addition of a considerable amount of strong acid, and therefore of a large number of free $H^{\bullet}$ ions, results in a very slight change in its reaction.

Hence the reaction of the blood, as L. J. Henderson and Hasselbalch (1912) have shown, is represented by the equation $C_H = K\frac{H_2CO_3}{NaHCO_3}$, in which the numerator indicates the concentration of HCO_3 ions, and is proportional to the tension of carbonic acid in the blood, the denominator is the amount of sodium bicarbonate in the plasma, and K is the dissociation constant of H_2CO_3.

The addition of carbonic acid to blood *in vitro* alters its reaction solely by increasing the number of $H^{\bullet}$ and HCO_3 ions, whereas fixed acid, when added to blood, increases its $H^{\bullet}$ ion concentration by reacting with sodium bicarbonate, thereby lessening the amount of this salt in the plasma, and at the same time increasing the carbonic acid in the blood. It is clear that, if the tension of carbonic acid in the blood is kept constant, the reaction of the blood will vary inversely with the amount of

sodium bicarbonate in the plasma, and that, on the other hand, if the bicarbonate remains unchanged, the reaction of the blood varies with the tension of carbonic acid.

When the blood is circulating in the body, the respiratory centre at once reacts to the slightest rise in the $H^{\bullet}$ ion concentration of the blood, whether this is effected by an increase in the numerator or a decrease in the denominator of the equation $C_H = K \frac{H_2CO_3}{NaHCO_3}$; and, if the centre remains efficient, the reaction of the blood cannot alter greatly, provided the bicarbonate factor has not been greatly decreased. For this reason, the bicarbonate of the blood has been termed its 'alkali-reserve' (Van Slyke).

The buffers of the blood can be described as substances holding in combination alkali which can be made available to carry CO_2 or any other acid. When CO_2 leaves the blood the alkalis recombine with the buffer substances. The buffer substances, dissolved in the plasma (bicarbonates, phosphates), are very weak as compared with the buffers concentrated within the red blood corpuscles. If the buffer action of the blood were exclusively determined by the salts dissolved in the plasma, a solution of these salts in water would be expected to have as an efficient buffer action as blood. It is found, however, that such a solution of salts has a buffer action very like the one of the plasma, but much less than that of the blood. This proves that the red blood corpuscles play a very important part in stabilising the reaction of the blood. Hæmoglobin is the chief buffer in the red cells. Van Slyke calculates that 80 to 95 per cent. of the alkali used to carry the excess of CO_2 in the venous blood over that of the arterial is furnished by hæmoglobin. Hæmoglobin liberates alkali, which is used to carry the CO_2 in two ways. A smaller part of the alkali is furnished by the unchanged oxyhæmoglobin which is itself an efficient buffer at the reaction of the blood. The greater part of alkali is set free when the relatively strong acid, oxyhæmoglobin, is changed by loss of oxygen to the much weaker acid, reduced hæmoglobin.

There is another mechanism by which the red blood corpuscles influence the reaction of the blood. Zuntz (1861), and, later, Hamburger (1897), have shown that addition of carbonic acid to the blood produces an alteration in the distribution of the anions between the corpuscles and the plasma. In these circumstances

acid radicles migrate from the plasma into the red cells. On evolution of the CO_2 from the blood a reverse change takes place, and anions migrate from the cells into the plasma, thus to some extent preventing the plasma from becoming too alkaline. Cl ions are the main ions concerned in this interchange. Under increased tension of CO_2 the red blood cells withdraw Cl ions from the plasma NaCl, thereby leaving an excess of Na to form $NaHCO_3$. The changes in Cl concentration in the plasma have been quantitatively demonstrated by Gürber, Hamburger, Van Slyke, and Cullen, and lately by Mukai, Dautrebane, and Davis.

TABLE VIII A.—(MUKAI.)

	CO_2 Tension in mm.	Per Cent. NaCl in Serum.
1.	Exposed to Air.	0·639
2.	143	0·602
3.	225	0·564
4.	263	0·554
5.	309	0·545
6.	347	0·489

Per cent. of NaCl in serum of dog's defibrinated blood exposed to different tensions of CO_2.

There is every reason to believe, as Van Slyke (1917) points out, that a similar interchange takes place between the plasma and the tissues, in which phosphates form a buffer salt system. The importance of the part played by the tissues and red cells, in preventing an excessive fall in the bicarbonate of the blood-plasma during exercise, will depend upon the rapidity with which this interchange occurs, but it is probable that, at least during prolonged exercise, it contributes considerably to checking any marked change in the reaction of the blood.

Anrep and Cannan have shown that the tissues play an important part in stabilising the reaction of the blood by furnishing to the blood or removing from the blood lactic acid. If an animal is kept for some time over-ventilated so as to diminish the CO_2 content of its blood, it is found that there is an accumulation of lactic acid in the blood. As soon as the CO_2 of the blood is artificially increased the lactic acid concentration of the blood begins to fall. The retention of the lactic acid in the blood and its disappearance did not depend in these experiments on any changes in the oxygen saturation of the blood, since, in the experiments of Anrep and Cannan, the blood was kept fully saturated with oxygen. It is to a large extent also independent of glycolysis of the blood sugar. No disappearance of lactic acid produced by glycolysis could be observed by sub-

mitting shed blood to high tensions of CO_2; evidently the removal and to a large extent the production of lactic acid is under these conditions a function of the tissues, which tends to keep the reaction of the blood nearer to its normal limits.

TABLE VIII B.—(ANREP AND CANNAN.)

Time from Beginning of Experiment.	Per Cent. CO_2 in Respired Air.	CO_2 Content of the Blood.	P_H	Lactic Acid mgm. Per Cent.	Sugar mgm. Per Cent.
1 hr.	air	12	7·78	85	221
1 hr.	6·3	—	—	—	—
2 hrs.	6·3	45	7·32	52	165
3 hrs.	6·3	51	7·34	32	120
4 hrs.	6·3	66	7·20	21	102
4 hrs.	air	—	—	—	—
5 hrs. 10 mins.	air	18	7·80	59	39

Experiment with a heart-lung preparation.

The Reaction of the Blood during Exercise.

The reaction of the arterial blood during exercise has never been directly investigated, but the observations of Douglas and Haldane (1913) have yielded data from which it is possible to calculate approximately the maximum extent to which this may alter during exercise. They found that, in the resting subject, a rise of 1·6 mm. in the alveolar tension of carbonic acid increases the total pulmonary ventilation by 10 litres a minute; and their observation has been confirmed in the later work of Campbell, Douglas, and Hobson (1914). Taking this figure in conjunction with Hasselbalch and Lundsgaard's (1912) work on the relation between the alveolar tension of carbonic acid and the C_H of the blood, they point out that it represents an increase of $0{\cdot}13 \times 10^{-8}$ in the C_H of the arterial blood, or a change of 0·02 in the P_H of the blood. Assuming, first, that this relationship holds good whatever the pulmonary ventilation may be, and, second, that the excitability of the respiratory centre remains constant, it is only necessary to determine the pulmonary ventilation during exercise in order to measure the effect of exercise upon the reaction of the blood.

The range of pulmonary ventilation is very large, and a short period of violent exercise, such as 100 yards' race, may lead to a ventilation of 150 litres per minute or even more. But, since a man may run 100 yards without taking a breath, the extreme dyspnœa, thereby produced, takes place after the exercise is over, and probably could not be maintained for any length of

time. During less severe work, which can be carried on for some time, the pulmonary ventilation does not usually exceed 100 to 120 litres per minute, and this figure is probably near the limit reached by most individuals during severe continued work.

If the premises just stated are correct, an increase of 100 litres in the pulmonary ventilation would result from a rise of $1{\cdot}3 \times 10^{-8}$ in the C_H of the blood which is equivalent to a decrease of 0·15 in its P_H value. But, owing to the greater sensitiveness of the respiratory centre during exercise, a much smaller change in the reaction of the blood would probably suffice to bring about such an increase in the pulmonary ventilation. The range of variation in the P_H value of arterial blood during exercise, unless this

TABLE VIII c.

	Alveolar CO_2 Tension.	Oxygen-Tension.	Percentage Saturation of Blood with O_2.	Value of K.
After the ascent . .	35 mm.	27·5	40 per cent.	0·000168
Normal	40	27·5	53 ,,	0·000292

In order to arrive at the change in the reaction of the blood which would cause this decrease in the affinity of hæmoglobin for oxygen, Barcroft makes use of what is known as the Barcroft-Peters curve (Fig. 4), which shows the P_H of the blood represented by the negative logarithm of any given value of K. K is a constant in the equation $\frac{y}{100} = \frac{Kx}{1 + K}$, where y = percentage saturation of the blood with oxygen, and x = the oxygen-pressure to which the blood is exposed.

is very severe, is therefore very small, being in all probability considerably less than 0·15.

The only other observations bearing upon this question are those of Barcroft (1914), who availed himself of the fact that any increase in the C_H of the blood, by lessening the affinity of hæmoglobin for oxygen, alters the form of the dissociation curve of oxyhæmoglobin. One of Barcroft's experiments consisted in climbing 1,000 feet, from sea-level in half an hour; and he notes that the rate of climbing entailed no sort of distress, and that "roughly speaking this meant going up at the fastest rate at which respiration could comfortably be performed through the nose." At the end of the walk samples of his blood and alveolar air were collected. The carbonic acid tension of the alveolar air was 35 mm. Hg, and the blood, when exposed in a tonometer to

this tension of carbonic acid and to an oxygen tension of 27·5 mm. Hg, became 40 per cent. saturated. The figures in Table VIII C. show the effect of the exercise upon the affinity of Barcroft's blood for oxygen.

When the P_H of the blood is plotted directly against the negative logarithm of the constant K, it is found that the latter is practically a linear function of the former (Fig. 5). In the experiment just described, the P_H of Barcroft's blood before exercise was 7·29 and after the exercise 7·09. Barcroft further determined that the change in the affinity of his hæmoglobin for oxygen, brought about by the exercise, corresponded with that produced by the addition to his blood of sufficient lactic acid to make its percentage in the blood 0·023 per cent.

The occurrence of a change of this magnitude in the reaction of the blood during moderate exercise is very difficult to understand, in view of Campbell, Douglas, and Hobson's observation that a fall of 0·02 in the P_H value of the blood increases the pulmonary ventilation by 10 litres a minute.

If this is the case, a fall of 0·2 in the P_H of the blood would certainly produce extreme dyspnœa, whereas it is clear from Barcroft's description of his climb that he experienced no respiratory distress.

TABLE IX.—Reaction of the Blood during Exercise as Calculated (*a*) from Haldane's Data and (*b*) from Barcroft's Experiment.

	(*a*) Haldane.		(*b*) Barcroft.	
	C_H.	P_H.	C_H.	P_H.
Rest	3×10^{-8}	7·52	5×10^{-8}	7·29
Moderate exercise .	—	—	8×10^{-8}	7·09
Severe exercise . .	$4·3 \times 10^{-8}$	7·37	—	—

The difficulty of reconciling these results is not lessened by Bayliss' observations on the actual change in reaction, produced by the addition of acid to blood, either *in vitro* or *in vivo*.

Bayliss (1918) added varying amounts of acid to cat's blood-plasma, this being exposed to a constant tension of carbonic acid (about 40 mm. Hg), so that any change in the reaction of the plasma was due entirely to reduction of the alkali-reserve. He found that the addition of sufficient acid to neutralise half the sodium bicarbonate in the plasma altered its P_H value from 8·0 to

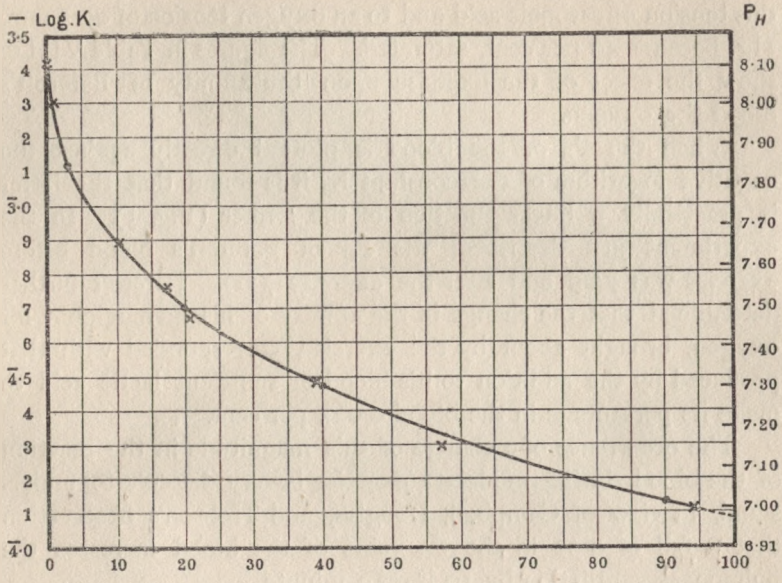


FIG. 4.—Barcroft-Peters curve. Abscissa = CO_2 pressure in millimetres.

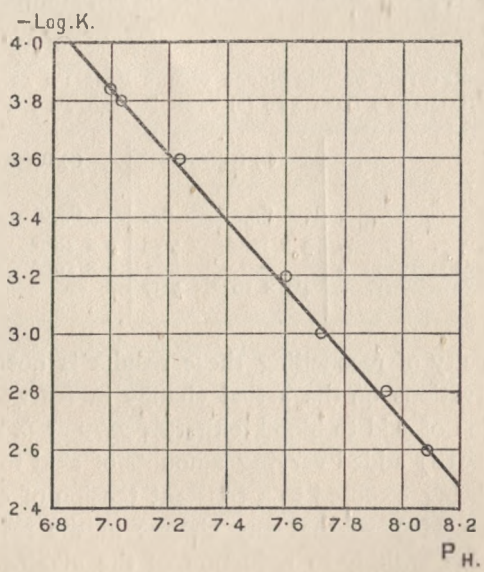


FIG. 5.—Barcroft-Peters curve (from Hasselbalch).

6·8, an increase of 3×10^{-8} in its $H^{\cdot}$ ion concentration. The same sample of plasma was then exposed to carbonic acid at a tension of only 20 mm. Hg, with the result that its reaction became the same as it had been before the addition of acid. This experiment demonstrates, first, the trivial change in the reaction of the blood produced by a considerable reduction of its content of sodium bicarbonate, and second, that, when the plasma bicarbonate and the tension of carbonic acid in the plasma are simultaneously reduced to half their normal value, the ratio $\frac{H_2CO_3}{NaHCO_3}$, and, therefore, the reaction of the blood are unchanged. In the normal animal, the sensitiveness of the respiratory centre is such that a very considerable fall in the alkali-reserve of the plasma may be completely counterbalanced by increased pulmonary ventilation, and the reaction of the blood may remain unchanged. Bayliss showed that, when acid was added to the circulating blood, no change in its reaction could be detected when one-third of the bicarbonate in the plasma had been neutralised, since the tension of carbonic acid was simultaneously lowered by increased pulmonary ventilation.

The reaction of the blood was determined by means of standard phosphate mixtures, using neutral red as an indicator. This indicator is particularly valuable for estimating the reaction of blood plasma, since it is but little affected by proteins and salts, and it changes colour when the $H^{\cdot}$ ion concentration is just above or below the normal reaction of the blood (Sörensen, Miss Homer).

Barcroft calculated that the amount of lactic acid added to his blood, during his climb of 1,000 feet, was such that it then contained 0·023 per cent. lactic acid. Bayliss finds that this amount of acid, if added to blood-plasma, combines with only one-eighth of the sodium bicarbonate in plasma, and that the change in the reaction of the blood, thereby produced, is imperceptible. The evidence brought forward by Bayliss suggests that the effect of exercise upon the reaction of the blood cannot have been so large as Barcroft's experiments led him to suppose. The method usually adopted by Barcroft for ascertaining the amount of lactic acid present in blood was that originally devised by Mathison. It consists essentially in determining the amount of acid which must be added to normal blood in order to render its dissociation curve identical with that of the blood under examination; both samples of blood are exposed to a constant tension of carbonic acid. Since the tension of carbonic acid

is kept constant, it is clear that Mathison's method merely measures the alkali-reserve of the blood and gives very little indication of the $H^{\bullet}$ ion concentration of the blood while yet in circulation.

Further, it has been observed by Hasselbalch (1917) that the relation between the P_H of the blood and the negative logarithm of the constant K in the formula $\frac{y}{100} = \frac{Kx}{1 + K}$ does not hold good for all individuals; and, under some pathological conditions, his results showed considerable deviation from the linear relationship represented in the Barcroft-Peters curve. A similar deviation was observed by T. R. Parsons and W. Parsons, in conjunction with myself, in a single experiment on the effects of exercise upon the reaction of the blood, Barcroft's method showing a greater rise in the C_H of the blood than did the gas electrode.

The occurrence of this deviation at once suggests that the key to the difference between Barcroft's results and those calculated from Haldane's data as to the reaction of the blood during exercise is to be found in the fact that Barcroft's method measures the reaction of the red cells, whereas the activity of the respiratory centre depends on the C_H of the plasma. While, in the resting individual, the red cells and the plasma are presumably in equilibrium, it seems possible, as J. W. Trevan[1] has suggested, that, owing to the interchange of acid-radicles between the red cells and plasma during exercise, the C_H of the red cells may increase more than does that of the plasma. The occurrence of such a change would account for the divergence between Barcroft's results and calculations based on Haldane's data. Again, as Barcroft and Camis (1909) have shown, the affinity of hæmoglobin for oxygen is influenced, not only by the reaction of the blood, but also by other factors and notably by electrolytes. It is conceivable, therefore, that during exercise changes may take place in the character of the salts in the red cells, and that these may disturb the normal resting relationship between the reaction of the blood and the constant K. There is no clear evidence, however, of such changes, and the actual alteration in the reaction of the arterial blood during exercise still awaits investigation, though it is probable that, partly owing to the efficiency of the respiratory centre, and partly as the result of the stabilising influence of the

[1] Private communication.

red corpuscles and of the tissues, this alteration is extremely small.

Whatever may be the extent to which it occurs, the change in the reaction of the blood during exercise must be effected, either by a rise in the tension of carbonic acid in the blood, or by a diminution of its alkali-reserve, or by a combination of these two processes. The active muscles produce both lactic and carbonic acids, though, if the exercise is gentle, the lactic acid is apparently completely oxidised in the muscles, and the rise in the C_H of the blood is due solely to a rise in the tension of carbonic acid in the blood.

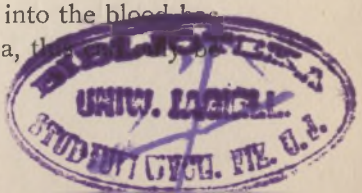
During vigorous exercise some lactic acid escapes oxidation and passes into the blood, and Ryffel (1909) showed, by direct

TABLE X.—(DOUGLAS AND HALDANE.)

Nature of Exercise.	Tension of Carbonic Acid in Alveolar Air.		
	Rest.	During Exercise.	After Exercise.
(1) C.G.D. walking 600 yds. at 5 miles per hour .	39·75 mm. Hg	45·4	10 mins. later, 39·6
(2) C.G.D. walking 600 yds. at 6 miles per hour .	39·75 mm. Hg	44·5	15 ,, ,, 36·8
(3) C.G.D. running 300 yds. in 52 seconds . .	39·50 mm. Hg	—	25 ,, ,, 34·1

analysis, that, after severe exercise, the blood may contain as much as 0·07 per cent. lactic acid. The acid, by reacting with the plasma bicarbonate, lessens the alkali-reserve of the blood and at the same time sets free carbonic acid. Vigorous exercise, therefore, alters the ratio $\frac{H_2CO_3}{NaHCO_3}$, and increases the C_H of the blood, and, consequently, the pulmonary ventilation, not only by raising the tension of carbonic acid, but also by lessening the bicarbonate in the plasma.

After the exercise is over, the hyperpnœa continues until sufficient carbonic acid is removed from the blood to bring back the *ratio* $\frac{H_2CO_3}{NaHCO_3}$, that is to say, the reaction of the blood, to its normal value; and, if the passage of lactic acid into the blood has lessened the bicarbonate content of the plasma, the



effected by a corresponding fall in the tension of carbonic acid in the blood (and alveolar air). Hence a low alveolar tension of carbonic acid, shortly after exercise, not only indicates that lactic acid has passed into the blood, but is to some extent a measure of the extent to which this has occurred; and Haldane and Douglas (1909) have demonstrated that after vigorous exertion, a considerable fall may take place in the alveolar tension of carbonic acid.

The Significance of Lactic Acid in the Blood during Exercise.

If the concentration of lactic acid in the skeletal muscles increases, some of the acid diffuses into the blood; and the presence of lactic acid in greater amount in the blood during exercise implies that lactic acid is being formed in the muscles more rapidly than it can be oxidised. The rate at which lactic acid is produced almost certainly varies directly with the activity of the muscles; the rate of its oxidative removal depends upon the ability of the oxidative mechanism in muscle to effect its oxidation, and upon the presence of an adequate supply of oxygen for this purpose.

It is not difficult to imagine that, even though the supply of oxygen is ample, the oxidative mechanism may be unable to deal immediately with the whole of the lactic acid presented to it during severe exercise. The nature of this mechanism is unknown, but, presumably, it is due to some catalytic process into which the factor of time must enter. However efficient the oxidative mechanism may be, the oxidation of lactic acid cannot be instantaneous, and, assuming that the rate at which lactic acid can be oxidised is a limiting factor, it is quite conceivable that the rate of production of lactic acid may outstrip the rate at which it is oxidised; and the excess will pass into the blood. If this view is correct, the process would be comparable with the hyperglycæmia which occurs, when the ability of the liver to form glycogen is overtaxed by the sudden entrance of an excess of glucose into the portal circulation.

The usually accepted view, however, is that the presence of lactic acid in the blood during exercise is the result of an inadequate supply of oxygen to the active muscles. It appears to have originated as the outcome of the work of Araki (1894), who found lactic acid in the blood of animals in which the oxygen-

carrying power had been diminished by the administration of carbon monoxide. Hill and Flack (1909) have brought forward good evidence that very violent exertion may lead to an acute and marked deficiency in the supply of oxygen to the body; and Barcroft and his co-workers (1915) observed that a combination of exercise with an inadequate supply of oxygen, namely, exercise at a high altitude and in unacclimatised individuals, caused a large increase in the amount of lactic acid in the blood. It seems clear, therefore, not only that lack of oxygen may occur during exercise, but that it may be sufficient to interfere with the normal oxidation of lactic acid; in these circumstances lactic acid will undoubtedly enter the blood in larger amount.

But the point at issue is not whether an acute and unmistakable lack of oxygen may cause the accumulation of lactic acid in muscle and its passage into the blood, but whether the appearance *during moderate exercise* of a small amount of lactic acid in the blood has necessarily the same significance. The evidence that this is the case is by no means convincing. Barcroft found that half an hour's walk, which entailed "no sort of respiratory distress," increased appreciably the amount of lactic acid in his blood; and, if this were the result of lack of oxygen, it would be necessary to believe that the circulatory and respiratory adjustments taking place during exercise fail to fulfil their function, except when the exercise is very gentle.

Again, there is a considerable body of evidence that a moderate lack of oxygen, unless this is prolonged, does not lead to the appearance of lactic acid in the blood. Ryffel 1909 (found) that, even when the percentage of oxygen in alveolar air was reduced to 4 per cent. for fifteen minutes, the amount of lactic acid in the blood was unchanged. In another experiment, he spent three hours and twenty minutes in a respiration chamber, in which the tension of oxygen was gradually lowered. At the end of the experiment, his alveolar air contained 4·15 per cent. of oxygen, but there was no increase in the lactic acid in his blood. The percentage of lactic acid rose only when experiments of this kind were prolonged for four hours or more.

Since lactic acid may pass into the blood during exercise under conditions which appear to preclude an inadequate supply of oxygen, and since, on the contrary, a considerable deficiency in oxygen-supply does not necessarily raise the percentage of

lactic acid, the appearance of lactic acid in the blood during moderate exercise hardly warrants the conclusion that the oxygen-supply to the active muscles is necessarily inadequate.

Although the available evidence scarcely justifies a decision as to the significance of the appearance of lactic acid in the blood during *moderate* exercise, the conception that it represents merely a lag in the working capacity of the oxidative mechanism, as compared with the production of lactic acid, is at least as reasonable as the view that a shortage of oxygen-supply exists during moderate exercise in a healthy man.

Summary.

The oxygen-consumption of the body per minute during exercise varies almost directly with the amount of external work performed, and an equally close relationship exists between the pulmonary ventilation and the oxygen-consumption of the body.

The greater pulmonary ventilation during exercise is due, partly to a rise in the $H^{\cdot}$ ion concentration of the blood, and, probably, partly to a greater sensitiveness of the respiratory centre to this stimulus, the latter being brought about by an outflow of impulses from the higher centres to the respiratory centre concomitantly with the passage of impulses from the cerebral cortex to the skeletal muscles. Since both the $H^{\cdot}$ ion concentration of the blood and the excitability of the respiratory centre probably increase *pari passu* with the severity of the muscular work, the correspondence between the pulmonary ventilation and the amount of muscular work can be adequately explained.

The $H^{\cdot}$ ion concentration of the blood is represented by the expression $K\frac{H_2CO_3}{NaHCO_3}$, where H_2CO_3 is proportional to the tension of carbonic acid in the blood, $NaHCO_3$ is the amount of sodium bicarbonate in the plasma, and K is the dissociation constant of H_2CO_3.

During exercise the $H^{\cdot}$ ion concentration of the arterial blood is increased, not only by a rise in the tension of carbonic acid in the blood but also usually by a decrease in the bicarbonate of the plasma, this being caused by the passage of lactic acid into the blood. The efficiency of the respiratory centre is such that the tension of carbonic acid does not rise greatly, and the

exchange of acid and basic radicles between the blood-plasma and the red cells and the tissues probably prevents any serious decrease in the bicarbonate of the plasma. As a result of these regulating processes, the reaction of the arterial blood alters very slightly during exercise.

The suggestion is put forward that the appearance of lactic acid in the blood during moderate exercise does not necessarily indicate an inadequate supply of oxygen to the muscles, but that it may merely represent a discrepancy between the rate at which lactic acid is produced and the rate at which it can be oxidised by the muscles.

CHAPTER IV.

THE OUTPUT OF THE HEART DURING EXERCISE.

The Diastolic Filling of the Heart. The Output per Beat. The Size of the Heart during Exercise.

IN order that the greater pulmonary ventilation during exercise may contribute effectively to meeting the requirements of the body for oxygen, two conditions must be fulfilled. In the first place, the arterial blood leaving the lungs must be as fully, or almost as fully, saturated with oxygen as during rest. In the second place, the rate of the blood-flow round the body as a whole (the circulation rate) must correspond with the degree of pulmonary ventilation. Assuming for the moment that the first condition is fulfilled, it is clear that the closer the correlation between the pulmonary ventilation and the circulation rate, the more efficiently will the respiratory and circulatory systems carry out their function of providing in the lungs, and transporting to the tissues, the oxygen needed during exercise. Greater pulmonary ventilation, for example, if unaccompanied by a more rapid circulation rate, would scarcely alter the amount of oxygen reaching the tissues in a given time.

That, during exercise, a definite relationship does exist, not merely between the pulmonary ventilation and the circulation rate, but also between these two processes and the amount of muscular work performed, is shown in Fig. 6. But, before entering on a discussion of the question as to how this relationship is brought about, it is necessary to consider the factors which regulate the circulation rate. The rate of the blood-flow round the body as a whole depends entirely upon the output of the heart per minute, and the other circulatory adjustments, occurring during exercise, are of value chiefly in that they enable the output of the heart to be utilised to the greatest advantage in supplying blood to the active organs.

The Output of the Heart.

Although the earlier observations of Loewy and v. Schrötter (1905) and of Plesch (1909) suggested that the output of the heart in man was increased by muscular work, the methods which they

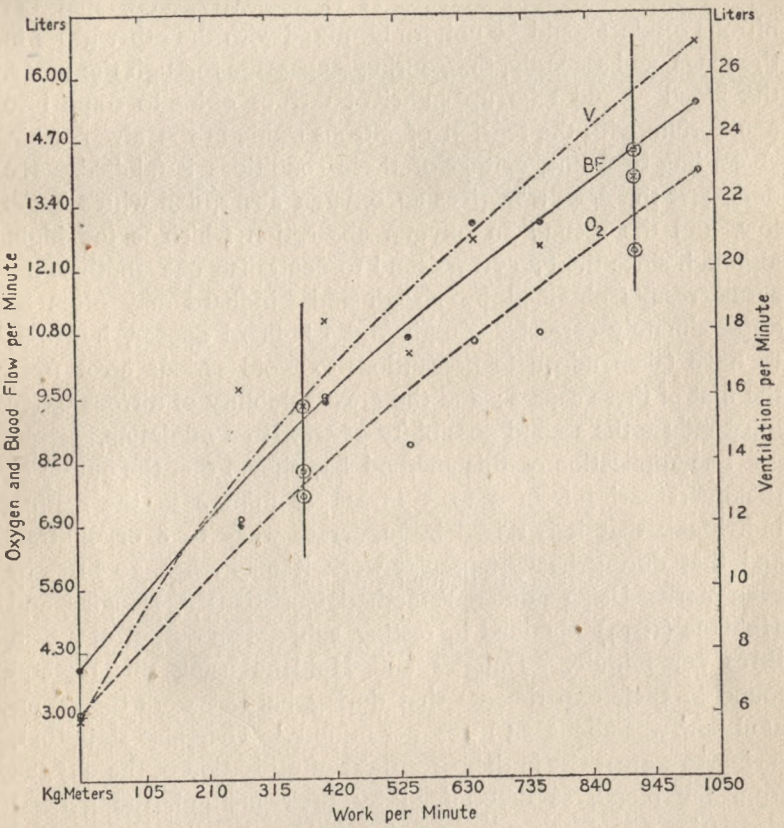


FIG. 6.—(Means and Newburgh.)
BF = circulation rate (blood-flow).
V = pulmonary ventilation.
O_2 = oxygen consumption.

adopted were so indirect that their results were inconstant and of rather doubtful value. Plesch calculated, for example, that during exercise the output of the heart might reach the almost incredibly high figure of 45 litres per minute. The first really accurate observations on the output of the heart in man were made by Krogh (1912), who employed, in a greatly improved

form, the nitrous oxide method first devised by Zuntz, Markoff, and Müller (1911). Its trustworthiness has been confirmed by Boothby (1915) and by Lindhard (1915), and the latter has improved it in some respects. The method has been criticised by Sonne (1918), who points out that two conditions are essential for its successful application. It is necessary, first, that the nitrous oxide should be uniformly mixed with the other gases in the lungs, and secondly, that, during its passage through the lungs, the blood should take up sufficient nitrous oxide to come into equilibrium with the tension of nitrous oxide in the alveolar air. According to Sonne, neither of these conditions is fulfilled. He finds that the first error gives an oxygen absorption which is too low, and the second an oxygen absorption which is too high, although since the two errors tend to neutralise one another, the actual results obtained by Krogh and Lindhard may often be approximately correct. Krogh and Lindhard appear, however, to have taken adequate precautions to avoid serious error from the first of these causes; and the great solubility of nitrous oxide must reduce the second possibility of error to a minimum.

The application of this method has shown that the output of the heart varies from 3 to 5 litres per minute in the resting individual, that it is raised by moderate work to 8 or 9 litres, and that during heavy muscular work it may reach 20 litres or even more. Using a different method, Christiansen, Douglas, and Haldane (1914) obtained in resting subjects an output of 5 to 8 litres per minute. Douglas and Haldane using this method found in their experiments that during hardest work the estimated flow was about 24 litres per minute. They also state that, owing to a great rise in the percentage of utilisation of the oxygen from the blood, as determined by their method, the general circulation rate does not increase in anything like direct proportion to the general metabolism, except when the work has already become so hard that little or no further increase in percentage utilisation occurs.

The blood output per heart beat is, according to Douglas and Haldane, in many subjects no greater during either moderate or hard work than during rest, and is about 120 c.c. for a man of average weight. In other subjects, however, the output per beat is considerably less than this during rest, and increases considerably during work.

Taking the oxygen-consumption of the body as a measure of its metabolic activity, Means and Newburgh (1915), Boothby (1915), and Lindhard (1915) further find that the output of the heart per minute runs practically parallel with the consumption of oxygen (Fig. 6); and, since the increased consumption of oxygen during exercise takes place mainly in the active muscles, including the heart, it is for practical purposes a measure of the work done by the body. In some of Lindhard's, and of Means'

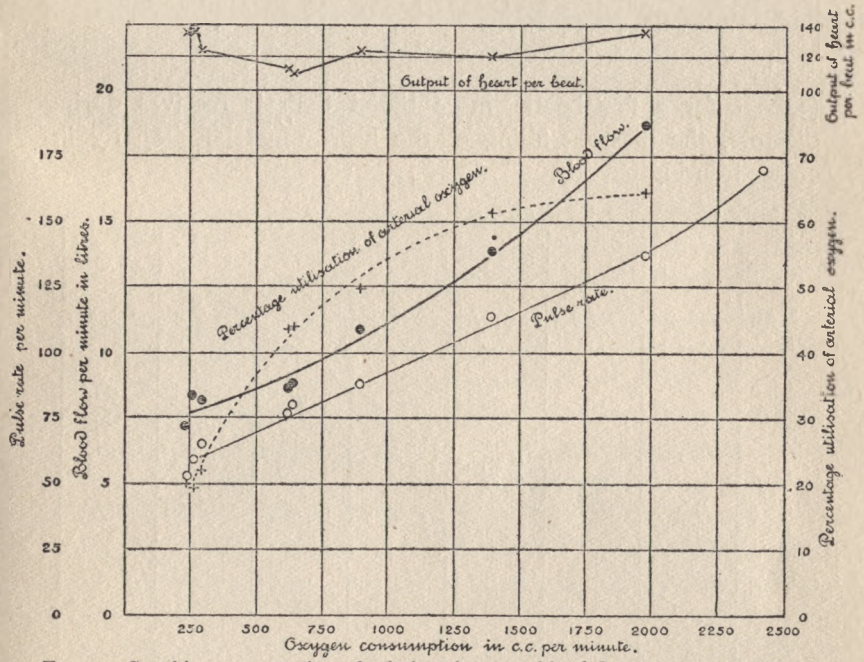


FIG. 7.—Graphic representation of relations between blood-flow, percentage utilisation of arterial oxygen, pulse-rate, and output of the heart per beat with varying general metabolism in the experiments on Douglas. (Douglas and Haldane.)

and Newburgh's experiments the external work, which consisted in pedalling a bicycle ergometer, was measured, and an almost linear relationship was observed between the work performed and the output of the heart (Fig. 8).

The highest figures in Table XI. must represent almost the maximal output of which the heart is capable, even in a powerful and highly trained man; and it is probable that, in the average man, the maximal output per minute does not often exceed 15 or 16 litres. Since the heart cannot discharge during systole

TABLE XI.—Relation of Oxygen-Consumption to the Output of the Heart. (From Lindhard's Data.)

	Oxygen-Consumption per Minute in c.c.	Output per Minute in Litres.	Pulse-Rate per Minute.
Rest . . .	330	4·9	72
Work . . .	606	6·3	86
,, . . .	1171	14·75	92
,, . . .	1759	16·65	128
,, . . .	1880	18·5	130
,, . . .	2407	22·6	148
,, . . .	2750	28·6	—

(except for a few beats) more blood than it receives during diastole, the diastolic filling of the heart must be similarly increased during exercise.

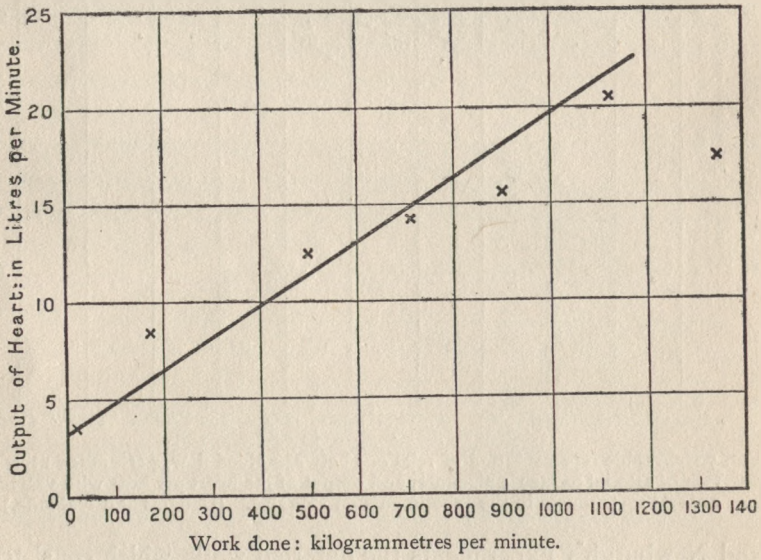


Fig. 8.—(Constructed from Lindhard's data.)

The Diastolic Filling of the Heart.

Apart from the duration of systole, the only two processes which can affect the diastolic filling of the heart are, first the venous pressure, and second, the rate and completeness of the relaxation of the muscular walls of the ventricles. Since all the evidence shows that the conditions on the two sides of the heart

are normally identical, it will be sufficient to consider only the right side of the heart.

Tone.—The idea that the heart muscle possesses *tone*, using this term to mean that the walls of the auricles and ventricles do not become completely relaxed and flaccid during diastole, originated from Gaskell (1880-1882), who found that perfusion of the frog's ventricle with alkaline saline solution led to less complete relaxation between the beats of the ventricle and finally to standstill in systole, whereas acid solutions brought about the converse effect, namely, diastolic standstill. This view appears to be generally accepted, as regards the human heart, by clinical writers (Clifford Allbutt, Mackenzie), and it has been adopted by Yandell Henderson (1909), who believes, not only that the heart muscle possesses diastolic tone in the sense that its relaxation is not necessarily complete, but also that this tone is variable, and that, under a given venous pressure, the distensibility of the ventricles, and hence the filling of the heart, is not always the same.

This belief rests, in part, upon the observations (Y. Henderson) that excessive pulmonary ventilation leads to very imperfect filling of the heart, and that, on the contrary, deficient pulmonary ventilation brings about dilatation of the heart. Janeway and Ewing (1914), however, have brought forward evidence that excessive pulmonary ventilation (with the chest open) lessens the filling of the heart by mechanically interfering with the return of blood to the heart; and Piper, Patterson, and Starling (1914), have shown that lack of oxygen causes the heart to dilate, in accordance with the law of the heart, in order to compensate for its decreased contractile power. They found no evidence of varying distensibility of the heart during diastole under a constant venous pressure; on the contrary, the filling of the heart was determined solely by the venous inflow.

In Yandell Henderson's experiments, an increase in venous pressure did not appreciably alter the curve of diastolic filling of the heart, and he believes this to be due to a compensatory rise of diastolic tone. Krogh (1912) has suggested in explanation of this result that the venous inflow was already so large that a further increase in venous pressure made but little difference to the rate of filling of the heart; and the similarity between Henderson's and Barringer's curves (Fig. 12) and those obtained

by Patterson, Piper, and Starling (Fig. 13) under a large venous inflow renders Krogh's suggestion very probable. It is possible, therefore, to interpret Henderson's results without invoking diastolic tone. Further, even when the experimental conditions are apparently similar to those in Henderson's experiments, a rise in venous pressure may increase the rate of filling and the output of the heart per beat, even though the pulse-rate at the same time becomes more rapid (Bainbridge, 1915). Nor do Gaskell's observations necessarily imply the existence of diastolic tone, since they can be equally well explained by assuming that alkali prolongs the systolic phase and cuts short the period of diastole, whereas acid has the converse action. The balance of evidence, therefore, is against the existence of diastolic tone, even in the normal heart, and the conclusion appears unavoidable that the heart muscle is normally completely relaxed during diastole, and that its filling is determined entirely by the venous inflow. The existence of a diastolic tone would be most uneconomical for the organism as it necessarily would cause a resistance to the venous blood returning to the heart.

The Venous Inflow.

The most important means concerned in increasing the venous inflow to the heart, and consequently its output, during exercise is undoubtedly the movements of the skeletal muscles. Tigerstedt (1909) has shown that tetanisation of the hind limbs, after section of the spinal cord in the lumbar region, brings about a larger output of the heart, as the result of a greater venous inflow; and this he regards as due to the mechanical action of the muscular movement on the return of blood to the heart. The importance of such movement in promoting the return of blood to the heart, by mechanically squeezing blood out of the veins of the muscles into the great veins, has been emphasised by Leonard Hill (1908); and the more vigorous the muscular movement, and the larger the number of muscles employed, the greater must be their effect upon the return of blood to the heart. Indeed it seems very probable that the increased rate at which blood reaches the heart during exercise varies almost directly with the amount of muscular movement. In this way, the muscles act as a subsidiary pump, and the combined action of the heart in driving blood into the

vessels of the muscles, and of the active muscles in sending blood back to the heart, must greatly increase its output per beat.

It is clear that the muscles can act in this way only if blood enters the vessels of the muscles from the arterial side as rapidly as it is forced out of these vessels into the great veins. The constriction of the splanchnic vessels, which occurs at the very outset of exercise, immediately diverts a large volume of blood into the muscles, and raises the pressure at which it is sent into their blood-vessels. The greater flow of blood into the active muscles, thus brought about, allows them at once to send more blood into the great veins, and thence to the heart. But the output of the heart does not increase during exercise, as Krogh has shown, until sufficient time has elapsed for this to take place. Hence the machinery, by which the output of the heart increases during exercise, is set in motion by the purely mechanical action of the active muscles, and in this manner the blood-flow to the muscles, at least so far as this depends upon the output of the heart, is very largely determined by their own activity. Dilatation of the blood-vessels in the muscles, in so far as it occurs during exercise, will allow still more blood to enter these vessels in a given time, and will thereby enhance the return of blood to the heart.

It is generally believed that the respiratory movements supplement the action of the skeletal muscles in this respect, and there seems to be no doubt that the movements of the diaphragm, by raising the intra-abdominal pressure and squeezing blood out of the vena cava, do increase the flow of blood to the heart. The extent to which costal respiration acts in this way is a matter of controversy. Y. Henderson found that more vigorous respiration had little or no effect on the filling of the heart, a result which is not surprising since (in his experiments) the venous inflow was already very large. Lewis (1908) showed that, in man, a pure costal inspiration lowers the arterial pressure, presumably by lessening the venous inflow, whereas abdominal respiration raises the pressure, and the actual effect of respiration upon the flow of blood to the heart therefore varies with the type of breathing. During short spells of violent exertion, the breathing is both costal and abdominal, and its effect upon the venous inflow is perhaps not very large. But, during prolonged steady exercise, such as a cross-country run, the breathing is chiefly abdominal (L. Hill),

and the respiratory movements must be of great importance in assisting the diastolic filling of the heart.

Krogh (1912) has suggested that the portal system also plays a considerable part in increasing the blood-flow to the heart during exercise. He regards the portal mechanism as consisting of two resistances, the first being the intestinal arterioles, and the second the portal vein and its tributaries; between these two resistances, the intestinal capillaries form a rather large reservoir. His view appears to be that stimulation of the splanchnic nerves, assuming it to cause, at the same time, contraction of the intestinal arterioles, dilatation of the capillaries of the liver, and contraction of the portal vein, will drive into the great veins more blood than could be driven out by contraction of the intestinal arterioles alone, since the contraction of the arterioles lessens the flow into the portal system, which therefore contracts and discharges blood into the central veins. The observations of Bainbridge and Trevan (1917), however, are not in favour of this view. They have shown that stimulation of a splanchnic nerve, or the injection of adrenalin, gives rise to some obstruction to the flow of blood from the liver into the general circulation, and, although the portal pressure rises, the pressure in the vena cava shows little or no alteration. It does not appear probable, therefore, that the portal mechanism can take any great share in increasing the flow of blood to the heart.

The efficiency of the muscular and respiratory movements, in increasing the venous inflow during exercise, is demonstrated by the fact that the venous pressure rises considerably (Hooker, 1911). Such a rise indicates that the venous inflow is sufficient, not merely to increase the output of the heart, but also to provide a head of pressure which ensures *rapid* filling of the heart during diastole.

The Factors which Determine the Output of the Heart.

The heart possesses two means of increasing its output per minute in response to the greater inflow of blood during exercise: these are a larger output per beat and acceleration of the pulse-rate.

According to Boothby's observations (1915), the increased output per minute is effected almost entirely by a rise in the pulse-rate; and he finds that the pulse-rate, like the output per

minute, has practically a linear relation to the oxygen-consumption (Fig. 9), and therefore to the intensity of the muscular work. In his experiments, the alternative method of increasing the output of the heart per minute (often termed the *minute-volume*), namely, a larger output per beat, plays a very small part, and, even when the consumption of oxygen is increased threefold, the

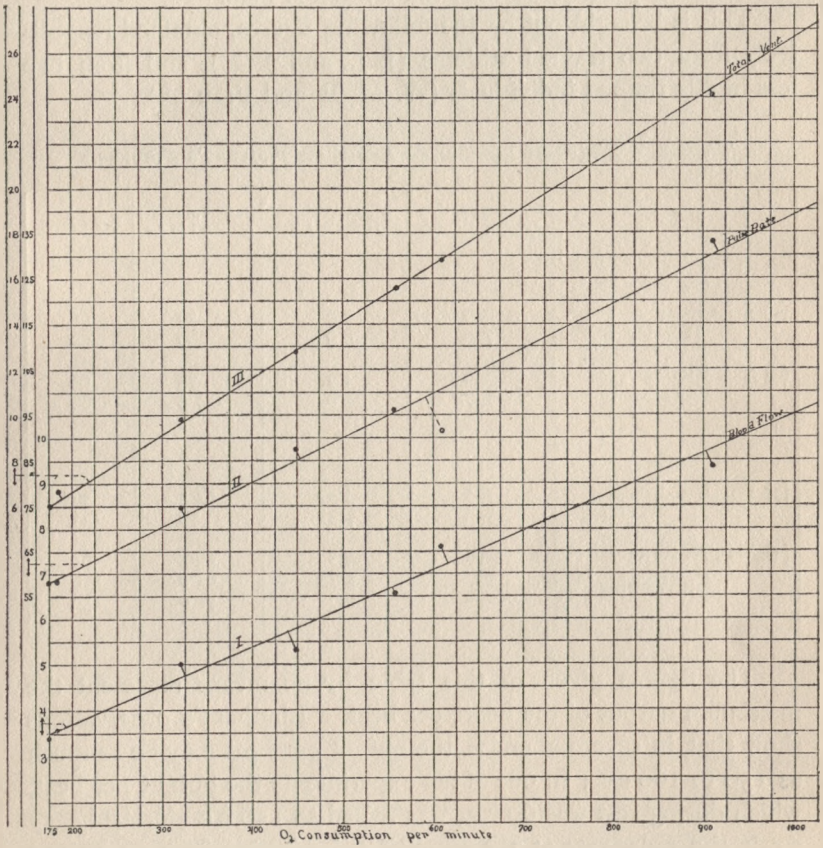


FIG. 9.—(Boothby.)

output per beat only rises 8·5 c.c. Boothby's observations were made on a single individual, and Krogh and Lindhard, who have studied the effects of exercise in a number of individuals, conclude that the relationship between the pulse-rate and oxygen-consumption is by no means so constant as Boothby supposed, and that it may even vary in the same individual at different times. They

found that, in highly trained men, the increase in the minute-volume of the heart during moderate exercise was obtained to a much greater extent by increase in the output per beat, and to a much smaller extent by acceleration of the pulse, than in the untrained person. They showed that, if the consumption of oxygen is the same in the two cases, the trained man almost invariably has a less frequent pulse than the untrained man.

This is brought out by the following figures, obtained respectively from two trained athletes (J. J., and J. L.), and from two less highly trained individuals (W. M. B. and Frau M.).

TABLE XII.—(From Lindhard's and from Boothby's Figures.)

Subject.	O_2 Consumption c.c. per Minute.	Minute-Volume of Heart in Litres.	Output of Heart per Beat in c.c.	Pulse-Rate.
Trained.				
(1) J. L. Resting	219	3·9	59	66
Working	782	9·0	100	90
(2) J. J. Resting	330	4·9	72	68
Working	797	11·0	127·5	86
Untrained.				
(3) W. M. B. Resting	185	3·57	61·5	58
Working	912	9·31	70	133
(4) Frau M. Resting	195	4·2	69·5	61
Working (*a*)	927	9·75	81·0	120
Working (*b*)	1070	10·7	71·0	150

The figures given in this table by no means represent the maximum output of the heart per beat. Lindhard's observations show that, in severe exercise, the output per beat may be as much as 150 to 160 c.c.; in one of his experiments the output per beat, which during rest was 69 c.c., was raised to 150 c.c. during heavy work, the pulse-rate at the same time increasing from 71 to 118 per minute. Means and Newburgh have recorded an output of 164 c.c. per beat, the pulse-rate being 107, and the consumption of oxygen being 1640 c.c. per minute.

Douglas and Haldane state that the output per heart beat, as determined by their method, is in many subjects no greater during moderate or hard work than during rest, and is about 120 c.c. for a man of average weight. In other subjects, however, the output

of arterial pressure, and, after a few beats, it becomes dilated to such an extent that it is able to maintain the same output against the higher pressure as that existing before the rise of pressure took place.

Dilatation of the heart, therefore, is an essential part of the

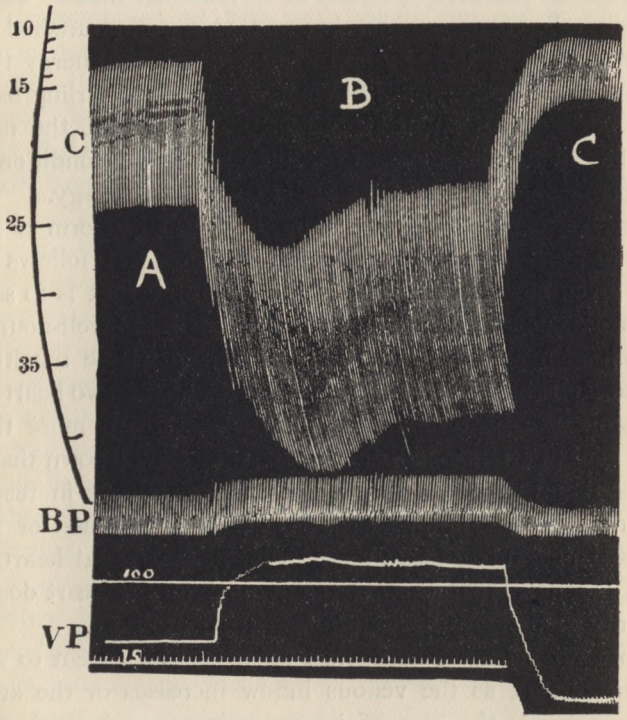


FIG. 11.—Effect of alteration in venous supply on volume of isolated heart. (Patterson, Piper, and Starling.)

	B.P.	V.P.	Rate.	O.P.	O.P. per Beat Calc.	O.P. per Beat Observed.
A.	124	95	22	86	3·9	5·7
B.	130	145	22	140	6·4	8·0
C.	122	55	22	33	1·5	2·5

BP = arterial pressure. VP = pressure in vena cava close to the heart in mm. water. OP = output of heart in c.c. per 10 seconds. Rate = number of beats in 10 seconds. C = cardiometer tracing of the volume of the heart.

mechanism by which it can increase or maintain its output in response to a greater venous inflow or to a higher arterial pressure. It is a perfectly normal process, and the extent to which it can take place, under physiological conditions, is ultimately limited by the pericardium.

to consider briefly the factors which determine first, the power of the heart to increase its output per beat, and second, the influence of the pulse-rate upon the output per minute.

The Output of the Heart per Beat.

Patterson, Piper, and Starling (1914) have recently proved that cardiac muscle resembles skeletal muscle in that the energy set free when it contracts, and therefore the force with which it contracts, is directly proportional to the initial length of its fibres; the phrase, initial length, means the length of the fibres just before they begin to contract. Since the heart is a hollow organ, the initial length of its fibres will vary directly with its volume at the end of diastole; consequently, the diastolic volume of the heart determines the energy set free, that is to say, the force with which the heart muscle contracts, during the following systole.

Upon this fundamental principle, which Starling has termed "the law of the heart," depends the ability of the heart to increase its output in response to a larger venous inflow of blood into the heart, and to maintain its output in the face of a raised arterial pressure. Theoretically, one might suppose that, when the venous inflow becomes larger, the greater diastolic filling of the heart would increase its contractile power to such an extent that it would, at the next systole, discharge into the arterial system all the blood entering it during the preceding diastole, and that its systolic volume would not alter. This is the case for the heart of the tortoise in which, as Kozawa (1915) has shown, the adaptation to increased filling of the heart is perfect, and the law of the heart is absolutely obeyed. But Patterson, Piper, and Starling find that, at least under experimental conditions, this is not perfectly true for the mammalian heart. If the venous inflow becomes larger the output of the heart increases, but for a few beats the output does not keep pace with the inflow. The result is that the diastolic (and systolic) volume of the heart gradually becomes larger, and there is a concomitant increase in the force with which the heart contracts at each successive systole. After a short time the diastolic volume, and, therefore, the contractile power of the heart, become so large that the output of the heart equals the inflow, while its volume at the end of systole has been increased (Fig. 11). The heart reacts in precisely the same way to a rise

The Contractile Power of the Heart.

Although every heart obeys the law just described, the actual amount of energy set free during each beat, or, in other words, the contractile power of the heart for any given diastolic volume, varies with the nutritive condition of its muscular fibres. Assuming its diastolic volume to remain constant, a well-nourished heart will contract more strongly and will set free more energy than a badly-nourished heart; and Patterson, Piper, and Starling use the term 'tone' to indicate the physiological fitness of the muscle fibres, this being the outcome of their nutritive condition and being manifested by their ability to develop energy. Tone, therefore, means a capacity of the heart to perform a given amount of work with a shorter length of fibres. It follows that, for any given increase in the length of its fibres, that is to say, in its diastolic volume, the contractile power of a well-nourished heart will increase more than that of a heart whose nutrition is impaired, and that, if the contractile power of the two hearts is to be the same, the badly-nourished heart must dilate more than a normal one. Patterson, Piper, and Starling have shown that this is the case, and that, in order to increase its output in response to a larger venous inflow, a heart, which is fatigued or badly nourished, must dilate much more than does a normal heart. It is clear, therefore, that the diastolic volume of the heart does not necessarily give any indication of its output per beat.

Another condition which must influence the extent to which the heart dilates, as the venous inflow increases or the arterial pressure rises, is the size of its musculature. A thick-walled ventricle will obviously be in a favourable position as compared with a thin ventricle, since the larger the number of fibres the greater will be the cumulative effect of a trivial increase in their length upon the contractile power of the heart; hence a thick-walled ventricle can increase its output with much less dilatation than can one whose walls are thin.

Although Barnard (1898) long ago pointed out that the primary function of the pericardium is to prevent over-distension of the heart, the idea that this function might be exercised in the ordinary course of daily life has never obtained general currency. The actual capacity of the pericardial sac, after deducting the space occupied by the heart-muscle, has been investigated by Hender-

son and Prince (1914), who found that it varied in different individuals from 450 to 600 c.c. Assuming that each ventricle is capable of holding a third of the total blood in the heart, they calculate that each ventricle can contain from 150 to 200 c.c., when the heart completely fills the pericardium; in one case, a very muscular man of nineteen years, the capacity of the left ventricle amounted to 230 c.c. Since the output of the left ventricle per beat rarely exceeds 150 c.c., Henderson and Prince concluded that the heart never dilates sufficiently to fill the pericardium. But they overlooked the fact that, as its output increases, the systolic as well as the diastolic volume of the heart becomes larger (Fig. 10), and that, in order to maintain an output of 150 c.c. per beat, the volume of each ventricle at the end of systole may easily be such that it contains 50 or 60 c.c. of blood; in that case its content of blood at the end of diastole might well be over 200 c.c., and the heart as a whole would completely fill the pericardial sac. Further, the less the contractile power of the heart-muscle the greater is the extent to which it must dilate in order to produce a given increase in output, and, therefore, the larger will be its residual content of blood at the end of systole. A feeble heart might, therefore, completely fill the pericardial sac, even though its output per beat was not greatly increased.

Starling (1922) has pointed out that the law of the heart, i.e. its power of response to increased demands, either absolute or relative to its functional capacity, is limited by the size of the pericardial sac. As the heart becomes fatigued, it maintains its output and the arterial pressure unchanged in virtue of its continual dilatation and the increased length of fibre thereby produced. As soon as the diastolic volume of the heart is equal to that of the pericardial sac, further dilatation becomes impossible. Increasing fatigue, i.e. diminution of functional capacity, will thus cause inadequate contraction with resulting diminution of output; unless there is a compensatory increase in the arterial resistance, the arterial pressure will also sink. In the intact animal the supply of blood to the muscles and to the brain will thus become inadequate, producing loss of muscular power, mental confusion, and even loss of consciousness. It is this condition of things which is probably responsible for the fainting which may occur in the course or at the end of a hard-fought race. The same conditions are present in the failure of

per beat is considerably less than this during rest, and increases considerably during work.

That the pulse-rate does not always correspond with the severity of the exercise is also very evident from the observations of Means and Newburgh (Fig. 10). In the experiment illustrated in this figure, the pulse-rate (after an initial acceleration) remained for a time almost steady, although the amount of work performed in a given time was steadily becoming larger, and the increased

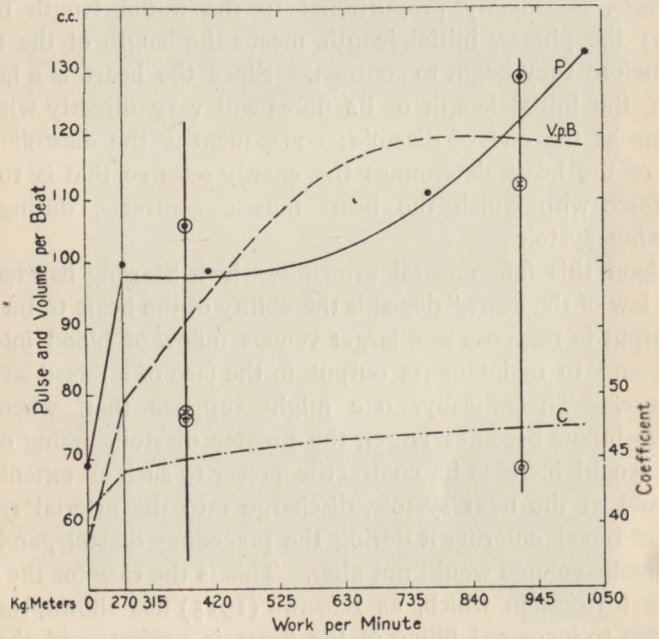


FIG. 10.—(Means and Newburgh.)

P = pulse-rate. VPB = output of heart per beat. C = coefficient of utilisation.

output of the heart per minute was effected entirely by a progressively larger output per beat. It may be concluded, then, that, in different individuals, during *moderate* exercise, the increased output of the heart per minute may be brought about either by a larger output per beat and a slight acceleration of the pulse or by acceleration of the pulse with little or no increase in the output per beat, and that every gradation may exist between these two extremes.

Before discussing the significance of the difference in the response of the heart in different individuals, it will be convenient

compensation of heart disease. In such cases one finds invariably diminished output of the heart. The arterial pressure is normal, or even raised above normal, since the brain, the master tissue of the body, must at all costs receive an adequate supply of blood. This it achieves, in the face of a diminished output from the heart, by arterial constriction and shutting off the blood from any or all of the other tissues of the body. The heart, which fills the pericardial sac at each diastole, has no margin left by which it can accommodate itself to any increased demands on the part of the organism. Any small movement may thus bring about fainting; the muscles, alimentary canal, kidneys, and all parts of the body, are inadequately supplied with blood. As a result, there is an increased intake of fluid with diminished urinary excretion, resulting in a condition of hydræmic plethora. The deficient oxidation of the blood may stimulate production of red blood corpuscles so that a real plethora results, involving both the corpuscular and the fluid parts of the blood. There is increased pressure in the large veins, while the deficient oxidation causes increased permeability of the capillary walls. There is thus increased transudation, resulting in œdema of dependent parts, together with all the other signs which are characteristic of failure of compensation and often grouped together as signs of backward pressure.

The Output per Beat during Exercise.

The difference in the behaviour of the heart in different individuals, as regards its output *per beat*, can be readily accounted for along these lines. It is easy to understand that the powerful heart of the althlete, while obeying the law of the heart, is able to respond to a moderate increase of venous inflow by a much larger output *per beat*, whereas the smaller heart of the sedentary person, even if dilated to its physiological limit, can only moderately increase its output per beat. This is the true explanation of the difference in the so-called reserve-power of the heart in different individuals. The calling up of the reserve is effected in accordance with the law of the heart, but the extent of the available reserve is determined by the contractile power of the heart, this depending partly upon its thickness of muscle and partly upon its nutritive condition; since the latter are the variable factors, it is upon them that the varied response of the heart to exercise depends in different individuals.

A further consequence of the greater dilatation necessary in order that the heart of a sedentary person may increase its output per beat, is that such a heart may dilate nearly to its physiological limit with very little increase in output per beat, and with only a moderate rise in venous inflow. As soon as this point is reached its ability further to increase its minute-volume depends solely on acceleration of the pulse-rate. Hence, in such an individual, increase in minute-volume is obtained, and must be obtained, almost entirely by acceleration of the pulse. On the contrary, the powerful heart of the athlete, with its greater reserve power, can double or more than double its output per beat before reaching its physiological limit of size. This doubtless explains the variation, shown in Table XII., in the behaviour of the heart in different individuals as regards the output per beat during moderate exercise.

The Size of the Heart during Exercise.

We should expect from the foregoing argument that severe exercise, and, in an untrained man, even moderate exercise, must considerably increase the diastolic volume of the heart; and it is almost certain that, in some of the examples just quoted, the heart dilated nearly up to the limits allowed by the pericardium. During recent years, however, the view has gained ground, and is now widely held, that in the healthy person the diastolic volume of the heart does not become larger during exercise. A necessary corollary to this view is that the output of the heart per beat is not greatly increased during exercise.

It rests upon evidence which at first sight appears unimpeachable, namely, direct measurement of the size of the heart, just before and after exercise, by means of the orthodiagraph or the teleo-Röntgen rays. Using the orthodiagraph Moritz (1908), Hoffmann (1902), and de la Camp (1903 to 1904) found that, in normal persons, severe exercise, even when carried to the point of exhaustion, produced no dilatation of the heart, and that sometimes its volume was actually diminished. The forms of exercise taken included wrestling, cycling, and work on the ergometer. On the contrary, Schott (1908) came to the conclusion that considerable dilatation occurred in these circumstances. It may be noted that in none of these experiments was the size of the heart observed during the actual exercise, although the record was taken as soon as

possible afterwards. With the object of minimising the interval between the cessation of the exercise and the observation of the size of the heart, Nicolai and Zuntz (1914), in their experiments, arranged the apparatus so that the Röntgen ray picture could be taken practically during the exercise, the subject merely stopping work for a few seconds during the actual period of exposure for the photograph. Their results indicated a small increase, amounting on an average to 4 mm., in the transverse diameter of the heart during work, and a definite decrease in size shortly after its cessation, the decrease in size taking place within three seconds of the cessation of exercise. As a result of calculations based upon the normal capacity and transverse diameter of the heart, they conclude that its output per beat is increased during exercise and may reach 150 c.c.

The most recent observations are those of Williamson (1915), who improved the technique by using the teleo-Röntgen method, and who paid considerable attention to the phase of respiration at which the photograph was taken. This is of importance since the position of the diaphragm appreciably affects the apparent size of the heart, and photographs, if they are to be strictly comparable, should always be taken at the same point in the respiratory cycle. The photographs were taken just before, and about twenty seconds after, fairly severe exercise. Williamson found that, taking thirty-three normal subjects, the heart diminished in size in twenty-nine cases, dilated in three cases, and in one case remained unaltered in size. In patients with compensated heart lesions, or in whom the heart was presumably weakened by some general disease, dilatation occurred in twenty-five out of fifty-seven cases. The average dilatation, when it occurred, was 4 mm.

Although Williamson appears to regard an increase of 4 mm. in the transverse diameter of the heart as trivial, the diastolic volume of the resting heart may exceed its systolic volume by about this figure. That is to say, the entrance of, on an average, 120 c.c. of blood into the two ventricles leads to quite a small change in its transverse diameter; and, since the heart is roughly spherical, a considerable addition to its content of blood at the end of diastole would produce a comparatively slight increase in its diameter. It is probable, in fact, that the presence of an additional 20 or 30 c.c. in the heart at the end of diastole could not be detected by observing

it with the Röntgen rays. In some of Lindhard's experiments, however, the amount of blood present in the two ventricles at the end of diastole during exercise must have exceeded their diastolic content of blood during rest by 120 to 180 c.c., a difference which could hardly escape notice.

The explanation of the divergence between the results of Krogh and Lindhard and the evidence derived from direct observation of the heart by Röntgen rays lies in the fact that de la Camp, Williamson, and even Nicolai and Zuntz, measured the size of the heart not during but *after* exercise. Immediately on the cessation of exercise the venous inflow to the heart diminishes owing to the stoppage of the pumping action of the skeletal muscles, while the pulse-rate falls very slowly for at least half a minute, and consequently, for a few beats, the output of the heart exceeds the venous inflow. The heart, therefore, begins to diminish in size almost instantly after the exercise stops, its diastolic volume falling to normal within three or four seconds (Nicolai and Zuntz); and if its rate declines slowly, its output per beat and its diastolic volume may for a short time be even less than normal. This sequence of events can be directly observed under experimental conditions. Patterson, Piper, and Starling have found that, when the venous inflow to the heart decreases, its output and diastolic volume reach a lower equilibrium point in seven or eight beats.

It may be concluded that, although orthodiagraphic records of the heart have demonstrated the rapidity with which it decreases in size after exercise, and have incidentally served to show the fallacious nature of the evidence derived from percussion and palpation as to the absolute size of the heart, these records throw very little light on the actual size of the heart *during* exercise, and do not in the least controvert the evidence of Krogh and Lindhard that the output of the heart per beat may be doubled, or more than doubled, during exercise.

The conclusion that the output of the heart can be increased either by a larger output per beat or by acceleration of the pulse, and that a large output per minute depends upon the co-operation of both these factors, is not accepted by Yandell Henderson (1906, 1909), who has examined directly the changes in the volume of the heart *in situ* by the plethysmographic method. Henderson brought forward evidence that, under normal conditions, the curve of diastolic filling of the heart is always of the same shape, and that shortening of the diastole merely cuts short the curve of diastolic filling without altering the form of the curve (Fig. 12).

This means that the rate at which the heart fills during diastole is always the

same, and does not vary with the venous pressure. Hence acceleration of the pulse, by cutting short the filling of the heart, necessarily lessens its output per beat, although, owing to the shape of the curve of diastolic filling, the decrease in output per beat does not (especially at first) fall off proportionately with the increase in pulse-rate. Consequently, acceleration of the pulse does increase to some extent the output of the heart per minute. The two most important deductions which Henderson draws from these observations are, first, that acceleration of the pulse-rate is the only means by which the output of the heart per minute can be increased, and, second, that the large output per beat and per minute, described by Krogh and Lindhard and others, cannot possibly occur. Henderson at first (1909) believed that the greatest minute-volume of which the heart is capable is less than double that occurring during rest. With such an output it would be impossible for the blood to carry to the tissues all the oxygen which is actually consumed during severe exercise. For example, if the output of the heart per minute were 8 litres, this amount of blood would only carry 1500 to 1600 c.c. of oxygen to the tissues, even if it were completely reduced in its passage through the capillaries, whereas the actual consumption of oxygen under these conditions may be 2500 to 3000 c.c. oxygen per minute. Henderson found it necessary, therefore, to assume that only a fraction of the oxygen taken

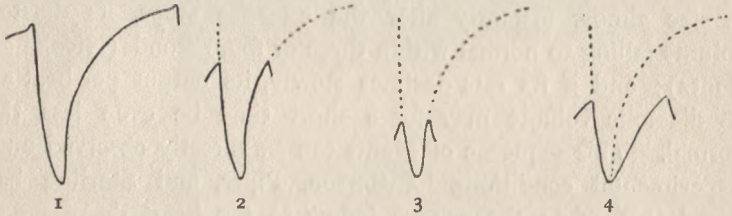


FIG. 12.—(Henderson and Barringer.)

Upstroke = diastole.

Curves representing the change in the volume of the heart during a cardiac cycle, 1, when the pulse is infrequent, 2 and 3, when the pulse is more frequent, 4 shows rate of diastolic filling with small venous inflow.

into the body is transported by the blood to the tissues, and that the remainder is utilised in the lungs themselves for the oxidation of metabolic products of muscular activity, a view which was first put forward by Bohr and Henriques (1897). But Evans and Starling (1913) have shown that the oxidation of metabolic products is carried out in the tissues themselves, and that the lungs do not complete the oxidation of metabolic products formed elsewhere in the body. The same conclusion has been reached by Henriques (1913) as the outcome of his more recent work. Henderson and Prince appear to have accepted this view, since they have recently (1914) used the oxygen-consumption of the body as a basis for calculating the output of the heart. They define the oxygen-pulse as the amount of oxygen taken into, and consumed by, the tissues from the blood expelled during one heart-beat. Thus, if the oxygen-consumption is 2100 c.c., and the pulse-rate is 140 per minute, the oxygen pulse is 15 c.c. Assuming the blood to lose half its oxygen during its passage through the tissues, and its oxygen-capacity to be 18 c.c. per 100 c.c. of blood, the output of the heart per beat would be 166 c.c. Henderson and Prince allow a smaller loss of oxygen from the blood, and conclude that, with a pulse-rate of 140 per minute, a powerful heart may put out 100 c.c. per beat and, therefore, 14 litres of blood per minute. During rest, with a pulse-rate of 60, the same heart might put out 150 to 160 c.c. per beat. Henderson and Prince regard these high

figures as possible only when the heart is very powerful, and consider that the average output per beat and per minute is distinctly less.

According to Henderson and Prince, therefore, the output of the heart during rest is much greater, and during exercise much less, than that which Krogh and Lindhard and others have described as occurring in man. If this were the case, the supply of blood to the tissues would be excessive for the resting individual and inadequate during exercise. If, for example, the output of the heart per minute were 14 litres, the maximum which Henderson and Prince believe possible, and the oxygen-capacity were 18·5 c.c. per 100 c.c. of blood, the total amount of oxygen available for the tissues would be just under 2600 c.c. per minute, assuming the blood to be completely reduced during its passage through the capillaries. Yet a highly trained man may consume as much as 2500 to 3000 c.c. of oxygen per minute, although it is impossible to believe that complete reduction of the blood ever occurs during exercise. This constitutes a fatal objection to the acceptance of Henderson's view that the venous inflow to the heart is constant, and that, in the normal individual, the output per beat decreases as the pulse-rate accelerates during exercise. The large output per minute, which may occur during exercise, is indeed only possible if the venous inflow is at the same time greatly increased. It must be remembered, however, that according to Douglas and Haldane there is in many subjects no increase in the output per beat during exercise.

Summary.

In order to meet the demands of the tissues for oxygen during exercise, not only a more rapid circulation rate but also a close correlation between the pulmonary ventilation and the circulation rate are required; and such a correlation is present during exercise.

The circulation rate round the body depends primarily upon the output of the heart, and this, which varies during rest from 3 to 5 litres a minute, may reach 20 litres or even more during heavy work.

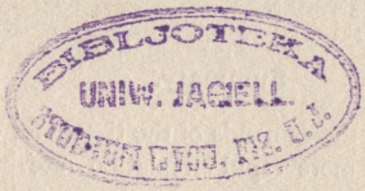
The larger output of the heart per minute involves a corresponding increase in the diastolic filling of the heart. It is concluded that the heart does not possess any diastolic tone and that its filling is determined entirely by the venous inflow.

During exercise the return of blood to the heart is increased partly by the active muscles, which mechanically squeeze blood out of their capillaries and veins into the great veins, and partly by the respiratory movements, particularly those of the diaphragm.

In response to a larger venous inflow, the heart can increase its output per minute either by a larger output per beat or by acceleration of the pulse-rate. The output of the heart per beat is shown to depend upon "the law of the heart," which states that the force with which the heart-muscle contracts during systole varies directly with the volume of the heart at the end of diastole.

The application of this law to the behaviour of the heart during exercise is discussed, as also is the influence of the nutritive condition of the cardiac muscle, and of the size of the cardiac musculature, upon its diastolic volume and output per beat.

The conclusion is reached that dilatation of the heart normally occurs during exercise and is a strictly physiological process, since dilatation of the heart, by increasing its contractile power in accordance with the law of the heart, enables the heart to increase its output per beat in response to a larger venous inflow. Such dilatation reaches its physiological limit when the heart at the end of diastole fills the pericardial sac.



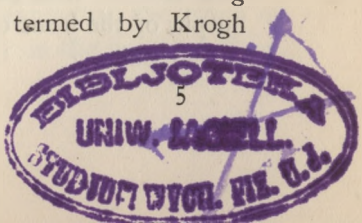
CHAPTER V.

THE OUTPUT OF THE HEART (*continued*)—THE INFLUENCE OF THE PULSE-RATE UPON THE OUTPUT OF THE HEART—THE BEHAVIOUR OF THE HEART DURING EXERCISE—THE MECHANICAL EFFICIENCY OF THE HEART.

The Influence of the Pulse-Rate upon the Output of the Heart.

THE diastolic filling of the heart, and therefore its output per beat, depends not only upon the rate at which blood flows along the great veins into the heart, but also upon the duration of diastole. Since the ventricular muscle is completely relaxed during systole, the rate at which the heart fills varies directly with the pressure under which blood flows from the great veins into the heart. If the changes in the volume of the heart at each beat under experimental conditions are graphically recorded (Patterson, Piper, and Starling), the form of the curves (Fig. 13) shows that, when the venous inflow is small, blood enters the heart at a fairly uniform rate throughout the diastolic period; consequently the length of this period determines the volume of the heart at the end of diastole and, therefore, its output per beat.

If the duration of diastole is constant and the venous inflow small, the heart will not fill completely during diastole. If the venous inflow increases, the heart fills more rapidly, though still at a uniform rate; and, since the fully relaxed heart-wall yields before the inflowing blood, the heart may fill to the limits imposed by the pericardium just at the end of diastole. But, as the venous inflow to the heart becomes still larger, a point is reached at which blood flows into the heart so rapidly that this fills to, or almost to, its maximal size before the end of diastole, and the curve of the changes in the volume of the heart alters in shape (Fig. 13). Any further increase in the rate of venous inflow then merely causes the heart to become full still earlier during the diastolic period. This condition is termed by Krogh "adequate" filling of the heart.



Since the maximum extent to which the heart can fill during diastole is fixed by the pericardium, it is clear that, if the pulse-rate remains unchanged, an increase beyond a certain point in the rate at which blood returns to the heart must lead to the accumulation of blood in the great veins. Krogh (1912) was the first to call attention to the significance of acceleration of the pulse in these circumstances. He pointed out that, if the venous inflow is so small that the heart slowly fills at a

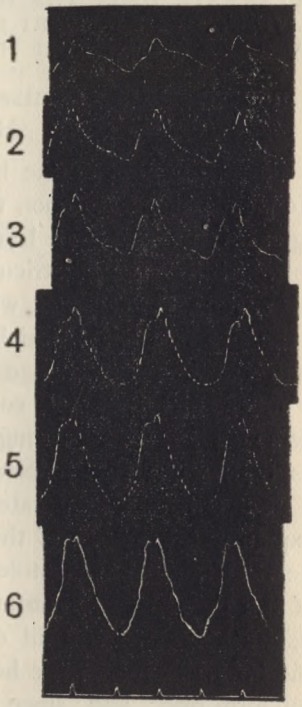


FIG. 13.—(Patterson, Piper, and Starling.)

Downstroke = systole.

Curve showing the change in ventricular volume during the cardiac cycle with varying venous inflow, this being smallest in curve 1 and largest in curve 6.

fairly uniform rate during diastole, an increase in the rate of the heart, though lessening its output per beat, will hardly affect its minute-volume. On the other hand, if the heart fills early in diastole, greater frequency of the pulse will very slightly diminish its output per beat, and its output per minute will increase almost in proportion to the rise in the pulse-rate. The correctness of this view has been demonstrated experimentally by Kuno (1915), who showed that, provided the venous inflow was adequate, the output of the heart could be doubled by increasing the frequency of the pulse.

TABLE XIII.—(KUNO.)

Height of Venous Reservoir in cm.	Venous Pressure in V. Cava (mm. in H_2O).	Pulse-Rate per Minute.	Output of Heart per Minute.	Output of Heart per Beat.
13	73	90	700 c.c.	7·8 c.c.
13	47	135	955 ,,	7·1 ,,
18	111	78	680 ,,	8·7 ,,
19·5	85	126	1300 ,,	10·3 ,,

The Venous Pressure.

So long as the blood enters the heart from the great veins as rapidly as it reaches these veins from the peripheral veins, the pressure in the great veins remains low, since a very slight pressure suffices to distend the relaxed ventricular walls. But, as soon as the amount of blood flowing into the great veins exceeds that which can enter, and be accommodated in, the heart during diastole, blood begins to accumulate in the great veins and the venous pressure rises. As a result of the higher pressure, the heart fills *earlier* in diastole and the diastolic pressure in the heart also rises. The higher pressure cannot appreciably increase the diastolic volume of the heart, since this is fixed by the pericardium; and, so long as the rate of the heart remains unchanged, a rise of venous pressure beyond a certain level has little or no influence upon the output of the heart. Hence a high venous pressure implies that blood is being returned to the great veins and heart faster than the heart can transfer it to the arterial side of the circulation. The gradual rise of pressure in the great veins and heart, as the venous inflow increases, has been observed experimentally by Evans and Matsuoko (Fig. 14), by Kuno, and by Patterson and Starling; in the experiments of Patterson and Starling the pericardium was open.

When these conditions are present, acceleration of the pulse at once lowers the venous pressure (Table XIII.), since, by increasing the output of the heart per minute, it lessens the accumulation of blood in the great veins.

The Relation Between the Pulse-rate and the Contractile Power of the Heart.

The part taken by the pulse-rate in extending the range of the output of the heart depends, not only on the venous inflow,

but also on the contractile power of the heart. Other things being equal, the absolute contractile power of the heart is proportional to the number and size of its fibres. Consequently, in response to a moderate increase in venous inflow, a comparatively slight dilatation enables a powerful (thick-walled) ventricle to increase considerably its output per beat and still to empty itself

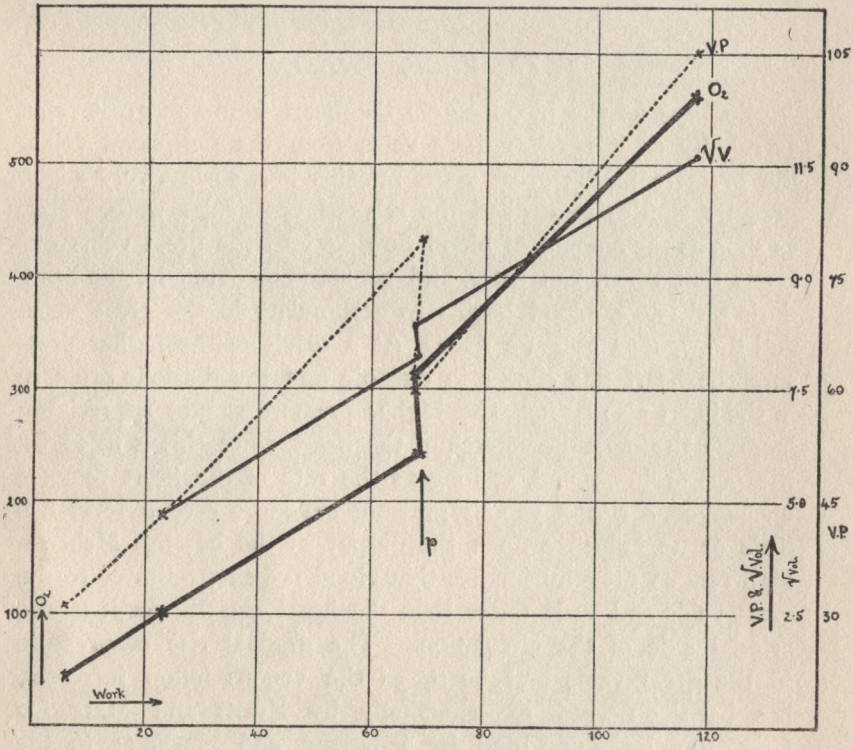


FIG. 14.—(Evans and Matsuoko.)

Vv = volume of the heart; V.P. = venous pressure in mm. of water.
O_2 = oxygen-consumption of heart in c.c. per hour. Work = kg.m. per hour.
At p the pericardium was opened.
The work of the heart was increased by increasing the venous inflow to the heart.

almost completely at each beat. Hence a slight increase in the pulse-rate will bring about a sufficiently large output per minute to prevent any accumulation of blood on the venous side and, therefore, to prevent an appreciable rise of venous pressure. Placed under the same conditions, a feeble (thin-walled) ventricle, even when dilated to its physiological limit, may be unable

greatly to increase its output per beat and may be far from empty at the end of systole. In these circumstances, considerable acceleration of the pulse will be necessary to increase the minute-volume of the heart sufficiently to balance the venous inflow. In this way acceleration of the pulse can compensate for lessened contractile power in maintaining the output of the heart per minute; and the less muscular the heart, the greater will be the pulse-rate required to maintain any given output per minute.

Again, if the venous inflow and pulse-rate are constant, the feebler the heart and the less its output per beat, the greater will be the venous pressure and the diastolic volume of the heart, and the more rapidly will it fill during diastole. Acceleration of the pulse increases the output of such a heart per minute, thereby lowering the venous pressure and lessening the rate of filling and the diastolic volume of the heart; and, if the pulse is sufficiently frequent, a comparatively feeble heart may maintain a considerable output per minute without much increase in its diastolic volume.

It may be concluded then, first, that the maximal output of the heart will be reached when the venous inflow and pressure are sufficient to fill the heart very *rapidly* and completely during diastole, and the frequency of the pulse is such that the next systole begins immediately the heart is full, and, secondly, that greater frequency of the pulse can compensate for lessened contractile power of the heart in maintaining or increasing its output per minute.

The minute-volume of the heart is the product of its output per beat and of the pulse-rate; its output per beat is the resultant of the rate of venous inflow, of the contractile power of the heart, and of the duration of diastole. It is clear that an intimate relationship must exist between the pulse-rate, the venous inflow, and the contractile power of the heart, if the optimal efficiency of the heart, as regards its minute-volume, is to be maintained. This relationship underlies, and furnishes the key to the interpretation of, the varying behaviour of the heart in different individuals during exercise. The question therefore arises, What is the link which correlates these three processes? The question is a difficult one because the venous inflow depends mainly upon the mechanical pumping action of the muscles, the contractile

power of the heart varies with its size and nutritive condition, and the pulse-rate is controlled by the central nervous system; and, before an answer is attempted, the factors which regulate the pulse-rate must be considered.

The Regulation of the Pulse-Rate.

Miss Buchanan (1909) was the first to show that, in man, the pulse quickens at the very outset of exercise, so that the first diastolic period, after exercise begins, is shorter than during rest. During the next few seconds, the acceleration of the pulse becomes progressively greater (Table XIV.), and, within one to two minutes, it reaches a fairly steady level, which is then maintained so long as the work continues. The rate finally reached depends upon the severity of the exercise, and upon the degree to which the subject is in training.

TABLE XIV.—(Miss Buchanan.)

Subject.	Resting.	½ Sec.	2 Secs.	10 Secs.	20 Secs.	1-2 Mins.	5-7 Mins. (After Hearing Signal to Begin Work.)
R. W. D.	42	74	84	90	105	120	120-127
W. B.	55	67	80	96	100	100	115
W. Ch.	58	78	85-90	100	100	140	150
C. G. D.	60	72	75	84	88	96-108	100
G. H. B.	64	72	80	90	90	100	100-103
R. P. H.	68	100	106	120	124	135-140	135-140
F. B. S. H.	72	90	96	105	108	110	120

The initial acceleration of the pulse is brought about solely by shortening of the diastolic period; and this, as Hunt observed (1899), is characteristic of loss of vagus tone as distinct from stimulation of the accelerator nerves, which leads to shortening of systole as well as diastole. This fact, and the promptness with which the acceleration begins at the outset of exercise, leave no doubt that the effect is due entirely to loss of vagus tone. Johansson (1893) found that in rabbits the initial quickening of the pulse was absent when the limbs were passively moved; and this observation has been confirmed for man by Krogh and Lindhard (1913), who accept Johansson's conclusion that the initial acceleration of the pulse in voluntary movement is the result of an outflow of impulses from the cortical motor centres to the vagus centre.

There is reason to believe, however, that increase of accelerator tone also contributes to the quickening of the pulse early in exercise, although, owing to the long latent period, this may not come into action for a few seconds after the beginning of exercise. Gasser and Meek (1914) found that, after section of the vagi and excision of the suprarenal glands, acceleration of the pulse occurred when the animal took exercise, and they regarded this as due to greater accelerator tone. Again, the reflex acceleration of the pulse brought about by stimulation of a sensory nerve is due, not merely to loss of vagal tone, but also to a concomitant increase of accelerator tone (Bainbridge, 1914). Since such stimuli normally evoke reflex movements, it is probable that the vascular changes induced by sensory stimuli are identical in character with those usually observed during exercise. Further, some observations of G. Bourne[1] indicate that loss of vagal tone alone would not account for the pulse-rate often observed during even the early stages of exercise. He found that, after the administration of a dose of atropin sufficient to eliminate the influence of the vagus on the heart, the pulse-rate in a number of healthy men at rest did not exceed 100 to 110. The acceleration of the pulse during exercise must, therefore, be looked upon as the outcome, partly of lessened vagal tone, and partly of greater accelerator tone.

The Continued Increase in Pulse-rate.

Although the initial increase in the pulse-rate is purely psychical in origin, the persistence of increased frequency of the pulse throughout the period of exercise is of very complex causation. It is almost certainly due in part to a continued outflow of impulses from the higher centres to the vagus and accelerator centres. There is no doubt, however, that, even when the psychical factor is excluded or reduced to a minimum, induced muscular movement increases the frequency of the pulse. Mansfeld (1910) showed that, in animals, after division of the spinal cord in order to exclude centripetal nervous impulses, tetanisation of the hind limbs led, after a few seconds, to a considerable acceleration of the pulse; the effect was obtained only if the vagi were intact. Mansfeld suggests that the acceleration is due to stimulation of afferent nerve-endings in the heart by

[1] Private communication.

a rise in the temperature of the blood. The evidence in support of this suggestion is, however, not very convincing, and there are other possible explanations of Mansfeld's results.

Apart from psychical influences, the possible causes of acceleration of the pulse during exercise are (1) the passage of adrenalin into the blood in larger amount; (2) rise of the temperature of the body; (3) irradiation of impulses from the respiratory to the vagus centre; (4) some effect of the increased $H^{\bullet}$ ion concentration of the blood upon the tone of the vagus centre, and (5) a rise of venous pressure.

The scanty evidence available does not suggest that a larger discharge of adrenalin into the blood contributes to the increased frequency of the pulse when exercise is carried out under the ordinary conditions of daily life. Gasser and Meek found that, when the heart was freed from all nervous control, exercise led to a slight increase in pulse-rate which could be accounted for by a rise of temperature. Marked acceleration of the pulse only took place if, owing to the condition of the animals, their oxygen-supply was inadequate. They conclude, therefore, that, during normal exercise, the discharge of adrenalin into the blood-stream is insufficient to affect the pulse-rate. The possibility that, when exercise is carried out under emotional stress, adrenalin may enter into the blood-stream in sufficient amount to quicken the heart will be considered later.

The temperature during exercise does not usually exceed 38·3° to 38·9° C., although a temperature of 40° to 40·5° C. has been recorded by L. Hill (1910) and by Savage and Barasch; and there is ample evidence, the most recent being that furnished by Markwalder and Starling (1913) and by Matsuoko and Evans (1915), that such a rise in the temperature of the circulating blood produces only a trivial acceleration of the isolated heart. But in the normal individual, as L. Hill and also Haldane and Boycott (1905) have shown, a rise of body-temperature (apart from exercise) may be accompanied by a marked increase in pulmonary ventilation and pulse-rate. Since the alveolar tension of carbonic acid falls and the $H^{\bullet}$ ion concentration of the blood is presumably not increased, the increased pulmonary ventilation must be the result of greater excitability of the respiratory centre; and it has been assumed (Pembrey) that the acceleration of the pulse is also due to some effect of the temperature upon the tone

of the vagus centre. It is not altogether easy to understand how a greater excitability of the vagus centre can lessen its tonic action except on the assumption that this tone is of reflex origin, and that the impulses which tend to increase, and those which tend to lessen, vagal tone normally balance, this balance inclining towards loss of vagal tone when the centre itself becomes more sensitive to afferent impulses. That the vagus tone is maintained reflexly under normal conditions is very probable, although it is difficult to prove that such is the case; but the cause of the diminution of vagal tone, which is associated with a rise of the temperature of the body, has not been fully investigated.

It might be suggested, however, that the acceleration of the pulse in these circumstances is really secondary to the greater activity of the respiratory centre which is also brought about by a rise of body-temperature. That a close correspondence often exists between the extent of the respiratory movements and the frequency of the pulse has already been pointed out; it holds good not only during exercise but under other conditions, such as at high altitudes and during apnœa. Since both the pulmonary ventilation and the pulse-rate usually vary directly with the oxygen-consumption of the body (Fig. 8), the increased pulse-rate during exercise might seem to be fully explained by supposing either that an irradiation of impulses takes place from the respiratory to the vagus centre, or that the vagus centre, like the respiratory centre, is affected by raised $H^{\bullet}$ ion concentration of the blood.

But the belief that such an irradiation or overflow of impulses can, or does, occur rests on very slender evidence, and, at least under experimental conditions, the relationship between the pulmonary ventilation and the pulse-rate is by no means so close as is often supposed. Even during exercise in man, Means and Newburgh (1915) find that the pulmonary ventilation and pulse-rate do not invariably run parallel. Moreover, Bainbridge and Hilton (1919) have brought forward evidence that, when the influence of the respiratory movements upon the circulation is excluded by opening the chest and cutting the phrenic nerves, increased activity of the respiratory centre does not alter the frequency of the pulse. Under the same conditions, the tone of the vagus centre is not lessened by a slight rise in the $H^{\bullet}$ ion concentration of the blood, although, as Hill and Flack (1908)

showed, a marked rise in the H• ion concentration of the blood slows the heart.

If these observations hold good, they point to the conclusion that neither irradiation from the respiratory to the vagus centre, nor the altered reaction of the blood, will account for the continued acceleration of the pulse during exercise, and that some other factor must be responsible for the acceleration. This factor appears to be the venous pressure. Bainbridge (1915) has shown that a rise of venous pressure brings about acceleration of the heart, which is due partly to loss of vagal tone and partly to increase of accelerator tone. The acceleration is reflex in origin, the afferent path being along the vagus nerves. The effective stimulus is either an adequate rise in venous pressure or, more probably, a sufficient increase in the diastolic volume of the heart to set up a slight diastolic tension in its muscular fibres. Lassa and Miyazaki find that this reflex acceleration of the heart-rate may be produced by afferent impulses arising in both auricles, left as well as right, and in the great veins close to their openings in the auricles, but not in any peripheral veins.

That the venous pressure rises during exercise was first observed by Hooker (1911). He found that the pressure in the veins of the hand, which varied from 28 to 80 mm. of water during rest, rose 100 mm. or more during exercise which, in his experiments, consisted in pedalling a bicycle ergometer. The rise in pressure took place very shortly after the exercise began and continued through its duration. Similar results have been obtained by Schneider, who also noted that the pressure did not return to normal for some time (eight to twelve minutes) after the conclusion of the exercise.

Since a greater venous inflow at the same time causes the heart to fill more rapidly and completely during diastole, and, by means of this reflex mechanism, leads to acceleration of the pulse, it is clear, not only that the larger venous inflow during exercise must bring about acceleration of the pulse, but also that it furnishes a link whereby the diastolic filling of the heart and the pulse-rate can be correlated in such a way as normally to ensure the optimal efficiency of the heart.

It should, however, be noted that deeper breathing, especially if this is mainly diaphragmatic, by bringing about a more rapid return of blood to the heart, will increase the diastolic filling

and volume of the heart; and it is quite probable that, in this indirect fashion, more vigorous respiration may contribute very considerably to acceleration of the pulse during exercise.

It may be concluded, therefore, that the greater frequency of pulse throughout the period of exercise is due to the interaction of three factors. The first is a continued outflow of impulses from the higher centres to the vagus centre, the second is reflex decrease of vagal tone and increase of accelerator tone induced by distension of the heart, and the third is a rise in the temperature of the body.

The Behaviour of the Heart during Exercise.

It has been shown, in the foregoing discussion, that the minute-volume, and the diastolic and systolic volumes, of the heart are determined by the venous inflow, the pulse-rate, and the contractile power of the cardiac muscle; and these facts may now be applied in the interpretation of the behaviour of the heart during exercise.

At the outset of exercise the heart dilates, partly in order to maintain its output in the face of the rising arterial pressure and, possibly, partly because, until the higher pressure drives more blood through the coronary vessels, the blood-supply to the heart is not quite adequate and its contractile power (for a given diastolic volume) decreases slightly. But the concomitant initial acceleration of the pulse keeps the dilatation within moderate limits, and the rapidly increasing coronary blood-flow quickly restores or even improves the tone of the cardiac muscle and tends to lessen the volume of the heart.

For a few moments the acceleration of the pulse, brought about by the higher centres, has little or no effect upon the output of the heart per minute, since the venous inflow to the heart does not increase for some seconds after the beginning of exercise. As soon as this occurs, the diastolic volume of the heart becomes larger, its output per beat increases, and the pulse-rate becomes still more rapid; and the output per minute soon varies almost directly with the oxygen-consumption of the body, that is to say, with the intensity of the exercise.

Two factors appear to be at work in bringing about the co-ordination between the output per beat and the pulse-rate which is necessary to maintain this relationship between the

minute-volume of the heart and the amount of muscular work performed. In the first place, the greater outflow of impulses from the higher centres to the vagus centre, as the exercise becomes more vigorous, accelerates the pulse concomitantly with the larger venous inflow to the heart produced by the more active muscular movements. In the second place, the more active the exercise, the greater will be the return of blood to the heart; and this, partly by increasing the diastolic volume of the heart, and partly by evoking reflex acceleration of the pulse, leads to a corresponding increase in the output of the heart per minute. The slightest failure in the normal correspondence between the output of the heart per minute and the amount of work performed by the active muscles at once leads to the accumulation of blood in the great veins, and hence to greater distension of the heart. This causes further acceleration of the pulse, thereby increasing the output of the heart and restoring the balance between the output of the heart and the severity of the muscular work. The accuracy of these adjustments is shown by the fact that the output of the heart is practically a linear function (Fig. 9) of the oxygen-consumption of the body during exercise.

Evidence of the co-ordinating action of these processes is also furnished by the observation that, when the amount of muscular work done and the output of the heart per minute are the same in each case, the pulse-rate is less in the trained than in the untrained man. In the former, the output of the heart per beat is such that a comparatively slight increase in pulse-rate is required to maintain the necessary relationship between the output of the heart per minute and the degree of muscular work, and to prevent undue rise of venous pressure or inadequate oxygen-supply to the muscles. In the untrained man, whose heart has less contractile power, the output per beat must be supplemented to a much larger extent by acceleration of the pulse in order that the output per minute may correspond with the severity of the muscular work, since his heart empties itself much less completely during systole than that of the trained man. Indeed, broadly speaking, the acceleration of the pulse for a given intensity of muscular exertion varies inversely with the contractile power of the heart.

The effectiveness of this mechanism will be modified by the extent to which the vagus (and accelerator) centres are directly or indirectly played upon by emotional impulses from the higher

centres or by a rise in the temperature of the body; and, owing to these processes, the pulse-rate during exercise is sometimes so rapid that it not merely supplements, but may actually replace, an increased output per beat in maintaining the minute-volume of the heart. In these circumstances, the diastolic volume of the heart for a given output per minute will naturally be less than would otherwise be the case.

During heavy muscular work, however, the venous inflow to the heart must be so large that every heart dilates almost to its full size during diastole, and its output per beat reaches its limit; the output of the heart per minute then becomes directly proportional to the pulse-rate. The maximal pulse-rate attained during exercise, whether the individual is trained or not, appears rarely to exceed 160 per minute, although Benedict and Cathcart have recorded a pulse-rate of 180 in a highly trained subject performing very heavy work. Since the maximum pulse-rate is comparatively constant, the maximal output of the heart per minute in different individuals must ultimately depend upon the capacity of the heart to increase its output per beat, or, in other words, upon its contractile power.

If the nutrition of the cardiac muscle is normal, the contractile power of the heart is proportional to its muscular development, and the more muscular the heart, the more completely will it empty itself at each beat. Hence the powerful heart of a trained man is capable of reaching an output per minute far exceeding that which can be attained by the heart of a sedentary person; and since, as will be seen later, the intensity of muscular exertion of which a man is capable is very largely determined by the maximal output of his heart per minute, no man can be an athlete who does not possess a powerful (i.e. muscular) heart. In the case of two subjects, one trained and one untrained, working near the limits of their power, and whose output was almost maximal, Lindhard obtained the following figures:—

TABLE XV.

Work Done, Kgm. per Min.	Output of Heart, Litres per Min.	Pulse-Rate per Min.	Oxygen Consumed per Min.
(1) Trained subject { 1084 / 1287	{ 22·6 / 28·6	148 / —	2583 / —
(2) Untrained subject 386	10·7	150	1070 c.c.

The Mechanical Efficiency of the Heart.

The ability of the heart to maintain or increase its output is determined partly by the total energy set free at each beat and by the pulse-rate, and partly by the fraction of this energy which appears as effective work; and the relation between the work done by the heart and its total expenditure of energy represents its gross mechanical efficiency.

Since, during violent exercise, the heart may send out per minute four or five times as much blood as during rest, and this against a much higher arterial pressure, its external work is very greatly increased. It becomes of interest, therefore, to inquire whether the total expenditure of energy by the heart is correspondingly increased, what is the effect of exercise upon its efficiency as a machine, and whether training or other conditions have any influence upon the efficiency of the heart.

Light has been thrown on these questions by Evans. Taking the oxygen-consumption of the isolated heart as a measure of its total expenditure of energy, and at the same time recording the mechanical work performed by the heart, Evans (1912), and Evans and Matsuoko (1915), have investigated the conditions which influence its total expenditure of energy and its efficiency.

The energy-expenditure of the heart was calculated in terms of work from the equation 1 c.c. oxygen consumed = 2·07 kilogrammetres of work. The work done by the heart was calculated from the formula Work $= \frac{7QR}{5} + \frac{wV^2}{g}$, where Q = volume of blood expelled in litres, R = arterial resistance in metres of blood, w = weight of blood expelled in kilogrammes, V = mean velocity of the blood at the root of the aorta, and g = acceleration due to gravity.

Evans and Matsuoko took V to represent the mean velocity of the blood-flow, but Starling has pointed out that the velocity with which the blood leaves the heart during systole is a more accurate basis for determining the share taken by the velocity-factor in the work of the heart. The velocity of the blood-flow during the period when blood is entering the aorta can be approximately calculated by multiplying the mean velocity of the blood-flow by the factor

$$\frac{\text{duration of cardiac cycle}}{\text{duration of period of ventricular expulsion.}}$$

Evans has recently (1918) applied this correction to his earlier results, and he finds that the fraction of the heart's energy used in imparting velocity to the blood is much larger than was previously supposed, and that, consequently, the mechanical efficiency of the heart is greater than his earlier observations led him to believe to be the case.

The main conclusion which they reach is that, in cardiac as in skeletal muscle, the total expenditure of energy during

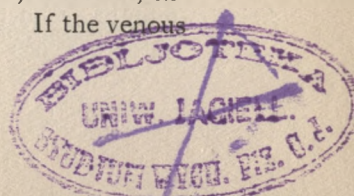
contraction varies directly with the initial length of the fibres, and that, if the pulse-rate is constant, the oxygen-consumption of the heart is proportional to its diastolic volume (Fig. 13).

Since the mechanical energy set free during systole is also proportional to the diastolic volume of the heart (Patterson, Piper, and Starling), the mechanical efficiency of the heart might be expected to remain constant, whether it is doing much or little work. But Evans and Matsuoko find that, when more work is thrown upon the heart either by a rise of arterial pressure or by a larger venous inflow, its efficiency *progressively* increases up to a maximum, which appears to be reached when the diastolic volume of the heart approaches its physiological limit. They attribute the greater efficiency, as the arterial pressure rises to the fact that, as Patterson, Piper, and Starling showed, the expulsion period of systole is prolonged and a longer time is available for the conversion of the heart's energy into mechanical work; and they consider that, when the venous inflow is increased (Fig. 15), the heart is more efficient, probably because the endocardiac pressure is greater and the velocity with which blood leaves the heart is correspondingly larger. In some of their experiments the optimal gross efficiency of the heart reached 28 per cent., a figure higher than is reached by the body as a whole even when working under favourable conditions.

TABLE XVI.—Efficiency of the Isolated Heart. (Evans and Matsuoko.)

Arterial Pressure.	Output per Hour.	O_2 Consumed per Hour.	Kg. Metres Work per Hour.	Mechanical Efficiency.
	Litres.	C.c.		Per Cent.
80	17·0	140	21·2	7·3
80	33·8	150	46·7	14·2
80	81	299	175·0	28·2

There are reasons for believing, however, that the varying efficiency of the heart observed by Evans and Matsuoko is largely the outcome of the conditions of their experiments, and that the efficiency of the normal heart is practically constant during rest and work. The energy-expenditure of the heart per minute is the product of the production of energy per beat and of the pulse-rate; and every rise in the pulse-rate, therefore, increases the total expenditure of energy of the heart. If the venous



inflow is small, greater frequency of the pulse lessens the diastolic volume of the heart and hence the production of energy per beat is less; but Evans' experiments on the influence of rate upon the consumption of oxygen by the heart indicate that the

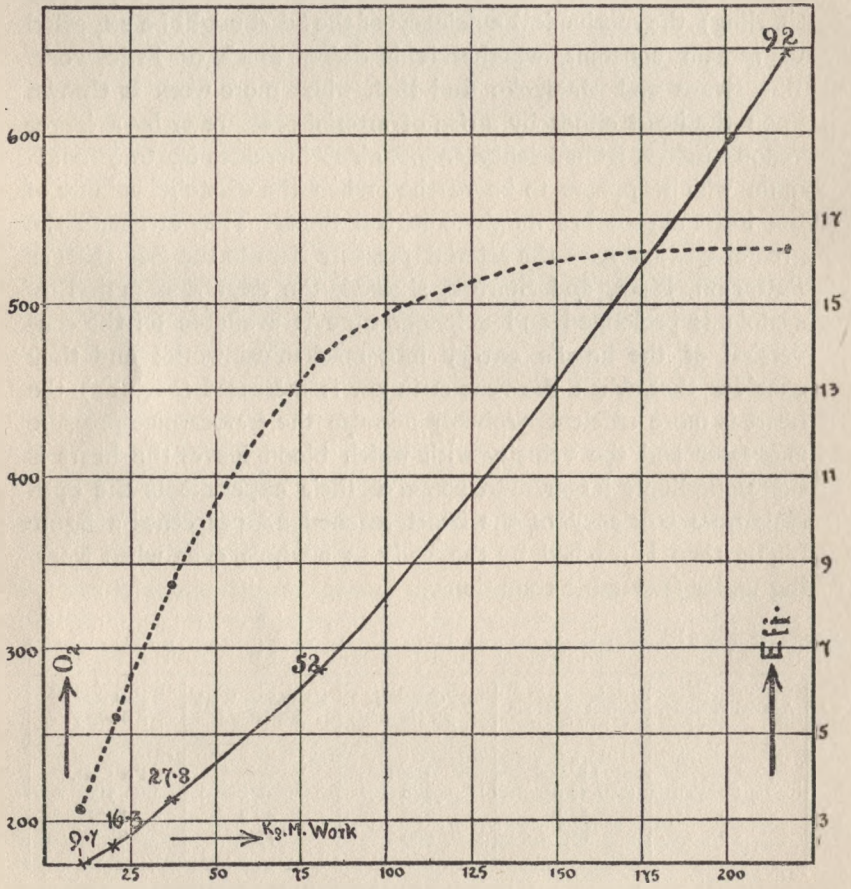


FIG. 15.—(Evans.)

Dotted line = percentage efficiency.

Continuous line = oxygen-consumption of heart in c.c. per hour. The figures on the continuous line indicate the output of the heart in litres per hour, kilogram-metre work = work per hour.

smaller consumption per beat is more than counterbalanced by increase in pulse-rate, and that the consumption of oxygen per minute is increased. With a large venous inflow, increase in pulse-rate has much less effect upon the diastolic volume, and

consumption of oxygen per beat and the energy-expenditure of the heart are almost a linear function of the pulse-rate.

Since, when the venous inflow is small, the output, and therefore the work, of the heart per minute are almost constant, whatever the pulse-rate may be, acceleration of the pulse by increasing the total energy-expenditure of the heart, but not its work, lowers its mechanical efficiency. On the contrary, when the venous inflow is large, both the output of the heart and its expenditure of energy are proportional to the pulse-rate. Hence it is clear that, in order to obtain a constant and optimal efficiency of the heart, the pulse-rate must correspond fairly closely with the venous inflow. Acceleration of the pulse, if unaccompanied by a larger venous inflow and output of the heart (or by a higher arterial pressure), is uneconomical and involves a useless expenditure of energy.

The varying efficiency of the heart, observed by Evans and Matsuoko appears, therefore, to be due to the fact that, in their experiments, the pulse-rate was constant and very rapid; consequently, with a small venous inflow, the heart was liberating energy in excess of its needs and its efficiency was low, whereas, with a large venous inflow, the energy was more effectively transformed into work. Their experiments were carried out on the heart-lung preparation, in which, owing to the elimination of nervous control, the rhythm of the heart is constant and much more rapid than that of the normal heart. In the normal heart, however, the pulse-rate and the output of the heart usually run almost parallel, and the efficiency of the heart is practically constant both during rest and during exercise, so long as the diastolic volume of the heart does not exceed the normal limits. The maximum efficiency recorded by Evans and Matsuoko was observed when the venous inflow was large and the pulse-rate rapid. This is comparable with the state of things existing during exercise, and it probably represents most truly the efficiency of the heart beating under ordinary conditions in the body. The ability of the heart to maintain this high efficiency, even when its work is enormously increased, is an excellent example of its powers of adaptation to the demands placed upon it during exercise.

It is also probable that the rise in efficiency, which Evans observed to follow a rise of arterial pressure, was also dependent

upon the great frequency of the pulse, and that, under normal conditions, the efficiency of the heart is unaffected by the arterial pressure, provided that the pulse-rate varies with the pressure as is the case during exercise.

Although the efficiency of the heart is constant in the same individual, it does not follow that in all individuals the mechanical efficiency is the same. It has been pointed out (p. 52) that, during moderate exercise, the trained individual increases the minute-volume of his heart by a larger output per beat rather than by an increase in the pulse-rate, and it might be anticipated that this would involve a smaller expenditure of energy, and that the heart of the trained man would be more efficient, in the technical sense, than that of the untrained man. The available data do not show decisively how far this deduction is justifiable, although there is some evidence (Table XVII.) that the consumption of oxygen by the heart is less, and its efficiency greater, when a given minute-volume is maintained by a larger output per beat than when it is effected mainly by increasing the pulse-rate. If this is the case, the greater the contractile power of the heart the higher will be its efficiency. In the experiments shown in Table XVII., however, the changes in the pulse-rate were produced by altering the temperature of the heart itself, and it has not yet been shown that the results hold good for the normal animal in which variations in the pulse-rate are effected through the vagi.

TABLE XVII.—(EVANS.)

Pulse-rate.	Output of Heart per Hour in Litres.	Oxygen-Consumption per Hour in c.c.	Efficiency.	Kgm. in Work per Hour.
162	24·3	165	10·8 %	37
64	24·3	117	15·2 %	37

The conclusion that the efficiency of the heart is constant and high holds good only for the normal heart in which the pericardial sac has not been stretched beyond its physiological limit. If, as a result of abnormal conditions, the pericardium has stretched, or if it has been opened under experimental conditions, the heart, as Starling has shown, can then dilate still further and can thereby greatly increase its expenditure of energy and its output. But

such a heart has crossed the boundary which divides the normal from the pathological; if called upon to do heavy work, it dilates more and more, and its energy is less and less completely transformed into mechanical work. The efficiency of the heart decreases because, with the giving way of the pericardium, the cardiac muscle is contracting at a mechanical disadvantage which is accentuated by every further dilatation.

The heart must, however, at all costs maintain its output if the circulation is to be carried on, although, in these circumstances, the performance of a given amount of work, and particularly of heavy work, necessitates a large and wasteful expenditure of energy; and, with increasing dilatation and steadily declining efficiency, a point will be reached at which it can no longer transform into work sufficient energy to increase its output or even to maintain a normal output. When this stage is reached, failure of the circulation is at hand.

Summary.

The influence of acceleration of the pulse upon the output of the heart per minute is determined by the rate at which the heart fills during diastole. If the venous inflow is small, the heart fills at a fairly uniform rate during diastole, and increased frequency of the pulse, while lessening the output of the heart per beat, scarcely affects its output per minute. If the venous inflow is so rapid that the heart fills almost completely early in diastole, acceleration of the pulse only slightly diminishes the output of the heart per beat, and its output per minute increases almost proportionately with the acceleration of the pulse. In these circumstances, the acceleration of the pulse, by enabling the heart to transfer blood more rapidly from the venous to the arterial side, also brings about a fall of pressure in the great veins.

The output of the heart per minute is the product of its output per beat, which ultimately depends upon the contractile power of its fibres, and of its rate. Hence, the smaller the output per beat, the greater will be the frequency of the pulse necessary to maintain a given output per minute, and in this way greater frequency of the pulse can compensate for lessened contractile power of the heart-muscle.

The initial acceleration of the pulse-rate at, or just before, the beginning of exercise is due to the passage of impulses from

the higher centres to the vagus centre whereby its tone is lessened; an increase of tone of the accelerator nerves is also partly responsible for the quickening of the pulse early in exercise.

The persistent acceleration of the pulse throughout the period of exercise depends, partly on a continuance of the outflow of impulses from the cerebral cortex to the vagus and accelerator centres, partly on the influence upon the vagus centre of the rise in the temperature of the body, and partly on the greater diastolic distension of the heart which reflexly lessens the tone of the vagus centre.

In each individual there is, as a rule, a close correspondence between the intensity of the muscular work and the frequency of the pulse. Reasons are given for concluding that this relationship is the result of two processes. In the first place, the outflow of impulses from the motor cerebral cortex to the skeletal muscles probably runs parallel with that to the vagus and accelerator centres. In the second place, the return of blood to the heart, and therefore the venous pressure, vary directly with the activity of the muscles.

Since the maximal pulse-rate during exercise is much the same (about 160) in different individuals, the maximum output of the heart per minute, which varies in different subjects, depends upon its capacity to increase its output per beat, that is to say, upon the contractile power of its fibres.

The gross mechanical efficiency of the heart (20 to 30 per cent.) is higher than that of the body as a whole, and in the normal man the heart is probably equally efficient both during rest and during exercise. The efficiency of the heart diminishes if acceleration of the pulse occurs without a corresponding increase in the output of the heart per minute or if the heart becomes dilated beyond its physiological limits.

CHAPTER VI.

THE BLOOD-SUPPLY TO THE ACTIVE ORGANS DURING EXERCISE —THE ARTERIAL PRESSURE.

ALTHOUGH the output of the heart is the most important means by which the blood-supply to the active muscles, the heart, and the brain is increased during exercise, other changes also occur in the circulatory system at the same time and add greatly to its effectiveness in this respect. These are an altered distribution of the blood, which is largely diverted from the abdominal organs into the active tissues, a rise of arterial pressure whereby the blood is driven more rapidly through the muscles, heart, and brain, and, in the case of the muscles and heart, local dilatation of their vessels.

Very few data are available either as to the actual blood-flow through the muscles during exercise or as to the share taken by these factors and by the output of the heart respectively in increasing this flow. Numerous observations have been made, under experimental conditions, upon the blood-flow through single muscles or small groups of muscles when resting or when thrown into contraction for a short time, and an increased rate of flow during contraction was almost invariably found. But the conditions existing in these experiments are so different from those present during normal exercise that the results are not of great value. The only investigation of this kind carried out under approximately normal conditions is that of Chauveau and Kauffman (1892), who observed a fivefold increase in the blood-flow through the *levator labii superioris* in the horse during mastication. The work of Krogh and Lindhard (1912), however, has yielded figures from which it is possible to make a rough calculation of the blood-flow through the muscles during heavy work. In one experiment the following figures were obtained by Lindhard :—

TABLE XVIII.

	Rest.	Work.
Output of heart per minute	5·0 litres	20·8 litres
Output per beat	72 c.c.	120·5 c.c.
Pulse-rate	70	166
Oxygen-consumption per minute . .	310 c.c.	1891 c.c.
Coefficient of utilisation	0·36	0·46

The early work of Ranke (1871) and of Spehl (1883) led them to conclude that, during rest, approximately one-third of the total blood is present in the skeletal muscles. Accepting this figure, which seems quite a probable one, one may make the further assumption that during rest one-third of the heart's output flows through the muscles, namely, in this case, 1·66 litres per minute. There is no doubt that most of the increased consumption of oxygen during exercise occurs in the active muscles (including the heart), and, in the present example, the additional oxygen which they consumed is taken to be 1,200 c.c. This involves the passage through the muscles of 12·69 litres of blood in addition to that flowing through them during rest, giving a total of 14·3 litres, which represents more than an eightfold increase of the blood-flow through the muscles.

As a result of such calculations from similar data in other individuals it appears that, during exercise, the blood-flow through the muscles may be from four to nine times greater in the trained man, and from three to six times greater in the untrained subject, than during rest.

TABLE XIX.

	Oxygen Consumed: c.c. per Minute.	Output of Heart: Litres per Minute.	Calculated Increase in Blood-flow through Muscles.
(1) *Trained man*—			
Rest . . .	248	4·3	—
Heavy work . .	2158	17·85	9·2 fold
(2) *Untrained subject*—			
Rest . . .	223	4·1	—
Moderate work .	1070	10·7	6 fold

Calculations of this kind can only furnish a rough indication of the magnitude of the blood-flow through the muscles. But, if

they are even approximately correct, they make clear the importance of the share taken by the altered distribution of the blood, the raised arterial pressure, the local vascular changes in increasing the blood-flow through the active muscles.

The Arterial Pressure.

Although the co-operation of all these factors is necessary for the maintenance of a sufficient supply of blood to the muscles, the most important is undoubtedly the rise of arterial pressure; and this appears to be particularly the case as regards the heart and the brain. So far as is known, the blood-supply to the brain is determined entirely by the mean arterial pressure; and, in the case of the heart, Markwalder and Starling (1913) have shown that the coronary blood-flow normally depends to a much greater extent upon the arterial pressure than upon any other factor, and that it may become inadequate for the nutrition of the heart, if the arterial pressure falls below 90 mm. Hg.

The extent to which the arterial pressure influences the blood-supply to the tissues is indicated by the work of Gesell (1918), who has found that the blood-flow through a single organ is not directly proportional to the blood-pressure, and that a comparatively small fall in arterial pressure brings about a relatively large decrease of the blood-flow through such an organ. This is also brought out by the observations of Robertson and Bock (1918). They have found that the supply of oxygen to the tissues can be maintained in spite of a greatly diminished oxygen-carrying power of the blood, provided the arterial pressure is kept up; and a man is better off, under these conditions, than one whose blood-pressure is low, even although, in the latter, the oxygen-carrying power of the blood is normal.

Since a normal arterial pressure is required to bring about a sufficiently rapid blood-flow round the body to meet its demand for oxygen during rest, it is clear that a rise of arterial pressure is absolutely necessary when this demand is increased by exercise, and that a high arterial pressure is an essential condition for the efficient performance of muscular work.

Direct evidence that the arterial pressure rises during exercise in man was obtained by Zadek (1881), but L. Hill (1898) was the first to measure the rise of pressure, his observations being made just after the conclusion of the exer-

little later (1904), Bowen followed out the course of the arterial pressure throughout the whole period of exercise. He observed a rapid rise of pressure at the very outset of exercise, succeeded by a more gradual further rise to a maximum, which was reached within five to ten minutes after the beginning of exercise. The pressure then remained fairly steady, though it showed a slight tendency to fall during the remainder of the period of work; and an abrupt fall almost to the resting level of pressure took place as soon as the work ceased. The maximum rise of arterial pressure in different experiments varied from 60 to 70 mm. Hg, although the exercise, which consisted in pedalling a bicycle ergometer, was not heavy and did not amount to more than 400 kilogrammetres per minute. These results were confirmed by Lowsley (1911), who adopted methods similar to those of Bowen.

The conditions under which continuous records of arterial pressure can be obtained during exercise are obviously limited, and the impossibility of recording the blood-pressure during the progress of most forms of exercise has led the majority of observers to measure the arterial pressure immediately after the conclusion of muscular work. Pembrey and Todd (1908) found that, in an untrained person, the arterial pressure was raised, in different experiments, from 16 to 34 mm. Hg by running up and down stairs for half a minute. In similar experiments carried out by Hill and Flack (1909) the rise of pressure amounted to 50 to 60 mm. Hg.

The results obtained in this way have hitherto been regarded as representing the actual rise of pressure during the exercise. But Cotton, Lewis, and Rapport (1917) have recently shown that, ten seconds after the end of a short period of vigorous exercise, the systolic pressure is little, if at all, above the normal resting level. It then rises rather steeply and reaches a maximum twenty to sixty seconds later; the pressure then gradually falls, and finally returns to the normal resting level from one to four and a half minutes after the cessation of exercise (Fig. 16). They explain these facts as follows. Immediately, at the end of exercise the muscles relax, and the veins, which they believe to be depleted *during* exercise, fill up with blood, thereby momentarily robbing the heart of its supply and lowering the arterial pressure until the veins fill and overflow; this overflow, by feeding the heart, again raises the arterial pressure, the rise representing

the continuance of the arterial pressure during exercise in so far as the latter is due to factors other than emptying of the veins into the arteries. The evidence already detailed (p. 48) goes to show, however, that the veins are full during exercise, and it seems more probable that the fall of pressure results from the

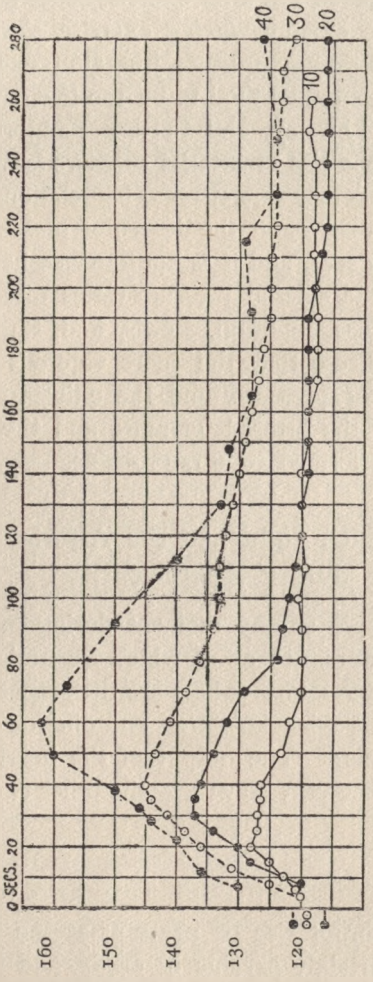


FIG. 16.—Systolic Blood-pressure (Cotton, Rapport, and Lewis). Showing the after-effect upon the blood-pressure of lifting 20 lb. dumb-bells once in two seconds: the number of lifts is shown on the right of the curve. The figures on the left represent B.P. in mm. Hg. The vertical zero (0 secs.) represents the cessation of exercise.

sudden stoppage of the muscular pump when the exercise ceases; this brings about a momentary stagnation of blood in the capillaries, which is rapidly succeeded by restoration of the venous inflow to the heart as the capillaries gradually empty themselves into the great veins. Cotton, Rapport, and Lewis further found

that, in ten healthy men, the average rise of systolic pressure, half a minute after walking briskly up a single flight of thirty steps, was 31 mm. Hg ; with rather more severe exertion, a rise of 40 mm. Hg was observed in some cases.

In the light of this evidence it is clear that a single record of the arterial pressure, taken just after exercise, does not necessarily represent the pressure existing *during* exercise, since there is no certainty that the maximum pressure just after exercise was recorded. The results obtained tend to be too low, and the figures recorded by Bowen, Lowsley, and Cotton, Rapport, and Lewis leave no doubt that the rise in arterial pressure is very considerable even during moderate exercise. The relationship between the rise of arterial pressure and the degree of muscular work has not been fully investigated, and it is not known whether, like the output of the heart, the arterial pressure varies directly with the severity of the exercise. Cotton, Lewis, and Rapport's observations, however, indicate that the more vigorous the exercise the greater the rise of pressure, and the existence of a direct relationship between the arterial pressure and the intensity of the muscular work performed appears probable.

The Factors which Influence the Arterial Pressure during Exercise.

The arterial pressure at any moment during exercise is the resultant of many factors, not all of which are under the control of the central nervous system. These are the output of the heart, vaso-constriction in the splanchnic area, and dilation of the vessels in the skin and muscles. The output of the heart has already been dealt with, and the part played by the other two factors may now be discussed.

Constriction of the Splanchnic Vessels.

The rapid and abrupt rise of pressure at the beginning of exercise is almost certainly psychic in origin, and is due to impulses passing to the vaso-motor centre, and thence to the splanchnic area, from the higher centres, and probably mainly from the motor area of the cerebral cortex. The fact that the initial rise of pressure is more pronounced when the exercise is carried out under emotional stress, and that, in these circum-

stances, it may occur even before the exercise begins; points clearly to this conclusion. Some indirect evidence of constriction of the splanchnic vessels during exercise has been furnished by Weber (1907), who found that certain emotions, or the thought of taking exercise (not followed by actual movement), led to shrinking of the abdominal viscera and to expansion of the limbs. The rise of arterial pressure and the altered distribution of the blood in the body, consequent upon constriction of the splanchnic vessels, would adequately account for the expansion of the limbs in this experiment, and there is, in point of fact, no evidence that, at the beginning of exercise, the vaso-motor centre directly lessens the tone of the vessels of the limbs.

To what extent, if at all, this initial effect persists throughout the period of exercise is uncertain, and direct evidence on the point would be extremely difficult to obtain. But, on general grounds, it seems quite probable that a continuous stream of impulses passes to the vaso-motor centre as well as to the other medullary centres during the whole period of muscular work. Indeed it seems almost inevitable that this must occur if the raised arterial pressure and altered distribution of the blood, which are so necessary for the blood-supply to the active organs, are to be maintained. Further, the question arises as to whether the vaso-motor centre is also stimulated during exercise by increased $H^{\bullet}$ ion concentration of the blood. Although it is well known that the vaso-motor centre can be excited in this way, it usually responds less quickly than the respiratory centre, under experimental conditions, when the $H^{\bullet}$ ion concentration of the blood is increased either by adding carbonic acid to the inspired air or in the early stages of asphyxia (Mathison, 1911). This difference may possibly be experimental in origin, since there is some evidence (Cathcart and Clarke) that the response of the vaso-motor centre to altered reaction of the blood is more easily dulled under the depressing influences of anæsthetics than that of the respiratory centre. But the change in the reaction of the arterial blood during exercise is so slight that, in the absence of any direct evidence as to the C_H of the blood required to excite the vaso-motor centre under normal conditions, the question whether the reaction of the blood normally affects the centre during exercise must be left unanswered for the present.

Local Changes in the Vessels.

The rise of blood-pressure and the altered distribution of the blood resulting from constriction of the splanchnic vessels, presuming this to continue throughout exercise, are in themselves sufficient to increase considerably the blood-flow through the muscles, heart, and brain. In the case of the muscles Anrep (1912) has shown that this is the case. But it is clear that the extent of this increase must be profoundly modified by the coincident occurrence of changes in the tone of the blood-vessels of the active muscles (including the heart). Such changes may be of nervous origin or may result from alterations in the composition of the blood.

Gaskell (1878) observed an increased blood-flow through the limbs on stimulating a motor nerve in a curarised animal; and Bayliss (1901) has shown that the limbs receive both vaso-constrictor and vaso-dilator nerves, although the extent to which these are distributed to muscles and skin respectively is not very clearly defined. Although the central nervous system clearly exercises some control over the tone of the arterioles in the muscles, it is not known how far, if at all, this controlling action is modified during exercise; and the comparatively trivial influence apparently exerted by the nervous system over the arterioles in the muscles early led Gaskell (1880) to examine the effect of chemical products of muscular activity upon the arterioles. His observation that these dilate, when lactic acid is added to the perfusing fluid, formed the starting-point from which has developed the current belief that the metabolic products of active organs lessen the tone of their arterioles, and thereby automatically increase the blood-flow through these organs.

The evidence recently brought forward by Dale and Richards and by Krogh makes it clear that this view must be extended to include capillary, as well as arterial, tone. Variations in capillary tone had previously been described by Roy and Graham Brown (1879), and by Langley (1911), but Dale and Richards, and especially Krogh, have examined the conditions necessary for its maintenance and the means by which it may be increased or decreased.

Krogh comes to the conclusion that the capillaries have a tone of their own and that this tone is not—at least not

principally—of nervous origin, but depends on the presence of some chemical substance or substances in the blood. The substance responsible for this tonic action of the blood has been found not to be oxygen. Local mechanical stimuli as well as local application of substances like iodine, cocaine, nicotine, cause dilatation of the capillaries and arterioles, and what is important, that in every case the dilatation could be observed over a greater area than that which had been stimulated. Local application of acids have also a pronounced dilator effect on capillaries and arterioles. The fact that the tone of the capillaries and arterioles diminishes under the influence of acid metabolic products must be constantly borne in mind in considering the extent to which the blood-supply to the muscles can be increased during exercise by alteration in the composition of the blood. The action of these substances and the spreading of the dilatation is according to Krogh based on an axon reflex mechanism. He finds that the effect is not changed by simple section of the nerves, but disappears when sufficient time is allowed for the nerves to degenerate. The reaction is probably due to local axon reflexes of the antidromic type along the fibres of sensory nerves which give numerous branches to capillaries and small arteries. During a normal resting condition of a muscle a large number of capillaries are closed. When the muscle begins to contract the capillaries dilate owing to the action of acid products of activity and the hitherto closed capillaries open—the active muscle receives in this way much more blood and regulates the supply of blood according to its needs.

Dale and Richards found that the capillary tone is lessened by the addition to the blood of small amounts of histamine.

It is reasonable to assume that the loss of capillary tone, which takes place when the circulating blood is deficient in oxygen, is really dependent upon an increased $H^{\bullet}$ ion concentration resulting from this deficiency. Further, Dale and Richards suggest that the action of histamine is probably typical of that of other metabolic products, whose formation is constantly taking place in the tissues, and whose production is "accelerated by every excitatory or injurious influence which intensifies metabolic activity." The fact that the capillaries, as well as the arterioles, are capable of variations of tone under the influence of metabolic products and of changes in $H^{\bullet}$ ion concentration must be

constantly borne in mind in considering the extent to which the blood-supply to the muscles can be increased during exercise by alterations in the composition of the blood.

Some indication of the degree of vaso-dilatation which may be produced by such metabolites, when muscular movement is carried out under more or less normal conditions and uncomplicated by changes in arterial pressure or in the output of the heart, has been furnished by Verzàr (1912). He examined the effect of a brief tetanus upon the blood-flow through a single muscle, cut off from the central nervous system but provided with its normal blood-supply, and found that, just after the tetanus, the maximal rate of blood-flow was five times greater than during rest. The magnitude of this change shows very clearly the important part taken by metabolites as a whole in increasing the flow of blood through muscles; and the local dilatation, induced in this way, must be especially valuable when muscular activity is limited to a few small muscles and the output of the heart remains almost unaltered.

The Action of Acid Metabolites.

The metabolites responsible for this change fall into two groups, namely, acid products of metabolism and metabolites other than acids. During normal muscular activity these are doubtless produced simultaneously, and it is not easy to assess the relative importance of these two factors. Gaskell's observation (1880) that the addition of lactic acid to the perfusing fluid dilates the arterioles in the muscles was confirmed by Bayliss (1901), who further found that the presence of an excess of carbonic acid in the perfusing fluid had the same effect. In these experiments the perfusing fluid was Ringer's solution, and the addition of lactic or carbonic acid to such a fluid produces a change in its $H^{\cdot}$ ion concentration far greater than would occur if the same amount of acid were added to blood. Assuming that the effective cause of dilatation of the arterioles by acids is the altered $H^{\cdot}$ ion concentration, it is evident that the passage of considerable amounts of these acids from the muscles into the blood during exercise may have comparatively little influence upon the arterioles and capillaries. It does not follow, therefore, that the addition of acids to the blood during exercise will necessarily dilate the arterioles. Indeed the reaction of the

arterial blood alters so little during exercise that it may be doubted whether it has any effect upon the arterioles generally, unless these are endowed with a sensitiveness to $H^{\bullet}$ ions almost comparable with that of the respiratory centre; and there is, unfortunately, no evidence as to the minimal increase in $H^{\bullet}$ ion concentration required to lessen the tone of the arterioles.

During exercise, however, the concentration of acid metabolites must be appreciably greater in the capillary blood, and in the

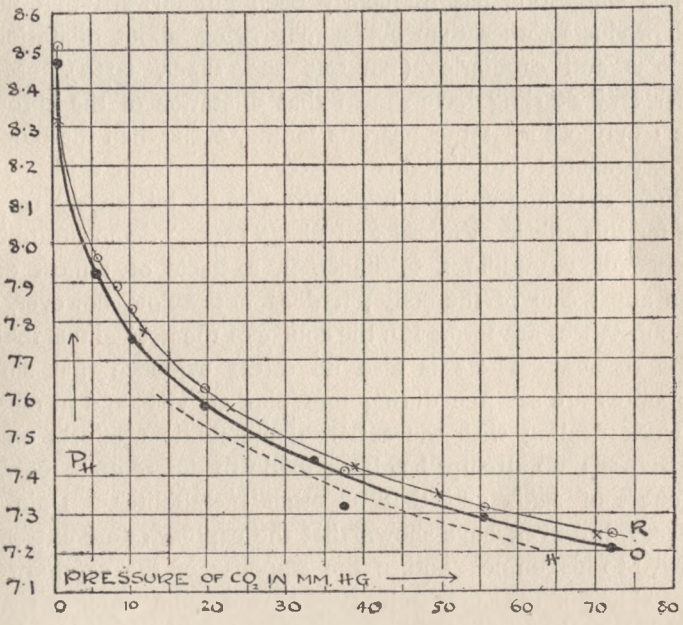


FIG. 17.—(Parsons.)

R = completely reduced blood.
O = fully oxygenated blood.
H = Hasselbalch's curve for oxygenated blood.

tissue-fluid bathing the arterioles and capillaries of the active muscles, than in the arterial blood, although the rapid diffusibility of lactic and carbonic acid and the increased velocity of the flow of blood and lymph through the active muscles probably prevent any considerable rise in the concentration of these acids in and around the capillaries, unless the exercise is severe or fatigue is setting in. Moreover, Christiansen, Douglas, and Haldane (1914) and Parsons (1917) have shown that, at a given tension of carbonic acid, reduced blood is less acid than oxygenated blood (Fig. 17).

and this will tend to minimise the rise in the C_H of the blood as it flows along the capillaries. None the less the local change in $H^{\cdot}$ ion concentration is probably sufficient to lessen the tone of the arterioles and capillaries in the active muscles. In this connection, information as to the C_H of the blood leaving the active muscles would be of great value.

Other Metabolites.

The suggestion has frequently been put forward that metabolic products, other than acids, may bring about dilatation of arterioles and capillaries (Barcroft and Piper, 1912). Markwalder and Starling have shown that dilatation of the coronary vessels may occur, if the heart is failing, even when the blood is well oxygenated and contains no excess of carbonic acid. They conclude that non-volatile metabolites must be largely responsible for this effect. Vincent and Sheen (1903) demonstrated the presence of vaso-dilator substance in extracts of almost every organ and tissue of the body; it does not follow, however, that such substances are formed in the course of the normal metabolism of the tissues. There is also no direct evidence that similar metabolites are set free during muscular activity, and in most of the work dealing with the action of metabolic products on the blood-vessels, no attempt has been made to differentiate between the effect of acids and that of other metabolites. Dale and Richards, however, have shown that the capillaries are extremely sensitive to histamine; and, if the response of the capillaries to the products of muscular activity is of the same order as that to histamine, their effect upon capillary tone in the muscles during exercise may be very considerable. There is no evidence that metabolites of this type are normally present during exercise in sufficient concentration in the general circulation to affect the tone of the arterioles and capillaries throughout the body as a whole.

It may be concluded, that although the metabolic products of muscular activity lessen the tone of the arterioles and capillaries during exercise, their action is purely *local* and is confined to the vessels of the active muscles; and the extent to which even this local loss of tone takes place will obviously correspond with the local production of metabolites or, in other words, with the intensity of the exercise. Such a decrease in tone, occurring

concomitantly with the rise of arterial pressure, will result not only in a much more rapid rate of blood-flow through the muscles, but also in the presence at any moment in the muscles of a much greater proportion of the total blood than during rest. At the same time the active muscles, owing to their mechanical action in driving blood into the veins, cause the blood to be returned more rapidly to the heart; and these two processes, namely, on the one hand, loss of arteriole and capillary tone, and, on the other hand, the mechanical pumping action of the muscles, will clearly run parallel with one another and with the degree of activity of the muscles.

The association of these two processes provides a mechanism whereby blood is driven under high pressure, and in large amount, into the relaxed vessels in the muscles, and is equally rapidly returned to the heart by the muscles themselves, thereby bringing about a very large increase in the output of the heart, in the circulation rate, and in the blood-supply, not only to the muscles, but also to the heart and brain. In this way decrease in the tone of the arterioles and capillaries in the muscles during exercise reacts upon the entire circulatory mechanism, and is, therefore, very advantageous to the body as a whole. It is only when the muscles are quiescent or toneless that such loss of capillary tone, as, for example, in the condition of shock, may be harmful, partly by lessening the peripheral resistance and partly by increasing the capacity of the vascular system.

The Influence of Adrenaline.—There is yet another factor, namely, the presence of adrenaline in the circulating blood, which plays a part in the regulation of capillary tone. Dale and Richards find that denervation of a limb produces a merely temporary loss of vascular tone, and that recovery and subsequent maintenance of capillary tone soon take place. If the limb is now artificially perfused with oxygenated, hirudinised blood, the tone of the capillaries is at once lost, but it can be restored by the addition of adrenaline to the perfusing blood. The presence of adrenaline is essential, therefore, for the maintenance of capillary tone; and, as Dale and Richards point out, a further inference from this experiment is that adrenaline must be present in the normally circulating blood in such amount as to maintain this tone. The possibility that an increase in the amount of adrenaline in the circulating blood may increase or decrease capillary tone,

according to the amount added, is discussed by them; and they have brought forward evidence that, in the normal animal, the sudden addition of small amounts of adrenaline to the blood lessens the tone of the capillaries. But, in view of the existing uncertainty as to the extent to which adrenaline is discharged into the blood during exercise, any conclusion in regard to the share which it takes in modifying the tone of capillaries during exercise would be premature.

Subsidiary Factors.

In addition to these factors, the circulation rate during exercise, and therefore the blood-supply to the body as a whole, is also influenced by other changes of subsidiary importance. These include dilatation of the vessels of the skin, rise of the temperature of the body, and concentration of the blood by loss of water. Dilatation of the vessels of the skin will tend to lower the blood-pressure by increasing the capacity of the circulatory system and by lessening the peripheral resistance. The rise of temperature also lessens the peripheral resistance in so far as it diminishes the viscosity of the blood. These effects will be, at least in part, counteracted by the increased viscosity of the blood brought about by the concentration of the blood which takes place during exercise.

Zuntz and Schumburg (1901) found that a long march led to an average increase of 9 per cent. in the number of red corpuscles. As a result of running, the increase varied in different subjects from 3 to 22·8 per cent. (Schneider and Havens, 1915) and 2·9 to 23·4 per cent. (Willebrand, 1903). Schneider and Havens found that the hæmoglobin value of the blood was also raised by running, the rise varying from 3·5 to 10·9 per cent.

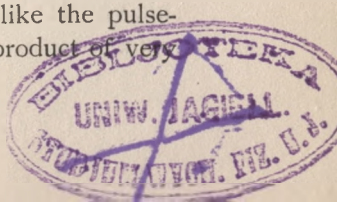
When the exercise lasts for some time, the loss of fluid from the body in the expired air and as a result of sweating must contribute to the concentration of the blood. Boothby (1915) regards it as being caused entirely in this way, since he did not observe any change in the blood before the onset of sweating; but, since a short run, such as a 100 yards' race, may bring about some concentration of the blood (Hawke, 1904), some other factor must also be concerned in its production. Schneider and Havens believe that, in the resting individual, a proportion of the red cells is not in active circulation, but is stagnating within the

splanchnic area, and that, with the onset of exercise, constriction of the splanchnic vessels forces these cells into the general circulation, thereby bringing about an almost immediate rise in the hæmoglobin value of the blood. They consider that the passage of adrenaline in larger amount during exercise is responsible for reducing the capacity of the splanchnic area, and driving hitherto stagnant blood into effective circulation. This view is based partly on their belief that an increased $H^{\cdot}$ ion concentration of the blood brings about a greater discharge of adrenaline, and partly on the observation of themselves and of others (Lamson) that the injection of adrenaline into the blood stream raises the hæmoglobin value of the blood.

The evidence brought forward by Kellaway (1919), however, goes to show that a rise in the C_H of the blood does not affect the discharge of adrenaline by the suprarenal glands. Further, Bainbridge and Trevan (1917) have found that, far from driving blood out of the splanchnic area, adrenaline leads to the accumulation of blood in the liver (at least in the dog), and that the rapid filtration of lymph, which occurs in these circumstances, furnishes an adequate explanation of the concentration of the blood. There is indeed every reason to believe that the raised capillary pressure during exercise, by increasing the formation of lymph, accounts for the initial rise in concentration (F. H. Scott, 1918), and must contribute to the persistence of this rise throughout the period of exercise. The withdrawal of water from the blood, in consequence of the raised osmotic pressure of the active muscles, must also have some influence in lessening the volume of the blood.

As regards their effect upon the viscosity of the blood, it is very probable that the rise of temperature and the concentration of the blood practically neutralise one another, since Determann (1906) has observed only an insignificant change in the viscosity of the blood during exercise. The concentration of the blood is obviously advantageous since, by increasing the oxygen-carrying power of the blood per unit of volume, it enables a given supply of oxygen to the tissues to be maintained with a smaller output of the heart per minute than would otherwise be necessary.

A review of the foregoing discussion leads to the conclusion that the arterial blood-pressure during exercise, like the pulse-rate and the minute-volume of the heart, is the product of very



varied processes, and that a balance is maintained between, on the one side, the minute-volume of the heart and constriction of the splanchnic vessels, and, on the other side, dilatation of the arterioles and capillaries in the active muscles and the skin. Every accession of muscular effort tends to raise the arterial pressure, partly by driving the blood more rapidly back to the heart and increasing its output, partly as a result of a stronger outflow of impulses from the vaso-motor centre to the splanchnic area in response to stimuli from the higher centres, and possibly in response to a greater $H^{\cdot}$ ion concentration of the arterial blood. At the same time the larger production of acid and other metabolites in the muscles (and heart) lessens the tone of the capillaries and arterioles in the muscles.

Under normal conditions, the rise of blood-pressure brought about by the interaction of these processes is such that the needs of the heart, brain, and muscles are satisfied. Disturbance of this balance by defective or excessive action of any of these adjustments will at once derange the normal relationship between the requirements of the heart, brain, and muscles for oxygen and the arterial pressure which is so largely responsible for meeting these needs. In these circumstances, the arterial pressure of the individual will be higher or lower, as the case may be, for a given amount of exercise than that of the normal man. It is said, for example, that one of the early signs of fatigue during exercise is an exaggerated rise of blood-pressure due in all probability to over-activity of the vaso-motor centre.

Summary.

The effectiveness of the larger output of the heart in increasing the blood-supply to the active muscles, to the heart and to the brain during exercise is greatly enhanced by constriction of the splanchnic vessels, and by dilatation of the vessels in the muscles (and heart). It is calculated that, as the outcome of these processes, the flow of blood through the active muscles may be from six to eight times greater than during rest.

The rise of arterial pressure during exercise is the resultant of (1) increased output of the heart; (2) constriction of the splanchnic vessels; and (3) dilatation of the vessels in the muscles and skin.

The constriction of the splanchnic vessels is brought about primarily and chiefly by the outflow of impulses from the higher centres to the vaso-motor centre. Whether the centre is also stimulated by the greater $H^{\cdot}$ ion concentration of the blood during exercise is uncertain.

Evidence is brought forward that the tone, not only of the arterioles but also of the capillaries, can be lessened by metabolic products, and that these metabolites are of two kinds, namely, acids and metabolites other than acids. There is reason to believe that, during exercise, the concentration of these metabolites in and around the arterioles and capillaries of the active muscles is sufficient to lessen the tone of these vessels, thereby increasing the flow of blood through the muscles.

The addition of small amounts of adrenaline to the circulating blood lessens the tone of the capillaries, but there is at present no evidence that adrenaline modifies capillary tone during exercise.

CHAPTER VII.

THE PASSAGE OF OXYGEN INTO THE TISSUES DURING EXERCISE—THE CONSUMPTION OF OXYGEN BY THE MUSCLES—THE CONSUMPTION OF OXYGEN BY THE HEART.

The Passage of Oxygen into the Tissues.

THE circulatory changes taking place during exercise, by increasing the rate of blood-flow through the active organs, place at their disposal a much larger amount of oxygen than is available during rest. But it is a physiological truism that the oxygen-consumption of every tissue varies with, and is primarily determined by, its functional activity. Each organ takes up from the blood flowing through it the oxygen required for its metabolic activities, and the amount of oxygen which each fraction of the blood gives up to the tissues, as it passes along the capillaries, depends partly upon the demands of the tissues and partly upon the rate of the blood-flow.

The extent to which the blood becomes reduced, as it traverses the capillaries, has been termed by Krogh (1912) the *coefficient of utilisation.* The coefficient is ascertained by finding the amount of oxygen taken up by the tissues from 1 litre of blood during its passage round the body, and dividing the figure, thus obtained, by the oxygen capacity (per litre) of the individual. If, for example, the amount of oxygen absorbed by the individual per minute is 270 c.c., and the minute-volume of the heart is 4·8 litres, each litre of blood gives off $\frac{270}{4{\cdot}8} = 56{\cdot}25$ c.c. oxygen to the tissues; and, if the oxygen capacity of the blood is 185 c.c. per litre, the coefficient of utilisation is $\frac{56{\cdot}25}{185} = 0{\cdot}30$.

Observations made by Lindhard (1915) on ten resting individuals showed a comparatively constant coefficient. In eight of the ten cases, the coefficient was between 0·29 and 0·31, and the extreme limits of variation lay between 0·25 and 0·31.

Lindhard assumes the arterial blood to be fully saturated with oxygen, whereas Boothby who has repeated these observations, takes it as being 94 per cent. saturated. Allowing for this difference in his calculations, his observations confirm those of Lindhard. Slightly higher figures were obtained by Means and Newburgh. The constancy of the coefficient is rather remarkable since, as Lindhard points out, the consumption of oxygen and the output of the heart varied considerably in the individuals whom he examined.

If the coefficient remained unchanged during exercise, the greater oxygen requirements of the active organs could be met only by a more rapid flow of blood through them. All the recorded observations, however, show a striking increase in the coefficient, which may be doubled or more than doubled during exercise. The following table is constructed from Lindhard's figures :—

TABLE XX.

	Oxygen-Consumption: c.c. per Minute.	Output of Heart: Litres per Minute.	Coefficient of Utilisation.
(1) Rest	310	5·0	0·30
Work (*a*)	1630	17·05	0·47
Work (*b*)	2089	19·65	0·55
(2) Rest	248	4·3	0·31
Work (*a*)	1410	12·1	0·63
Work (*b*)	1893	14·4	0·70
(3) Rest	329	6·0	0·30
Work (*a*)	606	6·3	0·52
Work (*b*)	1759	16·6	0·57

Working with a single muscle, the gastrocnemius, Verzàr (1912) also found a rise in the coefficient during tetanus, as is seen from the following figures :—

	Blood-flow per Minute.	Coefficient of Utilisation.
Rest	1·16 c.c.	0·24
Tetanus	2·4 c.c.	0·40

Douglas and Haldane, using their method, also found a great rise in the coefficient of utilisation of the oxygen in the blood.

TABLE XXa.—(Douglas and Haldane.)

Condition.	Coefficient of Utilisation.
Lying down	0·190
Sitting upright on chair	0·225
Ergometer 103 kilogrammetres per minute	0·430
,, 264 ,, ,, ...	0·496
,, 512 ,, ,, ...	0·610
,, 752 ,, ,, ...	0·640

The effect of muscular exercise on the coefficient of utilisation of oxygen.

Lindhard's calculations are based on the assumption that the arterial blood is as fully saturated with oxygen during exercise as during rest, and, if this is the case, the hæmoglobin in the venous blood reaching the heart during exercise may be only 30 to 50 per cent. saturated with oxygen. Since the blood in the great veins comes not only from the active organs but also from others which are at rest, it is quite probable that the blood leaving the active muscles is at times even less than 30 per cent. saturated with oxygen.

On the other hand, the suggestion has been put forward (Barcroft, 1914) that, owing to the rapid rate at which the blood flows through the lungs and to the slightly lessened affinity of hæmoglobin for oxygen during exercise, the blood may not have time to become as fully oxygenated as during rest, and that the arterial blood may not be more than 85 per cent. saturated with oxygen. During exercise, however, the tension of oxygen in the venous blood reaching the lungs is considerably lower than during rest, and may fall to 25 mm. Hg, whereas the tension of oxygen in alveolar air remains practically as high as during rest. Hence, oxygen must diffuse more rapidly from the alveolar air into the blood during exercise than during rest. Further, M. Krogh (1915) has shown that the diffusion-coefficient, namely, the amount of oxygen which will diffuse from the alveolar air into the blood in one minute at a tension-difference of 1 mm., is considerably greater during exercise than during rest. The combination of a larger diffusion coefficient with a greater difference in the tension of oxygen in alveolar air and in blood respectively must hasten considerably the passage of oxygen into the blood as this flows through the lungs. The extent to which the arterial blood in man is saturated with oxygen during exercise is not known, but it is possible that the more rapid diffusion of oxygen into

the blood completely counterbalances the effect of the faster blood-flow through the lungs, and that Lindhard's assumption is at least approximately correct.

Krogh has shown that the increased supply of oxygenated blood is greatly helped by the dilatation of the capillaries in an active muscle. The large number of capillaries which are tonically contracted and closed during rest, open widely as soon as the muscle becomes active. In this way the surface of contact between the blood and the active tissues is enormously increased.

It is clear, then, that, although any one fraction of the blood traverses the capillaries several times faster during exercise than during rest, the active muscles are able to take up twice as much oxygen, or even more, from each fraction ; and the question arises How is this effected? There appear to be only two possibilities, namely, first, more rapid dissociation of oxyhæmoglobin as the blood traverses the capillaries, and, second, a greater avidity of the tissues for oxygen.

The influence of exercise upon the dissociation curve of hæmoglobin has been studied mainly by Barcroft and his co-workers. There are no direct observations as to the effect of severe exercise upon the dissociation curve, but Barcroft (1914) found that moderate exercise, such as a climb of 1,000 feet from sea-level in half an hour, produced a comparatively small change in his dissociation curve (Fig. 18); when examined at an oxygen-pressure of 27·5 mm. Hg, the saturation of his blood was 13 per cent. less just after exercise than during rest.

In these experiments the saturation of the blood was determined after equilibrium between blood and oxygen had been attained. During exercise, however, the blood is flowing through the muscles several times as fast as during rest, and it is very unlikely that the dissociation of oxyhæmoglobin reaches the equilibrium point. Consequently, the *rate* at which oxyhæmoglobin dissociates is the really important factor in this connection, and it is significant that, in Barcroft's experiment, the exercise doubled the velocity of dissociation of oxyhæmoglobin relatively to the velocity of association. Mathison (1911) was the first to show that the addition of small amounts of acid to blood greatly accelerates the rate at which its oxyhæmoglobin dissociates under a low tension of oxygen. He suggested that this was caused by the increased $H^{\cdot}$ ion concentration of the blood, produced by the

addition of acid; and the later work of Barcroft and his collaborators has not merely confirmed Mathison's view, but has demonstrated the marked extent to which even a trivial increase in the $H^{\bullet}$ ion concentration of the blood hastens the velocity with which oxyhæmoglobin can dissociate.

The samples of blood, examined in Barcroft's experiment, were obtained from the general blood-stream; and there are good reasons for believing that the $H^{\bullet}$ ion concentration of the

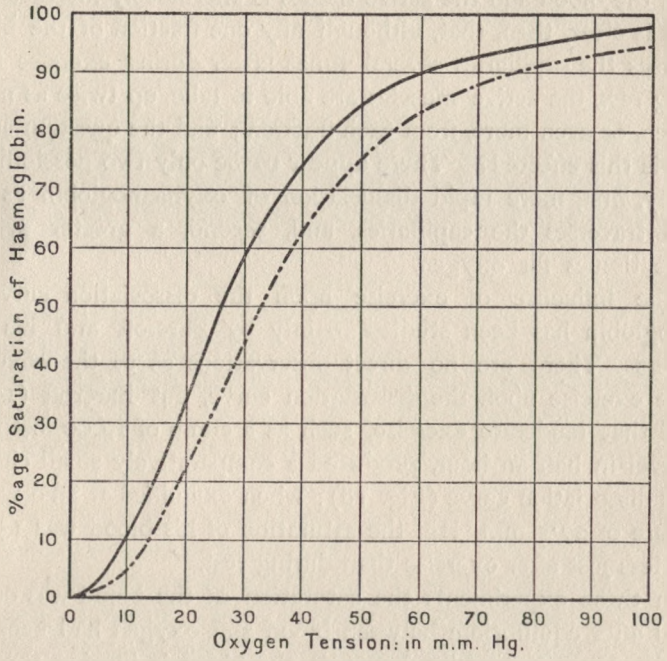


FIG. 18.—Dissociation curve of Barcroft's blood (Barcroft).
—— at sea-level.
. . . . . just after climbing 1,000 feet.

blood as a whole is distinctly less than that of the blood leaving the active muscles. It is probable, therefore, that, even during moderate exercise, as in Barcroft's experiment, the rate of dissociation of oxyhæmoglobin in the blood flowing through the active muscles may be much more than doubled, and that, during violent exercise, the local $H^{\bullet}$ ion concentration of the blood in the active muscles may increase sufficiently to bring about very rapid dissociation of oxyhæmoglobin.

Since the production of lactic and carbonic acids in the

muscles normally runs parallel with the intensity of the muscular exertion, a similar relationship probably exists between, on the one hand, the intensity of the exercise and, on the other hand, the local $H^{\bullet}$ ion concentration of the blood in the capillaries of the muscles and, consequently, the rate at which oxyhæmoglobin dissociates in the capillaries of the muscles. The more rapid the dissociation of oxyhæmoglobin, the higher will be the tension of oxygen in the plasma, and the more quickly will oxygen diffuse into the tissues; and, as the outcome of this series of inter-related processes, the active muscles (and heart) are enabled to take up oxygen in accordance with their varying requirements.

Further, the rate at which oxyhæmoglobin dissociates is increased, not only by changes in the reaction of the blood, but also by a rise of temperature (Barcroft and Hill, Oinuma, 1911). The influence of temperature is so considerable that a rise of 10° C. may double, or more than double, the rate of dissociation. The rise in the temperature of the body during exercise, must, therefore, exert an appreciable influence upon the rate at which the blood parts with oxygen as it flows through the tissues.

Incidentally, it may be noted that the lessened affinity of hæmoglobin for oxygen, which occurs during exercise, is much more effective in increasing the passage of oxygen from the blood to the tissues than in decreasing the extent to which the blood takes up oxygen as it flows through the lungs. There are two reasons for this difference. In the first place, the rate at which blood flows through the lungs depends entirely upon the output of the heart and, even during the heaviest work, is only four or five times greater than during rest, whereas the blood-flow through the muscles, in these circumstances, may be eight or ten times greater than during rest. In the second place, the tension of oxygen in the alveolar air is so high that a slight increase in the $H^{\bullet}$ ion concentration of the blood scarcely affects the amount of oxygen taken up in the lungs; on the contrary, in the tissues, where the oxygen tension is very low, a similar increase in the C_H of the blood enables the oxyhæmoglobin to dissociate much more readily.

During vigorous exercise, the rate at which the blood flows through the active organs becomes so rapid that the time spent by any one fraction of the blood in the capillaries is considerably shortened. Consequently, although each red corpuscle

gives up its store of oxygen more rapidly to the tissues, it has less time at its disposal for this purpose. The widening of the capillary bed allows the amount of blood flowing through the active muscles to be greatly increased with only a comparatively small acceleration of the rate at which the blood traverses the capillaries. Moreover, the dilatation of the capillaries, by increasing the surface area of the blood flowing through them must facilitate the diffusion of oxygen into the tissue-fluid and muscle-fibres.

But the coefficient of utilisation is often so large that some writers believe that the increased C_H of the blood is insufficient to account for the very marked reduction which the oxyhæmoglobin may undergo during exercise, and that other factors must be also at work. Lindhard, for instance, has suggested that possibly some catalase or reductase is produced during exercise, and that this lessens the affinity of hæmoglobin for oxygen. There is, however, no evidence for the existence of such a catalase.

Again, some observations of Verzàr (1912) appear to indicate that a small but definite tension of oxygen is present in resting muscle, and, if this is the case, a fall in this tension during muscular activity would enable the muscle to take up oxygen more quickly from the blood. It is not easy, however, to understand how muscle can possess an oxygen-tension, since the evidence goes to show that no free oxygen is present in muscle or any other tissue (Fletcher and Brown), and Verzàr's observations may perhaps be capable of some other interpretation.

There is at present no ground for believing that oxygen enters the cells of the tissues except by diffusion from the blood by way of the tissue fluid; and, if it is admitted that the tension of oxygen in the tissues, whether these are resting or active, is almost nil, the speed with which oxygen can diffuse into the tissues must depend entirely upon the rate at which oxyhæmoglobin dissociates as the blood flows through the tissue. But it is obvious that, unless the oxygen diffusing into the cell at once enters into some form of chemical combination, for example a peroxide, the tension of oxygen in the cell will tend to rise. The rate at which the tissues seize upon the oxygen presented to them varies, of course, with their metabolic activity. It is conceivable, therefore, that a resting organ may not use at once all the oxygen reaching it, and that a small tension of oxygen may exist. But the avidity of

the active tissues for oxygen is so large that the oxygen entering them is at once utilised, and the oxygen tension is kept at zero, even though the rate at which oxygen is diffusing into the tissues is much greater than during rest. Krogh, on the other hand, believes that during work the blood flow through the muscle increases, owing to dilatation and opening of the capillaries, to such an extent that the oxygen tension of the muscle must be well above zero.

It may be concluded, that the increased consumption of oxygen by the muscles (and heart) during exercise depends upon two factors. In the first place, the active muscles utilise so rapidly, for oxidative processes, the oxygen reaching them by diffusion that the tension of oxygen within them is zero. In the second place, they increase the amount of oxygen reaching them from the blood by an indirect means, namely, a rise in the C_H of the capillary blood, this being normally brought about by the acid products of their metabolic activity and varying *pari passu* with their activity. There is no doubt that, as the outcome of these two processes, in conjunction with a larger blood-flow through the muscles, the consumption of oxygen by the muscles during exercise may be very large. But the direct measurement of the oxygen-consumption of the muscles, under conditions approximating to those present during exercise, presents such difficulties that comparatively few observations have been made.

The Consumption of Oxygen by the Muscles.

The problem was first attacked by Chauveau and Kaufmann (1887), who measured the blood-flow through the *levator labii* of the horse, and determined the oxygen-content of the blood entering and leaving the muscle. In these experiments no anæsthetic was necessary, and the muscle was contracting under normal conditions and was not being artificially stimulated; but the methods of blood gas analysis then available left much to be desired. They found that the oxygen-consumption of resting muscle varied from 0·0028 to 0·0079 c.c., and that of the active muscle from 0·01 to 0·05 c.c. per gramme of muscle per minute.

The same question has recently been investigated by Verzàr (1912), who determined the oxygen-consumption of the cat's gastrocnemius muscle, making use of Barcroft's technique. The

muscle was thrown into activity by brief stimulation of the sciatic nerve. Verzàr found the average oxygen-consumption of resting muscle to be 0·0044 c.c. per gramme per minute. A brief tetanus increased the consumption of oxygen during, and for some little time after, the tetanus; and the total consumption of oxygen for the whole period, in one experiment, was at the rate of 0·0089 c.c. per gramme per minute as against 0·003 c.c. during rest. The maximum consumption of oxygen occurred fifteen seconds after the tetanus, and reached the high figure of 0·02 c.c. per gramme per minute.

The character of Verzàr's results is shown in the following table:—

TABLE XXI.

	Per cent. Saturation of the Blood.		Rate of Blood-Flow per Min. c.c.	C.c. Oxygen Used by Muscle.	
	Venous.	Arterial.		Per Min.	Per Gram. per Min.
Normal (resting) .	69	93	1·16	0·050	·003
Tetanus . .	53	—	2·40	·178	·010
15 secs. later .	62	—	6·00	·336	·020
11 „ „ .	60	—	3·52	·208	·012
11 „ „ .	58	94	2·40	·154	0·009
146 „ „ .	60	96	0·90	0·059	0·0035

Further, the recent work of Krogh and Lindhard, and of Lindhard, has furnished data which make it possible to form an estimate of the oxygen-consumption in the muscles of man during exercise. In one experiment, the output of the heart increased fourfold during exercise and the coefficient of utilisation rose from 0·30 to 0·46. Even on the assumption that the distribution of the blood in the body does not alter, this involves a six-fold increase in the amount of oxygen consumed by the muscles. In order to arrive at the actual amount of oxygen consumed by the muscles in man, it is necessary to make two assumptions, namely, first, that, in a trained healthy man, the muscles form approximately 40 per cent. of the body weight, and second, that, in the resting individual, about one-third of the total consumption of oxygen takes place in the muscles. For the purpose of the calculation, the following data from Lindhard are used. They were obtained in three highly trained individuals:—

TABLE XXII.

		O_2 Consumpt. per Min.	Output of Heart per Min.	Coefficient of Utilisation.
(1) J. J., wt. 75 kg.	Rest	329	6·0	0·30
	Work (*a*)	1973	20·15	0·53
	(*b*)	3204	35·0	0·495
(2) J. L., wt. 63 kg.	Rest	248	4·3	0·31
	Work	2158	17·85	0·65
(3) V. M., wt. 64 kg.	Rest	310	5·0	0·30
	Work	2157	18·05	0·58

The oxygen-consumption during rest, and the *minimum* oxygen-consumption during work calculated from these figures are as follows :—

	Rest.	Work.
(1) J. J.	0·0036 c.c.	0·0178 (*a*) c.c. per gram. per min.
		0·034 (*b*) ,, ,, ,,
(2) J. L.	0·0032 ,,	0·0278 ,, ,, ,,
(3) V. M.	0·0040 ,,	0·027 ,, ,, ,,

When one remembers that, owing to the altered distribution of the blood during exercise, the increase of the blood-flow through the muscles may be twice as great as that represented by the minute-volume of the heart, it is clear that during heavy work the consumption of oxygen may be 0·05 c.c. per gramme per minute or even more.

It is evident, therefore, that, during severe exercise, the muscles may call for ten to fifteen times as much oxygen as they require during rest, and that they meet this demand by taking up more oxygen from each portion of the blood flowing through them. The additional amount of oxygen which they can obtain in this way is obviously dependent upon the rate of the blood-flow through the muscles. There is probably some degree of adjustment between these two processes, and the muscles may obtain a given quota of oxygen, either by means of a large blood-supply and a comparatively small coefficient of utilisation or by a large coefficient of utilisation and a moderate increase in blood-supply. But the range of this adjustment is limited, and, during vigorous exercise, the avidity of the muscles for oxygen is such that both

a larger coefficient of utilisation and a very rapid flow of blood through the muscles are necessary to satisfy their needs.

Although all the circulatory adjustments, discussed in the preceding chapters, contribute to this end, the duty of providing the blood-supply to the muscles primarily devolves upon the heart, and, so long as the output of the heart keeps pace with the work done by the muscles, their functional capacity is fully maintained. The work thrown upon the heart during exercise, however, entails a large increase in the consumption of oxygen by the heart itself and the ability of the heart to keep up an adequate blood-supply to the brain and muscles during heavy muscular work is conditional upon a corresponding increase in its own blood-supply. The blood-supply to the heart is, therefore, one of the decisive factors which determine a man's capacity to perform muscular work.

The Blood-supply to the Heart during Exercise.

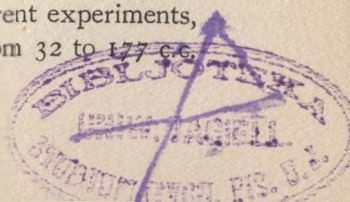
The work done by the human heart during heavy muscular work, with an output of 21 litres per minute and an arterial pressure of 130 mm. Hg, may amount to 44·6 kilogrammetres per minute (Evans). If the mechanical efficiency of the heart in these circumstances is assumed to be 25 per cent. (not an unduly high figure), its consumption of oxygen would be 86 c.c. per minute. It is probable that, during extremely severe work, the consumption of oxygen by the heart may in some individuals reach 100 c.c. per minute, since an output of 28 litres per minute has been recorded (Lindhard) and the arterial pressure often exceeds that taken as the basis of Evans' calculations.

Lewis (1914) found the weight of the muscular tissue of the two ventricles in normal human hearts to be about 150 grammes; and, allowing 50 grammes for the weight of the auricles, the average weight of the muscular, that is to say the oxygen-consuming, tissue of the human heart is approximately 200 grammes. Its maximum requirement of oxygen therefore appears to be about 0·5 c.c. per gramme per minute. In all probability, however, a heart, capable of an output of 28 litres, or even of 21 litres, per minute, would be more muscular than the average heart, and possibly the maximum consumption of oxygen by the heart seldom exceeds 0·4 c.c. per gramme per minute.

The extent to which the blood gives up its oxygen as it flows through the coronary vessels has not been fully investigated. A few observations made by Evans (1914), on a heart doing a moderate amount of work, showed a mean coefficient of utilisation of 0·46, and it is almost certain that, during severe exercise, the coefficient of utilisation for the heart is at least as great as that of the body as a whole, and may reach 0·66 to 0·7. In that case, a blood-flow of 800 to 850 c.c. per minute through the coronary vessels would enable the heart to take up 100 c.c. of oxygen.

Assuming its efficiency to be 25 per cent., its output per minute to be 4 litres, and the arterial pressure to be 100 mm. Hg, the consumption of oxygen by the resting human heart would be about 12·5 c.c. per minute, a figure which agrees fairly well with Evans' estimate of 10·5 c.c. The coronary blood-flow through the heart in a resting man appears to be about 140 c.c. per minute (Starling and Evans). It is clear, that, during heavy muscular work, the oxygen-requirements of the heart may undergo an eight or ninefold increase, and that a sixfold increase in the blood-flow through the coronary vessels is necessary. Two questions therefore arise. First, by what means can the blood-supply to the heart be increased, and, second, are these means equal to the task imposed upon them?

The factors which control the blood-flow through the coronary vessels have been investigated for the dog's heart by Evans and Starling (1913) and by Markwalder and Starling (1913). Evans and Starling showed that the blood flowing along the coronary vessels reaches the right auricle, partly along the coronary sinus and partly along the vein of Thebesius and other small veins, and that approximately three-fifths of the total blood-flow through the coronary system escapes along the coronary sinus. Having established this fact, they proceeded to measure directly the blood-flow from the coronary sinus in the heart-lung preparation, and the figures which they obtained, when multiplied by the factor $\frac{5}{3}$, gave the total blood-flow through the coronary system. Similar observations by Markwalder and Starling showed that in different experiments the ratio of the outflow from the coronary sinus to the total coronary flow varied only from 0·51 to 0·6 per cent., although, in the different experiments, the total circulation through the heart ranged from 32 to 177 c.c.



per minute; thus the factor $\frac{5}{3}$ is fairly accurate whatever the rate of the blood-flow through the heart.

Making use of these data, they found that the blood-supply to the heart like that to the muscles, is governed by two factors, namely, the arterial pressure, and changes in the tone of the coronary vessels. Broadly speaking, their observations go to show that a rise of 50 per cent. in the arterial pressure may treble the blood-flow through the coronary vessels.

TABLE XXIII.

MARKWALDER AND STARLING—

Arterial Pressure, mm. Hg.	Output from Coronary Sinus, c.c. per Min.	Total Coronary Flow = Sinus Outflow × $\frac{5}{3}$, c.c. per Min.
77	35	58
96	63	105
116	96	160

EVANS—

Arterial Pressure.	Total Coronary Flow, c.c. per Min.	Coronary Flow in c.c. per gramme of Heart per Min.	Work done by Heart, kg. per Hour.
80	39	0·71	10·0
106	71·4	1·3	41·4
120	115·5	2·1	56·2

Since the arterial pressure often rises 50 to 60 mm. Hg during vigorous exercise, this factor alone will greatly increase the coronary blood-flow.

Further, the tone of the coronary vessels is markedly lessened by the presence of adrenaline or of metabolic products in the circulating blood. Both Evans and Starling and Markwalder and Starling observed that a striking increase in the coronary blood-flow followed the addition of adrenalin to the blood. In one experiment (Evans and Starling) in which the arterial pressure was kept constant, the presence of approximately 1 in 3,000,000 adrenalin in the blood doubled the coronary flow. Similar results have been obtained by Patterson (1915).

The effect of increasing the $H^{\cdot}$ ion concentration of the blood or of an accumulation of metabolic products, such as is induced by asphyxia, is even more marked. On one occasion Evans

and Starling found that asphyxia produced a fivefold increase in the coronary flow which, in this instance, reached 5·0 c.c. per gramme of heart per minute. The susceptibility of the coronary vessels to metabolites is evidently quite as great as that of the arterioles and capillaries in the muscles, and it is probable that, during vigorous exercise, the local concentration of these substances in and around the coronary vessels may bring about a sufficient loss of arteriole and capillary tone to double or more than double the coronary blood-flow.

The possibility that, when exercise is carried out under emotional stress, a greater discharge of adrenalin into the blood stream may still further dilate the coronary vessels will be considered subsequently.

There seems every reason to believe that, during exercise, the raised arterial pressure, aided by a concomitant decrease in the tone of the coronary vessels, normally ensures a sufficiently large flow of blood through these vessels to meet the needs of the heart, however great these may be. But this is only true so long as the mechanical efficiency of the heart remains high. If its work remains constant, the oxygen-requirements of the heart vary inversely with its mechanical efficiency; and, if its efficiency declines during exercise, or if it is low from the outset of exercise, the heart will expend more energy, and will consume more oxygen, in performing a given amount of work than would a normal heart. It is evident that such a heart, if called upon to perform heavy work, will consume a very large amount of oxygen, and, in these circumstances, its demand for oxygen may exceed the supply provided by the coronary circulation, even though the coefficient of utilisation rises considerably. If this happens, metabolic products will accumulate within the cardiac fibres, thereby bringing about a still further decline in the efficiency of the heart and limiting its output. Whether this sequence of events ever occurs in the perfectly normal heart, even during very heavy work, is doubtful. But any disturbance of the nutritive condition of the heart lessens its mechanical efficiency (Patterson, Piper, and Starling), and it appears probable that, in a man whose heart is less efficient than normal, the supply of oxygen to the heart may become inadequate during exercise, thereby curtailing the range of its output and limiting the capacity of the individual to perform muscular work.

Summary.

During severe exercise the active muscles may take up from each fraction of the blood flowing through them twice as much oxygen as during rest, and, since the circulation rate is at the same time very rapid, the muscles may consume from ten to fifteen times as much oxygen as during rest.

The passage of oxygen from the blood into the tissues takes place solely by diffusion, and the avidity of the active tissues for oxygen is such that the oxygen reaching them at once enters into chemical combination, and their oxygen tension is zero. Consequently the rate at which oxygen can diffuse into the tissues varies directly with the tension of oxygen in the plasma, and this depends upon the extent to which oxyhæmoglobin dissociates as the blood traverses the capillaries. During exercise the increased $H^{\cdot}$ ion concentration of the blood in the capillaries of the active muscles and heart leads to more rapid dissociation of oxyhæmoglobin, thereby raising the tension of oxygen in the plasma, and accelerating the rate at which oxygen can pass into the tissues.

The work thrown upon the heart during exercise involves a large increase in its expenditure of energy and its consumption of oxygen; and the ability of the heart to increase its output sufficiently to meet the needs of the brain and muscles is conditional upon an adequate supply of blood to the heart itself. It is probable that, during severe exercise, the heart may consume 100 c.c. of oxygen per minute, and that the flow of blood through the coronary vessels may be six times greater than during rest.

The increased supply of blood to the heart is brought about partly by the rise of arterial pressure and partly by dilatation of the coronary vessels, and it is concluded that these two factors normally ensure a sufficient coronary blood-flow to meet the needs of the heart for oxygen even during very heavy muscular work.

CHAPTER VIII.

THE CO-ORDINATION OF THE CHANGES OCCURRING DURING EXERCISE.

The Initial Co-ordinating Mechanisms—Later Co-ordinating Mechanisms—Exercise Under Emotional Stress—The Limits of Muscular Exertion.

THE foregoing analysis of the changes taking place in the circulatory and respiratory systems during exercise has served to indicate the wide range of the adjustments possessed by these systems and the conditions under which the adjustments are brought into action. But, if the exercise is to be efficiently carried out, something more than the mere existence of these adjustments is required. It is essential that the extent to which they are called into play should be correlated with the activity of the muscular system, and that the supply of oxygen, which is the outcome of these adjustments, should neither outstrip nor lag behind the needs of the body during exercise. In point of fact, such a relationship is normally observed between the amount of work performed and the pulmonary ventilation, the pulse-rate, and the output of the heart (Fig. 8). Some mechanism must, therefore, exist, whereby the activities of the muscles, the nervous system, the heart and the lungs are co-ordinated and linked together in such a way that the resources of the body are utilised to the best advantage and the body acts as a physiological whole. The completeness of this co-ordination is a measure of a man's efficiency as a muscular machine, and any disturbance or failure in this correlation at once lessens the range of his activities. It is necessary then to consider the means whereby this co-ordination is effected.

Initial Co-ordination.

Foremost among these is the central nervous system, and its influence is most clearly seen at, or even before, the beginning of

exercise. The outflow of impulses from the motor cerebral cortex to the muscles is accompanied by a simultaneous outflow to the respiratory, vaso-motor, and cardio-inhibitory centres in the medulla, and there appears to be a very close correspondence between the intensity of the impulses to the muscles and to the medullary centre respectively, so that, for example, when a man starts to run, the immediate increase in his pulse-rate, blood-pressure, and respiration is more marked than if he starts to walk slowly. Voluntary movement, however, is initiated by antecedent psychical processes of the most varied nature and intensity, and these, particularly when they are mainly emotional, may bring about a rise of blood-pressure, and an increase of pulse-rate and of pulmonary ventilation, which has been termed 'anticipatory.' Simultaneously there occurs a toning up both of the muscles and of the whole nervous system, which causes them, so to speak, to stand to attention. These changes are very noticeable in a runner who is waiting for the signal to start in a race.

Further, there is some evidence (Bainbridge) that the medullary centres may be set in action as an anticipatory process even without the intervention of the higher centres, and that an afferent impulse, for instance, one which evokes pain, may lead to a reflex movement, and may at the same time bring about changes in the respiration, pulse-rate, and blood-pressure almost before the individual is consciously aware of the stimulus, and certainly before the higher centres could affect the medullary centres. This may often be seen during anæsthesia, when the higher centres are presumably out of action, and although the sensory stimulus is not strong enough to call forth a reflex movement (Fig. 19). A similar correlation is probably evoked in ordinary life when movement is brought about unexpectedly in response to afferent stimuli.

Another illustration of the anticipatory nature of the respiratory and circulatory adjustments is afforded by the well-known influence of violent emotion upon the medullary centres, even though, by an effort of will, any voluntary expression of the emotion is checked. Cannon (1915) has suggested that these anticipatory effects are brought about by an outpouring of adrenaline into the circulation; but, apart from the fact that adrenaline is not known to increase the respiratory movements, the onset of the circulatory and respiratory changes is often

too abrupt to be accounted for in this way. The almost invariable occurrence of these respiratory and circulatory changes, under the conditions just described, is evidence of a rather remarkable correlation between the nervous system and the nutritive requirements of the muscles. It may perhaps be regarded as one aspect of generally heightened activity of the nervous system during muscular exercise.

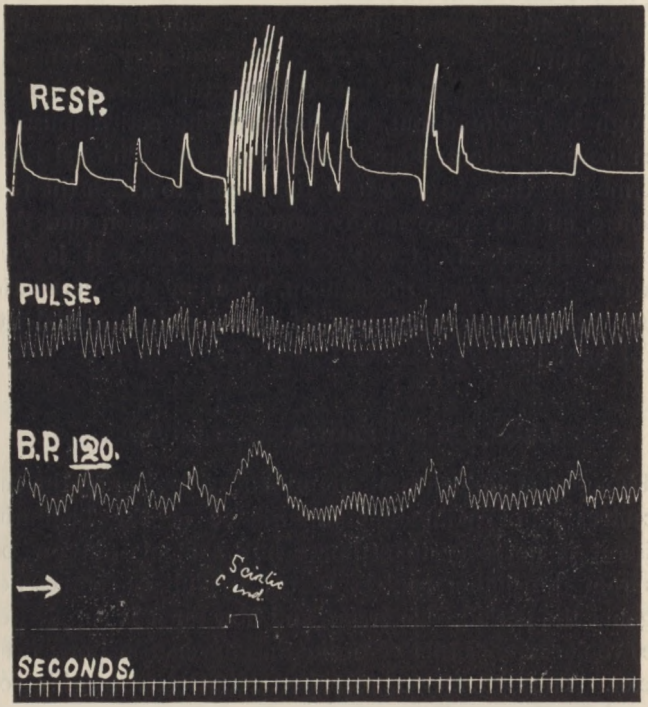
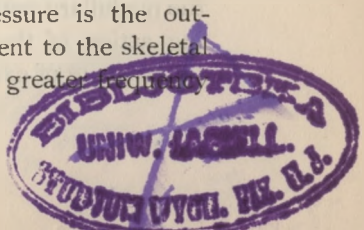


FIG. 19.—Shows the rapid response of the respiratory, vaso-motor and vagus centres to a weak sensory stimulus.

The effect of the initial changes is to provide for an increased supply of oxygen to the muscles, brain, and heart from the outset, and at a time when the other mechanisms, which regulate the respiratory movements and the minute-volume of the heart, have not yet come into action. The vaso-constriction in the splanchnic area, of which the raised blood-pressure is the outward sign, at once causes more blood to be sent to the skeletal muscles, to the heart, and to the brain. The greater [illegible]



of the pulse enables the heart to maintain its output against the rising arterial pressure without undue dilatation, and to increase its minute-volume the moment the venous inflow is increased by the more rapid return of the blood to the heart; and the deeper breathing, in addition to increasing the supply of oxygen, must tend to bring about a larger venous inflow to the heart. Krogh and Lindhard (1913) find that the output of the heart does not begin to increase until two to three seconds after the beginning of exercise, but it seems possible that this interval may be shortened when the respiratory and circulatory changes just described have taken place before the actual onset of exercise. As Krogh has pointed out, the needs of the active muscles for oxygen increase before there is time for the additional carbonic acid formed by them to pass into the blood, to reach the respiratory centre, and to evoke more vigorous respiration and thereby to increase the supply of oxygen to the body. It is for this reason that the nervous mechanism, whereby the ventilation is increased at the very beginning of exercise, is essential at this stage of exercise.

Later Co-ordinating Mechanisms.

Although the influence of the higher centres upon the medullary centres is of paramount importance at the beginning of exercise, it is not easy to estimate how far this outflow of impulses from the higher centres to the medullary centres persists throughout the period of exercise, and how far it is supplemented, or even replaced, by other co-ordinating mechanisms of a different character. The difficulty of reaching a conclusion on this point is enhanced by the possibility that, at least during severe exercise, the vaso-motor centre may be directly stimulated by a rise in the C_H of the blood, and that even a slight deficiency in the supply of blood to the brain during exercise would affect not only the vaso-motor, but also the respiratory, centre. But the arguments brought forward in the earlier chapters lead on the whole to the conclusion that the higher centres do send out a continuous stream of impulses, not only to the skeletal muscles, but also to the medullary centres, throughout exercise, and that the co-ordinating action of the central nervous system is not confined to the initial stage of exercise.

At the same time, other mechanisms play a large, and often predominant part in co-ordinating the activity of the rest of the body with that of the skeletal muscles during exercise. Krogh and Lindhard (1917) have found, for example, that, during induced muscular work, the increase in the pulmonary ventilation, in the output of the heart per minute, and in the pulse-rate, may be quite as marked as that produced by voluntary exercise of equal intensity. In their experiments, the muscles of the legs and back were thrown into activity by electrical stimulation, and the presence of some degree of *reflex* excitation of the medullary centres cannot be altogether excluded. But, as the outcome of these experiments, Krogh and Lindhard draw the conclusion that (after the initial phase is over) the pulse-rate and the minute-volume of the heart are mainly regulated by some chemical mechanism, whether the muscular work is induced or voluntary.

The $H^{\bullet}$ Ion Concentration of the Blood.

It is obvious that, so far as the respiratory centre is concerned, the $H^{\bullet}$ ion concentration of the arterial blood must be of the utmost importance in correlating the activity of the muscles with the pulmonary ventilation, since it is the only stimulus to the respiratory centre. And the question naturally arises, does the increased C_H of the blood during exercise also furnish the means whereby the circulatory adjustments are correlated with the activity of the muscles? Boothby (1915) believes that the answer is in the affirmative, and that the circulation rate, like the pulmonary ventilation, is directly related to the $H^{\bullet}$ ion concentration of the blood. He considers that "the same regulatory factor—the C_H of the arterial blood—controls with equal delicacy the ventilation of the lungs and the rapidity of the circulation rate. If we assume that the same regulatory factor governs both processes, it is only necessary to show a correspondence between the two processes to estimate the delicacy and sensitiveness of what may be looked upon as a 'centre' governing the circulation." Boothby thinks it possible that the circulatory centre forms a part of the respiratory centre, and that this performs the double function of controlling both the respiration and the circulation.

Although the coincident occurrence of two processes under

similar conditions does not in itself prove that they have a common origin, its simplicity renders this hypothesis very attractive; and Boothby points out that, during the apnœa which follows forced breathing, the circulation rate is also slowed, so that here again there is a correspondence between the pulmonary ventilation and the circulation rate. Before accepting this view however, it is necessary to consider whether the many factors which influence the circulation rate are, or can be brought, under the control of such a circulatory centre.

The circulation rate through the body as a whole is determined by the output of the heart per minute, and this again depends partly on the venous inflow during diastole, and partly on the ability of the heart to deal with this inflow by transferring blood from the venous to the arterial side of the vascular system. The increased venous inflow to the heart during exercise, though aided by the more vigorous respiratory movements, is due mainly to the mechanical action of the active muscles which drive the blood back to the heart. In this way the muscles act as a second pump; and the combined action of the heart, which drives blood into the arterial system and into the blood-vessels of the muscles, and of the active muscles which rapidly return blood to the heart, results in a large acceleration of the circulation rate round the body. Further, the rise of venous pressure, which plays so important a part in regulating the diastolic filling and output of the heart, and in correlating the frequency of the pulse with the rate of filling of the heart, is also due to mechanical factors, and it is difficult to imagine any means by which a medullary circulatory centre (activated solely by the C_H of the blood) could directly control the venous inflow to the heart.

Again, the response of the heart to an increased venous inflow is governed primarily by the 'law of the heart,' which is the expression of an inherent property of cardiac muscle, and is independent of any nervous influence. Indeed, granting that, as the outcome of the mechanical action of the muscles in returning blood to the heart, the venous inflow to the heart is proportional to the activity of the muscles, the output of the heart per minute will vary directly with the amount of muscular work, so long as the work is not excessive and the heart remains mechanically efficient, and this without the intervention of any nervous

mechanism other than reflex acceleration of the pulse in response to diastolic distension of the heart.

The pulse-rate, however, is entirely under the control of the central nervous system, and it might be expected that, if a medullary, circulatory centre does exist, the closest relationship would be observed between the $H^{\bullet}$ ion concentration of the blood and the pulse-rate. But the available evidence (p. 77) goes to show that, when extraneous factors are excluded, changes in the C_H of the blood, so long as these are within small limits, are without influence upon the frequency of the pulse, and that the altered reaction of the blood is not the primary cause of the normal correspondence between the activity of the respiratory and circulatory mechanisms. Further, the fact that the pulmonary ventilation and the pulse-rate do not always show a parallel increase during exercise (Means and Newburgh) is against their being controlled by a single centre, whose activity is aroused by the C_H of the blood. This discrepancy removes the main argument on which rests the conception that the frequency of the pulse is regulated during exercise by the reaction of the blood.

It is true that, as a rule, the relationship between the consumption of oxygen and the pulse-rate is extremely close. Even a change of position from lying down to sitting or standing up has a definite effect on both the consumption of oxygen and the pulse-rate, as the following table shows :—

TABLE XXIV.—Influence of Attitude upon the Pulse-Rate. (From Benedict and Cathcart's Data.)

Attitude.	Pulse-rate (average).	Oxygen-Consumption: c.c. per Minute.
(1) Lying on couch	66	247
Sitting on ergometer	88	292
(2) Lying on couch	60	245
Sitting on ergometer	81	376
(3) Lying on couch	67	252
Sitting on ergometer	80	312

But this is fully explained on the assumption that the greater outflow of impulses from the cerebral cortex to the skeletal muscles, when an individual sits or stands up instead of lying

down, is accompanied by a similar outflow to the medullary centres, identical in nature with, though less in extent than, that occurring at the outset of ordinary exercise.

The conclusion seems inevitable that the output of the heart per minute, and, therefore, the circulation rate, is the resultant of processes most of which cannot be brought under the control of any single nervous centre, and this constitutes a grave objection to the acceptance of Boothby's hypothesis in its present form. All the evidence goes to show that, partly in virtue of the law of the heart, partly by increase of the pulse-rate in response to diastolic distension of the heart, the output of the heart per minute automatically increases with the venous inflow. Consequently, the correlation between the work done by the muscles and the output of the heart can be effected by a purely mechanical process, namely, the rate at which blood is driven from the active muscles back to the heart.

There is no doubt that the $H^{\bullet}$ ion concentration of the blood is one of the means by which the supply of oxygen to the muscles is brought into relation with their needs during exercise. But the greater C_H of the blood produces this effect mainly through its direct action on the tone of arterioles and capillaries and on the rate of dissociation of oxyhæmoglobin, and only to a limited extent through the intermediation of the central nervous system. An adequate increase in the *local* $H^{\bullet}$ ion concentration of the blood flowing through the active muscles will simultaneously lessen the tone of their arterioles and capillaries and increase the rate at which the blood gives up its oxygen to the muscles; and a sufficient rise in the C_H of the *arterial* blood will stimulate the vaso-motor centre and tend to raise the mean arterial pressure. These processes bring about a larger flow of blood through the active muscles thereby enabling them—by their mechanical action—to increase still further the venous inflow to the heart, and its output per minute.

As the outcome of this concerted action, the circulation rate as a whole becomes more rapid, the blood gives up more oxygen to the tissues, and the effectiveness of almost all the factors concerned in increasing the supply of oxygen to the active muscles is enhanced. The rise in the $H^{\bullet}$ ion concentration of the blood required to bring about the changes is not known with certainty, but it is obvious that, when once this point is reached, these

changes will be accentuated by every further rise in the local or general $H^{\bullet}$ ion concentration of the blood. There is reason to believe that the $H^{\bullet}$ ion concentration of the arterial blood corresponds fairly closely with the severity of the exercise (Boothby, Douglas, and Haldane); and probably this also holds good for the local $H^{\bullet}$ ion concentration of the blood in the vessels of the active muscles and of the heart. Consequently, the $H^{\bullet}$ ion concentration of the blood must contribute considerably, in the way just described, to the correlation of the circulation rate and of the supply of oxygen to the muscles with the degree of muscular activity.

It is evident, then, that, during exercise, the co-ordination of the activity of the muscles with the circulatory and respiratory adjustments, which is necessary for the efficient performance of muscular work, can be effected to a large extent by changes initiated by the muscles themselves. Hence, partly by their mechanical action, partly by increasing the local (and general) $H^{\bullet}$ ion concentration of the blood, the skeletal muscles regulate their blood-supply in accordance with their needs.

The co-ordination brought about by these processes furnishes, however, a comparatively coarse adjustment, since they probably do not bring into action the vaso-motor and vagus centres until the $H^{\bullet}$ ion concentration of the blood and the venous pressure respectively have risen appreciably. A further and more delicate adjustment between the activity of the skeletal muscles and that of the medullary centres is required, in order to maintain, on the one hand, an adequate blood-pressure for the nutritive requirements of the heart and brain, and, on the other hand, the correlation between the venous inflow and the pulse-rate which is necessary to keep up the mechanical efficiency of the heart. This is effected through the intervention of the higher centres, and every outflow of impulses from the cerebral cortex to the muscles is accompanied by a correspondingly large outflow to the medullary centres and thence into the sympathetic system. These impulses, by rendering the respiratory system more excitable and by stimulating the vaso-motor centre, do away with the need for more than a trivial rise in the $H^{\bullet}$ ion concentration of the blood; and, by lessening the tone of the vagus centre, they permit the necessary acceleration of the pulse to occur with a moderate increase in venous pressure.

Since both their mechanical action on the return of blood to the heart and the $H^{\cdot}$ ion concentration of the blood vary automatically with the degree of activity of the muscles, and since a similar relation almost certainly holds between the intensity of the impulses passing respectively to the skeletal muscles and to the medullary centres from the cerebral cortex, it is clear that all the co-ordinating mechanisms at work during normal exercise are directly connected with the work performed and are ultimately dependent on the activity of the motor cerebral cortex. Although artificially induced movement can be carried out fairly efficiently, the co-operation of the higher centres appears to be necessary not only for the complete co-ordination of the activity of the muscles with that of the body as a whole, but also for the full development of the beneficial effects of exercise. The controlling influence of the higher centres is present at every stage of exercise, though it is seen most clearly at the outset of exercise and during emotional stress; and the ability of a man to make the fullest and most efficient use of his muscles is determined by the accuracy with which this higher co-ordination is effected. A man's nervous organisation is as important as the size of his muscles, and his muscular development is by no means the only criterion of a man's capacity for muscular exertion.

An illustration of this truth is found in the greater efficiency, and lessened sense of effort, with which a man performs muscular work when this is done under the stimulus of interest or is accompanied by pleasure. Conversely, the influence of boredom or of 'staleness' upon the amount of exertion which an athlete can make is well known; and the striking differences, which may occur on successive days, in the performance of a man training for a race, must be attributed almost entirely to variations in the extent to which the nervous system is co-ordinating his muscular movements with the adjustments of the respiration and circulation. It is partly for this reason that a man often runs or rows so much better in a race than in practice.

Exercise Under Emotional Stress.

The importance of the part played by the higher centres in co-ordinating and integrating the activity of the skeletal muscles and the adjustments of the circulatory and respiratory systems during exercise is most strikingly evident when the exercise is

carried out under emotional stress. Every one is familiar with the fact that, in these circumstances, a man may perform feats of strength or endurance of which he would usually be incapable. For example, McDougall quotes a story of an athlete who, when pursued as a boy by a savage animal, leaped over a wall which he could not again clear until he reached his full growth; and instances of intense and prolonged exertion, such as the dances of dervishes, carried out under the stimulus of religious or military enthusiasm, abound in literature. Again, it is a frequent experience of athletes that, when they are apparently exerting themselves to the utmost limit of their powers, a sudden emotional stimulus, such as the shouts of spectators, enables them to develop an unexpected reserve of strength.

The supreme muscular efforts occurring under these conditions are only possible if they are accompanied by a corresponding increase in the blood-supply to the muscles, the heart, and the brain. For this purpose, a stronger outflow of impulses to the medullary centres, concomitantly with that to the muscles, is necessary to bring about a sufficient increase in pulmonary ventilation, and to enable the heart to cope with the work thrown upon it. From this point of view, the striking augmentation of cardiac accelerator tone is especially valuable since, as Gaskell showed, stimulation of the sympathetic supply to the heart not only accelerates the pulse but increases the contractile power of the heart; and a considerable accession of accelerator tone has been observed during severe exercise (Gasser and Meek, 1914).

In this way, when exercise is performed under the stress of emotion, the higher arterial pressure, brought about by greater activity of the vaso-motor centre, improves the flow of blood to the muscles, the heart, and the brain; and the better contractile power and greater frequency of the heart, induced by stronger accelerator and augmentor impulses, enables the heart to increase its output per beat and per minute, and thus to deal with the larger venous inflow following upon the more intense muscular exertion. Nor is the influence of emotion limited to the vaso-motor and vagus centres, since there is a concomitant outflow of impulses along the greater part of the visceral sympathetic system; and these impulses, by bringing about dilatation of the coronary vessels and a greater discharge of glucose from the liver into the blood, will contribute still further to the working efficiency of

the body during exercise. Thus the mobilisation of the reserves of energy in the body during emotional stress finds expression, partly in a simultaneous and proportional increase in the muscular movements, and partly in a stronger discharge of impulses to the medullary centres and along the visceral sympathetic system.

During the last few years, however, the view has steadily gained ground that a more rapid passage of adrenaline into the blood-stream during states of violent emotion not only occurs, but is the essential factor in enabling the individual to extend the range of the exertion of which he is capable; and some writers appear to regard the action of adrenaline as replacing, rather than supplementing, the outflow of impulses from the brain along the sympathetic system.

According to this view, which has been vigorously advocated by Cannon (1915), adrenaline is thrown into the blood-stream just at the moment when its stimulating influence on the circulation, the liver, and the muscles will increase the functional capacity of the muscles and heart sufficiently to enable them to meet the additional demands made upon them by the nervous system. It serves, therefore, both to supplement and to reinforce the co-ordinating processes ordinarily at work during exercise; and, just as the accelerator of a motor car, at a touch from the driver, increases the supply of petrol to the engine, when the latter is required to do more work, adrenaline, suddenly entering the blood-stream in response to an impulse from the central nervous system, increases the oxygen-supply and consequently the functional capacity of the whole body.

The Action of Adrenaline.

Before entering into any discussion of this view it will be convenient to consider briefly some of the effects of such a discharge of adrenaline into the blood-stream, assuming it to occur. As regards its action upon the heart, Evans (1914, 1917) has recently confirmed and extended the earlier work of Barcroft and Dixon (1907), who found that the expenditure of energy by the isolated heart, as measured by its consumption of oxygen, was greatly increased by the addition of adrenaline to the blood. An example of Evans and Ogawa's results is shown in the following table:—

TABLE XXV.—(EVANS AND OGAWA.)

Pulse-Rate.	Output Litres per Hour.	C.c. O_2 used by Heart per Hour.	Kgm. Work Done.	Efficiency.	
46	11·5	58	17·5	14·6	No adrenaline.
67-86	11·5	176	17·5	4·8	Adrenaline added.

The larger consumption of oxygen is not simply the result of greater frequency of the pulse, since a similar or greater change in pulse-rate, brought about by raising the temperature of the heart, increases the consumption of oxygen to a much smaller extent; and Evans concludes that adrenaline directly stimulates the metabolic processes in the cardiac muscle fibres, and increases the energy developed at each heart-beat. Hence, for any given diastolic volume of the heart, more energy is set free during the succeeding systole when adrenaline is present than when it is absent, or to express the same fact in another way, the presence of adrenaline enables the heart to develop a given amount of energy with a smaller diastolic volume. Anrep (1912) has shown that, under experimental conditions, this is actually the case. One result of its diminished systolic volume is to extend the range of possible dilatation of the heart during diastole, and to enable the heart to increase its expenditure of energy still further, if it is called upon to perform more work.

Adrenaline, then, calls out the reserve-force of the heart, and adds to its power to mobilise its stores of energy. This effect is presumably produced through its action upon the endings of the sympathetic fibres to the heart, since Gaskell long ago proved that stimulation of the sympathetic supply to the heart leads to a similar augmentation of its contractile power.

Further, as Patterson (1915) has shown, adrenaline shortens the systole, both absolutely and also relatively to the diastolic period; at the same time it intensifies the contractile stress, and the rate at which this develops during systole, with the result that the endocardiac pressure is high and the blood is expelled more forcibly into the aorta. These changes enhance the power of the heart to maintain its output against a high arterial pressure.

There is no doubt, therefore, that a sudden addition to the circulating blood of sufficient adrenaline to bring about the changes

just described will be advantageous to the circulatory system in every way. In the first place, partly by accelerating the pulse and partly by improving the contractile power of the heart-muscle, adrenaline extends the range of the output of the heart per minute, and enables it to deal with a larger venous inflow than would otherwise be possible. If a man is doing such heavy work that the output of his heart is almost at its maximum, a sudden inflow of adrenaline into the circulating blood, occurring coincidently with a greater muscular effort, will permit of a corresponding increase in the output of his heart. At the same time, the greater and more quickly developed endocardiac pressure evoked by adrenaline enables the heart to maintain this output in spite of the raised arterial pressure. In the second place, the concurrent rise of arterial pressure, brought about mainly by the action of adrenaline on the splanchnic arterioles, increases the blood-supply to the brain, and to the muscles. Finally, adrenaline brings about a larger coronary blood-flow, not only by raising the blood-pressure, but also by dilating the coronary vessels.

Whether adrenaline has any direct effect upon skeletal muscle, apart from that brought about by increasing its blood-supply, is uncertain. Oliver and Schafer (1895) stated that the contraction of isolated frogs' muscle was prolonged in the presence of suprarenal extract, but Schafer has since shown that adrenaline itself does not produce this effect. More recently, Cannon and Nice found that the contractile power of fatigued muscle was improved by an intercurrent stimulation of a splanchnic nerve, and drew the conclusion that this was due to a direct action of adrenaline upon skeletal muscle. They obtained the same result when adrenaline was injected into the blood-stream. This observation was confirmed by Gruber, who states that it is not due merely to an improved blood-supply to the muscle, since, even when the muscle is perfused with Ringer's solution, the addition of adrenaline improves the contractile power of fatigued muscle, although the flow of fluid through the muscle decreases. Gruber concludes that adrenaline has a twofold action on muscular contraction, one by improving its blood-supply, the other depending upon its chemical action upon the muscular fibres. Further observations are desirable, however, on this question.

The Part Played by Adrenaline during Exercise.

If a sudden discharge of adrenaline from the suprarenal glands is to occur when it is most useful, namely, during exercise carried out under emotional stress, this must be controlled by the central nervous system. That adrenaline might pass in larger amount into the blood-stream as a reflex response to certain afferent impulses was first suggested by the observation of Cannon and de la Paz (1910) that the adrenaline content of the vena caval blood was increased in cats during emotional excitement induced by the barking of a dog. In 1911, Cannon and Hoskins found that a similar increase occurred during the excitement stage of anæsthesia, or as a result of stimulation of sensory nerves. In 1912, Elliott showed that, in cats, emotional excitement, anæsthetics, and the stimulation of sensory nerves, lessened the adrenaline content of the suprarenal gland if this retained its normal connection with the central nervous system, but not if it was isolated from the nervous system. Elliott concluded that emotion leads to a more rapid secretion of adrenaline into the blood-stream, the efferent impulses reaching the suprarenal glands by way of the splanchnic nerves.

The evidence just detailed is entirely in favour of the view advocated by Cannon and others, first, that a sudden discharge of adrenaline into the blood is necessary for the complete mobilisation of the individual's energies during exercise, and, second, that such a discharge does take place when exercise is carried out under the influence of emotion. The correctness of this view has recently been denied by Stewart and Rogoff (1916-17), who have traversed most of the ground upon which it rests. They find that morphia, which was used by Elliott to evoke emotional excitement in cats, also lessens the adrenaline content of the suprarenal glands in dogs, although it does not excite them. Again, they failed to confirm Cannon and de la Paz' statement that the adrenaline content of the vena caval blood is increased during emotional excitement, although the conditions, in their experiments, were apparently identical with those present in Cannon and de la Paz' experiments. Further, they found that the external manifestations of emotional excitement, and presumably, therefore, the visceral concomitants of emotion, could be evoked in a perfectly normal manner in animals whose suprarenal glands had

been isolated from the central nervous system. On these and other grounds, Stewart and Rogoff conclude that the passage of adrenaline into the blood is not increased during emotional stress, and is not necessary to evoke the external signs of emotion; and the comparative constancy of the discharge of adrenaline from the suprarenal glands leads them to suggest that it exerts a continuous rather than a spasmodic influence upon the sympathetic system.

In this controversy there are really two questions at issue. The first is whether an increased discharge of adrenaline actually takes place, and the second is whether a greater discharge of adrenaline is essential for the development of the intense energy displayed by individuals working under emotional stress. Stewart and Rogoff would appear to have answered the second question in the negative, and, in that case, the greater efficiency of the circulatory and other adjustments under these conditions must be due mainly to a larger outflow of impulses from the brain along the sympathetic system.

Whether an increased discharge of adrenaline also occurs, and supplements the nervous outflow of impulses into the sympathetic system, is a difficult question. But the fact that both operative procedures, which necessarily involve some degree of stimulation of sensory nerves, and anæsthetics are in themselves capable of evoking the activity of the suprarenal glands must detract from the value of conclusions based on experiments in which these conditions are present.

Dr. Kellaway has made some observations in which the influence of these disturbing factors was eliminated by excising one superior cervical sympathetic ganglion, and allowing the animals (cats) to recover. After an interval of some weeks, it was observed that, in some cats, emotional excitement, induced under normal conditions, led to preferential dilatation of the pupil of the denervated eye. In other experiments in which, in addition to removal of a superior cervical ganglion, both suprarenal glands were cut off from the central nervous system by division of the splanchnic nerves, emotional excitement led to no dilatation of the denervated pupil. These experiments appear to show conclusively that emotion is associated with a greater discharge of adrenaline into the blood, so long as the connection between the central nervous system and the suprarenal glands is intact.

But the iris, when deprived of its sympathetic supply, is so sensitive to adrenaline, that a concentration of adrenaline in the blood, equivalent to one part of adrenaline in 100 millions, is capable of evoking distinct dilatation of the pupil, although it does not appreciably affect the heart or blood-vessels. Consequently, Kellaway's observations do not suggest more than a very minute addition of adrenaline to the circulating blood during a moderate grade of emotional excitement.

On the whole, however, the evidence, while not substantiating the extensive claims put forward by some writers on behalf of adrenaline as a predominant factor in co-ordinating the activities, and mobilising the energies, of the body in states of emotional excitement, does furnish very strong reasons for concluding that some additional adrenaline is discharged into the circulation under these conditions, although the amount of adrenaline thus set free appears to be extremely small. It appears probable, therefore, that emotional excitement extends the range of a man's physical powers, primarily because it quickens the activity of the whole central nervous system, and enables a larger volume of impulses to flow, not only to the skeletal muscles, but to the circulatory system and to other organs, and that adrenaline merely enhances, to an uncertain and possibly very slight extent, the effect of the co-ordinating and stimulating impulses passing from the brain along the sympathetic system. There is at present no unequivocal evidence that the additional adrenaline sent into the circulation takes any large share in bringing about the rise of arterial pressure, acceleration of the pulse, and other visceral changes associated with emotion.

The suggestion that, apart from sudden outbursts of adrenaline secretion into the blood, a slight but steady increase may occur in the rate at which adrenaline enters the circulation during exercise has been accepted by some writers (Schneider and Havens), although the evidence in its favour is of a very inconclusive character. This suggestion arises out of the belief that the increased $H^{\cdot}$ ion concentration of the blood during exercise stimulates the vaso-motor centre, thereby leading to an outflow of impulses along the splanchnic nerves to the suprarenal glands. Kellaway (1919) has shown, however, that even a rise in the C_H of the blood, sufficient to cause marked dyspnœa, is without effect upon the amount of adrenaline entering the circulation from

the suprarenal glands. Nor did Gasser and Meek find any evidence that exercise is normally accompanied by a greater discharge of adrenaline into the blood stream. It is very doubtful, therefore, whether the suprarenal glands, as regards the secretion of adrenaline, take any share in bringing about the circulatory and other changes occurring during exercise under ordinary conditions. A comparatively slight deficiency, however, in the blood-supply to the brain at once leads to a greater discharge of adrenaline into the blood-stream (Kellaway); and there is no doubt that, during intense exertion, symptoms of cerebral anæmia sometimes make their appearance. In these circumstances, the greater concentration of adrenaline in the blood will tend to increase the rate and contractile power of the heart and to raise the arterial pressure, and may contribute effectively to improving the supply of oxygen to the brain and to maintaining or extending the working powers of the individual.

The Limits of Muscular Exertion.

The effectiveness of the correlation between the activity of the skeletal muscles and that of the rest of the body is demonstrated by the intense muscular exertion of which a healthy man, and particularly a trained man, is capable. One of Benedict and Cathcart's subjects frequently performed external work equivalent to 1,000 kilogrammetres per minute for an hour or more, and this amount of work (as they point out) is approximately the same as that involved in climbing 2,500 feet in an hour up a mountain side. During very severe exertion, such as running rapidly upstairs, which can only be maintained for a few seconds, the work may be equivalent to 4,000 to 9,000 kilogrammetres per minute (Blix, 1903, A. V. Hill). Blix calculated that during less intense exertion, which could be continued for several hours, the effective work might amount to 500 kilogrammetres per minute. While these figures probably represent fairly accurately the maximal working capacity of an athletic man under ordinary conditions, it is quite possible that they are not infrequently exceeded when work is done under the stimulus of enthusiasm or excitement, although, under these conditions, accurate measurement of the amount of work performed may be almost impossible.

There is a limit, however, to the individual's capacity for muscular work, and this will be reached either if the force and rate with which the muscles are contracting reaches its maximum, although their supply of oxygen and of nutritive material is ample, or if the supply of oxygen, provided by the respiratory and vascular systems, becomes insufficient for the demands of the skeletal muscles, the heart, or the brain.

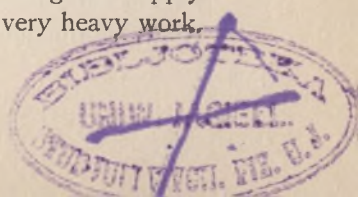
The available evidence goes to show that this limit is imposed by the supply of oxygen to the muscles and brain rather than by the functional capacity of the skeletal muscles. Hill and Flack (1909, 1910) have found, for example, that, if pure oxygen is breathed for a few minutes just before exercise, not only is the individual capable of greater exertion, but the dyspnœa and cardiac distress are lessened, the frequency of the pulse is lowered, and the arterial pressure is higher. Further, cerebral symptoms of lack of oxygen, such as dizziness, dimness of vision, and even faintness, do not appear when the exercise is carried out after inhalation of oxygen.

TABLE XXVI.—Effects of Oxygen. (Constructed from Hill and Flack's Data.)

		Blood-pressure. Mm. Hg.	Pulse-rate.	Rate of Resp.	Pulmonary Ventilation. Litres per Min.
I. Breathing air	(*a*) Rest	110	68	29	9
	(*b*) Just after running up and down 26 stairs 8 times in 1′ 34″	120	156	42	42
	(*c*) 1 minute later	130	140	41	40
II. Breathing oxygen	(*a*) Rest: breathing oxygen	120	64	24	7·5
	(*b*) Just after running 8 times up and down 26 stairs in 78″	160	116	55	40
	(*c*) 1 minute later	170	104	57	32

Both sets of observations were made on the same individual.

Hill and Flack calculate that, by breathing oxygen, the total volume of oxygen present in the body, partly dissolved in the body-fat and water, and partly in the lungs and the blood, may be increased by nearly 5 litres. This alone is enough to supply the tissues with oxygen for two minutes during very heavy work.



Its value is greatest during the early part of a long bout of exercise, or in a sprinter who may run 100 yards without taking a breath.

Douglas and Haldane (1909) found that, after forced breathing of ordinary air just before exercise, this was more efficiently carried out, and they therefore suggested that the beneficial effect of inhalation of oxygen just before exercise was due to the lowering of the alveolar tension of carbonic acid by the deeper breathing rather than to excess of oxygen in the blood. But Hill and Mackenzie (1909), and Hill and Flack (1910), have furnished good evidence that the important factor is the larger amount of oxygen present in the body as the result of inhalation of oxygen. They find that excess of oxygen in the air breathed enables a man to stand a much higher percentage of carbonic acid in the inspired air before reaching "breaking point," and that it also lessens the discomfort induced by forced breathing; it is partly for these reasons that inhalation of oxygen extends the range of a man's working power.

The possibility that, even during the heaviest work, the respiratory mechanism ever fails to provide in the lungs sufficient oxygen to meet the needs of the body may almost certainly be dismissed, since the alveolar tension of oxygen, under these conditions, scarcely falls below that present during rest (p. 28); and the cause of the inadequate supply of oxygen must be sought in the circulatory system. It might be suggested that, during very severe work, the circulation rate may become so rapid as to set a limit to the amount of oxygen which can be taken up by the blood flowing through the lungs and can be given up to the active tissues. Any further increase in the circulation rate would then lead to less and less complete saturation of the arterial blood with oxygen, while not adding to the amount of oxygen reaching the tissues. Marie Krogh (1915) has shown, however, that, given a coefficient of utilisation of 0·73 and a diffusion coefficient of 56, both of which may be present during heavy work, as much as 3,760 c.c. of oxygen could enter the blood from the lungs per minute by diffusion, and that the arterial blood would be almost fully saturated. Since an oxygen consumption of this magnitude must be almost as large as is required for the carrying out of the heaviest work which the body could ever perform under any conditions, it does not appear probable

that too rapid a circulation rate is usually, if ever, responsible for imposing a limit to the supply of oxygen to the body.

Marie Krogh considers that the heart is as a rule the limiting factor for a man's working capacity, and this is also the view of Hill and Flack, who hold that inhalation of oxygen, by maintaining or restoring the vigour of the heart, adds to a man's power to perform muscular work. All experience, clinical and other, confirms this conclusion, and goes to show that it is upon the heart that the stress of violent exertion falls most heavily. For example, some recent observations of Maitland (1916) on soldiers in the field have shown that prolonged and intense exertion under the conditions of war often leads to marked symptoms of circulatory embarrassment or failure; these include cyanosis or extreme pallor, a feeble very frequent pulse, and a low arterial pressure. It seems clear, then, that, during very severe exercise, the output of the heart, and therefore the circulation rate, ultimately fail to keep pace with the muscular work, and that the supply of oxygen becomes insufficient for the requirements of the body, thereby limiting the working powers of the individual.

Every voluntary movement adds to the work of the heart, not only because the greater venous inflow impels the heart to send out more blood, but also because it has to put out blood against a higher arterial pressure; and, when violent exercise is associated with emotional excitement, the burden of work laid on the heart may become so heavy that one is surprised, not that the heart reaches the limit of its powers, but that the range of its power is often so large.

Thus a man reaches the limit of his working powers as soon as the output of his heart fails to correspond with the demands of the tissues for oxygen, and this discrepancy may be brought about, in a healthy man, in one of two ways. One is that, as Hill and Flack suggest, the output of the heart is limited by its blood-supply. The other is that, even though its blood-supply is ample, the output of the heart per minute may reach the maximum of which it is capable, and that this may become insufficient to provide for the needs of the rest of the body during intense exertion.

Hill and Flack consider that, by placing more oxygen at the disposal of the heart, inhalation of oxygen enables the heart to develop the energy required to keep up an adequate circulation

rate, and that, in the absence of such assistance, the heart is insufficiently supplied with oxygen during intense exertion. But these experiments are capable of another interpretation. The additional oxygen taken into the body during the inhalation of oxygen is equally accessible to the skeletal muscles and to the brain; and, in so far as they use this adventitious supply, they make a smaller demand upon the heart, thereby lessening the strain placed upon it. On this view, oxygen relieves cardiac distress during exercise, not only by increasing the supply of oxygen to the heart, though this doubtless does occur, but also by lessening its work. Benedict and Smith have shown that, even in the resting man, the inhalation of pure oxygen lessens the frequency of the pulse and, therefore, in all probability the work of the heart; and the supply of oxygen to the heart is certainly not inadequate when a resting man breathes ordinary air. Consequently, although Hill and Flack's experiments point to the conclusion that the supply of oxygen to the body is the decisive factor in setting the limit to exercise, they do not furnish unequivocal proof that this is primarily caused by an inadequate supply of oxygen to the heart.

Except that the maximal output of the heart per minute, and, therefore, a man's capacity for exertion, will be greater if the supply of oxygen to the heart remains adequate, the question whether its oxygen-supply does, or does not, set a limit to the output of the heart may not seem of material importance for the body as a whole. But it is of great importance as regards the effect of exercise upon the heart itself. In the one case, the nutrition of the heart is perfectly normal, although the body asks more than the heart can give. In the other case, the insufficient supply of oxygen leads to the accumulation of metabolic products in the cardiac muscle fibres, to the appearance of fatigue, and hence to a diminution of both the output and the efficiency of the heart. Possibly because it is always at work, even a transient shortage of oxygen appears to depress the functional power of the heart even after the immediate cause has passed away, and this effect will be more marked and prolonged the more acute the temporary insufficiency of oxygen.

It seems possible that, in a perfectly trained and healthy man, the supply of oxygen to the heart is adequate even during the most intense exertion, since the experience of many athletes

is that they reach the limit of their powers with comparatively little subjective feeling or outward evidence of cardiac distress. The blood-supply to the heart is the weak link, however, in the chain of circulatory adjustments during muscular exercise; and, as the intensity of muscular exertion increases, a point is probably reached in most individuals at which the supply of oxygen to the heart falls short of its demands, and the continued performance of heavy work becomes difficult or impossible. Moreover, the coronary blood-flow depends to a greater extent on physical factors, the chief being the arterial resistance, the effect of locally developed metabolites comes in probably only as a second line of defence.

Summary.

In order that exercise may be efficiently carried out, it is necessary that the activities of the skeletal muscles, the nervous system, the heart, and the lungs should be co-ordinated and linked together in such a way that the resources of the body may be utilised to the best advantage and the body may act as a physiological unit.

At the outset of exercise, this co-ordination is effected entirely by means of the central nervous system. Impulses passing from the higher centres to the medullary centres bring about greater pulmonary ventilation and a rise of arterial pressure, and thus provide at, or sometimes even before, the very beginning of exercise a more abundant supply of blood to the skeletal muscles, the brain, and the heart.

The view that the raised $H^{\bullet}$ ion concentration of the blood during exercise is entirely responsible for co-ordinating the respiratory and circulatory adjustments with the activity of the muscles is discussed, and reasons are brought forward for not accepting it.

The processes whereby, during exercise, the activity of the skeletal muscles is correlated with that of the rest of the body are three in number. The first is the mechanical action of the active muscles in returning blood more rapidly to the heart. The second is the increased $H^{\bullet}$ ion concentration of the arterial blood, and still more of the blood flowing through the muscles. These two changes vary directly with the degree of muscular activity, and bring about a corresponding increase in the pulmonary

ventilation and the circulation rate. By these means the active muscles to a large extent regulate their own blood-supply. The third process is a greater outflow of impulses from the higher centres to the medullary centres, concomitantly with the flow of impulses to the muscles; and this adds to the effectiveness of the first two processes.

Under the stress of violent emotion a man can often carry out muscular efforts of which he is normally incapable, and this not only involves greater muscular activity, but also places a greater strain on the circulatory and respiratory systems. The fuller mobilisation of the resources of the body, under these conditions, is only possible if the greater muscular effort is accompanied by a corresponding increase in the blood-supply to the muscles, heart, and brain, and in the efficiency of the circulatory and respiratory adjustments. This is effected mainly by a larger outflow of impulses from the higher centres, not only to the medullary centres but along a large part of the sympathetic system, thereby bringing about greater ventilation of the lungs, a rise of arterial pressure and acceleration of the pulse, and augmentation of the contractile power of the cardiac muscle. The question as to how far a more rapid discharge of adrenaline into the blood-stream occurs, and supplements the purely nervous factor, is discussed: and the conclusion is reached that the share taken by adrenaline in bringing about the circulatory and other changes taking place during exercise, even when this is carried out under emotional stress, is comparatively small.

A man's maximum working power is determined, not only by the functional capacity of his skeletal muscles, but also by the supply of oxygen to the muscles, heart, and brain. Since the supply of oxygen ultimately depends upon the output of the heart, the limit to the exertions of which a man is capable is reached, when the output of his heart fails to correspond with the demands of the tissues for oxygen.

CHAPTER IX.

TRAINING.

The General Effects of Training—Exercise in the Trained and Untrained Man—Second Wind.

THE greater strength and efficiency of the body, brought about by regular physical training, are the product of two processes which normally go hand in hand. One is the development of the muscular system as a whole, and more especially of the muscles employed in the form of exercise carried out; the other is an increase in the range and delicacy of the adjustments of the circulatory and respiratory systems whereby the supply of oxygen to the body is assured. The attention of trainers and athletes has naturally been directed almost exclusively to the first of these processes; and the traditional methods adopted in a regular course of training, for example, before a boat-race, are regular and progressive exercise, and a particular form of diet, which includes the consumption of large quantities of meat.

The growth in the size of the muscles during training clearly demands the presence in the diet of a considerable amount of protein in order to provide the material required for this purpose. Possibly, also, in virtue of its specific dynamic action, protein may increase the intensity of the whole metabolic activities of the muscles, including those occurring during exercise. It may, in fact, lead to a more rapid combustion of the fat and carbohydrate, the oxidation of which provides the energy for muscular work, and may thereby increase the work of which the muscle is capable in a given time. On this view, a liberal protein diet, so to speak, makes the fire hotter in which the carbohydrate and fat are consumed. But it is very difficult to determine whether such a process actually takes place, and no definite facts can be adduced in support of this suggestion.

There is no doubt, moreover, that many men have been successfully trained on a diet consisting largely of carbohydrate

and eggs, and there is no consensus of opinion as to what form of diet is the most useful. Many athletes appear to find that a rigid or specialised training and diet are unnecessary, so long as the ordinary rules of health are observed and regular and progressively increasing exercise is taken.

The growth in the size of the muscles during training leads to some increase in the oxygen-consumption of the body during rest (Lindhard). Benedict and Smith (1915) found that in athletes the basal metabolism was slightly higher than in untrained individuals, the average production of heat in twenty-four hours being 26·0 calories per kilogram of body-weight in athletes and 24·4 calories in non-athletes.

Hyde, Root, and Curl (1917) have examined quantitatively the influence of practice upon the amount of work which a single muscle can perform. The work was carried out with an ergograph, the flexor muscles of one finger being employed, and was continued in each experiment until the subject stopped from exhaustion. At the end of a month's daily training one subject—an athlete—had more than trebled, and the other, who was not an athlete, had almost trebled, his capacity for work.

TABLE XXVII.—Work Done with Ergograph. Weight Lifted was 5 kgm. (Hyde, Root, and Curl.)

		Duration of Work in Minutes.	No. of Contractions.	Distance in cm. to which Weight was Lifted.	Work Done in Kilogram-metres.
A. Non-Athlete	Nov. 19	9′ 18″	279	253	12·65
	Dec. 20	26′ 54″	798	726	36·30
B. Athlete	Nov. 19	8′ 55″	273	375	18·75
	Dec. 20	30′ 18″	918	1205	60·25

The greater size and power of the skeletal muscles, which results from regular physical training, is accompanied by a similar development of the lungs and heart. The greater expansion of the chest increases the vital capacity and the range of pulmonary ventilation, and these changes must be of value, not only in adding to the oxygen reserve in the lungs, but also in increasing the surface which the pulmonary capillaries offer to the alveolar air, and thereby raising the individual's coefficient of diffusion.

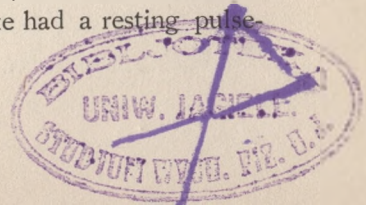
It is generally recognised that the heart is larger, that is to say, more muscular, in athletes than in sedentary individuals, and that the heart grows in size as the result of all forms of regular

exercise or during the course of military training (Nicolai and Zuntz, 1914). Carefully graduated exercise, in fact, is a recognised method of improving the nutritive condition, and developing the muscular power, of the heart. Further, Hirsch (1899) has shown that, apart from disease, the weight of the heart, observed post-mortem, is directly related to the general development of the skeletal musculature. Indeed there appears to be no doubt that the growth of the muscles in response to regular physical training finds its counterpart in a corresponding development of the muscular tissue of the heart, and that, as the muscular machine becomes more powerful, the heart, upon which the supply of oxygen to the muscles ultimately depends, also becomes stronger.

Hence, for the making of an athlete, a large and muscular heart is just as much a physiological necessity as a highly developed muscular system, since, whatever the size of his muscles, a man's capability to perform muscular work is determined by the output of his heart. The notion that the large heart of the athlete is in any way abnormal is entirely erroneous, and the term, hypertrophy of the heart, should be limited to those conditions, almost invariably pathological in origin, in which the muscular development of the heart, as compared with that of the skeletal muscles, is unusually large.

Incidentally it may be noted that any considerable increase in the size and number of the skeletal and cardiac muscular fibres necessitates either a formation of fresh capillaries or the opening up of hitherto unused capillary channels, if the nutrition of the muscles and heart is to be maintained. The difference in the size of the heart furnishes the key to the difference in its behaviour in trained and untrained individuals respectively, during both rest and work. An infrequent pulse has often been regarded as characteristic of well-trained men, and some observations by Michell (1909) go to show that, in under-graduates who take up games vigorously, the average rate of the pulse during rest tends to decrease year by year.

Michell found (excluding school athletes from his record) that the average resting pulse-rate of the men examined was: First year, 74; second year, 68; third year, 58·3. Similar observations have been made by other writers, and Miss Buchanan (1909) records that a famous Oxford stroke had a resting pulse-rate of 45.



Since, during rest, the output of the heart per minute is slightly larger (Lindhard), and the pulse less frequent in the trained individual than in the untrained man, the output per beat is probably greater. For a given venous inflow, the powerful heart of the athlete sets free more energy, and empties itself more completely at each beat, than does the feebler heart of the untrained individual; consequently the output per minute can be maintained with a less frequent pulse.

TABLE XXVIII.—Effect of Training in Same Individual. (From Lindhard.)

	Minute-Volume of Heart.	Output per Beat.	Pulse-rate Per Minute.	Coefficient of Utilisation.
(*a*) Untrained . .	4·8 litres	62 c.c.	77	0·30
(*b*) When fully trained .	5·65 „	103 „	55	0·46

The systolic arterial pressure, according to most observers (Michell) is not higher during rest in trained than in untrained men.

Exercise in the Trained and Untrained Man Respectively.

Reference has already been made to some of the differences in the changes taking place in the circulation during exercise in trained and untrained men (p. 8), and all the evidence goes to show that, when the same amount of work is performed, the pulse is less frequent (Fig. 20), the blood-pressure is lower, and the output of the heart per minute is usually smaller, in the trained than in the untrained man. The effect of a brief period of vigorous exercise upon the pulse-rate is shown in the following table:—

TABLE XXIX.—Effect of Exercise upon the Pulse-rate per Minute. (Pembrey and Todd.)

Trained Man.		Untrained Man.	
Rest.	Just after Exercise.	Rest.	Just after Exercise.
64	132	68	152
56	120	82	160
60	104	68	152

The following figures probably represent fairly accurately the difference in the output of the heart per beat and per minute in an athlete and a non-athlete, when the work done by the two subjects is approximately the same, and is not excessive even for the non-athlete :—

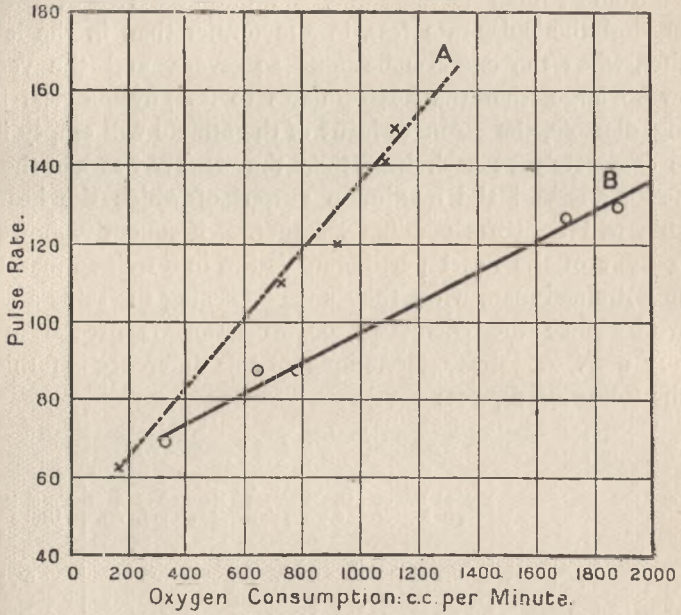


FIG. 20.—(Constructed from Lindhard's data.)

A = untrained subject.

B = trained subject.

The oxygen consumption indicates the severity of the exercise.

TABLE XXX.—(LINDHARD.)

	Non-athlete.		Athlete.	
	Rest.	Work.	Rest.	Work.
Oxygen-consumption .	195 c.c.	1051	3·30	1171 c.c.
Pulse-rate per minute .	72	144	68	92
Output of heart per min.	3·9 litres	11·4	4·9	14·75
,, ,, per beat	54·5 c.c.	79	72	160·5
Coefficient of utilisation	0·31	0·50	0·36	0·43
Weight of subject . .	50 kg.	—	75 kg.	—

It has been shown (p. 82) that the total energy expended in maintaining the output of the heart per minute, whether

during rest or during exercise, is the product of the energy set free at each heart-beat, and of the number of beats per minute. Since physical training, by increasing the size (i.e. the muscular tissue) of the heart, enables it to develop more energy per beat, it is clear that, if the minute-volume of the heart in the trained and untrained man is the same, the output per beat will be larger, and the pulse-rate less, in the former than in the latter. Further, when the exercise becomes so severe, and the venous inflow so large, that the heart dilates to its physiological limit during diastole, the stronger heart of the athlete will empty itself more completely at each beat than the weaker heart of the untrained man; and the maximum output of which the heart is capable will be correspondingly larger. Frequently, however, the output of the heart per minute is less in a trained man than in an untrained man, when they are performing the same amount of work, since the coefficient of utilisation is greater in the trained man. A striking example of this difference is furnished by the following figures:—

TABLE XXXI.—(KROGH AND LINDHARD.)

	Work Done: Kgm. Metres.	O_2 Consumed: c.c. per Minute.	Minute-Volume of Heart in Litres.	Coefficient of Utilisation.
J. L. trained . .	458	1350	9·8	0·73
A. K. untrained . .	446	1320	16·0	0·47

Whether the larger coefficient of utilisation in the trained man is the result of some modification in the rate at which the blood flows through the muscles, or whether the ability of the muscles to take up oxygen from each fraction of the blood flowing through them is increased, is not known. But the larger coefficient lessens considerably both the strain thrown upon the heart and the amount of work which it is called upon to perform, thereby adding to the reserve power of the heart and making possible a larger supply of oxygen to the muscles during heavy work.

Again, training increases the red corpuscles and the hæmoglobin value of the blood (Michell). Schneider and Havens (1915) observed, in one subject, an increase of 9·4 per cent., and in another subject, an increase of 3·6 per cent. in the hæmo-

globin value of the blood. The rise is of importance chiefly as an indication of the improved physical condition of the subjects, and it is known that, in men undergoing training, a fall in the hæmoglobin value is often a sign of 'staleness' or of their being below par. But the greater oxygen-carrying power of the blood must also assist appreciably in lessening the output of the heart necessary to keep up the oxygen-supply to the muscles for any given amount of muscular work.

The advantages of training are not confined to the circulatory system, and the mechanical efficiency with which work is performed is greater in the trained than the untrained man (Lindhard, Benedict and Cathcart). Bürgi (1900) found that, for the same individual, training reduced the output of carbonic acid from 2,430 to 2,103 c.c. per kilogrammetre of work performed. Zuntz (1903) showed that a dog, trained for one form of exercise, carried this out more efficiently than another form of exercise to which it was unaccustomed, and concluded that the muscles actually employed in any particular kind of exercise work more economically when trained. These effects are almost certainly brought about mainly through the intermediation of the central nervous system, with the result that the co-ordination and adjustment of the movements involved in any form of exercise is more perfectly effected and useless movements of other muscles are eliminated.

Thus the trained man can perform a given amount of work with a smaller consumption of oxygen and a smaller output of carbonic (and lactic) acid than the untrained man. The smaller consumption of oxygen lessens the output of the heart necessary to provide an adequate supply of oxygen to the muscles; and the decreased output of carbonic (and lactic) acid leads to less change in the C_H of the blood in the trained, than in the untrained, man for the same amount of external work.

It seems probable, too, that the smaller muscular effort necessary for the performance of a given amount of work in the trained, as compared with the untrained, man is associated with a lessened outflow of impulses from the higher centres, not only to the muscles, but also to the medullary centres; and this, if it occurs, will tend to keep down both the pulse-rate and the blood-pressure.

Training leads, then, to increase of power and economy of

effort, and the trained man is better equipped at almost every point to perform muscular work than is the untrained man. By developing his skeletal muscles, his heart, and his lungs, training extends very greatly the range of the exertions of which a man is capable; and, by bringing about better co-ordination of his movements, it enables a man to take moderate exercise with a minimal expenditure of energy and with scarcely any sense of effort. Nor are the advantages conferred by training purely physical, since the sense of strength and well-being, which it usually engenders, colours and reacts upon the individual's outlook and actions as a whole.

Second Wind.

The transition, during vigorous exercise, from a state of respiratory and, to a less extent, of cardiac distress to one in which the individual breathes easily and comfortably, and feels able to continue the exercise almost indefinitely, is known as getting one's 'second wind,' and is a familiar event in the experience of most people. But the conditions under which it usually occurs render investigation and analysis of its real nature very difficult. Indeed, beyond the facts that the transition may be gradual or may be fairly abrupt, and that it takes place both in the trained and in the untrained man, very little is known about it. The only observations which throw any light on it are those of Pembrey and Cooke (1913). They found that, during the period of laboured breathing before second wind, the pulmonary ventilation and the percentage of carbonic acid in the alveolar air were higher than after second wind had occurred (Table XXXII.). Further, while the onset of second wind was not accompanied by any constant change in the pulse-rate or the arterial pressure, they noted a close association in time between the onset of sweating and of second wind.

The only possible explanations of the decrease in the pulmonary ventilation, as second wind supervenes, are either a fall in the $H^{\cdot}$ ion concentration of the blood reaching the respiratory centre, or a diminution in the excitability of the respiratory centre; and the latter possibility would appear to be excluded by the fact that the alveolar tension of carbonic acid falls concomitantly with the pulmonary ventilation. Pembrey and Cooke's observations,

while pointing clearly to the conclusion that the $H^{\bullet}$ ion concentration of the blood falls during the establishment of second wind, throw no light on the means by which this is effected; and, although, from time to time, various suggestions have been offered in explanation of this fall, none of them appears to have been put to the test of experiment. Some discussion of these suggestions is, however, not altogether unprofitable, since the processes which regulate the $H^{\bullet}$ ion concentration of the blood are much better understood than was the case a few years ago.

TABLE XXXII.—(PEMBREY AND COOKE.)

	Alveolar Air.		R. Q.	Respiration.	
	CO_2 Volume per Cent.	O_2 Volume per Cent.		Volumes Breathed at 17° C. in Litres per Minute.	Rate.
(1) Rest	5·91	13·85	0·80	8·5	12
After running 9 laps, Dyspnœa . .	7·55	14·07	1·10	35·5	21
After running 13 laps second wind had supervened . .	5·77	13·63	0·74	19	22
(2) Rest	—	—	—	8	21
Dyspnœa; 8 laps .	—	—	—	23	37
Second wind; 16 laps	—	—	—	18·5	26

32 laps = 1 mile.

In considering the causation of second wind it is of importance to bear in mind the fact that second wind, when once established, tends to persist through the period of exercise, even though this becomes more severe. This fact suggests very forcibly that the fall in the $H^{\bullet}$ ion concentration of the blood is the outcome of some process or processes which remain effective throughout the exercise, and that a state of equilibrium is set up between the factors which tend respectively to raise and to lower the $H^{\bullet}$ ion concentration of the blood. It is possible, therefore, that second wind may be brought about by the interaction of a variety of mechanisms, and even that the relative importance of these mechanisms in its production may not be the same in all individuals.

The fall in the $H^{\bullet}$ ion concentration of the blood may result either from a lessened production of lactic and carbonic acid in

the active muscles, or from more rapid removal of these acids from the blood, or from more rapid oxidation of lactic acid. In favour of the first possibility is the observation that, owing to the elimination of unnecessary movements and improved co-ordination of the active muscles, exercise is carried out more efficiently as the exercise proceeds, and that the individual does the same amount of work with a smaller expenditure of energy. A man, in fact, takes a little time to 'get into his stride.'

In so far as this occurs it will tend, by lessening the total production of acid in the muscles, to minimise the rise in the C_H of the blood during exercise. The gradual rise of the temperature of the body early in exercise also leads, as has been pointed out (p. 20), both to greater efficiency of the muscles and to more complete oxidation of lactic acid within the muscles themselves, and must contribute in this way to a gradual fall in the amount of this acid escaping from the muscles into the blood. Hence the association between the onset of sweating and that of second wind may perhaps indicate the part played by an adequate rise of the temperature of the body upon the reaction of the blood.

The amount of lactic acid entering the blood from the muscles is dependent, however, not only on the rate at which this acid is produced, but also on the rate at which it is oxidised in the muscles, and for this latter purpose the supply of oxygen must be sufficient. It is conceivable that, at the outset of exercise, the co-ordination between the circulatory adjustments, which provide the supply of oxygen to the muscles, and the activity of the muscles themselves may not be quite perfect, and that, for a short time, the supply of oxygen to the muscles may lag behind their demands. If this happens, the amount of lactic acid passing into the blood may be so great as to lower the alkali-reserve of the blood very rapidly, and to bring about a progressively increasing $H^{\bullet}$ ion concentration of the blood and severe dyspnœa. As soon as the blood-flow through the muscles becomes more accurately adjusted to the extent of their activity, less lactic acid will escape oxidation and enter the blood, the reaction of the blood will swing slightly towards its normal level, and the dyspnœa will decline into hyperpnœa. Whether, at the beginning of exercise, a temporary discrepancy exists between the needs of the active muscles and their blood-supply is not known. But the output of the heart, the blood-pressure and the pulse-rate

rise so early during exercise, and their efficiency in increasing the flow of blood through the muscles is so great, that the occurrence of such a discrepancy does not appear very probable, except, perhaps, in the untrained man during severe exercise.

There is yet another factor which may contribute to the lowering of the $H^{\bullet}$ ion concentration of the blood associated with second wind, namely, an interchange of acid radicles between the blood-plasma and the red corpuscles and tissues. That such an exchange is not only possible, but actually does occur, has already been pointed out (p. 34), and, since the reaction of the blood cannot differ appreciably, except very temporarily, from that of the tissues, this interchange must come into play whenever the reaction of the blood alters. The passage of bases into the blood will increase its alkali-reserve, whereas much of the lactic acid diffusing into the tissues (other than the active muscles) is probably oxidised; and, since the tissues also contain a phosphate buffer-system, which stabilises their reaction, this interchange between the tissues and the blood may account, at least to some extent, for the fall in the $H^{\bullet}$ ion concentration of the blood which brings about second wind.

Although direct evidence is lacking, one may surmise that all the processes just discussed may be involved in the causation of second wind; and its earlier, sometimes almost imperceptible, onset in the trained man may be ascribed to the greater efficiency, not only of his heart and his circulatory adjustments, but also of his muscles and, from the point of view of exercise, of his nervous system. Indeed the very existence of second wind throws into relief the complexity of the regulating processes at work during exercise, and demonstrates the exactness of the co-ordination between its different parts, which is necessary for the smooth working of the body generally.

Summary.

Regular and progressive exercise is the essential feature of training, and the character of the diet, provided this is ample and is properly digested, is of subsidiary importance.

Training develops not only the skeletal muscles, but also the heart, and, in a healthy man, the development of his heart corresponds with that of his muscular system. Owing to the increase in its contractile power, the output of the heart per beat

is often larger, and the pulse-rate less frequent, in the trained, than in the untrained man, even during rest.

When a trained, and an untrained man, take the same amount of exercise, the pulse is less frequent, the arterial pressure is usually lower, and the minute-volume of the heart is smaller in the former than in the latter. These differences are due partly to the fact that the output of the heart per beat is larger in the trained man, and partly to the greater coefficient of utilisation and oxygen-carrying power of the blood in the trained man, which lessen the output of the heart per minute necessary to provide a given supply of oxygen to the muscles. The better co-ordination of movement, which is brought about by training, also improves the mechanical efficiency of the body. The effect of these changes is not only to increase a man's power of doing muscular work, but also to enable such work, whether heavy or light, to be performed with the utmost economy of effort.

The characteristic features of 'second wind' are a simultaneous fall in the alveolar tension of carbonic acid and a decrease in the pulmonary ventilation; and they are caused, in all probability, by a diminution in the $H^{\bullet}$ ion concentration of the blood. The possible causes of the diminished $H^{\bullet}$ ion concentration of the blood are greater mechanical efficiency of the body, an improved blood-supply to the muscles, and the exchange of acid and basic radicles between the blood and the tissues. It appears probable that all these processes are concerned in bringing about 'second wind.'

CHAPTER X.

EXERCISE AT HIGH ALTITUDES.

The Process of Acclimatisation—The Passage of Oxygen into the Blood—The Changes during Exercise.

AMONG the various symptoms of 'mountain sickness' a lessened ability, or complete inability, to carry out active physical exertion is conspicuous. As acclimatisation to lowered oxygen-pressure takes place, this disability passes off to a considerable extent; and a man, who is acclimatised to high altitudes and in good physical training, can, as the experience of mountain climbers shows, perform very severe exercise. But, in all individuals, exercise at high altitudes exhibits two characteristic features. In the first place, the respiratory and circulatory changes produced by a given amount of exercise are greater than at low levels, and, in the second place, the maximum amount of work, which can be carried out by the individual in a given time, is less than at low levels. These features are most noticeable in the unacclimatised subject, and, after acclimatisation has taken place, the response to gentle exercise may scarcely differ at high altitudes from that at low levels; but, however complete the adaptation may be, they always appear during severe exercise. The effects of exercise upon the pulmonary ventilation have been worked out by Douglas, Haldane, Henderson, and Schneider (1912), on Pike's Peak, which is 14,109 feet above sea-level, and are illustrated in the following table:—

TABLE XXXIII.—PULMONARY VENTILATION IN LITRES PER MINUTE. (AT 37° C. MOIST AND PREVAILING BAROMETER.) (DOUGLAS, HALDANE, HENDERSON, AND SCHNEIDER.)

	At Oxford.	On Pike's Peak.
Rest, standing	10·4 litres	14·89 litres
Walking 2 miles per hour . .	18·6 ,,	27·9 ,,
,, 4 ,, ,, . .	37·3 ,,	57·5 ,,
,, 5 ,, ,, . .	60·9 ,, .	110·2 ,,

The consumption of oxygen for each grade of exercise was not appreciably different at Oxford and on Pike's Peak respectively.

With regard to the circulatory changes, Schneider, Cheley, and Sisco's observations (1916) show that the acceleration of the pulse and the rise of arterial pressure during exercise are greater at high altitudes than at low levels, and that there is a corresponding delay in the return of the pulse-rate and blood-pressure to the normal after the exercise. Although, in a trained and acclimatised man, these effects are not brought out by walking slowly, they appear during walking at four miles an hour, and become very striking when the exercise consists in rapid running.

TABLE XXXIV.—Effect of Exercise on Pulse-Rate and Arterial Pressure. (From Schneider, Cheley, and Sisco.)

		Pulse-rate.		Arterial Pressure.	
		Resting.	Just after Exercise.	Resting.	Just after Exercise.
Walking 3 miles per hour	Colorado Springs	69	80	113	112
	Pike's Peak	76	102	124	132
Walking 4 miles per hour	Colorado Springs	71	100	114	120
	Pike's Peak	82	132	116	142
Short run uphill	Colorado Springs	70	108-160	130	166 (average)
	Pike's Peak	85	206 (average)	130	197 ,,

Exercise also causes a greater rise of venous pressure at high altitudes. There is no evidence regarding the output of the heart or the coefficient of utilisation.

Lack of oxygen is the cause of the lessened ability of the individual to perform work at high altitudes, and the exaggerated circulatory and respiratory response to exercise is undoubtedly a compensatory process. But, before discussing the causation of these compensatory changes, it is necessary to consider briefly the nature of the processes which constitute acclimatisation.

Fortunately for this purpose it happens that most of the more recent investigations have been made at much the same barometric pressure, those of Douglas, Haldane, Henderson, and Schneider (1912), of Schneider and Sisco (1914), and of Schneider, Cheley, and Sisco (1916), on Pike's Peak at an average barometric pressure of 457 mm. Hg, of Barcroft and others in the Peruvian Andes, chiefly at Cerro de Pasco, at a barometric pressure

of 458 mm. (1921-22), and those of Hasselbalch and Lindhard (1915), in a pneumatic chamber at a pressure of 448 to 462 mm. Hg. The results obtained on Pike's Peak in the Peruvian Andes, and in the pneumatic chamber, agree so closely that the greater intensity of the sunlight, the fall of temperature, and other changes incidental to life on a mountain, clearly do not take any active part in the process of acclimatisation.

The Process of Acclimatisation.

The Respiratory Changes.—After acclimatisation had taken place, the two main respiratory changes observed, both on Pike's Peak and in the pneumatic chamber, were, first, an increase of approximately 50 per cent. in the pulmonary ventilation as compared with that at or near sea-level, and, second, a fall in the

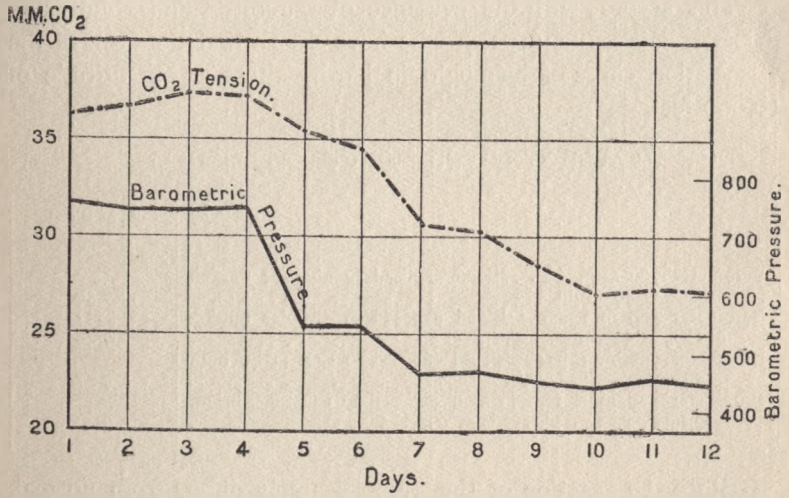


FIG. 21.—Influence of barometric pressure upon the alveolar tension of carbonic acid. (Hasselbalch and Lindhard.)

alveolar tension of carbonic acid (Fig. 21 and Table XXXV.). The result is that the tension of oxygen in the alveolar air is from 16 to 18 mm. Hg higher than otherwise would be the case.

These changes clearly point to the existence of a very slight rise in the $H^{\cdot}$ ion concentration of the blood, but the increase in the pulmonary ventilation is so trivial that the actual alteration in the C_H of the blood must be almost inappreciable. Direct observations by the gas electrode method have been made by Hasselbalch and Lindhard (1915), who find that, at a

TABLE XXXV.

	Douglas, Haldane, Henderson, and Schneider.		Hasselbalch and Lindhard.	
	Near Sea-level. Bar. 747.	Pike's Peak. Bar. 457.	Near Sea-level. Bar. 755.	Pneumatic Chamber Bar. 454.
Pulmon. ventilation	7·67 litres	10·29 (Douglas)	5·25 litres	8·0 litres
Alveolar CO_2 tension	39·6 mm. Hg.	26·9 ,,	36·3 ,,	24·4 ,,
,, oxygen tension . .	100·4 ,,	54·7 ,,	—	—

low barometric pressure, the reaction of the blood is practically unaltered, when it is exposed to the alveolar tension of carbonic acid existing in the subject at that pressure.

This accords with the evidence of Barcroft, Camis, Mathison, Roberts, and Ryffel (1915), who have shown that the form of the dissociation curve of hæmoglobin hardly alters at an altitude of 10,000 feet.

TABLE XXXVI.—(Hasselbalch and Lindhard.)

	P_H of Blood.
Barometer 760 mm. Hg. Blood exposed to alveolar tension of CO_2 = 40·8 mm. Hg.	7·50
Barometer 589 mm. Hg. Blood exposed to alveolar tension of CO_2 = 32·2 mm. Hg.	7·48
Barometer 760 mm. Hg. Blood exposed to CO_2 at 40 mm. Hg tension	7·51
Barometer 589 mm. Hg. Blood exposed to CO_2 at 40 mm. Hg tension	7·44

Since the reaction of the blood scarcely differs from normal, whereas the fall in the alveolar tension of carbonic acid is considerable, there must necessarily be a decrease in the sodium bicarbonate content of the blood. That this is the case is clear from Hasselbalch and Lindhard's observation (Table XXXVI.) that, when the blood of an individual living at a high altitude is compared with that of the same individual living at sea-level, the two samples being exposed to the *same* tension of carbonic acid, the former is distinctly the more acid.

The same fact is brought out in the experiments of Barcroft, Camis, Mathison, Roberts, and Ryffel in which, testing the blood in the absence of carbonic acid, they observed, by Mathison's

method, that it was uniformly more acid at a high altitude. In short, there is, at a high altitude, a simultaneous fall in the alveolar tension of carbonic acid, and in the alkali-reserve of the blood, though, since these two changes almost counterbalance one another, the reaction of the blood scarcely differs from the normal value.

Douglas, Haldane, Henderson, and Schneider look upon the fall in the alveolar tension of carbonic acid as secondary to a primary reduction in the alkalinity of the blood. They reject the view that this is brought about by the passage of lactic acid into the blood, since the tension of carbonic acid remains low, even after the symptoms of oxygen-want have almost entirely disappeared. They conclude that the change is due to some adaptive alteration in the regulation of the alkalinity of the blood, and they suggest that an alteration in the reaction of the urine excreted by the kidneys would account for the facts.

Barcroft and his co-workers consider that the change in the blood at moderate altitudes is due mainly or entirely to some other cause than lactic acid, whereas, at high altitudes, the amount of lactic acid present in the blood is increased. Their observations at high altitudes, however, were made on the day of their arrival, and before acclimatisation had taken place; it seems doubtful, therefore, whether lactic acid takes any share in reducing the alkali-reserve in the fully acclimatised person during rest.

It should be remembered, however, that Anrep and Cannon have shown that there exists a definite correlation between the CO_2 and the lactic acid in the blood. They found that in every case when CO_2 is removed from the organism there is an accumulation of lactic acid in the blood. On addition of CO_2 the lactic acid disappears. Direct determinations of lactic acid in the blood at high altitudes should be included in the programme of future expeditions.

Hasselbalch and Lindhard's interpretation of the facts under discussion is the converse of that just stated. They hold that the primary change takes place, not in the blood, but in the respiratory centre. They believe that, at high altitudes, the respiratory centre becomes abnormally sensitive to the $H^{\bullet}$ ion concentration of the blood, this change bringing about increased pulmonary ventilation and a fall of the alveolar tension of carbonic

acid. The lowered tension of carbonic acid must be compensated by a secondary fall in the sodium bicarbonate content of the blood, and Y. Henderson has shown that greater pulmonary ventilation does lower the alkali-reserve of the blood.

If such a change in the excitability of the respiratory centre is admitted, it would undoubtedly account for the observed facts, and, in this connection, Hasselbalch and Lindhard's (1916) observation that the amount and percentage (relatively to the total nitrogen) of the urinary ammonia are diminished at high altitudes is very significant. An increase in the ammonia in the urine is one of the recognised means by which the body compensates for a greater production of acid in the body; conversely, the addition of alkali to the body is known to decrease the excretion of ammonia. Although Hasselbalch and Lindhard regard the decreased output of ammonia as dependent on some metabolic alteration induced in the tissues by the increased C_H of the blood, it may equally be taken as evidence that more alkali than usual is available in the tissues to combine with the acid formed in the body and that, in consequence, less ammonia is required for this purpose.

The possibility that the excitability of the respiratory centre might be greater at high altitudes had previously been rejected by Haldane (1912) on the ground that it would diminish, and not increase, the supply of oxygen to the tissues. He supposed that the dissociation curve of oxyhæmoglobin would be shifted to the left, and that the blood would therefore dissociate less readily and completely than usual during its passage through the capillaries. In their earlier work (1914) Barcroft and his co-workers found that the dissociation curve of the blood was practically unaltered in form, and that such shift as did occur was towards the right. But in the expedition to Peru (1921-22) it was found invariably that in the natives, and in the members of the expedition after acclimatisation, the dissociation curve of the blood for oxygen was actually shifted towards the *left*, i.e. in the direction of increased saturation for any given oxygen-pressure. It is evident that such a change must favour the taking up of oxygen in the lungs, while in itself retarding the giving up of oxygen to the tissues.

Hasselbalch and Lindhard believe that the greater sensitiveness of the respiratory centre is a direct result of the lessened

tension of oxygen in the blood, and Haldane and Poulton's observation (1908) that oxygen-want produces this effect, probably by bringing about a greater production of acid within the centre itself, seems to offer an adequate explanation of such a change. In the resting individual, it is the nervous system, and not the muscles, which is most readily affected by lack of oxygen; and such a lack, while too slight to increase the passage of lactic acid into the blood from the muscles, might well lead to a sufficient formation of acid in the nervous system to heighten the excitability of the respiratory centre. In that case the greater pulmonary ventilation, by raising the alveolar tension of oxygen, would enable the blood to become sufficiently saturated with oxygen to maintain an adequate supply both to the brain and to the body as a whole. Thus, in the process of acclimatisation, a position of equilibrium would be reached, at which the pulmonary ventilation would be just sufficient to keep the production of acid in the respiratory centre from exceeding the minimal level necessary to ensure an adequate ventilation. Such a process is certainly more intelligible than an adaptive alteration on the part of the kidney since, so far as is known, the kidney blindly responds to every change in the reaction of the blood, and there is no evidence that it initiates such changes. Hasselbalch and Lindhard (1916) have determined the P_H of the urine during the process of acclimatisation; but their results show no significant alteration from the normal P_H value.

Whatever its cause may be, the increased pulmonary ventilation raises the tension of oxygen in the alveoli, at 457 mm. Hg barometric pressure, from 35·8 mm. Hg to 52 to 55 mm. Hg. Taking the dissociation curve of Barcroft's blood as a standard, this means that the hæmoglobin of the blood as it leaves the lungs may be 86 per cent. saturated with oxygen instead of 65 per cent. saturated. Since the hæmoglobin value of the blood in a fully acclimatised man may be from 120 to 130, and occasionally as high as 150 (Douglas, Haldane, Henderson, and Schneider), it is evident that the amount of oxygen reaching the tissues may be greater than at low levels, and that a *resting*, acclimatised man may be over-compensated.

In summarising the results of the Peru High Altitude Expedition of 1921-22 Barcroft points to three principal factors which have positive influence in acclimatisation.

(*a*) The increase in total ventilation, which usually raises the alveolar oxygen-pressure 10 to 12 millimetres higher than it would otherwise be; (*b*) the rise in the oxygen-dissociation curve so that at any oxygen-pressure the hæmoglobin will take more oxygen than before; (*c*) the rise in the number of red corpuscles, and correspondingly in the quantity of hæmoglobin.

Barcroft and Ugeno (1923) found that blood can be made artificially to resemble high-altitude blood, by shaking out CO_2 and then withdrawing a portion of the plasma, so that the blood is richer in corpuscles. Such blood has been found to give, at the alveolar CO_2 pressure of the Ades (27 mm. CO_2), an oxygen-dissociation curve which rises apparently out of proportion to the change in reaction.

In every case there is an increase in the hæmoglobin value of the blood and in the red cell count. On nearing the ascent, there was a marked increase in the number of reticulated red cells; after the descent these cells fell to below their normal percentage. The increase in these cells indicates a hyper-function of the bone marrow. The increase in the red cells is such as to cause an absolute increase in the amount of oxygen in each cubic centimetre of blood in spite of the decrease in saturation (80 to 85 per cent.). Moreover, the increase in the red cells accounts for the fact that the oxygen-dissociation curve is higher than normally. The latter is explained by Barcroft and Ugeno by the assumption that the quantity of chlorine which migrates at a given CO_2 tension into each corpuscle is markedly less than would be the case if the number of corpuscles had not increased. Otherwise the interior of the corpuscle will be more alkaline than originally, when exposed to a given tension of carbonic acid. In accordance with the works of Barcroft and of Kato (1915) the oxygen-dissociation curve should under these conditions be higher.

The Circulatory Changes.

In confirmation of earlier observers (Zuntz, Durig, and Kolmer), Douglas, Haldane, Henderson, and Schneider, and also Schneider and Sisco, find that, on Pike's Peak, the pulse-rate, even after acclimatisation, is greater than at low levels. The individual variations are considerable, some men showing acceleration of only a few beats, and others an increase of ten beats or more; in exceptional cases the acceleration may be

replaced by a decrease in pulse-rate. The systolic arterial pressure is practically unchanged, but Schneider and Sisco record a lower venous pressure on Pike's Peak than at low altitudes; and they attribute the fall of pressure to the increased pulse-rate. These changes persist even after complete acclimatisation, as is shown by the following figures obtained in one of their subjects, who spent six months in each year on Pike's Peak, and six months at Colorado Springs:—

TABLE XXXVII.

	Average Pulse-rate.	Arterial Pressure:		Venous Pressure Cm. Water.
		Systolic.	Diastolic. Mm. Hg.	
Colorado Springs (6,000 feet) .	71	116	83	13·6
Pike's Peak (14,109 feet) .	87	110	83	9·9

The output of the heart per minute appears to be practically the same at high as at low levels. The methods used by Douglas, Haldane, Henderson, and Schneider for estimating the output per beat were first, the pulse-pressure, and, second, the recoil board devised by Yandell Henderson. Both these methods indicate that the output per beat is diminished on Pike's Peak, but that, owing to the acceleration of the pulse, the minute-volume of the heart is the same as at Colorado Springs. Schneider and Sisco (1914) have measured the rate of blood-flow by Stewart's method, which consists in determining the amount of heat given off by the hand in a certain time, the hand being immersed in a water calorimeter. They found that the circulation rate through the hands was from 30 to 76 per cent. greater on Pike's Peak than at low levels, and, since their observations with the recoil board indicate a larger output of the heart per minute, they concluded that the circulation rate as a whole was more rapid. Hasselbalch and Lindhard, however, employing Krogh and Lindhard's method, have found that the output of the heart is not increased at high altitudes during rest, thereby confirming Douglas, Haldane, Henderson, and Schneider. Similar results were obtained in the Peru expedition.

In a later paper, Schneider and Sisco (1914) attribute the increased blood-flow through the limbs partly to dilatation of the arterioles and partly to greater rapidity of the circulation as

a whole, this being brought about by acceleration of the pulse and fall of venous pressure. But, as has been pointed out (p. 70), acceleration of the pulse increases the circulation rate only in so far as it increases the output of the heart, and, during rest, the diastolic filling of the heart is so slow that increase in the pulse-rate usually has no influence on its output. The fall of venous pressure, again, is merely an incidental sequence of the greater frequency of the pulse, and does not in itself indicate any change in the circulation rate as a whole. It must be concluded, then, that, at high altitudes, the circulation rate is the same as at low levels, and that the greater blood-flow through the limbs is due to dilatation of the limb-vessels. Since the arterial pressure is practically unaltered at high altitudes, the dilatation of the limb-vessels must be counterbalanced by vaso-constriction elsewhere, presumably in the splanchnic area. There is at present no evidence to show which of these is the primary process. Schneider and Sisco regard the increased frequency of the pulse as an adaptive change in response to oxygen-want, since they found that the inhalation of oxygen slowed the pulse. But a similar decrease in pulse-rate has been observed to take place as a result of inhalation of oxygen at low levels, although, in these circumstances, oxygen-want did not previously exist. There is at present no satisfactory explanation of the greater frequency of the pulse in the resting individual at high altitudes, and it is not easy to understand how the acceleration at high altitudes can be in any way advantageous to the circulation.

The Passage of Oxygen into the Blood.

It has been found both by Douglas, Haldane, Henderson, and Schneider, and by Hasselbalch and Lindhard that, in the resting individual, the consumption of oxygen at high altitudes is the same as at ordinary levels.

TABLE XXXVIII.—Oxygen Consumption in c.c. per Minute.

	Barometric Pressure 750-760 mm. Hg.	Barometric Pressure 450 mm. Hg.
Douglas, Haldane, Henderson, and Schneider .	237	248
" " " " .	330	345
Hasselbalch and Lindhard	219	220

Durig and Zuntz observed a greater consumption of oxygen at high altitudes than at low levels. It is probable, however, that the individuals in whom this occurred were not fully acclimatised, since Hasselbalch and Lindhard have also found that the consumption of oxygen is increased during the transitional stage before adaptation has become complete.

Since the minute-volume of the heart is also unaltered, it is clear that, in the resting individual at a high altitude, the blood must take up its normal amount of oxygen from the lungs, and that, unless it undergoes much greater reduction than usual during its passage through the tissues, the blood must leave the lungs almost as fully saturated with oxygen as at low levels. Opinion is sharply divided, however, as to the means by which the passage of oxygen into the blood at high altitudes is effected. Krogh holds that oxygen enters the blood, both at low levels and at high altitudes, solely by diffusion through the pulmonary epithelium, whereas Douglas and Haldane, while accepting diffusion as the only process concerned in the resting man at low levels, consider that, at high altitudes, diffusion will not account for the intake of oxygen, and that this is brought about by active secretion on the part of the pulmonary epithelium.

The Diffusion Theory.

On the diffusion hypothesis, the amount of oxygen entering the blood per minute is the product of the diffusion-coefficient of oxygen through the membrane separating the alveolar air from the blood and of the mean difference between the tension of oxygen in the alveolar air and in the blood flowing through the pulmonary capillaries. The diffusion-coefficient is defined as the amount of oxygen in c.c. which can diffuse through the alveolar membrane in one minute, when the difference of oxygen-pressure on the two sides of the membrane is 1 mm. In 1911, A. and M. Krogh found that the diffusion-coefficient might be 25. More recently (1915), M. Krogh has shown that the coefficient varies from 23 to 43 in different individuals during rest, and that, when the surface area of the lungs is increased by greater pulmonary expansion, for example, during exercise, it ranges from 37 to 56.

In the determination of the coefficient, the assumption is made that the alveolar membrane is watery; and some observations of Cushny on the exhalation of volatile

substances through the lungs favour this view. But it is not certain that such is the case. Lipoids exist in almost all membranes in the body, and as Bayliss has pointed out, the presence of lipoid in the alveolar membrane would greatly increase the diffusion-coefficient. The values of the coefficient, as determined by M. Krogh, must, therefore, be minimal values.

On Pike's Peak, Douglas absorbed during rest 345 c.c. oxygen per minute. Taking an average value for the diffusion-coefficient, namely, 33, this amount of oxygen could enter the blood by diffusion, if the difference between the tension of oxygen in the alveoli and that in the blood were $\frac{345}{33} = 10{\cdot}5$ mm. Assuming the blood leaving the lungs to be in equilibrium with the alveolar tension of oxygen, it would be 85 per cent. saturated; and, if the blood lost 32 per cent. of its oxygen in passing round the body, the venous blood would be 53 per cent. saturated, this representing an oxygen-tension of 32 mm. Hg. If the blood, instead of coming into equilibrium with the alveolar air, becomes only 80 per cent. saturated in the lungs, the oxygen-tension of the venous blood would be 28 mm. Hg. The maximum tension-difference then is 22 or 26 mm. Hg. The tension-difference falls, however, as the blood travels along the capillaries, and the *mean* tension-difference, when roughly integrated by the method described by Bohr, is about 12 or 13 mm. Hg; this is more than sufficient to provide for the absorption of 345 c.c. of oxygen by diffusion alone.

The relationship between the oxygen-consumption of an individual and his diffusion-coefficient has not been worked out, but, since the former corresponds roughly with the muscular development of the individual, it is not improbable that a large oxygen-absorption is associated with increased alveolar surface and, consequently, with a large diffusion-coefficient. Assuming that the oxygen-absorption and the diffusion-coefficient are related in this way, the evidence for the diffusion theory is more convincing than that indicated by the foregoing example, since an oxygen-absorption of 345 c.c. per minute is rather large for a resting man, and it seems quite possible that Douglas' diffusion-coefficient might be 40 or thereabouts. In this case, a mean difference of 8·5 mm. Hg between the tension of oxygen in the alveolar air and in the capillary blood in the lungs respectively would provide for the required absorption of oxygen. Moreover, the increased pulmonary ventilation at high altitudes

would tend to raise the diffusion-coefficient still further, and, in these circumstances, a still smaller mean difference of tension would be adequate.

The assumption that the venous blood loses one-third of its oxygen in passing through the tissues is, however, not always correct. Taking the consumption of oxygen per minute to be 240 c.c., the output of the heart to be 4 litres per minute, and the oxygen capacity of the blood, when 96 per cent. saturated, to be 181 c.c. per litre, the blood would lose one-third of its oxygen if each litre gave off 60 c.c. to the tissues. If, at high altitudes, the blood left the lungs 80 per cent. saturated, and the hæmoglobin percentage rose to 118, the oxygen-carrying power of the blood would be almost unchanged, and the percentage saturation of the venous blood would be 53 per cent. But if, as might well occur, the hæmoglobin percentage rose to 134 the oxygen-carrying power of the blood would be 201 c.c. per litre; the removal in the tissues of the usual 60 c.c. of oxygen would then leave the venous blood 56 per cent. saturated, and its oxygen-tension would be 33 mm. Consequently, the difference between the tension of oxygen in the alveoli and in the venous blood reaching the lungs would be lessened.

Hence, any excess of hæmoglobin (per unit volume of blood) beyond that required to compensate for the diminished saturation of the blood at high altitudes has the effect of raising the venous oxygen-pressure, and thereby *reducing* the mean difference of oxygen-tension upon which the diffusion of oxygen depends. This could, of course, be met by a slight fall in the saturation of the arterial blood, and, consequently, of the venous blood, which, while not affecting the absorption of oxygen, would tend to produce, or to accentuate, cyanosis. Douglas, Haldane, Henderson, and Schneider state indeed that blood which is 85 per cent. saturated with oxygen is distinctly darker in colour than that saturated to 95 per cent., and they consider that the absence of any sign of blueness of the mucous membranes in acclimatised individuals is a strong argument against the diffusion theory. But in the Peru expedition cyanosis was found both in natives and in acclimatised Europeans.

The direct comparison of two samples of blood, examined side by side *in vitro*, is, however, a much more delicate method of observation than inspection of a mucous membrane. Further

owing to its greater content of hæmoglobin, the saturation of the blood in the capillaries of the mucous membranes probably differs less from that of arterial blood at high altitudes than at low levels. It is not certain, therefore, that, when the arterial blood is only 85, or even 80, per cent. saturated, this will produce any recognisable change of tint in the mucous membranes, and the absence of cyanosis in acclimatised men on Pike's Peak, as noted by Haldane, is not inconsistent with the diffusion theory. Moreover, even though the venous oxygen-pressure is raised by an excess of hæmoglobin, the mean difference of oxygen-tension is probably sufficient to allow the blood, as it flows through the lungs, to become saturated almost to the alveolar oxygen-tension, unless the diffusion constant in any individual is unusually small relatively to the absorption of oxygen.

The explorations of the Duc d'Abruzzi and his companions in the Himalayas probably provide the most severe test to which the diffusion hypothesis has been subjected. The barometric pressure was 312 mm. Hg, and the oxygen-pressure of the alveolar air is calculated by Haldane and his colleagues as being about 30 mm. Hg. They point out that blood, when in equilibrium with alveolar air at this pressure, is not quite half saturated with oxygen, the percentage of saturation corresponding with that found in the arterial blood of animals just before death from asphyxia, and that, on the diffusion theory, the saturation of the blood would be even less. Since the explorers felt no discomfort during rest and were even able to take a moderate amount of exercise, Haldane and his colleagues conclude that the diffusion hypothesis breaks down.

This figure for the alveolar tension of oxygen is not accepted by M. Krogh. On the basis of Haldane's assumption that the members of the expedition were doing work involving an oxygen consumption of 1,000 c.c. per minute, and assuming further that the ventilation per minute measured 111·3 litres, M. Krogh finds that the alveolar oxygen-tension would be 47 mm. Taking the diffusion-coefficient as 56, the absorption of 1,000 c.c. of oxygen could be obtained with a mean tension difference of 17·8 mm., which would be possible if the arterial blood were 60 per cent. saturated. M. Krogh concludes, therefore, that the results of the d'Abruzzi expedition are not incompatible with the diffusion theory, although marked cyanosis must have been present.

It appears then that, even at high altitudes (up to 24,000 feet), the passage into the blood of sufficient oxygen to enable a man not merely to exist, but to live with comparatively little discomfort, and even to take exercise, when once he has become acclimatised, can be effected by diffusion alone, and that, at least on Pike's Peak, the diffusion hypothesis not only avoids being wrecked on the Scylla of secretion, but also, in the resting individual, evades the Charybdis of cyanosis.

A height of 27,000 feet was reached in the 1922 expedition to the Mount Everest. Some of the members of the expedition reached this height without using oxygen. They found that acclimatisation occurred very quickly.

The Secretion Hypothesis.

This conclusion deprives the secretion hypothesis of one of the two main arguments advanced in its support, namely, the inadequacy of the diffusion theory to account for the facts. But there remains the direct evidence brought forward by Douglas, Haldane, Henderson, and Schneider that, on Pike's Peak, the tension of oxygen in the arterial blood is considerably higher than that in the alveolar air. Employing the carbon monoxide colorimetric method, they found that the average pressure of oxygen in the arterial blood was 88·3 mm. Hg, and, since the average alveolar pressure of oxygen was 52·5 mm. Hg, the tension of oxygen in the arterial blood was 35·8 mm. Hg higher than that in the alveolar air. In one subject, who had just ascended the Peak, and who was cyanosed, the pressure of oxygen in the arterial blood exceeded that in the alveolar air only by a few millimetres.

On the ground of these observations, Haldane and his colleagues hold that increased secretory activity of the pulmonary epithelium, by raising the tension of oxygen in the arterial blood, makes acclimatisation possible, and that the development of secretory activity is a gradual process. At an oxygen-tension of 88 mm. Hg, the blood will be 95 per cent. saturated; in that case, the process of compensation for the high altitude is so complete that there is no obvious reason why, on Pike's Peak, the individual should differ in any respect (apart from the activity of his pulmonary epithelium) from a man at sea-level. What, then, is the explanation of the progressive increase in the percentage

of hæmoglobin in the blood, an increase which continues even after the secretory activity of the pulmonary epithelium has had time to develop? Haldane and his colleagues believe that, at low barometric pressures, easily oxidisable metabolites pass through the lungs into the arterial blood in abnormally high proportions, that these substances are oxidised in the blood on its way through the body, and that the rise in the percentage of hæmoglobin, by increasing the oxygen-content of the arterial blood above the normal level, permits this oxidation to take place without any reduction in the supply of oxygen to the tissues.

It is difficult to understand, however, how, if the saturation of the blood is normal and its oxygen-carrying power greater than normal, the metabolism of the subject can be affected, and how the oxidation processes in the tissues can be less efficient than usual. Nor does it seem possible (on the secretory view) to account for the change in the reaction of the blood, which Haldane and his colleagues regard as being responsible for the increased pulmonary ventilation, although this doubtless renders easier the task of the pulmonary epithelium. Even if the pulmonary ventilation were unaltered and the alveolar oxygen-tension remained at 38 mm., an excess of 35·8 mm. in the tension of oxygen in arterial blood over that in alveolar air would enable its hæmoglobin to become 92 per cent. saturated with oxygen, a value quite sufficient at low levels.

Further, the occurrence of periodic (Cheyne-Stokes) breathing in the acclimatised man, sometimes only on slight exertion, but in some individuals even during sleep, does not accord with the view that the blood is normally saturated with oxygen, since Douglas and Haldane (1909), have clearly shown that it is usually caused by lack of oxygen, and Pembrey and Allen (1905) found that it was abolished by inhalation of oxygen.

Apart from these objections to the views of Haldane and his co-workers, Hartridge's (1912) evidence appears to throw some doubt on the validity of the colorimetric method employed by Haldane. Hartridge's observations indicate that, when the air breathed contains a diminished percentage of oxygen, the tension of oxygen in the arterial blood is not higher than that of the alveolar air. But these experiments are hardly relevant, since the lack of oxygen was very temporary, whereas Douglas, Haldane, Henderson, and Schneider hold that prolonged lack of oxygen is necessary to develop the secretory activity of the pulmonary epithelium. Bayliss (1915) has suggested that possibly the greater percentage of hæmoglobin in the blood may interfere with the accuracy of the carbon monoxide method.

To quote a remark made by Gibbon in another connection, "it is not the duty of the (writer) to interpose his private judgment in this nice and important controversy," which will, perhaps, be finally settled only by direct determination of the oxygen-tension and percentage saturation of the arterial blood of a completely acclimatised individual at a high altitude. In the meantime, however, M. Krogh's evidence appears to have weighted the scales heavily in favour of the diffusion theory.

Definite evidence in favour of the diffusion theory was given by the recent expedition to Peru (1921-22), when a number of tests were made for the purpose of discovering whether the pressure of oxygen in the blood was or was not higher than that in the alveolar air. In all cases they were so nearly the same that the passage of gas through the pulmonary epithelium could be only attributed to diffusion.

The Changes during Exercise.

Rapid walking on Pike's Peak may increase the oxygen consumption to 2,000 c.c. per minute, and, during a short run, this figure may doubtless be exceeded, though only for a few moments. Such a rise in the consumption of oxygen can take place only if the mean difference between the tension of oxygen in the alveolar air and that in the blood reaching the lungs is greatly increased; this is effected partly by a rise in the tension of oxygen in alveolar air, and partly by greater reduction of the blood during its transit round the body. At low levels, the increased pulmonary ventilation during exercise leaves the alveolar oxygen-tension almost unaltered, whereas, on Pike's Peak, the pulmonary ventilation during exercise is exaggerated to such an extent (Fig. 22) that the alveolar tension of carbonic acid falls and the tension of oxygen may increase to 68 or 69 mm.

At the same time the coefficient of utilisation rises considerably, the result being that the tension of oxygen in the venous blood falls and the mean difference of tension between the alveolar air and the venous blood may reach 38 to 40 mm. Taking the diffusion-coefficient during muscular work to be just over 50, this difference of tension will allow of the passage into the blood of roughly 2,000 c.c. of oxygen per minute, which is almost the highest figure recorded by Haldane and his co-workers.

The hyperpnœa or dyspnœa induced by exercise at high

TABLE XXXIX.—(COTTON, RAPPORT, AND LEWIS.)

Work.			Pulse.			Systolic Blood-pressure.				Remarks.
Lifts 20 lb. Bells.		Duration in Seconds.	Before Exercise.	After Exercise.		Before Exercise.	After Exercise.			
				Max. Reading.	Fall to Normal in Secs.		Max. Reading.	Rise.	Fall to Normal in Secs.	
Subject 1	40	80	78	170	280+	121	162	41	230	Considerably breathless, fatigued, palpitation.
	30	60	72	127+	280+	119	145	26	220	Breathless, slight fatigue.
	20	40	74	118	160	116	137	21	120	Slight breathlessness.
	10	20	80	112	60	119	128	9	50	" "
Subject 2	60	120	85	158	280+	120	169	40	270	Considerably breathless, fatigue, palpitation.
	40	80	85	130	120	117	139	22	210	Some breathlessness.
	30	60	95	130+	100	118	137	19	110	Slight breathlessness.
	20	40	98	123	80	116	134	18	110	" "

Martin, Gruber, and Lanman (1914) also found that, although the pulse-rate rapidly decreased after exercise, it did not return to normal for more than an hour. Their observations were made both on a trained and on an untrained individual, and the exercise consisted in running up and down stairs for three to six minutes. Similar results were obtained by Benedict and Cathcart (1913). In Benedict and Cathcart's experiments, the

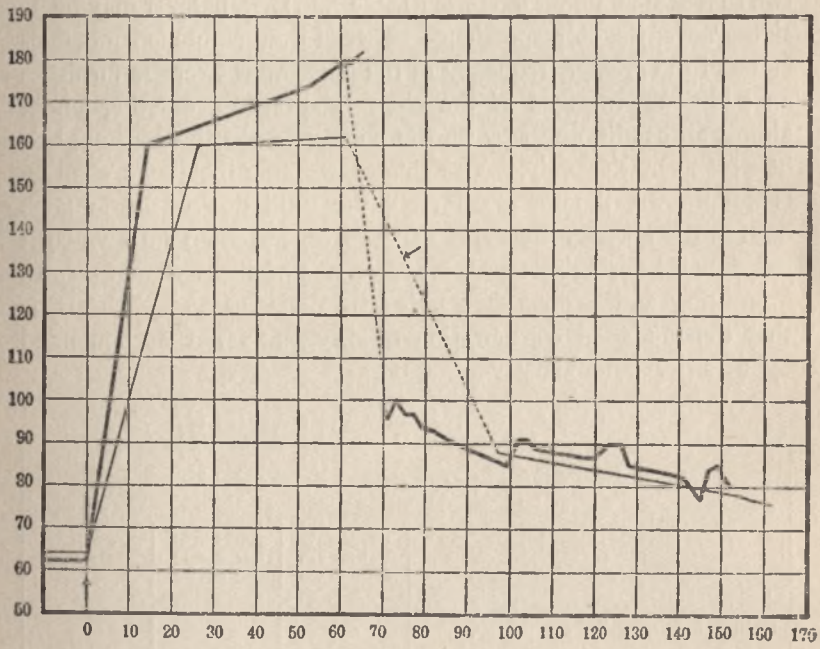
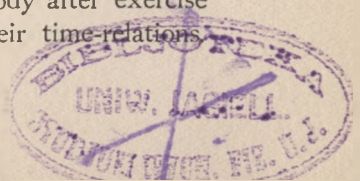


FIG. 23.—(From Benedict and Cathcart.)

Figures along abscissa = time in minutes.
Figures along ordinate = pulse-rate per minute.
Arrows indicate the beginning and end of the exercise.

exercise was severe and rather prolonged; at the end of the exercise the pulse-rate fell rapidly at first, and then remained, sometimes for several hours, at a distinctly higher rate than before the exercise (Fig. 23).

The prolonged slight acceleration of the pulse after exercise is not associated with raised temperature of the body, since Martin, Gruber, and Lanman found that the decline in the pulse-rate and the fall in the temperature of the body after exercise did not necessarily correspond as regards their time-relations.



altitudes is, therefore, necessarily greater than at low levels; it is due, partly to heightened excitability of the respiratory centre, and partly to the greater rise in the C_H of the blood during exercise under these conditions.

The actual effect of exercise on the passage of oxygen into the blood, however, is not so simple as these figures seem to indicate, since the circulation rate through the lungs also becomes greater during exercise. In consequence of the smaller

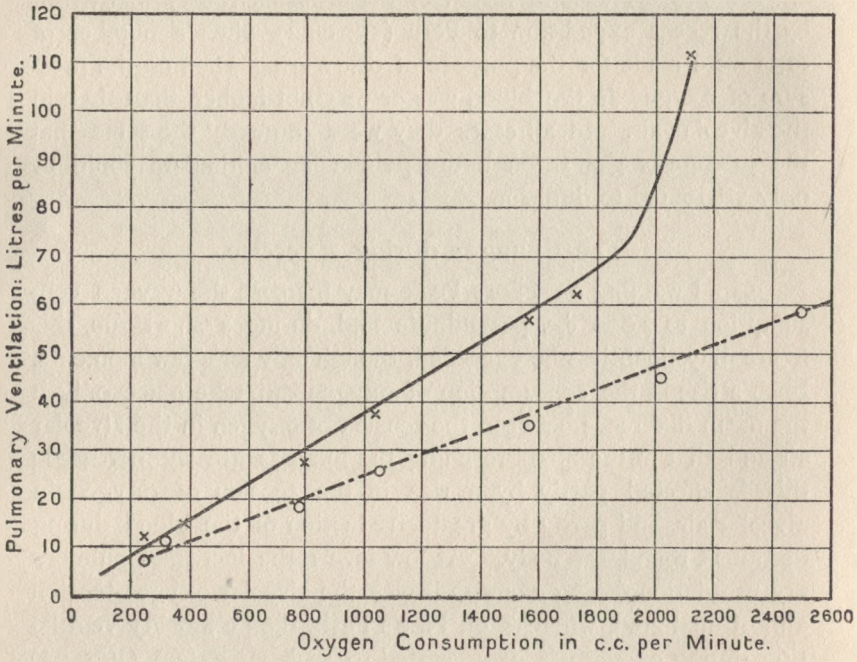


FIG. 22.—(Constructed from Douglas, Haldane, Henderson, and Schneider's data.)

Upper curve = ventilation on Pike's Peak.
Lower curve = ventilation at Oxford.

difference between the pressure of oxygen in the alveolar air and that in the venous blood at high altitudes, the *rate* of diffusion must be slower than at low levels. Consequently, as the flow of blood through the lungs becomes more rapid, less and less time is available for the passage of oxygen into the blood, and the percentage saturation with oxygen of the hæmoglobin in the blood leaving the lungs inevitably falls. The fall in the tension of oxygen in the arterial blood brings about two effects.

In the first place, it tends to lessen the amount of oxygen carried from the lungs to the tissues. In the second place, it slows down the rate at which the blood gives up its oxygen to the tissues.

It is from this point of view that the hæmoglobin content of the blood, and its rate of dissociation, become of such importance for the maintenance of an adequate difference of tension between the alveolar air and the blood. Barcroft and his associates (1915) have shown that a given amount of exercise increases the $H^{\cdot}$ ion concentration of the blood to a greater extent at high altitudes than at low levels; and, in all probability, the local concentration of acids in the capillaries of the active muscles is also greater under these conditions. The dissociation of oxyhæmoglobin, as the blood flows through the active tissues, is thereby accelerated, and the venous blood is more fully reduced. The fall in the oxygen-tension of the venous blood favours the more rapid diffusion of oxygen into the blood in the lungs, although this will be accompanied by cyanosis.

Again, the higher the percentage of hæmoglobin in the blood, the slower is the circulation rate necessary for the transport of a given amount of oxygen from the lungs to the tissues, and hence the higher will be the pressure of oxygen in the arterial blood.

The hæmoglobin content of a man's blood is, therefore, of vital importance in determining the intensity of the exercise which he can perform at a high altitude, and, from this point of view, the hæmoglobin value of his blood is probably the truest index of the extent to which a man is acclimatised to high altitudes.

It might be anticipated that, owing to the greater hæmoglobin content of the blood, the circulation rate would increase less rapidly at high altitudes than at low levels. On the other hand, the higher arterial pressure and greater concentration of acid metabolites in the muscles will presumably cause a more rapid flow of blood through the muscles than at low levels, and the mechanical pumping action of the muscles will bring about a correspondingly larger venous inflow to the heart, which will tend to increase its output and hence the circulation rate. The available data do not permit of any conclusion as to whether, for a given amount of exercise, the circulation rate at high altitudes differs from that at low levels. Nor is there at present any

evidence that failure on the part of the circulatory system is responsible for the lessened ability of the individual to perform exercise at high altitudes.

It is clear, then, that since, on the one hand, a more rapid circulation rate is required to carry oxygen from the lungs to the tissues, and, on the other hand, such an increase in rate gradually lowers the tension of oxygen in the arterial blood, the limit of exercise at high altitudes is reached when the tension of oxygen in the arterial blood becomes inadequate for the needs of the tissues. In other words, the amount of oxygen passing into the blood sets the limit to the amount of exercise which a man can perform at high altitudes, whereas, at low levels, the decisive factor is the rate at which oxygen can be carried from the lungs to the tissues.

The first tissue to suffer visibly from the lowered tension of oxygen in the arterial blood is the central nervous system. It is for this reason that, even in the acclimatised subject, severe exercise brings on the characteristic symptoms of "mountain sickness." It is probable, indeed, that many climbing accidents are caused, not by failure of the muscles but by a sudden aberration of judgment or disturbance of co-ordination induced by an insufficient supply of oxygen to the brain. Short of manifest signs of lack of oxygen, such as giddiness or faintness, the exaggerated respiratory movements and the high arterial pressure, may be looked upon as directly or indirectly the result of increased sensitiveness of the central nervous system to lack of oxygen. The effect may depend upon greater $H^{\bullet}$ ion concentration of the blood reaching the brain, or may be secondary to the production of acid within the brain itself. It is possible, too, that a larger discharge of adrenaline into the blood-stream may be in some measure responsible for the excessive circulatory response to exercise, since a comparatively slight anoxæmia evokes a greater outflow of adrenaline into the circulation (Kellaway).

Although a man, when taking active exercise at a high altitude, must almost invariably be hampered to some extent by lack of oxygen, the deficiency of oxygen may be almost imperceptible, so long as the pulmonary ventilation continues to increase. But the margin of safety during exercise is so slight that the adapting mechanisms, which maintain the supply of oxygen, soon reach the limit of their effectiveness, and even a trained and

acclimatised man cannot perform as vigorous exercise as at low levels. None the less a trained man is better equipped than an untrained man, assuming both men to be acclimatised, partly because, in all probability, his diffusion-coefficient for oxygen is larger, and partly no doubt owing to the better co-ordination of his muscles during exercise. The greater range of pulmonary ventilation, which seems to exist in the trained subject, must also add to his capacity for exercise by making possible a larger alveolar tension of oxygen, and consequently more rapid diffusion of oxygen into the blood. There is also some evidence that the hæmoglobin value of the blood is normally higher in the trained, than in the untrained, man. This confers a still further advantage on the trained man at a high altitude since, even before acclimatisation has taken place, he will be less liable than an untrained man to suffer from mountain sickness.

Summary.

The characteristic features of exercise at high altitudes are, first, that the circulatory and respiratory changes produced by a given amount of exercise are greater than at low levels, and, second, that the maximum amount of work which a man can perform is less than at low levels. These features are present even in the acclimatised individual, and are very conspicuous in a man suffering from mountain sickness.

Even in the acclimatised subject, the pulmonary ventilation is approximately 50 per cent. greater (and the alveolar tension of carbonic acid is lower) than at low levels, although the reaction of the blood scarcely differs from that at, or near, sea-level. The question whether the greater pulmonary ventilation is brought about primarily by a rise in the C_H of the blood, or by greater excitability of the respiratory centre to a normal chemical stimulus, is discussed.

The greater pulmonary ventilation raises the alveolar tension of oxygen from 35·8 mm. Hg to 52 to 55 mm. Hg (the barometric pressure being 457 mm. Hg), thereby rendering it possible for the blood leaving the lungs to be 85 per cent. saturated with oxygen instead of only 65 per cent. saturated.

After acclimatisation to high altitudes, the output of the heart and the arterial blood-pressure are the same as at low levels,

whereas the pulse is more frequent and the venous pressure is less than at low levels.

At a high altitude, a resting acclimatised man consumes as much oxygen per minute as at low levels. The question whether, not only in the resting man, but also during exercise, the passage of oxygen from the lungs into the blood is effected solely by diffusion, or whether it involves secretory activity on the part of the pulmonary epithelium, is discussed.

During exercise at high altitudes the pulmonary ventilation is exaggerated to such an extent that the tension of oxygen in the alveolar air rises considerably (10 to 15 mm.), thereby allowing oxygen to diffuse more rapidly into the blood. At the same time, the more rapid flow of blood through the lungs tends to lower the saturation with oxygen, and the oxygen-tension, of the blood leaving the lungs. The limit of exercise is reached when the percentage saturation of the arterial blood with oxygen falls to such a level that the tissues can no longer take up sufficient oxygen for their requirements and suffer from lack of oxygen.

CHAPTER XI.

THE AFTER-EFFECTS OF EXERCISE—CIRCULATORY AND RESPIRATORY CHANGES—FATIGUE—THE BENEFICIAL EFFECTS OF EXERCISE.

Circulatory and Respiratory Changes.

MOST of the circulatory and respiratory changes associated with the carrying out of exercise pass off remarkably quickly after the conclusion of exercise, and, at least as regards the output of the heart, the circulation rate, and the blood-pressure, the transition to the resting state may often be completed, even after severe and prolonged exertion, within a quarter of an hour. Immediately on the cessation of exercise, the skeletal muscles send back the blood to the heart less rapidly, and its diastolic volume and output per minute begin to diminish within a few seconds. At the same time there is a sudden relaxation of nervous tension and of muscular tone, and the man stands or sits passive with slack muscles. Further, partly owing to the stoppage of the muscular pump, partly in consequence of lessened activity of the medullary centres, the arterial pressure falls rapidly, and, after a short bout of exercise, it may reach its normal resting level within three or four minutes (Cotton, Rapport, and Lewis). Even after prolonged and severe exertion, the arterial pressure soon falls to, or, for a short time, below, its normal level.

The frequency of the pulse also decreases very rapidly after exercise, and, according to the observations of Cotton, Rapport, and Lewis, it may return to its resting rate within five minutes after the conclusion of a brief period of exercise (Table XXXIX.). It is clear, however, from some of Pembrey's (1909) observations that, after more prolonged exercise, such as running half a mile or more, the pulse-rate may remain above its normal level for an hour, or even longer, after the conclusion of the exercise. In one of Pembrey's experiments the pulse-rate during rest was 68. Immediately after a run of one mile the subject had a pulse-rate of 164, and an hour later it was 82.

Benedict and Cathcart believe that the higher pulse-rate after exercise is correlated with the increased metabolism which is one of the after-effects of exercise, and to which attention was first called by Speck (1892). Benedict and Cathcart showed that the total metabolism of the individual, when measured either by the consumption of oxygen or by his production of heat, might remain distinctly above his ordinary resting level for as long as two to four hours after exercise (Table XL.). Whatever may be its significance, the correspondence between the heightened metabolism and the greater frequency of the pulse after exercise furnishes an additional instance of the close relationship, existing under almost all conditions, between the pulse-rate and the consumption of oxygen by the body. The character of the metabolic changes is not known, though presumably the oxidation of lactic acid, both in the muscles themselves and in other tissues into which it has diffused during exercise, must be one of these changes. An interesting and curious fact, noted by Benedict and Cathcart, is that the increased consumption of oxygen is not accompanied by a larger pulmonary ventilation.

TABLE XL.—(Benedict and Cathcart.)

Metabolism of Subject Lying on a Couch Before and After Work.

	Oxygen Absorbed: c.c. per Minute.	Heat Output per Minute in Calories.	Pulse-rate.
Resting before work	233	1·15	62
Duration of Work—One Hour.			
5 minutes after end of exercise . .	407	1·93	100
54 ,, ,, ,, ,, ,, . .	311	1·46	88
78 ,, ,, ,, ,, ,, . .	306	1·44	85
102 ,, ,, ,, ,, ,, . .	293	1·38	83

The period required for the pulmonary ventilation to return to its normal level after exercise depends almost entirely upon the reaction of the blood at the conclusion of exercise. If little or no lactic acid has been added to the blood, the excess of carbonic acid in the blood is very quickly removed by the lungs. If, however, lactic acid is present in the blood in considerable amount, the hyperpnœa continues until, by the washing out of

carbonic acid, the alveolar tension of carbonic acid falls sufficiently to bring the reaction of the arterial blood to its resting value. At this point the *ratio* $\frac{H_2CO_3}{HNaCO_3}$ is normal, although both the tension of carbonic acid in the blood and the bicarbonate of the plasma are reduced.

This condition, which Hasselbalch terms "compensated acidosis," gradually passes off, and the alkali-reserve of the plasma and the tension of carbonic acid regain their normal level. The restoration of the alkali-reserve is effected partly by the excretion of lactic acid and of acid phosphate by the kidneys, thereby setting free base which can form bicarbonate, and partly, no doubt, by interchange of acid radicles between the plasma and the tissues. Anrep and Cannon have shown that all the tissues have a powerful action in restoring the alkali-reserve. In cases of reduced amount of CO_2 in the blood lactic acid is retained in the blood and thus the alkali-reserve and the P_H is kept down. On addition of CO_2 lactic acid is gradually removed from the blood and the alkali-reserve is restored. This effect is independent of the secretion of urine. After a brief period of moderate exercise, the restoration of the alkali-reserve and the alveolar tension of carbonic acid to their normal resting level takes place fairly rapidly as the following figures show :—

TABLE XLI.—(From Douglas and Haldane.)

	Alveolar Tension of CO_2 in mm. Hg.
Rest	38·2
Just after running 300 yards	45·7
10 minutes later .	35·6
15 ,, ,, .	33·0
25 ,, ,, .	33·8
43 ,, ,, .	37·8
60 ,, ,, .	38·4

Mettenleiter (1915) states that, after prolonged and severe exertion, a slight compensated acidosis, as indicated by a lowered alveolar tension of carbonic acid, may persist for twenty-four hours or even longer.

The temperature of the body falls rapidly after the conclusion of exercise (Fig. 1). Bardswell and Chapman (1911) made the interesting observation that it almost invariably falls to normal

within an hour after exercise, however high it may rise during the course of the exercise. A subnormal temperature for a short time has also been noticed after exercise (Pembrey, 1909). The time taken for the temperature of the body to fall to its resting level, however, naturally varies to some extent with the conditions under which the individual is placed, and, what is even more important, with his general health.

Fatigue.

The changes just described represent the gradual subsidence of the processes invariably associated with the carrying out of muscular work, whereas fatigue is not a necessary result of exercise and appears only when this is severe or prolonged. Fatigue, as it occurs in man, presents two aspects, the one objective and the other subjective. Its outward manifestation is a diminished capacity for doing effective work; its chief subjective symptoms are defined by MacDougall (1908), as (1) a feeling of local tiredness in the active muscles; (2) a general sensation of tiredness; and (3) sleepiness.

The causation of the sensation of fatigue is rather obscure. Joteyko (1904) has suggested that the local feeling of fatigue is the result of impulses set up in sensory structures, such as the muscle spindles, which subserve muscle sense, and that these endings are stimulated by the chemical products of muscular activity. Frumerie (1913) points out that the sense of fatigue is referred at first to the joints and tendons, in which there is no accumulation of these products, and he suggests that it is more likely to be due to prolonged mechanical stimulation of nerve-endings in joints and tendons. If this view is correct, the local sense of fatigue is in no way related to the actual processes taking place within the muscle itself. One difficulty in accepting this suggestion is that, after the same amount of exercise and, presumably, approximately the same degree of mechanical stimulation of nerve-endings, an untrained man may feel fatigued, whereas a trained man is not tired. Possibly, however, the mechanical stimulation of nerve-endings is really greater in the untrained than the trained man, since the latter utilises his muscles more efficiently.

Whatever its origin may be, the sense of fatigue is often a very fallacious index of the working capacity of the body.

Johansson (1902) and, more recently, Frumerie have found that, when a single group of muscles is examined, there is not necessarily any correspondence between the subjective feeling of fatigue and the capacity of the muscles to perform work. A man is not always as tired as he feels, and an almost normal capacity for work may coexist with marked subjective fatigue (Myers, 1918). On the contrary, in certain circumstances, the sensation of fatigue may be slight or absent, although the output of work is falling off. None the less, it is probably true that a subjective feeling of fatigue does, as a rule, indicate a lessened capacity for work, and that, as Pembrey (1909) has suggested, it is a protective feeling, which tends to restrain a man from continuing to perform muscular work when this would react injuriously upon his whole system. This sensation may be temporarily annulled by strong emotion, and, simultaneously, the amount of work which a man can perform may be increased. But, when a man, who is already tired, is spurred on by emotion to fresh effort, the subsequent fatigue, both subjective and objective, is often extreme and out of all proportion to the exertions made.

The only trustworthy measure of fatigue, however, is the diminution in a man's capacity of performing work, and it has long been recognised that, in daily life, the main seat of fatigue after muscular exercise is the central nervous system. Even in ergographic experiments, Mosso long ago stated that "nervous fatigue is the preponderating phenomenon, and muscular fatigue also is at bottom an exhaustion of the nervous system." There appear, however, to be two types of fatigue, one arising entirely within the central nervous system, the other in which fatigue of the muscles themselves is superadded to that of the nervous system.

Every resting muscle possesses a store of potential energy, and the setting free of its energy is intimately bound up with the liberation of lactic acid; hence the possible sources of fatigue of a muscle are, on the one hand, exhaustion of its store of energy, and, on the other hand, clogging of the muscular machine by its metabolic products. Up to a certain point, greater concentration of lactic acid, or strictly speaking $H^{\bullet}$ ions, on the surface of the colloidal system of muscle fibrils increases the tension change and the setting free of energy within the muscle (Mines, 1913).

Beyond this point, the accumulation of acid prevents the complete restoration of the fibrils to their resting condition after each contraction, and the discharge of energy at each successive contraction diminishes.

The restoration of a muscle's store of energy depends partly on the oxidation of lactic acid within the fibres (Hopkins and Fletcher), partly upon the replacement of this acid in some unstable chemical complex (A. V. Hill). Consequently, the accumulation of the lactic acid within the muscle, not only hampers the discharge of energy at each contraction, but implies that its store of energy is diminishing.

In order that the muscle may remove lactic acid almost as rapidly as it is formed, and may renew its potential energy by utilising the crude energy presented to it as fat or carbohydrate, an adequate supply of oxygen is essential. Although this is normally provided during exercise, it is probable, as has been pointed out (p. 25), that, during severe prolonged exertion, the supply of oxygen is sometimes inadequate; in these circumstances, lactic acid is produced much more rapidly than it can be removed by oxidation or otherwise, and the muscles themselves become fatigued. Fatigue, induced in this way, may occur during a boat-race or in long-distance running, for example, a Marathon race, although even here fatigue of the nervous system must play an important and perhaps predominant part, since, under these conditions, the brain is apt to suffer quite as much as the muscles from lack of oxygen.

Another factor, which may contribute to the production of this type of fatigue, is fatigue of the heart itself. Although the occurrence of fatigue of the heart in health is not very clearly established, a temporary lowering of the functional capacity of the heart, induced by fatigue of its muscular fibres, might gradually bring about during exercise an insufficient blood-supply to the skeletal muscles and the brain. The lassitude and disinclination for exertion, often experienced on the day after a strenuous bout of exercise, has also been ascribed to fatigue of the heart as its primary cause.

The type of fatigue in which the muscles, as well as the nervous system, are involved is not the most common type, since, at least in a man accustomed to physical exertion, it demands an intensity and persistence of muscular effort, which is not usually

called for under the ordinary conditions of life among manual workers. In many forms of manual work, there is no evidence, either that the production of lactic acid in the muscles appreciably outruns its destruction, or that the heart fails to meet the needs of the muscular and nervous systems for oxygen; and, in the more strenuous kinds of industrial work, the accumulation of waste-products within the muscles is usually delayed or prevented by the interposition of brief rest periods at frequent intervals. The possibility that, in these workers, a gradual accumulation of waste products in the muscles may occur as the day goes on, and that this may ultimately clog the activity of the muscles, appears to be negatived by the rapidity with which the muscles get rid of these products and with which purely muscular fatigue can disappear. And it seems unlikely that as a rule changes in the muscles themselves take any real share in the production of industrial fatigue.

There is, indeed, good reason to believe that, broadly speaking, fatigue, as it occurs among industrial workers, has its origin entirely within the central nervous system (Report of Health of Munition Workers' Committee, 1918), although this conclusion does not exclude the possibility that occasionally, for example, under abnormally severe stress of very heavy work, fatigue of the muscles themselves may also supervene.

Admitting, however, that, as a rule, fatigue after muscular work is essentially a nervous phenomenon, the view has been advanced (McDougall, McKenzie, Hedvall), that metabolic products of muscular activity are responsible, at least in part, for bringing about fatigue of the central nervous system.

These products are of two kinds, namely, lactic and carbonic acids and metabolites other than acids. Neither lactic nor carbonic acid ever attains during exercise such a concentration in the blood as to be directly toxic, and the only possible way in which, so far as is known, they can influence the nervous system is by altering the reaction of the blood. The rise in the $H^{\bullet}$ ion concentration of the blood during ordinary physical work is so slight that it is difficult to believe that it produces any harmful effect upon the central nervous system, the more so since a trivial rise in $H^{\bullet}$ ion concentration is stimulating rather than depressing. It is conceivable that, during intense exertion, the reaction of the blood might alter sufficiently to disturb the nervous

system as a whole. There is no positive evidence, however, in support of this view, and the efficiency of the mechanisms which regulate the reaction of the blood is so great that such an occurrence seems improbable.

There is some evidence (p. 100) that metabolites, other than acids, are, or may be, formed during muscular activity, and may enter the blood-stream. The evidence of their existence is almost confined, however, to the fact that a neutral extract of muscle may bring about loss of tone of arterioles and possibly of capillaries, when injected into an animal (Vincent and Sheen, Bayliss). Nothing is known as to their chemical nature, nor is there any reason to believe that they have any action upon the central nervous system.

There appears, therefore, to be at present no secure foundation for the belief that the products of muscular activity take any share in bringing about fatigue of the nervous system, either directly or by altering the reaction of the blood. Such evidence as is available points rather to failure of the heart as underlying the comparatively rare cases of extreme nervous collapse described as occurring during intense exertion. Short of actual collapse, the frequent occurrence of giddiness, faintness, or nausea, indicate some degree of cerebral anæmia, and it is not improbable that a still slighter shortage in the supply of oxygen to the brain may accelerate or even induce fatigue.

It is doubtful, however, whether this factor contributes to the production of fatigue under ordinary industrial conditions, and the origin of fatigue, either after exercise or among industrial workers, must be sought in changes taking place entirely within the nervous system, and arising as the outcome of the activity of the nervous system. The real nature of these changes is still almost unknown, but, during prolonged exercise, the steady outflow of impulses to the muscles, the complex neural processes involved in the co-ordination of skilled movements, and the focussing of the attention upon the work, must involve a considerable fatigue of the central nervous system. Hence it is not surprising that, at the end of a day's manual work, most men not only feel tired, but are unequal to further sustained muscular or mental effort.

Industrial Fatigue.

The conclusion that fatigue, as observed among industrial workers, is essentially nervous in origin, is of considerable practical importance. In the first place, it explains the mode of action of many of the factors which influence the occurrence of industrial fatigue. In the second place, it indicates the channels into which practical efforts to prevent excessive fatigue should be directed. There appears to be no doubt (Health of Munition Workers' Committee, 1918), that industrial fatigue is induced much more rapidly by work involving great mental concentration, and by skilled work, than by work which is more or less automatic and makes only slight demands upon the central nervous system. Another factor of great importance is the speed at which the work is performed. Not only is there a rate of work at which the efficiency of the individual is greatest, but also, what is probably the same thing, a rate which is least liable to cause fatigue. The optimal rate of working, as already pointed out (p. 17), is determined mainly by the natural rhythm of the nervous and muscular systems of each worker, and the policy of 'speeding up' of workers is not necessarily an economical one since, by inducing excessive fatigue, it may lessen rather than increase the output of work. Further, not only the sensation of fatigue, but real (objective) fatigue, as measured by output of work, are very greatly modified by psychical processes, some, for example, the feeling of monotony, tending to hasten the onset of fatigue, others, such as 'interest,' improving the working capacity of the individual. Apart from the character of the work performed, the effect of depressing emotions, such as fear and anxiety, on the one hand, or of the stimulus of emulation or monetary considerations, on the other hand, in causing or abolishing fatigue is generally recognised. Finally, the general health of the individual reacts, not only upon his working powers at the beginning of the day, but also upon the rate at which his store of nervous energy becomes depleted and his output of work declines.

Some degree of fatigue at the end of a day's work is a normal event and has no ill-effects, since it quickly passes off. But a characteristic feature of nervous fatigue is that the rapidity with which recovery takes place, if a man rests as soon as fatigue

appears, is only equalled by the slowness of recovery, if he continues working until fatigue becomes excessive. And there is a growing body of evidence that, if the working hours are too long or the conditions under which the work is carried on are unsuitable, the individual does not completely throw off the fatigue induced by each day's work, and a condition of cumulative fatigue is gradually induced, which impairs his working capacity and health. In these circumstances, not only is the output of work diminished, but the mechanical efficiency of the body declines, since even the smaller output is only maintained by an extravagant expenditure of energy.

Tests of Fatigue.

Fatigue to this extent is clearly undesirable in the interests both of the individual and of the community, and, in order to prevent its occurrence, trustworthy means of detecting fatigue in its earlier stages are necessary. The most satisfactory test of a man's capacity for work is his output of work, and, if a man were merely a machine, this test would be quite accurate. The output of work from day to day is influenced, however, by many factors other than fatigue, and these must be taken into account in the application of this test. An extremely familiar illustration of the influence of extraneous factors upon a man's output of work is the difference in output on time-work or on piece-work respectively. In the instance given in Table XLII., the improved output at the end of the week appears to exclude fatigue as a cause of the different output in the two cases.

TABLE XLII.—(From P. S. Florence.)

Output of 17 Girls Drilling Fuses in Successive Weeks.

	(1) Time-work.	(2) Piece-work.
Monday	2266	2567
Tuesday	2050	2959
Wednesday . . .	2037	3143
Thursday . . .	2610	3066
Friday	3188	3291
Average daily output .	2430	3005

It is necessary, therefore, if the output of work is to serve as a reliable index of fatigue, to maintain uniform conditions of work,

and to eliminate individual variations as far as possible by studying the output of groups rather than that of single workers. When these precautions have been adopted, valuable results have been obtained as to the optimal length of the working day for work of varying intensity (Vernon, 1917). Vernon has shown very clearly that, the heavier the type of work, the shorter is the optimal length of the working day, and that, in some of the occupations which he studied, the working hours were too long.

TABLE XLIII.—(VERNON.)

27 Men Sizing Fuse Bodies (Heavy Labour).

	Average Hours of Work per Week.	Average (Relative) Output per Hour.	Output per Week, Hours × Output per Hour.
(1) Period of 6 weeks .	61·5	100	6150
(2) ,, ,, 6 ,, .	51·1	109	5570
(3) ,, ,, 8 ,, .	55·4	122	6759
(4) ,, ,, 3 ,, .	56·2	124	6969

The results shown in Table XLIII. point to the conclusion that, at least in this particular occupation, the maximal working week, consistent with the avoidance of cumulative fatigue, is fifty-six hours. For lighter forms of work, Vernon found that longer hours could be worked without loss, or even with improvement, of output. It is evident, therefore, that the establishment of a uniform length of working day for all classes of manual workers would lead in many cases to inefficiency.

Earlier writers (Galbraith) had called attention to the value of one or more brief rest-periods in each day's work, as a means of lessening fatigue and improving output of work; and their results are confirmed by Vernon.

The evidence, furnished by the group method, goes to show, therefore, that, when properly safeguarded and controlled, the output of work affords a satisfactory test of the conditions under which cumulative fatigue occurs and of the extent to which it is present in an individual.

Since most forms of work involve the activity of the greater part of the nervous system, it might be anticipated that fatigue, induced by a particular kind of work, will extend to the nervous system as a whole. In this connection, Stanley Kent (1916) has

studied the effects of industrial fatigue upon the readiness with which the individual reacts to certain sensory stimuli, and upon his acuity of sight and of hearing. His results, as a whole, accord with those obtained by other methods, and indicate that, as fatigue develops, the nervous system becomes less responsive, and reacts less readily, to afferent impressions. But the subjective element enters to a considerable extent into such tests as that of acuity of vision or of hearing; and, although, serving to indicate its presence, these tests do not necessarily give in every case a very accurate measure of the actual *degree* of fatigue.

The Beneficial Effects of Exercise.

In addition to the after-effects just described, regular exercise reacts, as every one knows, upon the whole life of the individual, since it almost always promotes, and in many people is necessary for the maintenance of health, this being understood to mean not only that the various organs of the body are working normally, but also that the activities of the body are so co-ordinated as to bring about the highest efficiency of both mind and body.

The means by which exercise brings about these beneficial effects are numerous and not altogether clear. In all probability, one factor is the more rapid circulation rate and the larger flow of blood and lymph through the muscles, the heart, and the brain. This will favour the more complete combustion of metabolic products and the removal of waste products, and will provide a more abundant supply of nutritive material for these organs. This factor appears, however, to be rather a subsidiary one. Violent emotion, for example, also leads to a greater flow of blood through the heart, brain, and muscles, yet few would maintain that repeated outbreaks of intense emotion are advantageous to the individual. The real value of exercise probably lies mainly in its effects upon the metabolism of the tissues themselves, and the vascular changes are useful chiefly in so far as they assist more active metabolism. The speeding up of the metabolic activity of the body, which is a characteristic feature of exercise, involves the more rapid utilisation of reserve nutritive material and probably also the more complete oxidation of these materials within the cells. In this way it prevents the cells from being clogged

with substances awaiting combustion, or with waste-products awaiting removal, and enables the lamp of life to burn more brightly.

During exercise the additional energy provided by the increased chemical activity of the tissues is expended as work or heat. But, after the exercise is over, the metabolic activity of the tissues, stimulated by the exercise itself, appears to be diverted to repairing and building up the tissues. From this point of view, exercise is particularly important in youth, since it is indispensable for the adequate development of the skeletal muscles, the heart, and the lungs, and, in a lesser degree, that of other structures in the body; and the almost incessant activity in a young child is a valuable asset for its normal growth and health. How functional activity brings about growth, whereas disuse leads to atrophy, is unknown, and the nature of the processes underlying hypertrophy is still unexplained. Bradley and Taylor (1916) have put forward the view that the $H^{\bullet}$ ion concentration within the tissues themselves is an important factor in bringing about building up or breaking down of the tissues as the case may be. They have adduced evidence that, when the reaction of the tissues swings towards the acid side, reserve protein is transformed into 'available' protein and that this undergoes autolysis. They regard it as possible that a larger blood-supply, and a more complete removal of acid products from the cells, may reverse this process, and may lead to the laying down of reserve protein and, therefore, to growth of the cell. This view is very suggestive, since the tissues are extremely susceptible to the reaction of the medium in which their activities are carried on; and it seems possible that slight changes in reaction, induced by the ebb and flow of acid and basic radicles into and, out of, the tissues during and after exercise, may bring about a shifting of the point of equilibrium between autolysis on the one hand and synthesis of new tissue on the other hand.

The influence of exercise upon the digestive and nervous systems is also an important element in maintaining health. The proneness of sedentary workers to suffer from dyspepsia is proverbial, and regular exercise aids digestion, partly by improving the appetite, partly by assisting mechanically the passage of food along the digestive tract, and partly by its general stimulating influence upon metabolism. Its effect upon the central

nervous system is less direct. Nevertheless, by diverting the attention into fresh channels and eliminating, for the time being, the ordinary activities of the mind, it reacts beneficially upon the mental attitude and indirectly upon the physical state of the individual; and this, at least in later life, is one of its most valuable effects. For this reason, the character of the exercise, and the circumstances and surroundings in which it is carried out, determine in some measure its beneficial effect upon the individual.

In some or all of these ways, exercise improves the efficient working of the body and, what is really its counterpart, the sense of well-being and of vigour which characterise a healthy man, and both current belief and direct evidence suggest that it is conducive to long life. Anderson observed that, in Yale University, the mortality was lower for athletes than for non-athletes. Meylan, who made a statistical study of the duration of life in a large number of Harvard oarsmen, found that the average length of life in these individuals was several years longer than the general average of the community. In drawing conclusions, however, from observations of this character it must be remembered that, in a sense, these oarsmen were selected lives since, to excel as an athlete, a man must possess from the outset a healthy body and a vigorous constitution.

Summary.

As a rule the circulatory and respiratory changes associated with exercise rapidly pass off after the cessation of exercise, whereas the return of the body to the resting state, as regards its metabolism, is more gradual.

Fatigue after exertion is characterised by a diminished capacity for performing work, this being usually accompanied by certain subjective sensations. The sensation of fatigue does not necessarily correspond with the actual fatigue of an individual, when this is measured by his capacity for work.

There are two types of fatigue, one originating entirely within the central nervous system, the other arising partly in the nervous system and partly within the active muscles. The former is of common occurrence, whereas the latter occurs comparatively infrequently. Industrial fatigue is usually of the first type.

There is no clear evidence that the products of muscular activity take any part in bringing about fatigue of the central nervous system.

Exercise appears to be beneficial mainly in so far as it stimulates the metabolic activity of the tissues, thereby promoting their functional efficiency. The better blood-supply, the improvement of digestion and other changes are also advantageous, since they favour the metabolic activities of the tissues themselves.

CHAPTER XII.

THE AFTER-EFFECTS OF EXERCISE (*continued*)—EFFORT-SYNDROME—OVER-STRESS OF THE HEART.

THERE is no direct evidence that, provided a man is physically sound and in good health, exercise, however severe, is ever harmful or followed by serious after-effects. From time to time cases crop up in which serious ill-effects follow, and are attributed to, severe exercise. After a long cross-country run, for example, an individual, previously presumed to be healthy, may suffer, not merely from temporary collapse but from prolonged impairment of health. In some of these cases, careful investigation often reveals the existence of some hitherto unsuspected bodily defect or disease; in others it is found that the individual has recently suffered from some infective disease.

Whatever may be the ætiological factors, the harmful after-effects of exercise when they occur, and this is comparatively seldom, can almost always be referred directly or indirectly to the heart. It is not surprising that this should be the case, since one conclusion which stands out clearly as a result of the preceding discussion is that the range of a man's ability to take exercise is usually determined by the functional capacity of his heart, and that the stress of exercise as a rule falls more heavily on the heart than on any other part of the body. Yet not only is the heart normally equal to the demands placed upon it, but, in a perfectly healthy man, even the most intense exertion of which he is capable has no harmful effect upon his heart. Clinical experience as a whole confirms this view, and may be summed up in Sir Clifford Allbutt's statement (1909) that "the importance of muscular effort as a factor in cardiac injury has been much exaggerated. In the sound adult organism the effects of physical stress on the heart are promptly counteracted by equilibrating machinery."

Effort-Syndrome.

There is abundant evidence, however, that, under certain conditions, severe or unwonted exercise may seriously impair the functional power of the heart, and that the lessened efficiency of the heart may then persist for weeks or months. This condition may arise suddenly as the result of a single bout of exercise in a sedentary individual or, as is more usual, may be developed gradually during the process of physical training or during a prolonged period of severe physical effort. Owing to the frequency of its occurrence among soldiers undergoing training or on active service, this condition has been termed 'soldier's heart,' although the manifold causes of this condition were clearly indicated by da Costa (1871). Moreover, as Lewis (1917) has pointed out, it is by no means confined to soldiers, and Lewis prefers to call it 'effort-syndrome,' since its characteristic symptoms appear chiefly during exercise.

The essential features of effort-syndrome are, first, lessened ability to perform muscular work, and, second, an exaggeration of the normal response of the circulatory and respiratory systems to exercise. If, for example, a healthy man and a patient suffering from effort-syndrome perform the same amount of exercise, the dyspnœa is greater and the pulse-rate and blood-pressure are higher in the patient than in the healthy man. Further, the pulse returns to its resting level after exercise much more slowly in cases of effort-syndrome than in health. When the patient is resting the pulse-rate and respiration are often normal, though some increase in pulse-rate and some degree of hyperpnœa may be present. Exhaustion, headache, palpitation, tachycardia, precordial pain, giddiness, and fainting are common.

The condition exhibits all grades of severity, some patients displaying symptoms only when subjected to severe exercise, whereas, at the other end of the scale, are those who, even in bed, are breathless and have a frequent pulse.

The extremely varied ætiology of effort-syndrome at once suggests the possibility that these cases are not all of one type and that the morbid, or at least abnormal, process, responsible for the symptoms grouped under this title, is not the same in every case. Indeed it is possible that each of the explanations offered as to the cause of effort-syndrome may be true for particular

cases. In 'gassed' men, for example, the symptoms could be accounted for by the existence of some change in the pulmonary epithelium, not necessarily of a gross nature, but sufficient to lessen the rate at which oxygen can diffuse into the blood. Again, many patients with effort-syndrome display marked hyper-excitability of the central nervous system; and over-activity of the medullary centres, either as a direct result of greater excitability of these centres, or brought about by exaggerated impulses from the higher parts of the brain, would explain the excessive circulatory and respiratory response to exercise exhibited by these patients. The view that abnormal excitability of the nervous system is the primary cause of effort-syndrome, and that the condition is purely nervous in origin, has been accepted by some writers, who apparently hold that effort-syndrome, either arises as the outcome of some shock to the nerve-centres in a neurotic subject or is simply a special manifestation of neurasthenia (Abrahams).

Although this may be the true explanation of some cases of effort-syndrome, there is evidence that, even among soldiers on active service, many of the patients suffering from effort-syndrome are in no way neurasthenic (W. E. Hume). Moreover, effort-syndrome occurs frequently in civil life under conditions in which a purely nervous origin can almost certainly be excluded. Lewis considers that as a rule over-excitability of the nervous system is not the primary factor in the causation of the symptoms of effort-syndrome, but is merely a manifestation of an underlying generalised disorder of metabolism or of actual intoxication of bacterial origin. He concludes that the symptoms may be caused "either by toxic products of bacterial origin or perhaps more often by the products of faulty metabolism induced by infectious disease." In default of any evidence of organic defect or disease of the myocardium, Lewis appears to regard the metabolism as a whole as being thrown into disorder, thereby bringing about certain changes in the body which are immediately responsible for the symptoms manifested by these patients. The arguments adduced in support of this view are, first, the close relationship between bacterial infection and effort-syndrome, second, the diminution or disappearance of symptoms when the source of infection is removed, and, third, the presence of certain changes in the blood and urine of the patients.

The belief that the character of the blood is altered in effort-syndrome rests almost entirely on the evidence brought forward by Barcroft, Cotton, Lewis, Milroy, Dufton, and Parsons (1916) that the extreme breathlessness on slight exertion, which is so characteristic of this condition, is due to a deficiency of buffer salts in the blood. Examining *in vitro* the blood of such patients, they found (1) that, when all the carbonic acid was shaken out of the blood, its reaction became slightly more alkaline than that of normal blood; (2) that, when it contained the amount of carbonic acid normally present in the body, it was just on the acid side of normal; (3) that any further addition of carbonic acid increased the $H^{\bullet}$ ion concentration of the blood to an abnormal degree. The reaction of the blood was apparently determined by noting the form of its dissociation curve in the various conditions just mentioned. In one instance these observations were confirmed by direct determination, by means of the gas electrode, of the effect upon its reaction of adding carbonic acid to normal blood and to that of patients. Further, it was found that, when small amounts of di-sodium phosphate and sodium bicarbonate were added to blood obtained from the patients, this behaved like that of a normal person as regards the change in its reaction produced by the addition of carbonic acid.

The deduction drawn from these experiments is that, owing to the deficiency of buffer salts, the normal passage of lactic and carbonic acids into the blood from the active muscles during exercise increases the $H^{\bullet}$ ion concentration of the blood, and therefore the respiratory movements, to an abnormal extent. Barcroft and his co-workers do not suggest, however, that a deficiency of buffer salts is responsible for the circulatory phenomena of effort-syndrome.

It is extremely difficult to reconcile this conclusion with the current view of the means by which the reaction of the blood is controlled and of the part played by the so-called buffer salts in determining its reaction. It has been shown (p. 32) that the reaction of the blood is represented by the equation $C_H = K\frac{H_2CO_3}{NaHCO_3}$, and, as Bayliss has pointed out, the only buffer salt, and indeed the only effective buffer substance of any practical importance, in blood-plasma is sodium bicarbonate. It is clear, therefore, that, when carbonic acid is removed from the blood, a

deficiency of sodium bicarbonate would render the blood less alkaline than normal blood, and that the observation of Lewis and his colleagues is not merely incompatible with a deficiency of buffer salts but suggests that the blood of their patients contained more bicarbonate than usual. It is in any case almost impossible to imagine how a deficiency of buffer salts could render the patient's blood more alkaline in the absence of carbonic acid, and more acid in the presence of carbonic acid, than normal blood.

Again, Drury has found that the tension of carbonic acid in the alveolar air of cases of effort-syndrome during rest is within the normal range (an observation which Bainbridge has confirmed). Since, in Bainbridge's cases, the patients were not breathless when resting, the $H^{\bullet}$ ion concentration of their blood must have been normal, unless the respiratory centre was less sensitive than usual, and, consequently, the third term of the equation, namely, the bicarbonate of the plasma must also have been normal in amount. That this is actually the case in some patients has been shown by direct measurement of the plasma-bicarbonate by the Van Slyke method. Bainbridge and Canti examined the blood of three patients,[1] who were resting in bed and not breathless, and obtained normal figures for their plasma-bicarbonate.

TABLE XLIV.—(Bainbridge and Canti.)

Case.	Volume of CO_2 obtained from Plasma.
1	64·2
2	61·3
3	62·3

The normal range is from 55 to 75 volumes. One control yielded 62 volumes of CO_2.

The conclusion appears inevitable that the blood of patients suffering from effort-syndrome is not lacking in sodium bicarbonate, and that the observations of Lewis, Barcroft, and their co-workers must be capable of some other interpretation than

[1] Dr. J. H. Drysdale very kindly allowed us to examine these patients who were under his care.

that which they offer. It is perhaps significant that the method adopted for determining a change in the reaction of the blood is an indirect one, namely, the affinity of hæmoglobin for oxygen. It has been pointed out earlier (p. 40), however, that the Barcroft-Peters curve which expresses the relationship between the affinity of hæmoglobin for oxygen and the $H^{\bullet}$ ion concentration of the plasma is not constant for all individuals or under all conditions. It is possible, therefore, that, in patients suffering from effort-syndrome, the normal equilibrium between the reaction of the red cells and that of the plasma may be disturbed.

The Circulatory Hypothesis.

In view of the evidence that the buffer salts, or at least, the bicarbonate, of the blood are not deficient, it seems necessary to look elsewhere for an explanation of the exaggerated circulatory and respiratory response to exercise which is so characteristic of effort-syndrome. Accepting Lewis' view that the primary cause of the symptoms is either toxic products of bacterial infection or products of faulty metabolism induced by infectious disease, there is clearly more than one point at which such products might exert their injurious influence. And the possibility at once presents itself that these may originate in some primary defect or impairment of the adjustments of the circulatory system normally occurring during exercise. From this point of view the following tables, which illustrate the effect of exercise upon the pulse-rate in the trained man, the untrained man, and the patient with effort-syndrome, are suggestive :—

TABLE XLV.—Pulse-Rate per Minute in Effort-Syndrome. (Meakins and Gunson.)

	Pulse-rate during Rest.	Just after Exercise.	Time of Decline.
Average figures—			
(1) 10 Healthy subjects . . .	75	109	1 minute
(2) 18 Patients presenting no material symptoms after exercise . .	79	120	1 ,,
(3) 21 Patients presenting symptoms after exercise	99	150	5 minutes

The exercise consisted in climbing at a brisk walk a group of 27 steps. Time of decline = time taken for return of the pulse-rate to within 5 beats of the resting value before the exercise.

TABLE XLVI.—Healthy Men. Pulse-Rate Before and After Exercise (¼ Mile Run). (Pembrey and Cook.)

	Rest.	Just after Exercise.	Counted during 1st Minute.	Counted in First Four Successive Periods of 15 seconds.			
				1	2	3	4
Trained . .	76	160	135	40	35	31	29
Untrained . .	80	180	165	45	41	40	39

It is clear that, as regards their response to exercise, a man suffering from effort-syndrome bears almost the same relation to a healthy untrained man that the latter does to a trained man. The same relationship appears to hold good for the blood-pressure and probably also for the pulmonary ventilation. Every gradation exists between the fully trained man on the one hand and the patient suffering severely from effort-syndrome on the other hand; and, whereas the trained man is more efficient than the average man, the patient with effort-syndrome is less completely equipped than the average man for the stress of ordinary life. It seems justifiable, therefore, to apply to the patients, in considering the causation of their symptoms, the conclusions which have already been reached as to the effect of training upon the circulatory response to exercise.

The trained man takes exercise with less circulatory and respiratory stress than the untrained man, chiefly because of the greater contractile power of his heart, and the suggestion naturally presents itself that, in the patient who displays during exercise the exaggerated respiratory and circulatory response known as effort-syndrome, the contractile power of the heart is less than normal.

Alike in the trained man, the untrained man, and the patient with effort-syndrome, the heart possesses only two means of increasing its output in response to a larger venous inflow during exercise. These are dilatation of the heart, with a corresponding increase in its contractile power, and greater frequency of the beat. If the nutrition of the heart is normal, and the diastolic length of the fibres is the same in each case, the heart of the trained man contracts more strongly at each beat than that of the untrained man solely because its fibres are larger and more numerous, or in other words, because it is more muscular. The

stronger contraction enables the heart to empty itself more completely, and to maintain a given output with a slower pulse-rate, than the heart of the untrained man.

In the same way if, either because it is less muscular or because the nutrition of its fibres is impaired, the contractile power of a man's heart becomes less than that of the heart of a healthy untrained man, then, assuming the same venous inflow in the two cases, the feebler heart will discharge less blood into the aorta at each beat than the normal heart. In order to maintain the same output per minute as the normal heart, the feebler heart must either beat more frequently or dilate more than the normal heart. The less its contractile power the greater will be the dilatation of the heart and the frequency of the pulse necessary to bring about a given output per minute; and, if it is very feeble, the heart, even on slight exertion, may keep up a normal output only when it is dilated almost to its physiological limit in order to obtain its maximum contractile power and when it is beating abnormally frequently. Hence, in a group of individuals, performing the same amount of muscular work, the extent to which the heart dilates and the pulse accelerates in each individual is a measure of the contractile power of his heart, provided that extraneous emotional factors are excluded. By the application of such a test, a trained man could be picked out from among a group of untrained men, and this test is actually used, as regards the pulse-rate, as one method of ascertaining the severity of the condition of effort-syndrome.

Observations made by the orthodiagraphic method led Lewis to the conclusion that, in his patients, the size of the heart during rest was certainly not greater, and on the average slightly less, than that of healthy young individuals, although he qualifies this conclusion by noting, first, that in the patients the pulse-rate was rather frequent, this tending to reduce the size of the heart, and, secondly, that most of the patients had been in a sedentary occupation for the greater part of their lives. Using the same method, Meakins and Gunson were unable to find any change in the size of the heart during exercise, although the normal decrease just after exercise was absent in severe cases of effort-syndrome. The limitations of the orthodiagraphic method have already been discussed (p. 64); and, since Lewis apparently regards a difference of less than 5 mm.

as being within the limits of experimental error, his observations are not incompatible with the conception of effort-syndrome, now under consideration.

In a healthy man, the co-ordinating mechanisms concerned in bringing about the normal correspondence between the degree of muscular activity and the pulmonary ventilation and circulation are extremely efficient; and it is probably only during intense exertion that an inadequate supply of oxygen to the brain and other tissues becomes an active factor in intensifying the respiratory and circulatory changes accompanying exercise. If, however, the contractile power of the heart is impaired, its efficiency as a pump falls off; and inefficiency of the most vital part of the mechanism concerned in supplying oxygen to the body during exercise, not only lessens the amount of work which a man can perform in a given time, but throws into disorder the co-ordination normally maintained between the demand for and the supply of oxygen. In consequence, the supply of oxygen to the active organs during exercise never quite keeps pace with the needs of the body; and, either because the medullary centres are not fully supplied with oxygen, or because the oxidation of lactic acid in the muscles falls abnormally short of its production and the $H^{\bullet}$ ion concentration of the blood becomes excessive, the activity of the respiratory and vaso-motor centres is exaggerated and the pulse accelerates still further.

According to this conception, the exaggerated circulatory and respiratory response, observed not only in effort-syndrome, but also during exercise at high altitudes, possesses the same significance, since it is the only means of preserving the normal relationship between the demands of the active organs for oxygen and the supply of oxygen, and of preventing a serious deficiency in the supply of oxygen. If this explanation of their causation is accepted, the symptoms characteristic of effort-syndrome merely furnish a further illustration of the idea, underlying all the preceding discussion, that, in the last resort, the requirement of the tissues for oxygen brings into action the mechanisms concerned in meeting that need.

Ætiology of Effort-syndrome.

What, then, are the grounds for believing that, in patients with effort-syndrome, the nutritive condition of the cardiac muscular

fibres, and hence the power of the heart to develop energy, is impaired or at least inferior to that existing in the normal heart?

The most important predisposing cause of the condition is infection. Lewis considers that, in at least 50 to 60 per cent. of his cases, "infectious disease may be held to play a chief part in promoting the disease (effort-syndrome) in its initial stages." If already present, the condition is exacerbated by an inter-current infection. The tendency of infective disease to injure the heart is notorious, the damage being often manifest as cloudy swelling, fatty change, or cellular infiltration; and there can be no doubt that, short of these relatively gross changes, the nutritive condition, that is to say, the metabolic activity of the heart-muscle, may be gravely impaired. In the case of the heart, as of every organ, impaired nutrition means lessened functional capacity, and this may arise either from a smaller power to store up potential energy or from an inability to convert this effectively into kinetic energy. In these circumstances the contractile power of the heart, or, in other words, the energy set free at each beat, will be abnormally small.

Extremely little is known concerning the nature of the metabolic changes which underlie what is termed the nutritive condition of an organ. But it is conceivable, for instance, either that the power of the muscle-fibres to take up into their substance the oxygen reaching them by diffusion may be impaired or that the normal oxidative processes may be carried out less completely or less rapidly. Some colour is lent to this suggestion, first, by the well-known action of many bacterial toxins in diminishing oxidative changes in the body, and, second, by the evidence of Krogh and Lindhard that the efficiency of the oxidative mechanism for lactic acid in muscle varies in different individuals. A change of this kind, assuming it to occur in cardiac muscle, would at once disturb the normal relationship between the production and destruction of lactic acid; and during exercise, though not necessarily during rest, the heart would tend to become rapidly fatigued and clogged by the accumulation of lactic acid, and possibly other metabolic products, within its fibres.

The readiness with which the contractile power of the heart is affected by disturbance of its nutrition may be observed under experimental conditions; Starling found that, when the heart

was fatigued or its supply of oxygen not quite adequate, its contractile power rapidly diminished. It is easy to understand, therefore, how an intoxication of bacterial origin, and perhaps especially a chronic intoxication, may bring about an impairment of the nutritive state of the heart muscle, though, unless the individual takes an amount of exercise to which the heart is unaccustomed, this may not only escape notice, but may eventually disappear, since the effect of infection upon the nutrition of the heart is usually transient.

Apart from infection, the large proportion of cases of effort-syndrome occurring amongst men normally engaged in sedentary work is very striking. Lewis notes that many of the patients found by experience that they were always unable to take violent exercise, although they were quite well when engaged in sedentary work. One is tempted to suggest that in these patients the nutritive level and inherent power of the heart muscle (and also their skeletal muscular development) are below the average just as that of other men is believed to be above the average, and that, in many cases, the patient with effort-syndrome, like the athlete, is born and not made. Under the ordinary conditions of life these men pass muster, but, when brought to the test of active physical training under military conditions or when subjected to unwonted stress, they fall into the hands of the physician and are labelled effort-syndrome.

Many of Lewis' patients, however, had adopted a sedentary life from choice and not from necessity; and it may be that, as Lewis suggests, a sedentary life in itself provides the conditions which predispose to effort-syndrome. If this is the case, a sedentary life will naturally accentuate any inborn deficiency in the contractile power of the heart.

It appears probable, then, that this condition is not a disease but a disability, which may be temporarily produced by infection (and by other means), or may be present from birth, or may be the outcome of a habitually sedentary existence. That its primary cause is impairment of the contractile power of the heart muscle is suggested not only by the reasons already advanced but by the fact that it is most effectively treated by carefully graduated exercise carried out under proper supervision. This has long been an accepted form of treatment in cases of myocardial defect.

Over-stress of the Heart.

Whatever may be the case in effort-syndrome, there is no doubt that, in some circumstances, a single bout, or repeated bouts, of violent exertion may be followed not only by prolonged, or even permanent, inability to take active exercise, but also by pathological dilatation of the heart or other signs of myocardial defect. This condition, often termed over-stress of the heart, may arise in young subjects when exercise is taken during the course of, or shortly after the cessation of, an infection, or in middle life when the heart is presumed to have lost its early vigour. The character of its predisposing causes indicates that some lowering of the nutritive condition of the heart muscle is a prerequisite to its occurrence, and it seems clear that severe exercise, though not injurious to a healthy heart, may actually damage the heart when this is already less efficient than a normal heart.

Many writers consider that the damage to the heart consists, in the slighter cases, in fatigue and loss of tone of the cardiac muscle, whereas, in the severe cases of over-stress, there occurs an actual strain of the muscle fibres, these being mechanically stretched beyond the limits of their elasticity. Such a strain, by altering the molecular condition of the fibre, permanently changes its molecular structure (Clifford Allbutt).

On this view, fatigue and loss of tone result in passive but remediable dilatation, whereas the altered molecular state of the strained fibres leads to irremediable dilatation.

In this connection the expression "loss of tone" is used by clinical writers (Clifford Allbutt, J. Mackenzie) to mean loss of diastolic tone. The evidence previously brought forward (p. 58) goes to show, however, that the normal heart does not possess diastolic tone; and, since the heart cannot lose what it has never possessed, loss of diastolic tone is not the cause of dilatation of the heart. The essence of the recent work of Patterson, Piper, and Starling, at least as regards its application to such conditions as that under consideration, is that in itself dilatation of the heart is not harmful but advantageous. The fatigued heart dilates, not because its muscular wall yields more easily before the inflowing blood during diastole but because its contractile power is weakened and only by dilatation can its contractile power,

be increased in accordance with the law of the heart. But the term "tone," as applied to the heart, does acquire a definite meaning if it is used to express the amount of energy which the cardiac fibres can develop during *systole*, or, in other words, the functional capacity of the heart for any given diastolic volume. According to this definition, loss of tone means feebler contraction of the cardiac muscle during systole; and the atonic heart dilates in order to develop more energy, since dilatation increases, instead of lessening, the power of the heart to carry on the circulation.

The milder forms of heart-stress (remediable dilatation) may, therefore, be fully explained as being the outcome of extreme and prolonged fatigue, and hence of diminished contractile power, of a heart already predisposed to fatigue by the ill-effects of recent infection, or of the other causes already considered, upon its nutritive condition.

The occurrence of molecular alteration of the muscular fibres as a result of mechanical stress is obviously very difficult either to prove or to disprove. But the pathological dilatation of the heart, which may be a sequence of exercise carried out under the conditions already described, clearly implies the existence of some change—not necessarily structural—in the muscle of the heart. The suggestion that strain of the muscular fibres, by altering their elastic state, allows the heart passively to dilate to excess, may appear to provide an adequate explanation of the dilatation and at the same time to place it in the category of pathological rather than physiological dilatation.

This hypothesis fails to take account of the facts that, unless the pericardium has given way, the mechanical efficiency of the heart is in no way lessened when its fibres are stretched during diastole to the limit allowed by the normal pericardium, and that the mechanical stress imposed upon the heart during exercise is not necessarily greater in the man who develops symptoms of over-stress than in the man whose heart remains normal. It might be argued that a degree of stretching, which would not harm normal cardiac muscle, might damage an ill-nourished heart. But, since the normal heart is completely relaxed during diastole, and its filling even to the physiological limit depends upon the venous inflow, any loss of elasticity on the part of its fibres would not influence its diastolic filling.

The hypothesis that intra-molecular changes in its fibres lead to dilatation of the heart by allowing it to fill to an abnormal extent during diastole under a given venous pressure appears, therefore, to be incompatible with the principles which underlie the filling of the heart. Any such change, assuming it to occur, must disturb not the filling but the emptying of the heart, since it lessens the ability of the cardiac muscle to develop energy or to transform energy into effective mechanical work. None the less, it seems quite conceivable that some subtle alteration in the structure of the delicate muscular machine might take place as a result of mechanical stress, and that such a change might interfere with the normal transformations of energy of which visible contraction is the outward sign. It is equally possible, however, that the stress might throw out of gear the chemical rather than the physical basis upon which this transformation of energy depends.

Whether structural or chemical in origin, the essential feature of over-stress is clearly lessened contractile power of the heart. The less its contractile power, the more must the heart dilate in order to obtain the energy necessary to maintain its output. If the power of the heart sinks to a level at which it can barely maintain the output necessary during rest, the heart will remain fully dilated long after exercise, and, under the steady pressure of the heart on the pericardium, the latter will give way. Further dilatation of the heart is then possible, but, with the yielding of the pericardium, the heart has crossed the border-line between physiological and pathological dilatation, since its mechanical efficiency has begun to decline.

It appears probable, then, that the principles, which underlie the working of the normal heart, also hold good for the behaviour of the heart during over-stress; and the application of these principles to other forms of cardiac disease, involving the myocardium, would probably be very fruitful since, as Sir Clifford Allbutt has said, "To go with physiology as far as we can is not only to tread so far on relatively firm ground, but also to provide a discipline and a preciser terminology."

Summary.

There is no evidence that, in a perfectly healthy man, even the most intense exertion produces any harmful effect upon the heart.

The term effort-syndrome is applied to a condition arising as the result of severe exercise or in the course of physical training, and characterised by a lessened capacity to perform muscular work and by exaggeration of the respiratory and circulatory changes normally occurring during exercise.

The view that the respiratory symptoms are dependent upon a deficiency of buffer salts in the blood in patients suffering from effort-syndrome is discussed, and reasons are given for not accepting this view.

The conclusion is reached that, in effort-syndrome, the contractile power of the heart is below the average, that, for this reason, either the muscles or the nervous system suffer from a slight deficiency of oxygen during exercise, and that the exaggeration of the respiration, pulse-rate, and blood-pressure is the outcome of an inadequate supply of oxygen to the active tissues.

The most important ætiological factors which cause effort-syndrome are, first, infective disease, and, second, a sedentary mode of life.

If the nutritive condition of the heart is impaired, violent exertion may be followed, not only by prolonged inability to take severe exercise, but also by pathological dilatation of the heart or by other signs of myocardial defect. This constitutes over-stress of the heart. The primary change in over-stress of the heart is lessened contractile power of its fibres, this being due in the milder cases to fatigue of the cardiac muscle, and in the more severe cases possibly to some chemical change in the fibres which lessens their power to develop energy. The dilatation of the heart is a secondary compensatory process, which enables the heart (in accordance with the law of the heart) to increase its contractile power by greater diastolic length of its fibres. It is not due to loss of diastolic "tone," since such tone does not exist even in the normal heart.

If the pericardium yields, thereby allowing the heart to dilate still further, the dilatation becomes pathological, because it is then accompanied by lowered mechanical efficiency of the heart.

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