THESIS

ON

THE MEASUREMENT OF EXERCISE TOLERANCE

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

by

E. A. HARRIS

M.B., Ch.B. (Liverpool), M.R.C.P. (London)

UNIVERSITY OF EDINBURGH

MAY, 1957.

EX BIBL UNIV EDINBURGEN

CONTENTS

	Page
INTRODUCTION	1
Chapter 1	
GENERAL CONSIDERATIONS	3
Form of exercise	5
Duration of exercise	6
Intensity of exercise	9
Correction of data	10
Chapter II	
PULMONARY FACTORS IN EXERCISE	13
Ventilatory volume	13
Respiratory frequency	18
Maximum breathing capacity	19
Chapter III	
THE RESPIRATORY DEAD SPACE	22
Definitions	25
The alveolar factor in the Bohr equation	27
The dead space in exercise and hyperventilation	31
"Series" and "parallel" dead space	36
The dead space in pulmonary emphysema ..	39
Classification of dead space	41
Chapter IV	
THE MEASUREMENT OF DEAD SPACE DURING EXERCISE	43
The respiratory quotient of end-tidal samples	45
The dead space for carbon dioxide and oxygen	46
End-tidal sampling methods	47
Chapter V	
CIRCULATORY FACTORS	48
Cardiac output	48
Heart rate	49
Arterial blood pressure	57
Chapter VI	
OTHER FACTORS IN O_2 AND CO_2 EXCHANGE	59
Pulmonary diffusing capacity	59
Blood vessels	59
Tissue enzymes	60
O_2 and CO_2 carrying capacity of blood ..	60
TESTS OF OVERALL EFFICIENCY	
Oxygen debt	61
"Physical fitness index"	63

Page

Chapter VII

THE PRESENT INVESTIGATION 64
Subjects 66
Procedure 68
Methods 72
Units 76

RESULTS

Chapter VIII

MECHANICAL EFFICIENCY 77

Chapter IX

THE COMPOSITION OF END-TIDAL AIR 79

Chapter X

VENTILATION 83
Healthy students 83
The effect of increasing age 90
Ventilatory behaviour in emphysema 93
Standardised ventilation 96
Discussion 96
Summary and conclusions 99

Chapter XI

HEART RATE 101
Course of heart rate during and after exercise 101
The heart rate during the steady state .. 106
Indices of performance based on heart rate during exercise 113
The recovery heart rate 115
The heart rate during early exercise .. 116
Summary and conclusions 117

Chapter XII

CONCLUDING REMARKS 119

ACKNOWLEDGMENTS 122

APPENDIX I
CARDIOTACHOMETER 123

APPENDIX II
APPARATUS FOR COLLECTING END-TIDAL AIR SAMPLES 127

APPENDIX III
SYMBOLS 129

TABLE OF RESULTS

INTRODUCTION

The assessment of a patient's capacity for physical exertion is an everyday requirement in clinical medicine. While much information about this can be obtained from a carefully taken history, the latter can never be objective, being coloured by the intelligence and personality of both patient and medical attendant. Most physicians will recall occasions on which, after a long and frustrating talk with a patient, they have been little wiser as to the degree of disability present, and even in doubt as to whether the patient's exercise tolerance is impaired at all.

Current textbooks of medicine (for example Beaumont, 1953; Chamberlain, 1951; Christian, 1947; Cecil & Loeb, 1951; Conybeare, 1954; Davidson, 1954; Garland & Phillips, 1953; Harrison, 1954; Musser & Wohl, 1951; Price, 1956) give no description of any objective test of exercise tolerance, and little indication that a history alone is not enough. Cardiology textbooks usually make brief reference to the use of exercise tests. Scherf & Boyd (1948) are uncompromising; "Medicine possesses no satisfactory test for estimating the functional capacity of the heart...All of the innumerable tests described...have little value." Evans (1948) gives details of a step-test, without reference to its source, and concludes with the opinion that it is worthless: "A patient with heart disease often performs the test satisfactorily...a healthy subject will frequently show a poor response." Friedberg (1950) refers to a few tests and discusses the principles underlying them. He is reserved in his opinion of their value: "The clinical

history is often a better guide." Levy (1951) uses the pulmonary oxygen extraction percentage as a guide to the state of the cardiac output in mitral stenosis and in some congenital heart disorders. White (1951) writes that when dyspnoea and angina pectoris "are clearly, singly and in a preponderant degree produced by tests of physical activity we may obtain valuable information about the heart. When a sense of exhaustion in local muscles or generally throughout the body, or when palpitation, dizziness and faintness appear...other factors then enter in, which prevent carrying the exertion far enough clearly to test the heart's strength; this is the usual situation, because of the general lack of physical training or because of the ready nervous fatiguability in most individuals tested. Hence the tests...amount to tests of training and of the nervous state, that is, of physical fitness, rather than of the cardiac condition."

This evidence of the present teaching of several leading clinicians, as well as experience of routine hospital practice, indicates that the majority of physicians make little or no attempt to measure exercise tolerance objectively. After half a century's intensive research into the physiology of exercise this is a remarkable state of affairs. The purpose of this thesis is to examine some of the exercise tolerance tests which have been proposed and to determine how far it is possible to estimate exercise capacity from measurements simple enough to be generally applicable in clinical work.

CHAPTER I

GENERAL CONSIDERATIONS

Any attempt to measure exercise tolerance involves a number of general problems at the outset. In order to establish the validity of an empirical test it is necessary to compare its results with an independent criterion of fitness. In the field of athletics this criterion has usually taken the form of some type of maximum performance. Taylor (1944), for example, used the "time-run to exhaustion" - the time required to exhaust the subject during treadmill work at progressively increasing gradient. Cureton et al. (1945) studied 28 different types of athletic performance (e.g. the mile run, floor push-ups, step test, 100-yard dash) and considered that a composite score including all of these was the best index of total fitness. The single event which correlated best with the composite score was the mile run, and this was used as the independent criterion for empirical tests of exercise tolerance (see later under "Harvard step test"). The use of these maximum performances as independent criteria is clearly appropriate in assessing a fitness test for athletic purposes, where the aim is precisely to determine how fit a man is for maximum effort.

In clinical work a maximum criterion, even if appropriate, is not suitable, because it is usually undesirable to exercise patients to the limit of their capacity. One patient at least, with mitral stenosis, has died following an attack of acute pulmonary oedema on the treadmill (Bruce

et al., 1951). Apart from actual risk, patients do not enjoy being exhausted in what they often consider to be the interests of the physician, and the observer can never be quite sure of full co-operation.

Perhaps for these reasons, clinical exercise tests have usually been assessed against an evaluation of the clinical history, an unsatisfactory procedure which largely begs the question of the need for an objective estimate. Master (1935) went even further; he asserted that his test would distinguish between grades of disability which were not otherwise distinguishable. In other words, the assumption of a difference in disability depended in these instances upon the results of a test which was itself under trial. The problem of the independent criterion is inherent in empirical exercise tests. It can be avoided only by basing the test on measurements of basic physiological functions which require no comparison with other and possibly spurious criteria.

Another difficulty arises when an attempt is made to define "exercise tolerance". Should this mean the highest exercise intensity which a subject can perform for a set period? As we have seen, there are theoretical and practical objections to such a definition for clinical purposes. Alternatively, as suggested by Wahlund (1948), exercise tolerance might be taken as the highest exercise intensity at which a "steady state" can be efficiently maintained. But what are the criteria by which we recognise efficiency or inefficiency? A third possibility is to estimate from submaximal data the "aerobic capacity" (Astrand & Ryhming,

1954). There is yet no agreement as to what should be the aim of a test of exercise tolerance, yet it is clearly a matter which merits close attention.

In view of these general problems the present review and experimental work have been planned on a wide basis. A priori one would expect that if a measure of exercise tolerance can be made, it should come from measurements of the components of the system whereby oxygen is supplied to, and carbon dioxide removed from, the active muscles during work. The chief of these components are as follows:

(1) Ventilation of the lungs and the distribution of air within them.

(2) Diffusion of gases across the alveolar membrane.

(3) Cardiac output and its distribution within the lungs.

(4) The O_2 and CO_2 carrying power of the blood.

(5) The functional state of blood vessels leading to and from the muscles.

(6) The efficiency of enzyme systems concerned with the utilisation of oxygen and liberation of CO_2 in the muscles.

The extent to which these can be measured under the conditions of the clinical laboratory will be considered in the chapters that follow; the rest of the present chapter is devoted to a short survey of some of the requirements to be fulfilled by the test-exercise itself.

Form of exercise

Stepping, walking, stationary cycling and arm exercise are all forms of exercise which are suitable for laboratory

study. Furusawa (1926) demonstrated that in arm exercise an unsteady state and an oxygen debt are more readily produced than in leg exercise, owing to the limited circulation of a small group of muscles. The heart and lungs are not put to the test by arm exercise unless their function is greatly impaired. In leg exercise peripheral fatigue occurs less readily and the heart and lungs are the chief arbiters of performance. Stepping (which usually includes stepping backwards) and cycling are forms of exercise to which not everyone is accustomed. Cureton et al. (1945) showed that practice influences the result of the Harvard step test quite markedly; Erickson et al. (1946) stated that in work on the bicycle ergometer the effect of practice may overshadow the effects of all other variables in its influence on physiological measurements. Cycle work may also restrict breathing if handlebars are used. ~~Hill (1922) found that~~ The maximum attainable O_2 uptake (aerobic capacity) is higher in running (Hill, 1922) ~~than in cycling~~, and ~~the same is~~ probably ~~true of~~ grade walking, (than in cycling. Bock et al. (1928) believed that muscle fatigue, not the heart or lungs, was the limiting factor in cycle work. Another major disadvantage of stationary cycling and stepping is that they require careful co-operation from the subject to maintain a steady rate of work. There can be little doubt that level and grade walking on a treadmill is the most suitable form of exercise for laboratory study.

Duration of exercise

The work of A. V. Hill and his colleagues (1924) established the concept of the "steady state" of exercise. Provided the rate of work does not exceed a certain limit

(the "crest-load", set by the aerobic capacity), a state is reached, soon after beginning exercise, in which the O_2 uptake remains almost constant and which may be maintained for a considerable time. During the steady state there is also approximate constancy of pulmonary ventilation, arterio-venous O_2 difference, cardiac output, heart rate and other variables. Above the crest-load O_2 uptake may become steady but the exercise can be maintained for only a short time and other variables do not reach a steady state. This is the so-called "pseudo-steady state". Hill & Lupton (1922) found that a trained runner reached a steady state of O_2 uptake in 3 minutes, even in exercise above his crest-load. Nielsen & Hansen (1937) demonstrated a constant O_2 uptake in healthy subjects after 5 minutes or less of bicycle ergometer work, up to a rate of 1620 mKg/min (about 3,500 ml. O_2 per minute). Donald et al. (1954, 1955) showed that O_2 uptake, arterio-venous O_2 difference and cardiac output were always steady after 4 minutes of mild to moderate work in normal subjects and in patients with rheumatic heart disease. Dexter et al. (1951) considered 2 minutes long enough to reach the steady state in health, in exercise up to 7 times the resting O_2 uptake. On the other hand Cournand et al. (1951) stated that 5 minutes are necessary for the attainment of a steady state even if O_2 uptake is only twice the resting level, and Eliasch (1952) noted fluctuation in the pulmonary wedge pressure up to 5 minutes after the start of exercise in cases of mitral stenosis. It is clear that these estimates depend largely on the criteria used to define the steady state. By including, for example, body

temperature and blood sugar concentration it would be possible to show that the steady state is never reached. For practical purposes, however, the O_2 uptake is the important criterion, and it would appear that this usually becomes stable within 4 minutes in both healthy subjects and patients.

In order to compare the responses to exercise of different people it is advantageous to continue the exercise into the steady state. In the first place there may be qualitative as well as quantitative differences in the way the steady state is reached: for example, a first-minute ventricular rate which is higher in subject A than in subject B might mean that A's stroke volume is impaired relative to B's, or that there is a lag in B's heart rate response. In the first case B is the fitter, in the second case A. By following the heart rate into the steady state the situation would become clear. The second, and perhaps main, advantage of continuing exercise into the steady state concerns the standardisation of the exercise. It is customary in stepping and bicycle work to calculate the rate of performance of external work as a measure of energy expenditure. However, the external work of walking is dependent upon an intricate system of variables, some of which have been discussed by Müller (1950a). It is wrong to suppose that the external work of walking can be determined from the distance by which the body's centre of gravity is raised in a given time, at least in level walking and in walking at a small gradient (Müller, 1950a; Starr, 1951). Even if it were possible to measure effective work in this way, it would bear an inconstant relation to energy expenditure because of variations in

the economy of movement between one person and another, and even in the same person at different times. Since the work of Boothby (1915) and of Bock et al. (1928) it has been common in work experiments to express energy expenditure in terms of steady state O_2 uptake, and this remains the most accurate measure of working intensity available. It avoids altogether the problem of variation in mechanical efficiency, for all physiological measurements may be related directly to oxygen uptake.

There are, however, important reasons for limiting the duration of the test-exercise. A test must not be unduly fatiguing. The observer's time may be important if several exercises are to be studied. Moreover, the longer exercise continues the more likely is a rise of body temperature to become a significant factor in determining some of the variables under study, particularly in heart disease in which temperature regulation may be disturbed by cutaneous vasoconstriction.

As a compromise between these conflicting requirements it would seem practical to adopt a 6-minute test-exercise, 4 minutes for the attainment of a steady state and 2 minutes to allow measurements in this state to be made.

Intensity of exercise

The use of a single standard exercise simplifies procedure. It is, however, impossible to tax a mildly handicapped person with a test-exercise which is within the reach of one severely disabled. Further, subjects with different degrees of disability may not be comparable at the same exercise intensity, which for them represents different

degrees of effort. Finally, Wahlund (1948) believes that it is possible to distinguish more sharply between different exercise capacities as the number of work rates available for comparison increases. It is, therefore, desirable to study a series of exercise intensities covering, as far as possible, the range of each individual's capacity.

Correction of data for body size

In order to compare physiological measurements made from persons of different stature it is necessary to allow for differences in body size. This is a matter which is still hotly debated (e.g. Tanner, 1949; Kleiber, 1950). Since the usual method is to correct data to unit body surface area, and since I have not adopted this procedure, it is necessary to state the grounds on which I have differed.

The surface area standard was originally applied to determinations of basal metabolism on the view that resting heat production just balances heat loss and resting oxygen uptake just supplies the necessary heat. Against this is the fact that heat is not lost at the same rate from different parts of the body surface. During exercise the energy released by tissue oxidation appears only in part as heat; for this reason alone it is quite irrational to correct working O_2 uptake to unit surface area, yet this is done. Resting cardiac output, too, is usually corrected in this way. The reason for this appears to be Grollman's finding that the cardiac outputs of healthy people, at rest, can be made to agree better (though not much better) in this than in any other simple way, e.g. by height or weight. It is hard to see a rational basis for this, and even harder when

it is applied, as it often is, to cardiac output determinations during exercise. At rest we have, at any rate, the authority of Grollman's empirical observation for such a correction; in exercise we have no authority whatever.

Correction according to body weight has at least as much in its favour as correction by surface area. It has the further advantage, in treadmill work, that the energy expenditure of level walking at a given speed is more closely related to gross body weight than any other variable; during stepping (and presumably gradewalking - see Müller, 1950a) the correlation is even more precise (Mahadeva et al., 1953). The results of the experimental work described in this thesis have been corrected on the basis of body weight.

The body weight correction is theoretically plausible if it be assumed that the proportional body composition is constant from one subject to another. In practice this is not so. The commonest gross variation is that found in obesity. A fat subject carries with him a quantity of tissue with a low O_2 consumption and a low blood flow, and compared with a lean person his O_2 uptake and cardiac output will be over-corrected by the body weight standard. One result will be a higher heart rate for the same corrected O_2 uptake, and the fat person will be judged unfit by indices based on heart rate. In one sense this is desirable, since obesity itself can be regarded as a form of unfitness. On the other hand, if heart or lung disease be present as well, it will be difficult to decide how far the observed result is due to obesity and how far to cardiorespiratory abnormality. To do this would require a separate set of standards

for "healthy" fat people grouped according to weight. In the studies to be described, markedly fat people were deliberately excluded. Obesity, is however, a problem which needs careful thought in relation to exercise tolerance tests, whatever type of test-exercise is used.

CHAPTER II

PULMONARY FACTORS IN EXERCISE

Dyspnoea is perhaps the symptom most commonly responsible for the limitation of exercise capacity. For the most part attempts to correlate dyspnoea with objective measurements have had little success. Many factors participate in producing dyspnoea and these may vary widely from case to case. "As a symptom, dyspnoea is not measureable" (Altschule, 1954). Nevertheless it is well established that patients with dyspnoea due to heart and lung disease show responses to exercise which are measurably outside the normal range. While these responses do not permit a strict assessment of any subjective symptom, it is possible to use them as indices of exercise performance.

VENTILATORY VOLUME

There are numerous recorded investigations in which the minute volume of ventilation (ventilation rate, $\dot{V}_E$) has been measured before, during and after exercise in disease of the heart and lungs. The essential facts are well documented and good reviews of the literature are available (Simonson & Enzer, 1942; Altschule, 1954).

In "decompensated" heart disease $\dot{V}_E$ may be normal or raised at rest, and increasesmore on exercise than in healthy subjects. It returns to resting levels, after exercise, more slowly than in health. Owing to limitation of tidal volume, the increase of $\dot{V}_E$ is often brought about predominantly by an increase of respiratory frequency. The maximum attainable minute volume is often less than normal, (Peabody

& Sturgis, 1922; Harrison et al., 1932; Campbell, 1934; Donald et al., 1954, 1955; Stock & Kennedy, 1953).

In pulmonary emphysema $\dot{V}_E$ is often raised at rest; it increases more than normally on exercise, though not usually as much as in heart failure; it returns more slowly than normally to resting levels after exercise. The maximum attainable minute volume is often grossly reduced (Campbell & Poulton, 1926a; Fishman et al., 1952; Hugh-Jones, 1952).

Other examples might be quoted, but the above suffice to show that measurement of ventilation rate in relation to exercise may be used to reveal abnormalities of the response to exercise. Since $\dot{V}_E$ varies with the rate of respiratory exchange, apart from the effects of disease, it has been customary to express it in relation to O_2 uptake and CO_2 output, as follows:

(1) Ventilatory equivalent for oxygen (Anthony, 1930, 1937; Knipping & Moncrieff, 1932).

$\dot{V}_E \times 100/\dot{V}_{O_2}$ (litres per 100 ml.)

(2) Percentage oxygen extraction or "utilisation" (Simonson & Gollwitzer-Meier, 1930).

$\dot{V}_{O_2} \times 100/\dot{V}_E$ (ml. per 100 ml.)

(3) Ventilatory equivalent for CO_2 (Marais & McMichael, 1937).

$\dot{V}_E \times 100/\dot{V}_{CO_2}$ (litres per 100 ml.)

The effect of exercise on the oxygen extraction (OE) was studied by Simonson & Gollwitzer-Meier (1930). At rest they found values of 2.2 to 6.0% in health. Other studies, collected by Lindgren (1953) gave a range of 2.2 to 5.5%.

Simonson & Gollwitzer-Meier found that during exercise the OE began to rise after 20 seconds and reached a plateau which was maintained until about 1 minute after exercise. It then fell rapidly to below the resting level, which was regained several minutes later. In nervous hyperpnoea OE was low at rest but increased normally on exercise. In heart disease OE was low at rest and rose less than normally, or even fell, on exercise; in emphysema it was low at rest but rose moderately on effort unless heart failure was also present. These changes in OE are, in fact, merely an expression of the behaviour of $\dot{V}_E$ in response to exercise in these conditions, as already noted. Simonson & Gollwitzer-Meier interpreted them as indications of various relationships between alveolar ventilation and pulmonary blood flow or cardiac output. A low OE, or one which did not rise normally on exercise, was held to show a low cardiac output or an inability to increase cardiac output on effort.

These findings have, in general, been confirmed by later work, for example by Donald et al. (1954, 1955) in mitral stenosis. The interpretation placed on them, too, seems to have found a measure of acceptance (e.g. Levy, 1951). In fact, the significance of the OE is not easy to assess in a given case. Eliasch (1952) found a normal OE with a low cardiac output in some cases of mitral stenosis; only when respiratory frequency, and therefore dead space ventilation, was increased did the OE fall. A priori reasoning suggests that OE depends upon a number of factors, such as cardiac output, venous saturation, dead space, depth and frequency of breathing, the efficiency of intrapulmonary gas and

blood distribution and alveolocapillary diffusion.

In an attempt to minimise one of these variables, that of voluntary alteration in the tidal volume and respiratory frequency, Marais & McMichael (1937) suggested the use of the ventilatory equivalent for CO_2. Transient changes of ventilation due to nervous hyperpnoea would result in more CO_2 being added to the expired air and this would tend to stabilise the CO_2 equivalent. McMichael (1939) found an approximate inverse log-log relation between the cardiac output and the CO_2 equivalent in a group of cardiac patients at rest. It is of interest to record that in 1920 Briggs proposed the use of the CO_2 concentration in expired air (the reciprocal of the CO_2 equivalent) as a measure of physical fitness. Simonson and Enzer (1942) stated that the changes in expired CO_2 content on exercise were not as pronounced as those of the OE in the conditions they investigated. This fits well with the results of several studies (e.g. Peabody & Sturgis, 1922; Campbell & Poulton, 1926a and b; Campbell & Sale, 1927) on the time-course of O_2 uptake and CO_2 output during and after exercise in heart and lung disease. Owing to the difference in shape of the blood dissociation curves for O_2 and CO_2, changes in ventilation rate have a marked (though transient) effect on CO_2 output but not on O_2 consumption. This obviously applies to hyperpnoea from causes other than nervousness; use of the CO_2 equivalent will therefore mask the effects of such conditions as diffuse pulmonary fibrosis in experiments lasting less than 5 or 6 minutes, whereas the OE will show more marked abnormality.

The significance of an abnormal ventilation rate at a particular level of gas exchange is thus difficult to appraise without additional information. Knowledge of the proportion of total ventilation expended in the dead space would go some way towards making ventilatory measurements more specific. This question will be considered later.

The Hugh-Jones test

Hugh-Jones (1952) introduced a new approach to ventilatory measurements during exercise. He made his subjects mount and descend a step, the height of which was adjusted for the subject's weight so that everyone performed vertical work at about the same rate. The exercise was stopped at the end of 5 minutes or, in the case of patients, when they could continue no longer. Expiratory volume was noted every half-minute from a gas meter through which the subject expired. The total ventilation for the whole of exercise and recovery, in excess of the mean resting ventilation, was calculated and termed the Excess Exercise Ventilation (EEV). The Standardised Excess Ventilation (SEV) was taken as the EEV divided by the number of minutes' exercise. The SEV plus the mean resting ventilation rate per minute gave what Hugh-Jones called the Standardised Ventilation (SV). The ventilation rate during the last minute of exercise was termed the Exercise Ventilation (EV). In health, and in those patients with emphysema who completed 5 minutes' exercise, SV was about equal to EV. This is a convenient way of expressing the fact that the "ventilatory debt" after exercise is, in these subjects, equal to the "ventilatory deficit" during the phase of adaptation; this in turn

seemed to depend upon the ventilation reaching an adequate rate (for the rate of exercise) before the end of the 4th minute of exercise. Emphysematous patients who could not finish the test showed an EV appreciably less than SV, indicating a ventilatory debt in excess of the adaptatory deficit. Stock &d Kennedy (1953) obtained similar results in patients with mitral stenosis.

This test is very simply carried out and will doubtless become more widely used in the routine assessment of exercise tolerance. It is, however, empirical, and what it measures is not fully understood. If, during exercise, alveolar ventilation is insufficient to prevent CO_2 retention and/or anoxia these must be corrected during the recovery period, and the ventilatory debt paid off during recovery will be greater than the apparent deficit of early exercise, since this is related to the highest ventilation actually attained, not to the true ventilatory requirement. This is very likely the mechanism by which SV exceeds EV in emphysema. There may be other factors at work, in mitral stenosis and other conditions, which are not so clearly defined; the OE (and all the factors which determine this), the oxygen debt and possible changes in lung rigidity need to be considered. Hugh-Jones's test appears to be a simple way of assessing ventilatory ability in exercise, but care is required before interpreting its results with any precision.

RESPIRATORY FREQUENCY

Wahlund (1948) suggested, as an index of working capacity, the work rate on a bicycle ergometer at which the respiratory frequency reached 30 per minute. This was a level

arbitrarily selected as the limit of efficient respiration. The test requires the counting of respiratory cycles at a number of different rates of work. The frequency is plotted against the rate of work and a regression line drawn, from which the appropriate value of work rate is read off. Respiratory frequency is, however, a very variable function. In treadmill work, for instance, it is often a submultiple of the stride rate (Bannister et al., 1954; personal observations) and is regulated almost consciously by the subject. Matthews (1954) found the respiratory frequency of no value as an index of exercise tolerance in mitral stenosis, owing to the individual variations in rate and depth by which a given ventilation rate is achieved.

In itself, therefore, respiratory frequency cannot be expected to give much information, and the same clearly applies to tidal volume. When combined with other data its value increases. The amount of ventilation "wasted" in the anatomical dead space varies directly with the frequency of breathing, and arguments will presently be advanced which suggest that the volume of the physiological dead space depends upon frequency as well as upon tidal volume.

THE MAXIMUM BREATHING CAPACITY

In health it may be that the limit of working capacity is set by factors other than the maximum ventilatory volumes of which an individual is capable. In disease, notably emphysema, breathing capacity may be the decisive factor. Hermannsen (1933) was the first to show that spontaneous forced respiration produces higher ventilation rates than either exercise or CO_2 inhalation in healthy subjects.

Breathing capacity is therefore commonly measured as the Maximum Voluntary Ventilation (MVV). The subject is asked to breathe as fast and as deeply as possible into a low-resistance recording system for a short time, usually 15 seconds. He is left to strike a balance between rate and depth himself (Gilson & Hugh-Jones, 1949). This balance must, however, influence the resulting ventilatory volume appreciably, and it seems likely that more informative figures for maximum ventilation can be obtained by measuring it at a number of set frequencies (Bernstein, et al., 1952). Moreover, the results of forced breathing at rest may not represent the maximum available ventilation during exercise (Stock & Kennedy, 1953). Owing to the difficulty of recording a period of forced respiration during exercise some have substituted the maximum expiratory flow-rate (Gaubatz, 1938; Kennedy, 1953). The validity of this substitution is still a matter for debate.

Methods for the measurement of breathing capacity are thus by no means standardised and need further investigation. Meanwhile, Hugh-Jones's test appears to give as good an indication as any of the ventilatory capacity during exercise. One of the factors in the result of this test is the relation between the ventilatory requirement of the exercise and the current ventilatory capacity. If SV is appreciably higher than EV it may mean that demand has exceeded supply, and by grading the exercise it might be possible to find the level at which this discrepancy begins.

SUMMARY

Ventilation rate, oxygen extraction and CO_2 concentration in expired air can be accurately measured during and after exercise, and may be used to show up differences between normal and abnormal responses to exercise, and between degrees and types of abnormality. Their usefulness would be enhanced by simultaneous measurement of other variables, notably respiratory frequency and dead space. The measurement of ventilatory capacity presents problems both at rest and during exercise and needs further study. Hugh-Jones's test, however, may give information about ventilatory capacity and has the advantage of being easily and quickly performed.

CHAPTER III

THE RESPIRATORY DEAD SPACE

A comprehensive account of dead space is not intended here, and the recent reviews by Bannister et al. (1954) and Rossier & Bühlmann (1955) are taken as a starting point for discussion. These authors outline briefly the main historical landmarks and the development of present ideas on dead space. They draw attention particularly to the following observations:

1) Measurements of dead space by non-respiratory gases (hydrogen, nitrogen, helium), as by Siebeck (1911), Krogh & Lindhard (1913, 1917), Fowler (1948) and Bartels et al. (1954), agree approximately with the results obtained from anatomical casts (Loewy, 1894) and by actual measurement of the conducting passages (Rohrer, 1915).

2) Non-respiratory gas methods show relatively small increases in dead space on lung distension, exercise and hyperventilation. Representative figures are 100 ml. resting to 180 ml. after an inspiration of 2 litres (Krogh & Lindhard, 1917) and during corresponding degrees of exercise (Fowler, 1948). Rohrer gave 180 ml. at the normal expiratory position to 260 ml. in full inspiration.

3) Methods using the respiratory gases CO_2 and O_2 give values similar to the above at rest, but during exercise or hyperventilation the dead space is found to increase very considerably. This is true whether "spot" samples of alveolar air (Douglas & Haldane, 1912; Haldane, 1915; Bannister et al., 1954), fractional whole-expiration analyses (Henderson et al., 1915; Aitken & Clark-Kennedy, 1928)

or arterial blood tensions (Cooper et al. 1953; Rossier & Bühlmann, 1955) are used to supply the "alveolar" concentration for the Bohr equation. Values of dead space between 600 and 800 ml. have commonly been reported under these conditions.

These results suggest a fundamental difference between the respiratory and non-respiratory gas methods. If the volume of the conducting passages does not exceed 180 ml. (Krogh & Lindhard) or 260 ml. (Rohrer) at full inspiration, the increase of the CO_2 and O_2 dead space to values of 600 ml. or more must indicate another kind of dead space which can increase at the expense of the respiratory units themselves.

Rossier & Bühlmann (1955) suggest that during exercise there is a partial pressure gradient for both CO_2 and O_2 across each alveolus. This gradient may be theoretically integrated into a portion of alveolar gas of uniform composition (they consider only the composition derived from arterial tensions) and a portion of pure inspired air. In effect, the alveoli contribute to the CO_2 or O_2 dead space, and this contribution is supposed to increase with increasing gas exchange.

If such gas pressure gradients account for the big increases of dead space when CO_2 or O_2 is the reference gas, it follows that in the non-respiratory gas methods there is no gradient of the reference gas, or that any gradient there is does not increase with exercise. We know that at rest there is a gradient under the conditions of the method (Krogh & Lindhard, 1913). The second proposition is

however plausible. Mixing beyond the anatomical dead space depends largely upon turbulence and this presumably increases with flow-rate, but increased turbulence would be offset to some extent by the shorter time occupied by each inspiration (Krogh & Lindhard, 1917). These two factors are, however, common to all reference gases. There is a third factor which is not; this is the gas exchange. Transfer of nitrogen, hydrogen and helium across the alveolar membrane is very slow compared with that of oxygen and CO_2, because of their low solubilities in blood. Table I shows the solubilities of these gases in water and oil. Solubility in blood approximates to that in water.

Table I

Volume of gas in ml. (STPD) which dissolves in 1 ml. of water or oil at 37°C (Lawrence et al., 1946).

	Water	Oil
Hydrogen	0.016	0.050 (cottonseed)
Nitrogen	0.013	0.067 (olive)
Helium	0.008	0.015 (olive)

The rapid and continuous interchange of O_2 and CO_2 at the gas-blood interface is a factor which would perpetuate a pressure gradient of these gases across the alveolar space (Fowler, 1952).

If it is true that the alveolar pressure gradient is the basis of the increase of CO_2 and O_2 dead spaces in exercise, this demonstration that a factor which maintains a pressure gradient does not apply to the biologically inert gases could be a sufficient explanation of the failure of

the inert gas dead space to increase significantly during exercise. Such increase as is observed can well be explained as a true increase of anatomical dead space consequent on an increase of tidal volume and FRC (Verzar, 1933; Huizinga, 1937) and on more complete washing out of the conducting airway. It remains therefore to examine further the problem of alveolar CO_2 and O_2 pressure gradients and the effect of these on dead space. At the outset some definitions are necessary.

DEFINITIONS

Difficulty arises at once if the term "alveolus" as used by Rossier & Bühlmann (1955) is taken literally to mean "alveolar sac", since this is too small for an appreciable gradient to exist across it, even when gas exchange is rapid (Rauwerda, 1946). But in an alveolar unit consisting of sacs, atria and duct (Miller, 1947) it is probable that a gradient exists under certain conditions, and that the sacs contain gas of a different composition from the duct gas. Haldane (1935) clearly recognised this. The term alveolar unit will be used in this sense, without imputing to it any rigid anatomical limits. It exists, indeed, in only a physiological sense, being that part of the respiratory tree in which inspired air mixes with alveolar air instead of displacing it.

Anatomical dead space, $V_D(An)$, is that part of the respiratory tract which is filled with pure inspired gas at the beginning, and with alveolar gas at the end, of expiration. The remainder of the lung volume is thus the sum of all the alveolar units defined above, and the rate at which

these are ventilated will be termed the alveolar ventilation $\dot{V}_A(An)$.

"Physiological dead space" is a term which will be reserved for the dead space for CO_2 or O_2. As will be seen, this dead space may have more than one meaning. It should be noted that the nitrogen dead space has been called "physiological" because of the way it is measured, whereas its value approximates to anatomical dead space. Physiological dead space will be designated V_D.

Just as $V_D(An)$ has its counterpart in alveolar ventilation, so V_D has its own in alveolar clearance, $\dot{V}_A$. This term, introduced by Rossier & Bühlmann, indicates the volume of gas of effective alveolar composition which is eliminated per minute.

Effective alveolar gas (Riley et al., 1946) contains gases at "those pressures which, if present continually and uniformly in all functioning alveoli, would permit the exchange of CO_2 and O_2 between the alveoli and blood, during a series of ventilatory cycles, in amounts exactly equal to the gas exchange as measured from analyses of the inspired and expired air".

The Bohr equation (Bohr, 1891) relates dead space to tidal volume and to the concentrations of any gas x in inspired, alveolar and expired air, as follows:

$$\text{Dead space} = V_T (F_{Ax} - F_{Ex})/(F_{Ax} - F_{Ix}).$$

The discussion will start with a consideration of the factor F_{Ax}.

Symbols follow accepted usage. For convenience the definitions of Pappenheimer et al. (1950) are set out in

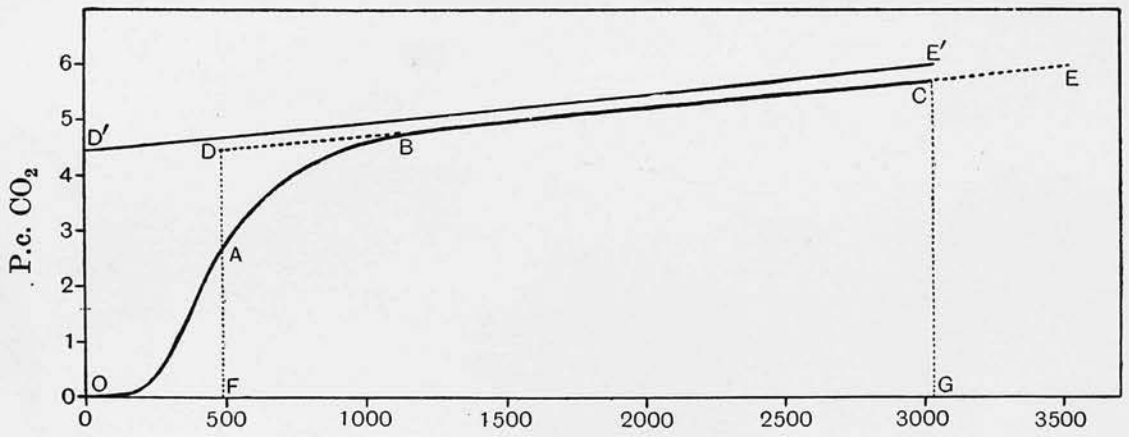

Diagram to show the method of deducing the alveolar CO_2 curve and the dead space from the experimental CO_2 curve (Exp. 12).

The flat part *BC* of the experimental curve *OABC* is prolonged to the left to *D* until the area *FDCG* equals the area *OABCG*, *DF* and *CG* being perpendicular to *OG*. *OF* then represents the volume of the dead space. *DC* is prolonged to the right to *E*, over a distance equal to *OF* (when measured horizontally). The whole line *DE* then represents the changing concentration of alveolar CO_2 throughout expiration.

Fig. 1

See text.

Appendix III which can be opened out to face the reader throughout the relevant sections of this thesis.

THE ALVEOLAR FACTOR IN THE BOHR EQUATION

Much controversy has arisen over the value to be assigned to the alveolar gas concentration in the Bohr equation. According to the basis of this equation the proper value is the mean concentration of the gas in the alveolar expired air (Krogh and Lindhard, 1913). Since the alveolar expired air cannot be collected it is possible to arrive at this value only indirectly, by means of continuous or fractional analysis of expired air. Fig. 1, taken from Aitken and Clark-Kennedy's paper (1928), shows how this may be done if it be assumed that the CO_2 concentration in the very first alveolar gas is represented by point D - in other words, assuming the validity of the extrapolation of the plateau CB. It is, however, certain that at the boundary between inspired air and alveolar air, just prior to expiration, the CO_2 concentration does not abruptly rise from zero to a value in the region of 4%. There must be a transition zone across which the concentration rises steeply to meet the plateau proper. The S-shaped part of Fig. 1 results, not only from mixing of alveolar and atmospheric air during the course of expiration, but also from a real gradient which exists at the mouth of each alveolar unit before expiration begins. At rest this gradient probably occupies a very small volume, and the configuration OFDC in Fig. 2a is an accurate representation for practical purposes. The midpoint of DC would therefore be the true mean CO_2 content of alveolar expired air, and this value when substituted in the Bohr equation

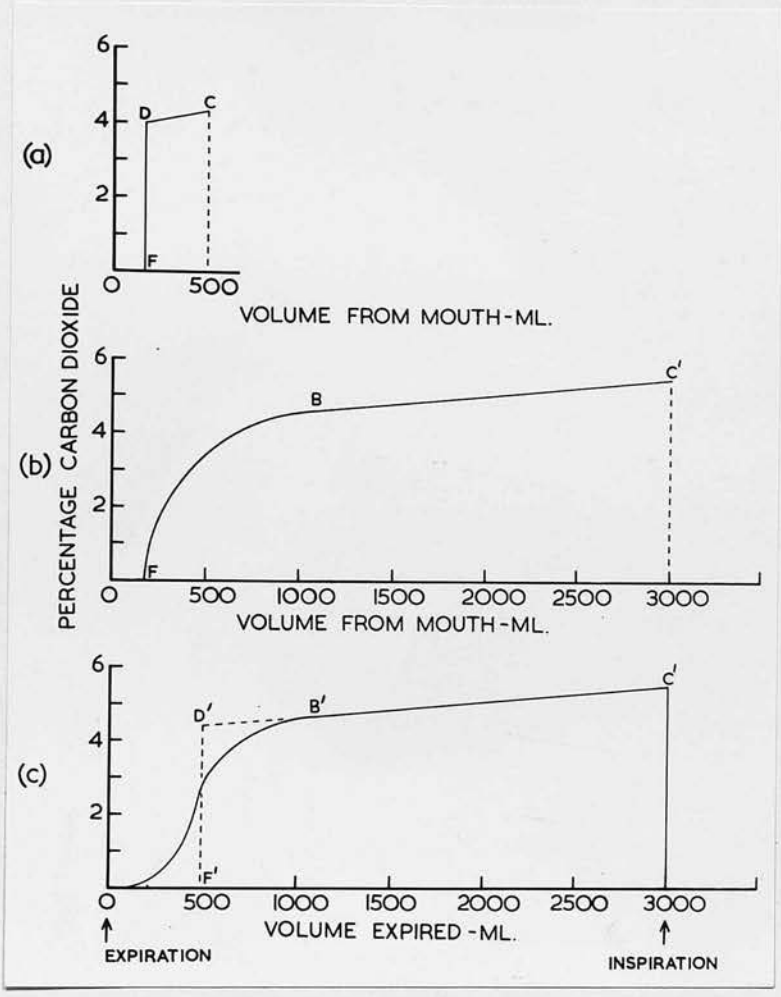

Fig. 2.

See text.

would give a dead space equal to OF.

If on the other hand the steep gradient of CO_2 concentration occupies an appreciable volume, then the situation just prior to expiration will be as depicted in Fig. 2b. As before, OF is the anatomical dead space; thereafter the CO_2 concentration rises more gradually than in Fig. 2a to reach the plateau after a substantially larger volume has been expired. The midpoint of the extrapolated plateau (Fig. 2c) is no longer the true mean concentration of CO_2 in the alveolar expired gas; it is higher than this, and gives, when substituted in the Bohr equation a value for dead space not of OF but of OF'.

It is only by the assumption of an extension of the steeper part of the CO_2 and O_2 gradients further and further into the alveolar units that the increase of V_D during exercise, found by Aitken & Clark-Kennedy, can be explained, for we know that $V_D(An)$ does not itself increase nearly as much. The increase of V_D depends, in fact, upon the alveolar CO_2 concentration determined by their graphical method not being the true mean alveolar concentration. The same applies to any direct sampling method in which gas is deliberately taken from some part of the plateau. This being so, have these direct samples any significance at all?

The answer to this question is that plateau samples, especially end-plateau samples, bear a fairly close relation to arterial blood tensions in health. This is true only when tidal volume is greater than about 750 ml., for otherwise the plateau proper is not reached. But the uncertainties of direct sampling, and particularly the additional

problems met with in certain abnormal pulmonary conditions, led Enghoff (1938) and later Riley et al. (1946) to dispense with direct samples and to introduce a new concept of "effective" alveolar air based on arterial CO_2 tension. At rest, as stated by Riley et al. (1946), effective alveolar air has the same composition as alveolar expired air, if this could be measured. It is, however, virtually certain, from the argument advanced above, that during exercise and hyperventilation effective P_{ACO_2} is higher than the true mean alveolar P_{CO_2}, and V_D calculated from effective alveolar air therefore increases with exercise just as does V_D calculated from end-plateau or even mid-plateau alveolar air.

In summary, the value of dead space obtained from the Bohr equation depends upon the value assigned to the alveolar factor. This has two definable meanings. The first is the true mean CO_2 concentration in alveolar expired air, using the latter term to mean the gas expelled from the anatomical boundaries of the respiratory units - or total lung volume minus anatomical dead space. This concentration cannot be experimentally determined, but if it could it would provide, by definition, a dead space equal to anatomical dead space under all conditions. The second meaning is "effective" alveolar CO_2 concentration, which is equal at rest to the mean alveolar expired CO_2 concentration, and gives the same dead space; during exercise it is higher, and gives an increasing value for dead space as exercise increases. Direct alveolar samples give values for F_{ACO_2} which theoretically have neither one meaning nor the other. It so happens, nevertheless, that end-plateau samples approximate to

"effective" alveolar air under certain conditions (see later). Furthermore, fractional techniques such as that of Aitken & Clark-Kennedy allow calculation of an apparent mean alveolar expired CO_2 concentration which could be said to have a physiologically determined meaning, and which gives values of V_D which increase with exercise and hyperventilation.

Both Haldane and Krogh were, of course, quite aware of the essentials of the foregoing argument, which was the basis of their famous controversy. Krogh objected because Haldane's samples did not represent mean alveolar expired air, while Haldane deliberately took his samples from the depths of the lung because he thought that these were more representative of arterial gas tensions. The latter are, in fact, the cornerstone of Haldane's conception of physiological dead space. In recent years there has been a clear tendency in writings on the subject to dispense altogether with direct alveolar samples in favour of arterial gas tensions. There is much to be said for this, but there are two reasons why direct samples are still useful. First, the accuracy of P_{aCO_2} estimations is only about one tenth that of alveolar gas analysis, and direct samples are more easily obtained than arterial blood. Secondly, a distinction exists, though it is seldom recognised, between true "parallel" dead space, due to unperfused or poorly perfused alveoli, and the extension of physiological dead space in exercise and hyperventilation, which takes place at the expense of all alveoli. Determinations based on arterial CO_2 tension include both of these. Those based on direct samples measure only the second, and will not detect true

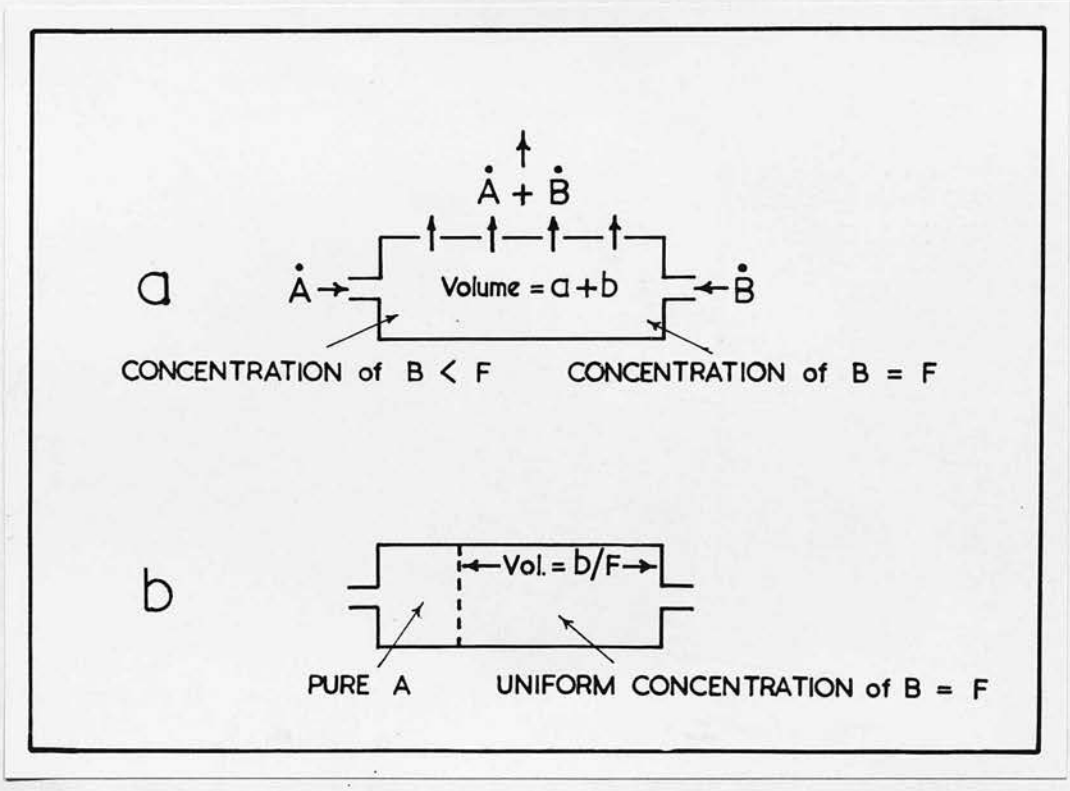

Fig. 3

See text.

"parallel" dead space if all alveoli empty more or less together. These matters will receive further attention in what follows.

THE EFFECT OF EXERCISE AND HYPERVENTILATION ON V_D

We have seen how modification of the alveolar gradient may give rise to an increase in V_D when this is measured from arterial CO_2 tension or an equivalent direct sample. Let us now examine this mechanism further in the special setting of exercise and hyperventilation.

Fig. 3a represents a chamber into which two gases are passing at constant rates, gas A from the left at a rate $\dot{A}$ vols. in unit time and gas B from the right at a rate $\dot{B}$. Gases A and B leave the chamber by diffusing through its side at a rate sufficient to keep the pressure inside the chamber constant. A volume $\dot{A} + \dot{B}$ must therefore leave the chamber in unit time. Within the chamber, during the steady state, there are volumes a and b of gases A and B respectively. If mixing is imperfect there will be a partial pressure gradient of gas B across the chamber, from a fractional pressure (or concentration) F at the extreme right, to a lower pressure at the left. This gradient may be simplified by imagining that all the molecules of B are collected at the right of the chamber at a concentration F, while the left-hand part of the chamber is filled with pure gas A (Fig. 3b.).

Then Total volume of chamber = a + b

Volume occupied by pure gas A = $(a + b) - b/F$..(1)

But $a/b = \dot{A}/\dot{B}$, therefore $(a + b) = b(\dot{A} + \dot{B})/\dot{B}$

If f is the number of times volume b is exchanged in unit

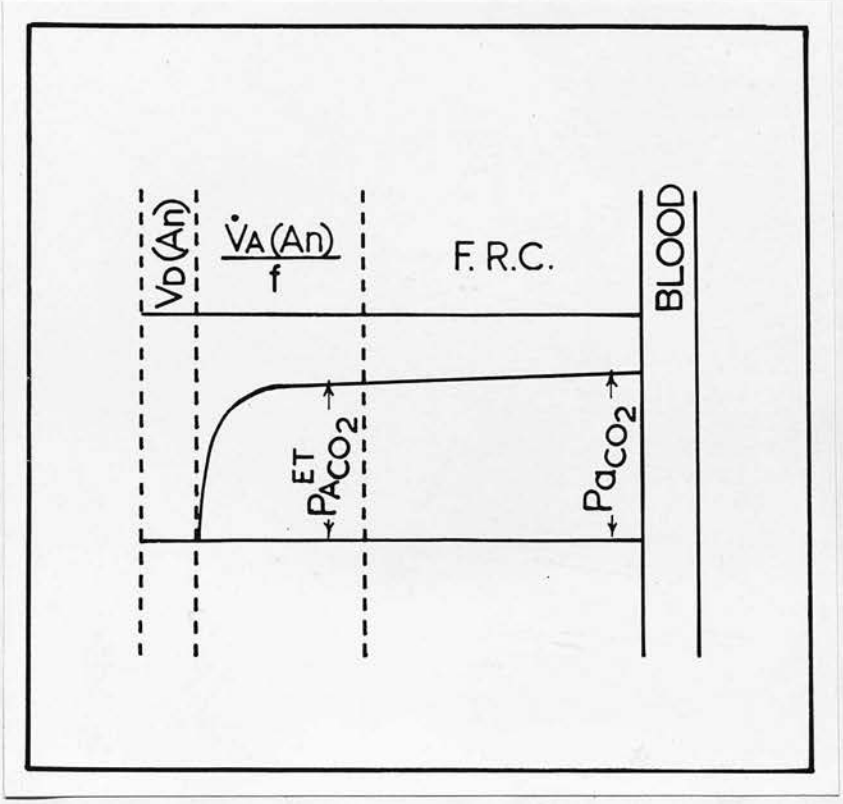

Fig. 4

See text.

My attention has been drawn to the paper by Nielsen, M. (1936). Skand Arch. Physiol. 74, suppl. 10, 87-208 in which an alveolar CO_2 gradient of this type was postulated.

time,

Then $\dot{B} = bf$ or $b = \dot{B}/f$

Substituting in equation (1), we have

$$\text{Volume occupied by pure gas A} = (\dot{A} + \dot{B})/f - \dot{B}/fF \quad \ldots\ldots(2)$$

The primary variables in this steady-state system are the rates at which the two gases enter the chamber, the degree of mixing between them and the volume of the chamber. The other variables are secondary to these. If mixing is perfect, $F = b/(a + b)$ and the volume occupied by pure gas A is zero, whatever $\dot{A}$, $\dot{B}$, f or the volume of the chamber.

The situation in the lungs just prior to expiration may be illustrated as in Fig. 4. By definition, $V_D(An)$ contains pure inspired gas at this moment. The "alveolar" space contains alveolar gas, which for simplicity is here regarded as a mixture of CO_2 and "non-CO_2". This space consists of an exchangeable portion which is due to be discharged at the next expiration and a portion corresponding to the functional residual capacity (FRC). CO_2 enters the alveolar space from the blood at a rate $\dot{V}_{CO_2}$. The CO_2 gradient is indicated diagrammatically.

In the general case with imperfect mixing, there is a parallel in Fig. 4 with the imaginary system depicted in Fig. 3. Instead of $(\dot{A} + \dot{B})$ we have $\dot{V}_E$, for $\dot{B}$ we substitute $\dot{V}_{CO_2}$, and we may replace F by either F_{ACO_2} or F_{aCO_2} according to whether we measure it from direct alveolar samples or by arterial tonometry. The respiratory frequency is f. The only difference from Fig. 3 is the addition of the FRC

and the anatomical dead space.

Equation (2), rewritten in terms of respiratory physiology, becomes

$$V_D = \dot{V}_E/f - \dot{V}_{CO_2}/f.F_{ACO_2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Restating, $V_D = V_T - V_T.F_{ECO_2}/F_{ACO_2}$ which is the Bohr equation for $F_{ICO_2} = 0$.

If we substract from both sides of equation (3) the anatomical dead space, we have

$$V_D^{alv} = \dot{V}_A(An)/f - \dot{V}_{CO_2}/f.F_{ACO_2} \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

This equation defines the factors which determine whether the (anatomical) alveolar space makes a contribution (V_D^{alv}) to the CO_2 dead space or not. As before, if mixing is perfect V_D^{alv} becomes zero. If mixing is not perfect, the alveolar space may contribute to V_D and the extent of its contribution will then depend upon $\dot{V}_A(An)$, $\dot{V}_{CO_2}$ and the volume of the exchangeable alveolar space.

An equation similar to (4) may be derived for O_2. Neglecting the correction for exchange ratio, this is as follows.

$$V_D^{alv} = \dot{V}_A(An) - \dot{V}_{O_2}/f(F_{IO_2} - F_{AO_2}) \quad \ldots\ldots\ldots\ldots (5)$$

Equations (4) and (5) may be derived very simply from the Bohr equation, as has been shown, and the reader may wonder how the imaginary steady-state system is necessary or helpful to discussion of the problem. It does, however, direct attention to the importance of time relationships in the genesis of dead space. The dynamic aspects of gas flow are not readily suggested by the Bohr equation, which rather implies that dead space is a matter of volumes and concen-

trations, unrelated to time.

It is now possible to re-examine the problems of exercise and hyperventilation in the light of equation (4). Voluntary hyperventilation may be performed by increasing alveolar tidal volume at constant frequency or by increasing frequency at constant tidal volume. If, in equation (4), we increase $\dot{V}_A(An)/f$ (alveolar tidal volume) and keep f constant, then if $\dot{V}_{CO_2}$ remains the same either V_D^{alv} must increase or F_{ACO_2} must diminish. If, on the other hand, we increase f, keeping $\dot{V}_A(An)/f$ constant, precisely the same conditions must hold at the same $\dot{V}_{CO_2}$. Whether V_D^{alv} increases or F_{ACO_2} diminishes will depend in each case upon whether intra-alveolar mixing alters as a result of the change in alveolar ventilation. Should the extra alveolar ventilation not "mix" at all, F_{ACO_2} will not alter. An increase of V_D^{alv} implies, in fact, that mixing of gases within the alveolar unit becomes less efficient at the higher rate of ventilation. In experimental hyperventilation, of course, both V_D and F_{ACO_2} alter. The theory is adequate to explain both happenings. It also shows that alveolar hyperventilation may increase V_D even if it is achieved entirely as a result of an increase of respiratory frequency. Experimental confirmation of this was provided by Williams and Rayford (1956).

Exercise presents a more difficult problem, for here, in addition to an increase of alveolar ventilation, there is an increase of CO_2 output, whereas in the steady state of voluntary hyperventilation at rest there is no such increase. In considering exercise, therefore, much depends on the relation of $\dot{V}_{CO_2}$ to $\dot{V}_A(An)$. Suppose $\dot{V}_A(An)$ is increased by increasing alveolar tidal volume at constant respiratory

frequency; then from equation (4), V_D^{alv} must increase unless (a) F_{ACO_2} diminishes or (b) $\dot{V}_{CO_2}$ increases at a rate greater than the increase of $\dot{V}_A(An)$. As a rule F_{ACO_2} increases, and could presumably only diminish if $\dot{V}_A(An)$ increased faster than $\dot{V}_{CO_2}$: thus (a) and (b) would appear mutually exclusive and even contradictory. In the opposite state of affairs, where f increases at constant $\dot{V}_A(An)/f$, an increase in V_D^{alv} requires either (i) a rise in F_A or (ii) an increase in $\dot{V}_A(An)$ greater than that of $\dot{V}_{CO_2}$, or both (i) and (ii). In this case the conditions for an increase of V_D^{alv} appear mutually exclusive or contradictory unless we assume that alveolar mixing deteriorates with the hyperventilation of exercise. That it does so appears likely from analogy with voluntary hyperventilation (discussed above)

There is a good example in the literature of how failure to realise the importance of the dynamic aspects of alveolar ventilation may lead to erroneous conclusions. Krogh & Lindhard (1917) set out to meet Haldane's criticisms of their use of hydrogen on the grounds that it was an unphysiological gas. They repeated their standard experimental routine, using oxygen instead of hydrogen to determine dead space at a number of levels of lung distension, and obtained results closely in agreement with their hydrogen method. Their studies were carried out at rest on the expirate from a single breath of suitable depth, and the co-operation required from the subject would ensure ample time for alveolar mixing before the expiration was made. It was assumed that

exercise and hyperventilation could increase dead space only by reason of the bigger tidal volumes involved. Haldane's work, on the other hand, had been based upon the expired air from a number of breaths, in subjects actively hyperventilating or exercising, and respiration was natural up to the moment of delivering the alveolar sample. Granting Krogh's contention that Haldane's alveolar samples were unrepresentative in these conditions, the experiments are still not comparable, for in Haldane's the alveolar space was hyperventilated - and in exercise $\dot{V}_{CO_2}$ also increased - whereas in Krogh's these conditions did not apply. They were measuring different things, albeit with the same gas.

"SERIES" AND "PARALLEL" DEAD SPACE

Pappenheimer et al. (1952) introduced a new method of determining dead space. Details of this "isosaturation method" may be found in their paper. They plotted P_{ECO_2} against $1/V_T$ at constant P_{aCO_2} and obtained dead space by extrapolating the regression line to the $1/V_T$ axis. The intercept represents the value of $1/V_T$ at which P_{ECO_2} should become zero with diminishing V_T. At this point V_T must therefore be the anatomical dead space as defined above. (In fact the tidal volume may be reduced experimentally to below this value before CO_2 disappears from expired air (Henderson et al., 1915; Briscoe et al., 1954) and Pappenheimer's extrapolation gives the value which would be obtained if the gas-front between alveolar and inspired air advanced towards the mouth as a plane rather than as a cone.) Since this dead space is in series with the alveoli, they call it the series dead space. When groups of alveoli are

present which have a high ventilation: perfusion ratio, the dead space calculated from arterial tensions is increased; since the increment of dead space lies in parallel with the normal alveoli, the increment is called the parallel dead space (Folkow & Pappenheimer, 1955).

The linear relation between P_{ECO_2} and $1/V_T$ over the range of V_T studied during exercise led Pappenheimer et al. (1952) to conclude that dead space (unspecified) remains constant with increasing exercise. As Folkow & Pappenheimer (1955) and Williams & Rayford (1956) point out, linearity is consistent with an increase of dead space provided that the increase is proportional to V_T. In this case, however, the intercept on the P_{ECO_2} axis would be less than the arterial P_{CO_2}, and Folkow & Pappenheimer (1955) quote Fishman (1954) to show that there is, in fact, a consistent difference, enough to account for a rise in the determined dead space of about 75 ml. at a tidal volume of 2 litres. This increment is of the order found in exercise by the non-respiratory gas methods and is further evidence that "series dead space" by the isosaturation technique approximates to the anatomical dead space.

Of special interest is the finding (Folkow & Pappenheimer, 1955) that positive-pressure breathing results in the appearance of a "parallel dead space" as well as an increase of series dead space of about the degree expected from the lung distension. They prudently make no firm statement as to the possible cause of this increase of parallel dead space, but imply that it may be due to an unevenness of lung perfusion set up by the positive-pressure breathing.

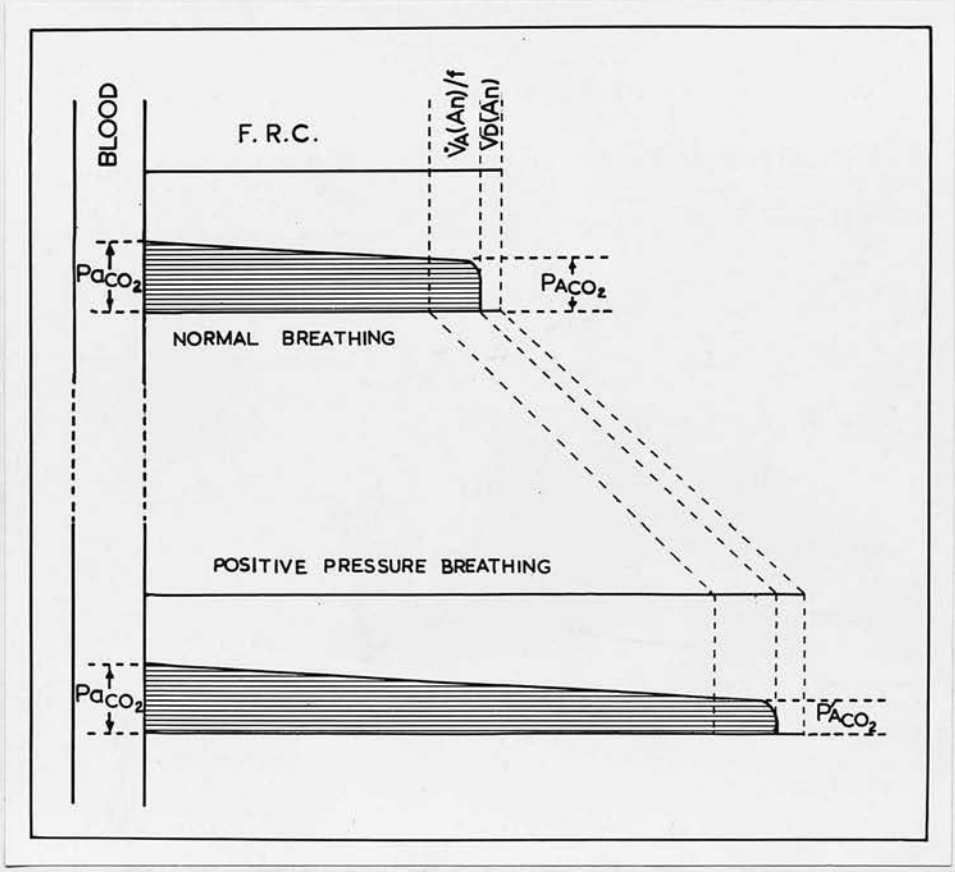

Fig. 5

See text.

It seems unnecessary to invoke this mechanism, since the parallel dead space effect is what might be expected on the basis of the alveolar gradient. Consider Fig. 5 a and b. Since (1) P_{aCO_2} is kept constant, (2) FRC increases much more than V_T in positive-pressure breathing and (3) the alveolar CO_2 gradient extends in each case from the alveolar membrane to the beginning of the series or anatomical dead space, it follows that the mean CO_2 pressure in the alveolar expired air must be lower in positive-pressure breathing than in ordinary breathing. But dead space calculated from mean alveolar expired CO_2 concentration, as we have seen, is the same as anatomical dead space, i.e. series dead space. The fall in mean alveolar expired CO_2 in positive pressure breathing is balanced by an increase in alveolar ventilation (about 25% in Folkow & Pappenheimer's study). Since P_{aCO_2} is unchanged, it must therefore give a dead space bigger than the anatomical or series dead space. The difference is attributed by Folkow & Pappenheimer to "parallel" dead space.

The above argument depends upon the assumption that the alveolar gradient exists in space as well as in time. It suggests, nevertheless, that it may be wrong to attribute the increase in V_D which occurs in positive pressure breathing to regional alterations in ventilation-perfusion ratios. It is desirable to reserve the term "parallel dead space" to mean the V_D increment due to such alterations and not to use it whenever V_D exceeds $V_D(An)$, for this may be due to a different cause.

THE DEAD SPACE IN PULMONARY EMPHYSEMA

It is in emphysema that the phenomenon of parallel dead space arises in its most marked degree, and since patients with emphysema were studied in the present investigation it is necessary to discuss the subject briefly.

When a number of alveoli are well ventilated but have a restricted supply of venous blood, their ventilation, as applied to the Bohr equation, is not balanced by a corresponding reduction of P_{aCO_2}, since the latter is weighted in favour of well-perfused alveoli. The poorly-perfused alveoli thus contribute to dead space when this is calculated from arterial CO_2 tension (Comroe et al., 1955). The alveolar air contributed by these alveoli to the total alveolar/$\overset{\text{expired}}{\text{air}}$ has a low CO_2 content. The "parallel" dead space effect does not therefore appear when dead space is calculated from mean alveolar CO_2 or from what was referred to on page 30 as apparent mean alveolar CO_2.

There are, however, a number of factors which influence the dead space, calculated from direct "plateau" samples, in emphysema. Firstly, the net effect of under-perfused, normal and under-ventilated alveoli is to give rise to the need for a high total alveolar ventilation in relation to the rate of CO_2 elimination. This situation is analogous to voluntary hyperventilation in health, and should increase V_D. Secondly, as is well known, the CO_2 plateau in emphysema is steeper than in health, partly at least because poorly-ventilated segments tend to empty later than well-ventilated ones. If end-tidal samples are used, the poorly ventilated alveoli will be preferentially sampled, F_{ACO_2}

will be high, and V_D will be high. Lastly, as a result of bronchial obstruction and "air-trapping", expiration takes longer than normal in patients with emphysema. When CO_2 output is rapid as in exercise there is thus more time for the addition of appreciable amounts of CO_2 to the alveolar air during the course of expiration. This is another factor which may increase the slope of the plateau.

The dead space calculated from direct samples does, in fact, often show an increase in emphysema. Moncrieff (1933, 1934) showed that in chronic tuberculosis, chronic bronchitis, asthma and emphysema the ratio of dead space to tidal volume was as high as 0.7 in severe cases, compared with the normal value of about 0.3. He used end-tidal samples at rest, assuming from preliminary analyses that after the expiration of 500 ml. or more the end-tidal sample contained no dead space gas. He surmised that the high ratios were due to poor mixing within the lungs and stated that this ratio "reveals a type of inefficiency which is quite hidden by the usual determinations of vital capacity" which were current at that time. Previously, Meakins & Davies (1925) had given some figures for pulmonary tuberculosis which yield ratios of about 0.5. These were obtained by the use of Haldane-Priestley samples.

Moncrieff's papers were soon followed by those of Enghoff (1938) and Riley et al. (1946) which drew attention away from the direct sampling method, and nothing more seems to have been done along the lines suggested by Moncrieff. In particular there have not, apparently, been any studies in which an end-tidal technique has been used during exercise

in emphysema. There is some evidence to suggest that unevenness of alveolar ventilation may become more marked during exercise. Otis et al. (1956) have presented theoretical arguments to account for this. End-tidal alveolar samples might be expected to give higher dead space figures in consequence, and it is conceivable that normal or borderline values at rest might become clearly abnormal during exercise.

To summarise, direct alveolar samples from patients with emphysema, while not providing evidence of a true parallel dead space, do give abnormal dead space values. These result from the high CO_2 content of end-tidal samples when the alveolar plateau is steep, from the high overall ratio of alveolar ventilation to CO_2 output, and possibly from defective gas mixing within the alveolar units (to be distinguished from defective <u>distribution</u> to the alveoli). There is reason to suppose that exercise may increase the deviation from normal.

<u>CLASSIFICATION OF DEAD SPACE</u>

It has been possible, in a thesis only partly concerned with dead space, to touch on but a few of the problems in this field. Enough has been written, however, to suggest that the nomenclature of dead space is at present unsatisfactory. By way of summarising the views advanced, the following classification is presented. It has seemed necessary to distinguish parallel dead space from the increase of V_D which occurs in health in positive pressure breathing, exercise and hyperventilation. The latter has therefore been called, for want of a better name, "extension dead

space".

DEAD SPACE

I. Anatomical

(a) By anatomical casts (Loewy, 1894).

(b) By direct measurement (Rohrer, 1911).

(c) By non-respiratory gases - H_2, N_2, He.

(d) By "isosaturation" - "series dead space".

II. Physiological

(a) By arterial P_{CO_2}. Includes anatomical, extension and parallel dead space.

(b) By direct "late plateau" samples. Includes anatomical and extension dead space, not necessarily parallel dead space.

(c) By fractional analysis of expired air (e.g. Aitken & Clark-Kennedy, 1928). Includes anatomical and extension dead space. Excludes parallel dead space.

CHAPTER IV

THE MEASUREMENT OF DEAD SPACE DURING EXERCISE

We have seen that anatomical dead space may be measured by any of the non-respiratory gas methods. These are technically difficult during exercise and some require highly specialised equipment. Anatomical dead space has not been measured in this study.

Physiological dead space can be measured in three ways:

(1) From arterial P_{CO_2}. The difficulty of obtaining arterial blood during exercise is not insuperable, but the technique of blood tonometry is subject to an error of ± 2-3 mm. Hg. When tidal volume is large, as in exercise, this may result in an error of several hundred ml. in dead space (Riley et al., 1954). For this reason, Riley assumes a dead space when V_T is above 2000 ml., and calculates effective alveolar tensions from this instead of from arterial blood P_{CO_2}.

(2) From continuous CO_2 analysis of single breaths (Aitken & Clark-Kennedy, 1928; DuBois et al., 1952). The "apparent" mean alveolar CO_2 content can be determined graphically from the CO_2 curve. Continuous analysis is expensive in equipment. It is also essentially a single-breath method and theoretically subject to random errors. The accuracy of physical methods of analysis does not yet compare with chemical methods.

(3) From "spot" samples of alveolar gas. Haldane-Priestley samples have random errors and tend to give too high CO_2 values in exercise; they also require much

co-operation from the subject. It is, however, possible to collect cumulative samples from any number of breaths during exercise, without disturbing respiration, by means of one of the end-tidal sampling methods. Such a method has been used in the present investigation and merits attention here.

The alveolar CO_2 plateau rises gradually even at rest, and in exercise it becomes steeper. In violent exercise it may rise from beginning to end by 10 to 15 mm. Hg. (Riley, quoted by Donald, 1956). There is thus much room for variation in the composition of a direct sample according to the point on the plateau at which it is taken. Nevertheless, the first requirement is to ensure that the plateau has been reached before the sample is taken. The volume of expirate necessary to wash out the (anatomical) dead space has been given by various authors as follows:

Krogh & Lindhard (1913)	600-800 ml.
Arsenijevic & Knipping (1930)	400-500 ml.
Moncrieff (1933)	400-500 ml.
Haldane & Priestley (1935)	800 ml.
Roelsen (1938)	700 ml.
Fowler (1948)	750 ml.

All these estimates are based on resting data, but since V_D(An) increases comparatively little with exercise the larger figures may be accepted as covering exercise as well.

Justification for the use of end-tidal samples depends upon empirical evidence that they reflect either "apparent" mean alveolar air composition or arterial P_{CO_2} with sufficient accuracy. So far they have been correlated only with P_{aCO_2}. Bannister et al. (1954) reviewed the available data, and agreed with Dill et al. (1927) that in health end-tidal samples during mild and moderately severe exercise show only

small random deviations from P_{aCO_2}. The evidence for severe or exhausting exercise is inadequate. Much remains to be established in this respect, and awaits further study of the CO_2 plateau under different conditions.

THE RESPIRATORY QUOTIENT OF END-TIDAL SAMPLES

Rahn (1949) made 27 resting determinations of end-tidal RQ and expired air RQ in 7 healthy subjects. At rest, tidal volume becomes important in the collection of end-tidal samples; Rahn does not state this but from one of his illustrations it seems to have been about 1000 ml. The mean expired air RQ was 0.828 (S.E. of mean, 0.010) and that of end-tidal air 0.829 (S.E. of mean 0.007). The difference is insignificant. Since the expired air RQ is the same as the alveolar expired air RQ and, by definition, as the effective alveolar air RQ, the implication was that end-tidal samples have the composition of alveolar expired air and of effective alveolar air.

This conclusion is no doubt correct under resting conditions. The alveolar plateau is almost horizontal and there cannot be much difference between the CO_2 content of "apparent" mean alveolar air, true mean alveolar air (alveolar expired air), end-tidal air and effective air. When we consider exercise, however, there arise considerable theoretical difficulties. Firstly, the plateau is steeper and CO_2 differences between various points along it may be substantial. Secondly, with extension of the pre-plateau alveolar gradient into the alveolar units the point at which the true mean alveolar expired air composition and RQ are reached should fall lower and lower on the plateau, while the point

at which the end-tidal sample is taken gets higher and higher as tidal volume increases. If P_{aCO_2} follows end-tidal CO_2, effective alveolar air cannot have the same composition as alveolar expired air; it has the same RQ only by definition. From the practical point of view, therefore, the RQ of a given alveolar sample is not helpful in deciding whether or not it gives a reliable measure of arterial P_{CO_2} or of "apparent" mean alveolar expired air composition.

As a result of sequential ventilation (Fowler, 1952) the less well ventilated alveoli empty later than the better ventilated ones, and the gas contributed by them to the alveolar expired air goes to form the last part of the alveolar plateau. The RQ of this gas is lower than the mean RQ. When tidal volume is large, end-tidal samples will be weighted more by gas of low RQ than when tidal volume is small. One would therefore expect that as tidal volume increases the end-tidal RQ should become lower and lower with respect to expired air RQ. Evidence will be presented later showing that this is so.

THE DEAD SPACE FOR CARBON DIOXIDE AND OXYGEN

As shown by Haldane (Haldane & Priestley, 1935) the dead space for oxygen is not the same as for CO_2 when Haldane samples of alveolar air are used. The difference depends (Rahn, 1949) on the RQ of the sample being different from that of expired air. When the alveolar sample RQ is lower than the mean RQ, as it usually is with end-tidal samples, during exercise, the O_2 dead space is bigger than the CO_2 dead space. This results from the fact that end-tidal air comes from alveolar units with a relatively low ventilation

perfusion ratio, which have a relatively low exchange ratio. End-tidal P_{CO_2} approximates more closely to mean end-capillary P_{CO_2} than end-tidal P_{O_2} does to mean end-capillary P_{O_2}, and the CO_2 dead space from end-tidal samples is closer to the dead space calculated from blood tensions than the O_2 dead space. For this reason the CO_2 dead space has been used in the present study, though the O_2 dead space might be preferable for specific purposes.

END-TIDAL SAMPLING METHODS

Manually operated devices were used by Krogh & Lindhard (1913), Loeb (1920), Trendelenburg (1921) and Schall (1921). Krogh & Lindhard also used an automatic fractional sampler, but Henderson & Haggard (1925) were the first to devise an automatic method for taking end-tidal samples. Various types of automatic end-tidal sampling apparatus have since been used by Clark-Kennedy & Owen (1927), Benzinger & Brauch (1934), Loeschke et al. (1939), Rahn et al. (1946) and Nielsen & Smith (1952). In general, a valve is made to open by the act of inspiration and allows a few ml. of gas to be withdrawn from the end of the previous expiration. This is repeatable over any number of breaths. A possible error is the occasional occurrence of a short expiration which does not clear the dead space. Only one of the devices described (that of Loeschke et al., 1939) made provision to avoid this. The apparatus used in the present work is described in Appendix II.

CHAPTER V

CIRCULATORY FACTORS

The vast literature on the cardiovascular responses to exercise in health and disease has been reviewed by Simonson & Enzer (1942) and by Altschule (1954). Circulatory measurements during exercise present greater technical difficulty than do respiratory measurements and few of them are suitable for an exercise tolerance test capable of routine application.

CARDIAC OUTPUT

There is now ample evidence for the view that a fundamental defect in heart failure is an inability to increase the cardiac output adequately, in amount or speed or both, in response to exercise. If heart output could be easily, accurately and safely measured it would occupy a place of importance in the routine assessment of cardiac function. Hamilton (1945) has criticised the available methods of output determination. He considered that reliable results are only to be had from the direct Fick method, using catheterisation of the heart, and from the dye dilution method of Hamilton et al. (1932) of which there have been a number of modifications. That these techniques can be used during exercise is shown by such studies as those of Donald et al. (1954, 1955), Wade et al. (1954) and Bishop et al. (1955) in which the direct Fick method was used. This method, however, imposes highly artificial conditions and the number of exercise levels which can be studied at one session is limited. Further, catheterisation of the heart cannot be performed more than three or four times on the same subject.

The dilution method is also unsuitable for routine exercise tests. The CO_2 method of Christiansen, Douglas & Haldane (1914) has been modified by Bock et al. (1928) and more recently by Forssander (1950, 1956) in a manner which might permit of routine application, but the accuracy of these modifications remains to be established.

HEART RATE

The relation between heart rate and stroke volume may be expressed as follows:

$$\frac{\text{Oxygen consumption}}{\text{Heart rate}} = \text{Stroke volume x Arterio-venous } O_2 \text{ difference.}$$

Henderson & Prince (1914) called this ratio the Oxygen Pulse. They showed that as exercise intensity increases the Oxygen Pulse (OP) increases also; this rise in OP becomes progressively less so that a plateau is reached. Few of the curves published by these workers showed a terminal fall of OP which might suggest that the limit of efficient heart action had been reached. In general, the highest oxygen pulses were attained by the fittest subjects. Radloff (1931) gave figures for OP, in a study of girl athletes, pointing to the same conclusion. Other published data (e.g. Donald et al., 1954, 1955) show that the OP is often lower in heart disease than in health, for the same exercise intensity. No doubt this is largely due to organic impairment of stroke volume in these patients. In any one subject, however, it is impossible to be sure that the primary disturbance is restriction of stroke volume and not an increase of heart rate brought about by other agencies, notably emotion. Moreover arterio-venous difference is an unknown and varying quantity.

These obvious criticisms seriously weaken the case for using heart rate or OP as an index of cardiac function in exercise. It may be that they lose some of their force as the intensity of exercise increases. Bock et al. (1928), using their modified CO_2 method for determination of cardiac output, showed that arterio-venous O_2 difference increased more and more slowly as oxygen uptake increased. There was little further rise in A-V difference beyond an O_2 uptake of 1600 ml./min. The results of Liljestrand et al. (1938) with Grollman's acetylene method were similar. Any error in these two studies due to recirculation would increase the calculated A-V difference, and this error would increase, rather than decrease, with greater work rate. There are no catheterisation studies, in which a sufficient number of exercises have been done by the same subject, with which to compare these results. Nor do these findings in healthy people, even if correct, necessarily apply in disease. Nevertheless, they suggest that in the higher range of exercise levels an increase in OP indicates an increase in stroke volume, and a fall in OP a fall in stroke volume. Regarding the effect of emotion, there is evidence that as work rate increases and the circulatory system gradually approaches its maximum performance, the influence of emotion diminishes (Cotton et al., 1915; Simonson & Enzer, 1942; Hickam et al., 1948). It is probable, therefore, that with increasing work the OP comes more and more to depend upon physical limitation of stroke volume, and it would follow that the value of heart rate as an index of the performance of the heart is highest at the upper range of exercise

intensity. This can be so only when heart rate is correlated with oxygen uptake; as Knehr et al.(1942), Taylor (1944) and Cogswell et al. (1946) have shown, the maximum heart rate attainable during exercise is of the same order in fit as in unfit people. The work rate achieved at this heart rate is, of course, higher in the fit subject.

Since Bowen's classical description of the effects of exercise on the heart rate in 1904, a number of tests of fitness for athletic and clinical purposes have been based upon measurements of the pulse rate. The athletic applications have been thoroughly appraised by Cureton et al. (1945), Cureton (1947) and Taylor (1944). The tests which are relevant to the clinical problem may conveniently be divided into two categories: 1) those based on pulse counts during recovery from exercise and 2) those which involve pulse counts during exercise itself.

1) Tests based on measurements of the recovery pulse rate

(a) Master's Step-test (Master & Oppenheimer, 1929; Master, 1935). This depends entirely upon a single pulse count taken sitting 2 minutes after stepping up and over a pair of steps of standard height, the number of journeys regulated by the subject's height and weight according to a predetermined scale. Normal performance was assessed in over 400 controls.

(b) The Harvard Step-test (Johnson & Brouha, 1942; Johnson et al., 1942). This test has been widely used as a measure of athletic and military fitness. Though too strenuous in its original form for clinical use, its underlying principle is relevant. The recovery curve of the pulse rate

EX BIBL UNIV ED IN

is approximately exponential and can be adequately characterised if three points on it are known. The pulse is counted from 1 to $1\frac{1}{2}$, 2 to $2\frac{1}{2}$ and 4 to $4\frac{1}{2}$ minutes after stopping a standard step-exercise, and the sum of these counts is incorporated into an index of fitnes. This procedure appears more acceptable than Master's single count.

Master's test has not, as far as I know, been critically re-investigated, but criticisms of the Harvard test might well apply more forcefully to Master's. Cureton et al. (1945) took the better of two Harvard tests and the better of two mile-runs in 117 students of mixed abilities, and found a correlation between these of only 0.310. In a further group of 71 trained men, experienced in the performance of fitness tests, the best step-test result and the best mile-run for each man during six weeks of successive testing were analysed; the correlation between these scores was 0.540. The question of motivation and skill can here be ignored. The correlation is not impressive. Taylor (1944) concluded that the recovery curve of the heart rate is not closely related to the working capacity as estimated by the "time-run to exhaustion" on the treadmill. "It seems clear" he writes, "that one must look to the responses <u>during</u> exercise....for critical measures of fitness for hard work." Baldwin et al. (1948) found that in pulmonary disease there was no relation between pulse counts, during recovery from exercise, and disability.

(c) <u>The "Erholungspulssumme"</u> (Recovery pulse sum, RPS) of Karrasch & Müller (1951), while not put forward as a

measure of fitness, introduced a new way of dealing with the pulse data during the recovery phase. The RPS was measured with a photoelectric pulse counter (Müller & Reeh, 1950). It consists of the total number of pulse beats in excess of the resting pulse level which occur between the end of exercise and the point at which the resting level is regained. The advantage of the RPS is that the precise time at which recovery is regarded as having ended is of little importance, provided it is overestimated rather than underestimated. Karrasch & Müller studied the effects of variations in fitness and of altering the intensity and duration of exercise on the RPS. Their results will not be considered further since it would appear that the RPS, like other derivatives of the recovery curve, is unlikely to be a sufficiently critical index of fitness. These workers admit that the causes of the raised pulse rate after exercise are poorly understood and probably related more to peripheral vascular conditions, muscle tone and posture than to the cardiac state.

2) Tests based on measurements of heart rate during exercise

(a) Wahlund's test (Wahlund, 1948) consists in counting, by auscultation at the cardiac apex, the heart beats for 30 seconds from the beginning of the 3rd, 5th and 7th minutes of exercise on a bicycle ergometer. The working load is increased at fixed intervals every $6\frac{1}{2}$ minutes and the same procedure carried out at each load. The mean heart rate at each load is plotted against the work rate in mKg/min. and the work rate corresponding to a heart rate of 170 is taken as the "working capacity". The rate of 170 beats per minute

was chosen, somewhat arbitrarily, as the limit of efficient cardiac performance. To avoid error from extrapolation the heart rate has to be pushed to somewhere near this level before the study ends - a procedure not without danger in some types of heart disease. Wahlund's paper contains a full statement of his basic data and their statistical analysis. Differences between groups of subjects, normal and abnormal, were found, but it is difficult to appreciate the value of this test in the individual subject. The cardiac and respiratory groups lack clear definition.

Bengtsson (1956) reported the results of an investigation in which Wahlund's test was applied to children.

(b) Astrand & Ryhming (1954), having found that the heart rate after 6 minutes of submaximal exercise could be correlated statistically with the maximum attainable O_2 uptake (the "aerobic capacity"), proposed a test of fitness as follows. The subject exercises by stepping, cycling or walking on a treadmill, and the heart rate after 6 minutes is determined. If the treadmill is used the O_2 uptake during the steady state of exercise is required. The aerobic capacity can then be read off directly from a nomogram constructed from the author's data. The exact work rate is not critical since the nomogram covers a range of rates. Alternatively, if several exercises be done at different rates, the aerobic capacity equals twice the O_2 uptake corresponding to a heart rate of 128 in males and 138 in females. This figure is obtained by interpolation. The basic data were obtained (Ryhming, 1954) from 15-second pulse counts by palpation of the radial artery during

exercise, a method which might seem liable to error. While there is general correlation between calculated and determined aerobic capacities, there is much individual scatter in the published figures. Astrand and Ryhming suggested that this test might find a place in clinical practice because it makes use of the lower range of exercise intensities.

(c) The "Leistungspulsindex" (Performance pulse index PPI) was proposed by Müller (1950b) as an index of fitness for use in the industrial and sporting fields. The heart rate was counted with the photoelectric pulse counter during several exercises of increasing severity on a bicycle ergometer. After correction of the pulse rate in each exercise for the fatigue-rise ("Ermudungsansteig") he plotted the corrected figure against working intensity in mKg/sec. The slope of the regression line was the PPI. The correction of the pulse rate appears rather arbitrary and difficult to apply to the pulse curves obtained in practice. However, Müller goes on to describe the test recommended for routine use, in which the correction plays no part. Exercise is performed against continuously increasing resistance and the pulse rate is recorded throughout. The slope of the pulse rate against work rate is taken directly as the PPI. The independent criterion of fitness with which the index was compared was an estimate of maximum performance on the bicycle ergometer. A group of 23 subjects showed a correlation coefficient between the index and the maximum performance of 0.70. The index was found to decrease (i.e. improve) during a training programme in 2 subjects. Müller did not suggest a clinical use for this test. It should be especially

noted that the absolute value of the heart rate has no part in the PPI; this concerns only the slope of the heart rate/work rate regression line.

These three tests have not been evaluated by other workers, and do not at present appear to be widely known. They merit attention because they differ in principle from the older tests. The accurate measurement of heart rate during exercise is now readily accomplished by the use of an automatic cardiotachometer (Austin & Harris, 1957), and from the technical point of view any of these tests could be applied in routine clinical work. They show, according to the published data, clear differences between dissimilar groups of subjects, but any one subject may deviate appreciably from his group and show poor correspondence between his test score and his independent criterion. These facts raise doubt as to whether the tests are sufficiently precise in the individual case to be clinically useful.

Two empirical observations may be mentioned in concluding this section. Bierring et al. (1936) noted a biphasic recovery curve in cases of angina of effort, the pulse rate falling transiently below the resting level shortly after the end of exercise, then rising and resuming its ordinary downward course. This was supposed never to happen in health, but there is some evidence that it does (e.g. Peabody & Sturgis, 1922; also personal observations). In 1934 Gilchrist pointed out that the usual correlation of high working heart rates with low exercise tolerance is reversed in heart block. He found the greatest disability in those patients

who showed the smallest increase in heart rate during exercise.

ARTERIAL BLOOD PRESSURE

The effect of exercise on the systemic blood pressure in man was studied by Barringer (1916a, 1916b, 1917). He recorded the systolic blood pressure (BP) by sphygmomanometry at frequent intervals after the end of a period of exercise and found that as the work rate increased there appeared a delayed rise in systolic BP, which reached a peak 1-2 minutes after stopping exercise. Patients with "cardiac insufficiency" began to show the secondary rise after lower work rates than healthy people. Barringer took his first BP reading 20-30 seconds after exercise. Cotton, Rapport & Lewis (1917), who took the first reading immediately afterwards, showed that the delayed rise is present in health after even small amounts of exercise, and it was clear that Barringer had missed this observation by a technical oversight. These papers illustrate the difficulty of following accurately the course of BP changes during and after exercise. The development of electronic methods of pressure measurement has made this easier. Eskildsen et al. (1950), using a capacitance manometer, found that BP rises rapidly after the start of work to reach a plateau. When exercise stops it falls, at first rapidly, then more slowly, until after 4-5 minutes it is often much lower than the previous resting level. Diastolic BP varies less than systolic, thus pulse pressure rises. These authors did not mention the rebound phenomenon during early recovery. Its absence may be due to the posture adopted: the subjects used a

"sofa-bicycle" and were presumably lying down. Fraser & Chapman (1954) used a strain gauge and their subjects exercised on a treadmill at 3 m.p.h. and 5% gradient. Rebound was noted in some cases. No patients were studied in either of these investigations. It is clear that more facts are needed before BP measurements can be used to assess exercise tolerance.

CHAPTER VI

OTHER FACTORS IN OXYGEN AND CARBON DIOXIDE EXCHANGE. TESTS OF THE OVERALL EFFICIENCY OF THE OXYGEN-TRANSPORT SYSTEM

The first and third factors listed in Chapter 2 have now been considered. There remain for discussion the pulmonary diffusing capacity, the state of the blood vessels to and from the active muscles, the tissue enzymes and the O_2 and CO_2 carrying power of the blood.

THE PULMONARY DIFFUSING CAPACITY

Diffusing capacity increases during exercise, presumably owing to an increase in the surface across which diffusion may occur. Available evidence (Riley et al., 1954) suggests that there is a maximum diffusing capacity which is reached during moderate exercise and then remains constant with further increase in exercise intensity. In pulmonary disease, the resting diffusing capacity and the maximum capacity elicited by exercise may both be lowered (Riley et al., 1952). This may therefore be an importance cause of limitation of exercise tolerance. At present, the determination of diffusing capacity requires an exacting technique and can be undertaken in few laboratories.

THE BLOOD VESSELS

Limitation of exercise tolerance due to obstruction of the limb vessels exhibits the features of intermittent claudication and is clinically characteristic. It merits attention here mainly because it may result in more general disturbances of gaseous exchange (Saha, 1956). Exercise of ischaemic leg muscles is physiologically akin to the exercise

of small muscle groups in the arms, the hallmarks of which are a lower maximum oxygen consumption and the contraction of an oxygen debt at lower rates of work. Since ischaemic pain may be an inconsistent accompaniment, such findings may be misinterpreted as evidence of cardiorespiratory failure.

THE TISSUE ENZYMES

There can be no doubt that the enzyme systems concerned with oxygen utilisation in the tissues constitute an important element in the compensatory mechanisms of heart and lung failure. Donald et al. (1954) found that the oxygen saturation of pulmonary artery blood fell during exercise to 6% in a patient with mitral stenosis and anaemia. Matthews and I studied a similar patient whose pulmonary artery blood showed zero saturation during exercise; this remarkable result was obtained by both photometric and van Slyke analysis. These findings imply that towards the venous end of the muscular capillary bed oxygen was being delivered to the cells at a negligible pressure gradient. It seems possible that impairment of the oxidation-reduction processes in muscle may sometimes be responsible for failure of this particular mode of adaptation to exercise, for example in vitamin deficiency states. This must remain, at present, imponderable.

OXYGEN AND CARBON DIOXIDE CARRYING CAPACITY OF BLOOD

Anaemia is a common cause of reduction of exercise tolerance and needs no further discussion. The CO_2 combining power of the blood as a factor in the adaptation to exercise is often overlooked but is also important. Clark-Kennedy & Owen (1927) were among the first to suspect failure

of CO_2 transport as a possible factor limiting exercise in health. During moderate and severe effort, acid metabolites from the active muscles are partly buffered by plasma bicarbonate, and CO_2 combining power diminishes (Barr et al., 1923; Bock et al., 1927). The addition of CO_2 to the blood thus causes a bigger change in pH under these conditions, and more blood (i.e. an increased blood flow) is necessary to carry the same amount of CO_2. A high alkali reserve is thus an advantage in that heavier exercise can be done before this point is reached. In all probability, as suggested by Clark-Kennedy & Owen, the limits of O_2 transport and CO_2 transport are normally reached more or less together. However, Robinson & Harmon (1941) and Knehr et al. (1942) found that the resting alkali reserve is no higher in athletes than in sedentary subjects, and does not increase with physical training. Pathological reduction of alkali reserve is unlikely to be an important cause of limited exercise tolerance.

TESTS OF THE OVERALL EFFICIENCY OF THE OXYGEN TRANSPORT SYSTEM

A. OXYGEN DEBT

The oxygen transport system may fail during exercise in two ways. As has been shown many times (e.g. Meakins & Long, 1927), the oxygen uptake in disease of the heart or lungs may reach its steady state more slowly than in health even when the O_2 consumption during the steady state is below the aerobic capacity. Alternatively, the exercise may be above the crest-load and a true steady state unattainable.

In either case work is done anaerobically, and therefore inefficiently (Christensen & Högberg, 1950). The oxygen debt must be repaid with interest during recovery. An excessive oxygen debt after standard exercise in cardiorespiratory disease has been demonstrated repeatedly; Simonson & Enzer (1942) give references. This observation is the basis of two tests of working capacity.

(a) The "Metabolic exercise tolerance test" of Katz et al. (1934). These workers measured the oxygen debt with a Benedict-Roth spirometer during a standard exercise and recovery. The exercise was done on a weight and pulley device operated by the arms and wheeled to the bedside when necessary. The O_2 requirement, O_2 debt and the time taken to regain the resting metabolism were all greater than normal in patients with heart failure, and increased progressively throughout the clinical grades.

(b) Nylin's test (Nylin, 1933, 1938). After a fixed amount of exercise on a spiral staircase the oxygen uptake was measured with a Krogh spirometer during the 2nd to 5th minutes of recovery inclusive, and the mean O_2 uptake during this time found by dividing by four. The percentage excess of this figure over the resting O_2 uptake was called the "relative oxygen debt" and this was worked out for three different exercise intensities in 265 normal subjects. Patients with various cardiac and respiratory disorders showed increases of relative O_2 debt which corresponded in general with their clinical severity. Cardiorespiratory neurotics gave normal results.

These two tests have firm theoretical support. They

comprehend in a single, simple measurement the final expression of failure at one or more points of the oxygen-transport mechanism, and it would seem impossible for the result to be influenced by psychoneurosis or malingering. Both tests can be done at a level of exercise intensity low enough to match the capacity of the most disabled person, or high enough to approach the borderline between health and minimum disability. With suitable modification of detail it should be possible to attain considerable precision. The measurement of O_2 debt does not, however, reveal the nature of the disturbance present, and could be useful only as a "blanket" test to distinguish real from imagined disability, or to follow the variation in exercise tolerance in the individual patient.

B. THE "PHYSICAL FITNESS INDEX"

Bruce et al.(1951) attempted to combine ventilatory and circulatory data during exercise in a "physical fitness index". Three standard treadmill exercises were used and the index calculated in a given case at one or other of these.

$$\text{Physical Fitness Index} = \frac{\text{Duration of exercise x Mean exercise OE}}{\text{Total number of heart beats for 3 minutes of recovery.}} \times 100$$

For repeatability, the PFI was determined in duplicate on successive days in 15 hypertensive subjects. Duplicates differed by up to 20%. The PFI was said to improve following surgical treatment of mitral stenosis (Bruce et al., 1953, 1956). The value of this index is as yet unproved by other workers.

CHAPTER VII

THE PRESENT INVESTIGATION

The original object of this work was to find out whether a reliable estimate of exercise tolerance could be made from simple measurements of the cardiorespiratory response to exercise, with particular reference to various indices of performance already proposed by previous workers. The problem of the independent criterion of fitness has been mentioned. To circumvent this in the present study required the comparison of healthy subjects known to differ in fitness; and, since the purpose of the study was primarily clinical, of patients known to differ in disability. The least objectionable way of doing this is to use each subject as his or her own control. So far as healthy subjects are concerned, this means following a group of unfit people through a programme of physical training. The practical difficulties of this method were considerable, and instead a number of subjects were studied whose fitness could be regarded as moderate, good or excellent. A group of fit old men was investigated to cover possible age differences. With patients, on the other hand, it seemed especially desirable to make each one his own control, since the comparison of different patients, however carefully they were selected to present differences only of severity and not in quality of structural disease, was likely to introduce difficulties not easily overcome. It was thus desirable to study each patient in two states of disability as far apart as possible, and to compare these.

A way in which these conditions might be satisfied at once suggested itself. Surgical valvotomy in suitable cases of rheumatic mitral valve disease may be expected to result in a rapid and substantial improvement of exercise tolerance. Physiological study of such cases before and after operation might be expected to provide objective evidence of improvement in patients who showed dramatic relief in other respects. At the time of this investigation there was no shortage of suitable patients in Edinburgh. They would, however, have had to travel a quarter of a mile from the hospital to the physiology laboratory which was housed in a non-clinical department. The physician in charge of these patients took the view that clinical physiology should be pursued within the hospital in so far as it involves experiments on hospital patients, and felt obliged to withhold his support and consent.

This decision, with which few would disagree, was finally made after half the time available for the study had elapsed. Alternative arrangements for the clinical part of the study had to be made. It happened that another investigation was being started in which the effect of hypothyroidism, induced by radio-iodine, on the exercise tolerance of patients with severe emphysema was to be studied, and for which treadmill experiments were desirable. An attempt was made to satisfy the needs of both studies simultaneously. The emphysema patients were , however, very badly handicapped since only such patients were thought suitable for initial study of an unproven method of treatment. One result of this was that the information obtained from

them was, from the point of view of the present investigation, very limited.

The practical usefulness of the results is, therefore, not as great as had been hoped, but enough of intrinsic interest emerged from the study to make a consideration of the data not altogether unprofitable.

EXPERIMENTAL SUBJECTS

Healthy subjects

Fifteen healthy University undergraduates were studied. All were examined clinically and no abnormality found, and all had had normal reports on recent chest X-rays. No deliberate attempt was made to select these subjects, except for A.J. They were, however, paid volunteers, and there was perhaps some bias towards the health-conscious and hard-up.

A.J., male, aged 22, was a middle and long distance runner of international standard. He won the 5000 metres event at the Mannerheim Games at Helsinki, 1956, in 14 min. 13.6 sec. The world record for this distance, set up by Pirie, stands at 13 min. 36.8 sec. A.J.'s gross weight (clothed as during the experiments) was 61.7 Kg and his height 168.6 cm. He was studied on 25th, 28th and 29th June, 1956.

Details of the remaining students are given in the following table. They were questioned about their recreational activities and their fitness arbitrarily classified as moderate or good. To attempt more precise classification than this seemed unwarranted.

Table II

Details of 14 healthy students

Subject	Age	Sex	Height (cm)	Weight (Kg)	Fitness
RKT	23	F	163	64.7	Good
PJ	22	M	183	86.0	Good
MP	26	M	182	74.4	Good
WGR	20	M	190	84.8	Good
John G	24	M	172	58.0	Moderate
HMM	20	M	186	77.5	Good
Janet G	19	F	159	56.3	Good
WGP	21	M	183	76.8	Good
CW	21	F	155	48.0	Good
BH	20	F	163	64.0	Moderate
JK	20	F	170	65.0	Moderate
FMcG	19	F	167	70.2	Moderate
MB	19	F	170	77.8	Moderate
RF	19	F	158	56.9	Moderate

There were two subjects, both doctors, of intermediate ages. MBM, aged 35, male, height 178 cm., weight 77.7 Kg.

JGT, aged 47, male, height 179 cm., weight 88.7 Kg.

Five old men were selected from a larger group on the basis of clinical, radioscopic, and electrocardiographic examinations. While there is no adequate definition of what constitutes good health in old age, these five men were, by any standards, very fit for their years. The principal findings in this group were as follows.

JW, aged 77, height 163 cm., weight 78 Kg. No relevant complaints. Heart normal, no signs of failure. BP 220/110. Moderate arteriosclerosis. Retinae grade 1 (Wagener & Keith, 1939). Lungs - occasional rhonchi. Moderate obesity. Radioscopy - Left ventricle moderately enlarged, aorta unfolded, lung fields clear, high diaphragm (obesity). ECG - horizontal heart.

AG, aged 79, height 170 cm., weight 72.6 Kg. Some "rheumatism" in the legs, without objective signs. Heart - systolic murmur, ? aortic sclerosis. BP 140/70. Moderate arteriosclerosis. Retinae grade 2. Radioscopy - Left ventricle slightly enlarged, aorta elongated, paradoxical

movement of left side of diaphragm, presumably dating from ? hydrothorax 23 years ago. ECG normal.

RE, aged 75, height 161 cm., weight 74.5 Kg. No complaints; regular walk of several miles most days. Heart and lungs clinically normal. BP 165/95. Retinae - bilateral senile cataract. Moderate obesity and arteriosclerosis. Radioscopy - high diaphragm, transverse heart, aorta unfolded, lungs clear. ECG - horizontal heart.

TS, aged 72, height 173 cm., weight 81.5 Kg. Still working as railway porter; some "rheumatism". Heart and lungs normal. BP 150/95. Retinae grade 1. Radioscopy - aorta elongated, no other abnormality. ECG - horizontal heart.

HD, aged 70, height 162 cm., weight 63 Kg. No complaints. Heart and lungs normal (heart rate 40/min.) BP 180/80. Retinae normal. Radioscopy - left ventricle slightly enlarged, lung fields clear. ECG - sinus bradycardia, horizontal heart.

Patients

Seven men suffering from chronic bronchitis and emphysema were investigated. They were all made breathless by very slight exertion. Details are given in Table III. I am indebted to Dr. I. W. B. Grant for the data on lung volumes, "mixing efficiency" and maximum breathing capacity. "Mixing efficiency" was determined by the closed circuit method of Bates & Christie (1950) as modified by Needham et al. (1954).

PROCEDURE

The subject attended the laboratory at 9.30 a.m., at least 1 hour after a light breakfast. He was warned not to smoke or drink coffee, or to hurry to the laboratory before the experiment. Loose clothing and fairly light shoes were the rule. For 5 to 10 minutes he was allowed to become accustomed to the motion of the treadmill and to the respiratory apparatus. During this preliminary period instruments were checked and a speed chosen at which the

Table III

Details of seven patients with emphysema

A = actual, P = predicted normal

SUBJECT		PC	SS	DC	JS	AM	WC	GS
Age		58	65	50	62	54	60	62
Height (cm.)		173	163	179	181	163	169	171
Weight (Kg.)		56	56	63	85	69	47	66
Total lung capacity (ml.)	A	7320	5410	6480	8260	5820	5980	6110
	P	5900	5600	6200	6500	5800	5750	5850
Vital capacity	A	1620	2000	2010	2610	1720	1600	2360
	P	3500	3200	3700	3700	3400	3250	3400
Inspiratory capacity	A	1270	1500	1170	2510	1370	1050	1510
	P	2600	2400	2700	2800	2500	2380	2550
Expiratory reserve volume	A	350	500	840	100	350	550	850
	P	900	800	1000	900	900	870	850
Functional residual capacity	A	6050	3910	5310	5750	4450	4380	4600
	P	3300	3200	3500	3700	3300	3370	3300
Reserve volume	A	5700	3410	4470	5650	4100	3930	3750
	P	2400	2400	2500	2800	2400	2500	2450
Mixing efficiency	A	80%	40%	50%	36%	60%	57%	50%
	P	>60%	>60%	>60%	>60%	>60%	>60%	>60%
Maximum breathing capacity (l./min.)	-A	16	22	31	25	24	14	22
	-P	101	92	110	98	115	98	97

subject could walk comfortably on the level. He then sat on a chair on the treadmill until heart rate, ventilation rate and respiration rate were steady; these were next recorded and expired air collected for 8 minutes, the subject remaining seated. No attempt was made to secure basal conditions.

The first exercise period then followed at the chosen speed with the treadmill level. Five seconds before the exercise was due to begin the order "Stand" was given, and second intervals counted aloud, ending with "Start" at zero time. An anticipatory rise in heart rate was usually seen during these five seconds, and a rise in ventilation rate no doubt occurred as well. However, all subjects went through the same routine. The exercise continued for 6 minutes. The last five seconds were counted aloud, and on the order "Stop" the treadmill was stopped and the chair replaced upon it. The subject sat quietly until heart rate, ventilation rate and respiration rate had returned to the previous resting level or until, after a recovery period of at least 20 minutes, these had been approximately constant for 5 minutes. A short rest then followed, during which the respiratory tubing could be washed out; the subject was asked to empty his bladder at this point if he wished, to avoid possible reflex circulatory effects from bladder distension. The next exercise followed immediately at a higher gradient, and the whole procedure was repeated. During the course of the morning up to 8 exercises were done, the gradient increasing for each exercise at regular intervals. The object was to cover the whole of the subject's range up

to the point of definite discomfort but not of distress. This aim was realised in most of the young people, but for various reasons the old men were not pushed as far as they probably could have been.

The patients were studied according to a slightly different plan, but in any case the number of exercise levels in this group would have been limited by their gross disability. In each case there were two exercises in which the data were suitable for inclusion in the present study. One patient (GS) was unable to complete the routine 6 minutes' exercise on preliminary testing, and in this case the duration of exercise was reduced to 5 minutes.

Throughout exercise and recovery the heart rate, ventilation rate and respiration rate were followed continuously every half-minute. During the last two minutes of exercise samples of expired and end-tidal air were taken and the temperature of expired air was noted.

The following calculations were made from the experimental data:

1. Exercise heart rate (EHR): the mean heart rate during the last two minutes of exercise.

2. Standardised heart rate (SHR): the total number of beats during the whole of exercise and recovery were calculated, and from this was substracted a figure representing the number of resting heart beats for this period. The result was divided by the duration of exercise in minutes and the quotient was added to the mean resting heart rate per minute. To determine mean resting heart rate the initial resting rate before exercise, and the final resting

rate after it, were averaged. The final resting rate was taken as the lowest number of beats over any two consecutive half-minutes in the last three minutes of recovery. This number served as the initial resting rate for the next exercise period unless a substantial time, or unavoidable activity, separated one exercise from the next. In the calculation of SHR a small error in the measurement of resting heart rate is largely eliminated in the final result.

3. Exercise ventilation (EV): the mean ventilation rate in l./min. during the last two minutes of exercise.

4. Standardised ventilation (SV): calculated as for SHR save that ventilation rate was substituted for heart rate. Final resting ventilation was the mean ventilation during the last two or three minutes of recovery; some discretion was necessary here because of slight resting fluctuation of ventilation rate and the small quantities involved.

5. Oxygen extraction (OE): $F^{c}_{IO_2} - F_{EO_2}$.

6. Carbon dioxide discharge (CO_2D): $F_{ECO_2} - F_{ICO_2}$.

7. Alveolar CO_2 pressure (P_{ACO_2}): $F_{ACO_2} \times (B-47)$. F_{ACO_2} was estimated from the end-tidal sample; B = barometric pressure.

8. Physiological dead space (V_D): CO_2 values were substituted in the Bohr equation.

9. Oxygen uptake and carbon dioxide output during the last two minutes of exercise.

10. Respiratory Quotient (R_{ET} or R_E) for end-tidal and expired air: $R_E = CO_2D/OE$.

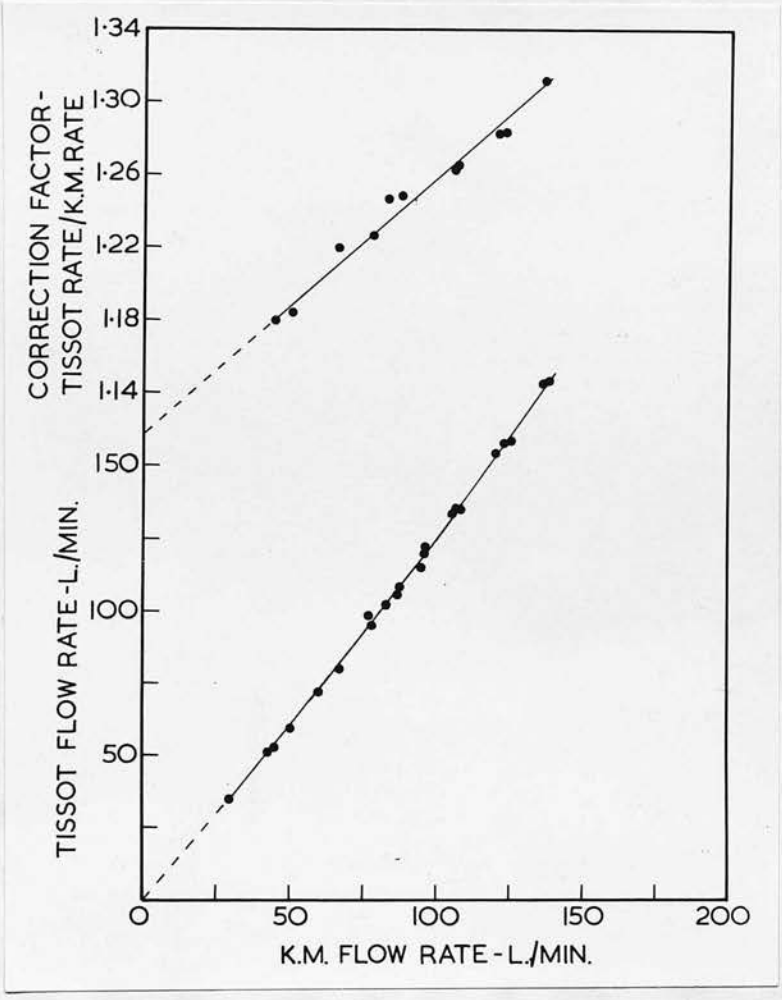

Fig. 6

Calibration characteristics of Kofranyi-Michaelis respirometer.

METHODS

Heart rate

An electronic cardiotachometer (Austin & Harris, 1957), described in Appendix I, was used to drive a ratchet and pawl mechanism coupled to a paper-drive. The paper thus moved forward a short distance with each heart beat. Time marks were inscribed every 30 seconds on the paper. Heart rate was proportional to the distance between time marks and could be read off directly on a calibrated rule. During experiments the rate could be quickly counted to within 3 beats per minute by a scaling device which marked every 10 beats on the paper, but the rule was always used for accurate analysis of the record. A Post Office counter, driven by the cardiotachometer, recorded heart beats over long periods.

Expired gas volumes

A dry gas meter (Kofranyi & Michaelis, 1940) was used. It was calibrated by passing air from a 100 l. Tissot spirometer through it at different rates measured by stopwatch. In Fig. 6 the flow-rate indicated by the Tissot scale is plotted against the flow-rate calculated from the meter readings. The meter progressively under-records as flow-rate increases. This is probably due to at least two causes: 1) a true instrumental calibration error which may or may not remain constant at all rates of flow; 2) the resistance of the meter, which sets up a back-pressure which increases as flow increases. Under conditions of turbulent flow the back pressure increases as the square of the flow-rate. At the moment of its measurement in the meter,

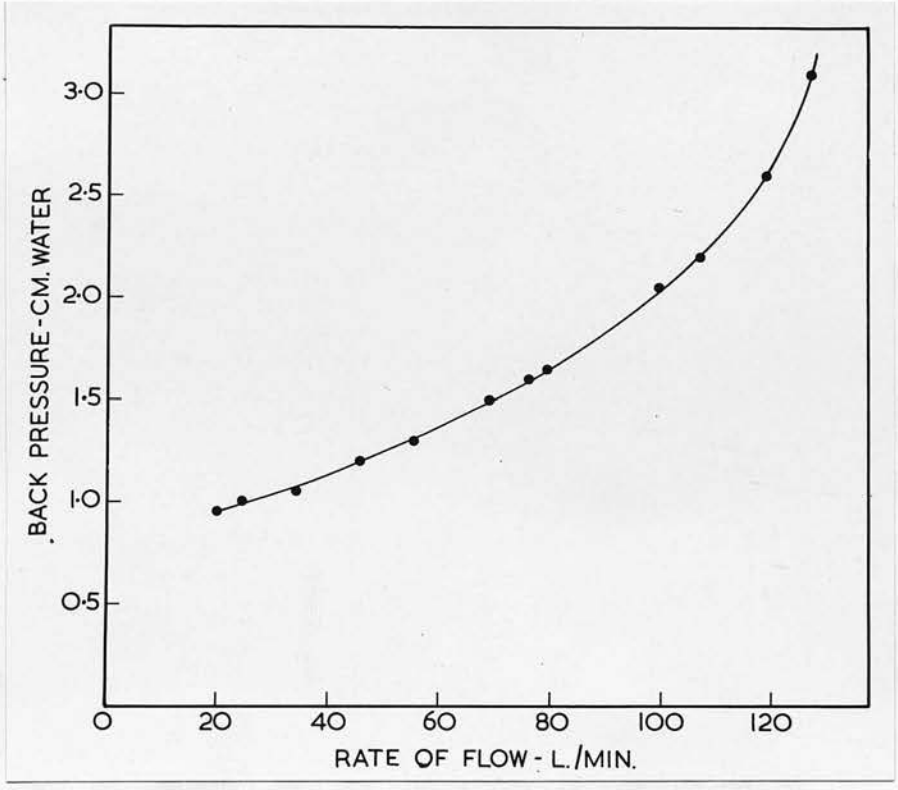

Fig. 7

Back-pressure exerted by respirometer at different rates of flow.

therefore, the gas is compressed, and the relative reduction in its volume must be proportional to the square of the flow-rate. According to this view, the progressive under-recording of volume by the meter is a direct result of its resistance.

In practice it is convenient to use the upper part of Fig. 6 where the ratio of true (Tissot) flow-rate to meter flow-rate is plotted against the meter rate, and the regression line calculated. This gives the appropriate correction factor to be applied to a given flow-rate as recorded by the meter. The data for Fig. 6 were, however, obtained at constant rates of flow, and cannot be applied as they stand to the intermittent flow of respiratory experiments. Assuming that expiration occupies half a cycle, the recorded flow-rate over an interval of time is half the effective mean flow-rate through the meter, since during inspiration the meter is idle. For a given recorded flow-rate, therefore, the correction factor used was the one corresponding to twice that rate. Short of calibrating the instrument by intermittent flow as described by Cooper (1955) I believe that the procedure outlined gives the most accurate results available. The meter was calibrated twice at an interval of three months and the data from both calibrations are combined in the lower part of Fig. 6. They are remarkably consistent.

Fig. 7 shows the back-pressure set up by the meter during steady flow. Beyond 120 l./min. (corrected rate) the back-pressure rises steeply. If we assume that the curve of volume-flow with time, during expiration, is half a

sine-wave (Cooper, 1955), the peak rate of flow through the meter is about 2.83 times the observed, corrected ventilation rate. At ventilation rates above 40 l./min the meter probably interfered significantly with breathing because of the back-pressure set up at peak rates. In fairness, it should be recalled that the meter was not designed for work involving such high ventilation rates.

The meter was fitted with a switch which closed a circuit each time 1 litre (meter dial) passed through. A pen was thus activated to mark each litre on the recording paper, and a Post Office counter provided counts over long periods.

Expired gas samples

The meter sampling tube delivered gas into small rubber bladders. The usual precautions were taken to minimise loss of CO_2 through the bladder wall and to compensate for instrumental dead space. From the bladders gas was transferred to glass sampling tubes immediately after the collection period, stored under slight pressure and analysed in the Haldane apparatus. Duplicate analyses were required to agree to within 0.05 vol. % for both CO_2 and O_2. Usually an accuracy of $\pm$ 0.03 vol. % was obtained without difficulty.

Reliability

To test the accuracy of the methods of recording ventilation and collecting and analysing expired air, the following experiment was done. A healthy trained subject walked for 5 minutes at 4 m.p.h. level and 4 m.p.h. up a gradient of 14%, on each of two occasions. Ventilation was recorded automatically and expired air collected separately

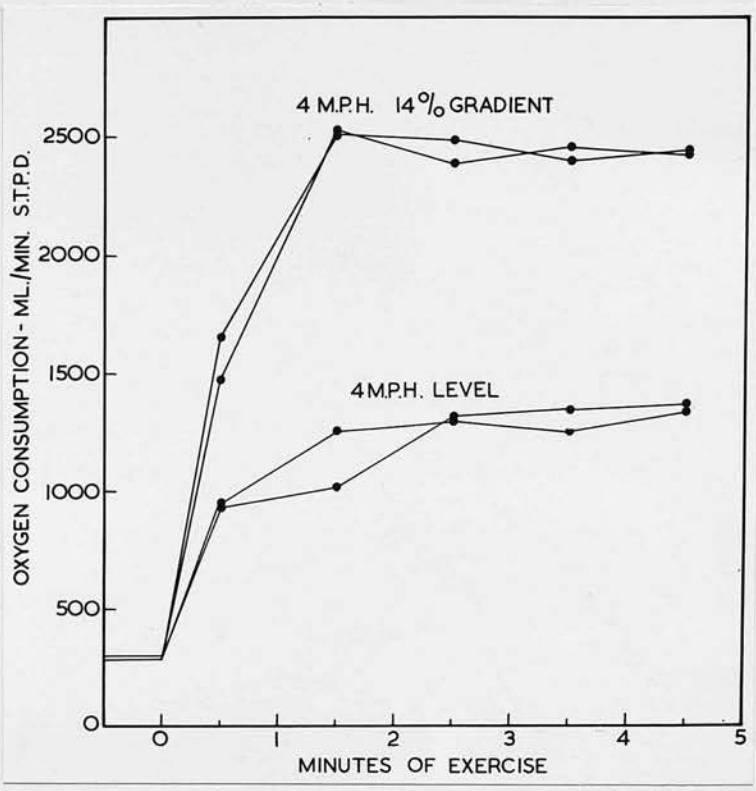

Fig. 8

Duplicate minute to minute determinations of oxygen uptake at two rates of work.

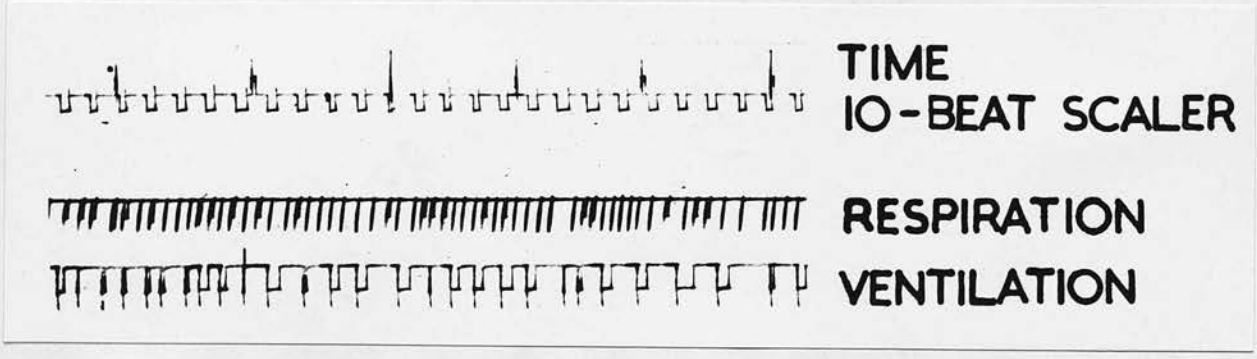

Fig. 9

Record of heart rate, ventilation rate and respiratory frequency.

for each minute of each exercise. In Fig. 8 the oxygen uptake has been plotted against time at the mid-point of each minute. The differences between the corresponding values of $\dot{V}_{O_2}$ during the last three minutes at both exercise levels were within physiological limits. This experiment suggested that the automatic record gave reliable minute-to-minute estimates of ventilation. In practice it was used only for long counts as a check on the meter readings. The meter dial was always read to the nearest half-litre at the beginning of exercise, after 4 and 6 minutes of exercise and at the end of recovery.

Mouthpiece

A conventional Siebe-Gorman mouthpiece was used. It contained two light rubber valves fixed at their centres. The right-angled bends of these mouthpieces give rise to unnecessarily high resistance but they were the only ones available which could be relied upon not to leak. In any case, the resistance of the meter was greater. The dead space of the mouthpiece was 50 ml., measured by filling it with water. Corrugated rubber rubing of 2.5 cm (smallest) internal diameter connected the mouthpiece to the respirometer.

Respiratory frequency

The trigger of the end-tidal sampling device (see Appendix II) provided a signal with each inspiration and this was made to move another recording pen and counter. Heart rate, ventilation and respiratory frequency were thus all recorded continuously on the same strip of paper. A specimen record is shown in Fig. 9.

UNITS

All ventilatory data have been expressed at body temperature, ambient pressure and saturated with water vapour (BTPS). Oxygen uptake and CO_2 output were corrected to 0°C, 760 mm. Hg, dry (STPD).

CORRECTION FOR BODY SIZE

All gas volumes were corrected, by simple ratio, to a standard body weight of 65 Kg. A corrected volume is indicated by adding a superscription to the appropriate symbol; e.g. $\dot{V}_{O_2}^{65}$ means the oxygen uptake per minute corrected to 65 Kg. body weight.

RESULTS

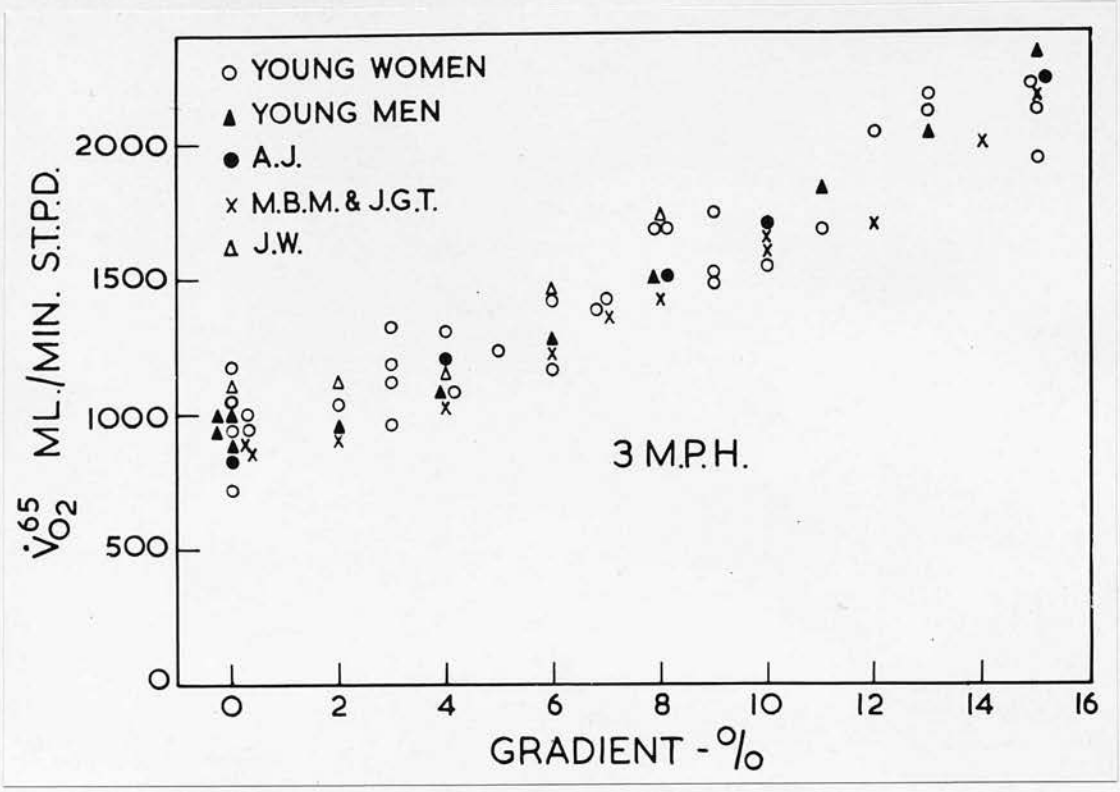

Fig. 10

Relation of oxygen uptake to gradient at 3 m.p.h.

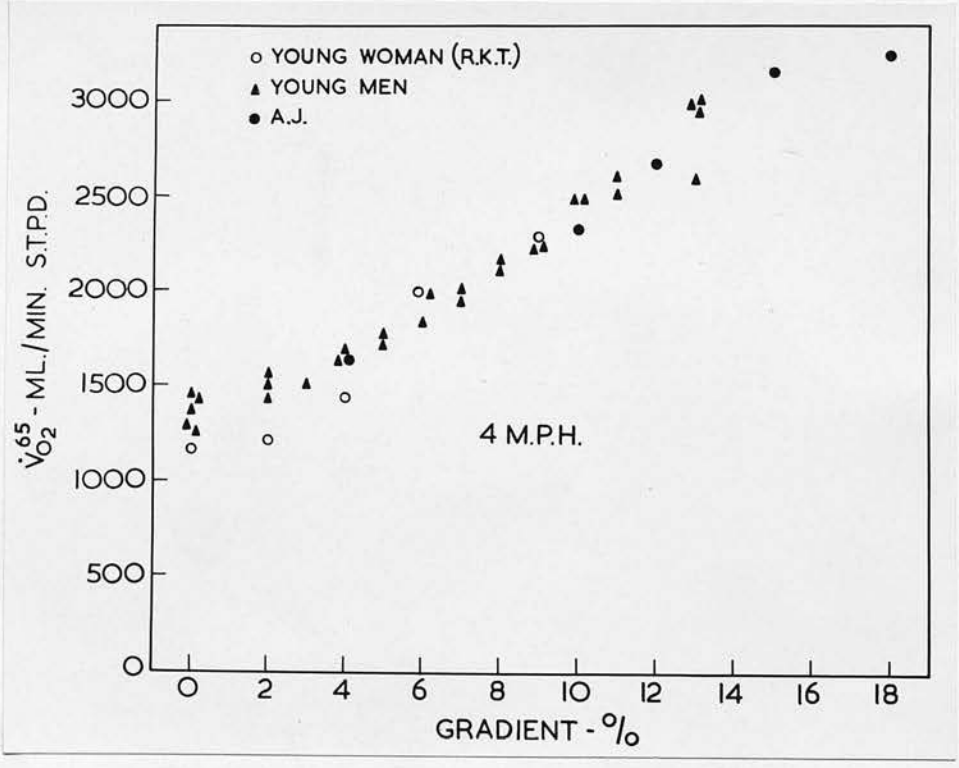

Fig. 11

Relation of oxygen uptake to gradient at 4 m.p.h.

CHAPTER VIII

MECHANICAL EFFICIENCY

One obvious way in which an individual may be capable of more work than another is by exercising more efficiently. It is worth examining the experimental data from this aspect.

The speed at which the subjects walked was largely a matter of convenience. Thus most of the young men walked at 4 m.p.h. and most of the women at 3 m.p.h. MBM and JGT both exercised at 3 m.p.h. At these speeds enough data are available for certain comparisons to be made. The old men, except for JW, were more at ease at 2.5 m.p.h. and the patients had to use the lowest possible treadmill speed, 1.375 m.p.h. Of these groups, therefore, only JW can be compared with the students.

Figs. 10 and 11 show the oxygen uptake, corrected to 65 Kg. body weight, plotted against gradient at 3 and 4 m.p.h. There is clearly no significant difference in mechanical efficiency between the young men and women, or between these and AJ, MBM, JGT or JW.

These figures show also the approximately linear relation between oxygen uptake and gradient. This relation was much more exact in the individual case, as has been shown many times (Passmore & Durnin, 1955). The scatter in Figs. 10 and 11 undoubtedly results in part from the imperfections of weight correction. Other factors are involved in the energy expenditure of walking. One of these, the stride rate (Lehmann, 1953), was measured in these experiments. It was not possible to improve the correlation by

introducing a correction for stride rate, and since it is not relevant to the subject of this thesis it is not discussed further.

CHAPTER IX

THE COMPOSITION OF END-TIDAL AIR

The factors which determine the composition of expired air at different phases of expiration, and the significance of the RQ of alveolar air samples, have been discussed. The composition of the end-tidal samples obtained in the present study is indicated in Table VII in the appendix. The RQ of each sample was calculated and compared with the RQ of the corresponding expired air sample. It was often found that when tidal volume was low the end-tidal RQ was higher than the expired air RQ and that as tidal volume increased this difference was gradually reversed. The following example shows this.

Subject J.K.

V_T (ml.)	Expired RQ	End-tidal RQ	$R_E - R_{ET}$
1384	0.794	0.813	-0.019
1412	0.768	0.779	-0.011
1619	0.848	0.851	-0.003
1646	0.867	0.854	+0.013
1652	0.804	0.806	-0.002
2397	0.935	0.886	+0.049

As tidal volume increases, the end-tidal sample is taken later and later with respect to the mean point of the alveolar plateau. One would therefore expect that the end-tidal RQ should differ more and more from the RQ of expired air, but that the former should always be less than the latter. In the above example the direction of change with increasing V_T is according to expectation. At the lower tidal volumes, however, end-tidal RQ is greater than expired RQ. This can be explained only by supposing that at low tidal

volumes alveolar air was sampled earlier than the mean point, and that as V_T increased the sampling time first came to coincide with the mean point and later came after it. This was thought to result from the method used to obtain end-tidal air, since with the manometer switch used originally (see Appendix II) the valve leading to the end-tidal sampling tube could sometimes be seen to open just before the end of expiration. However, when the manometer switch was later replaced by a tambour-operated one, which caused the sampling valve to open only at the onset of inspiration, the same pattern of RQ differences was found. This is well illustrated by the findings in A.J., for whom the tambour switch was used.

Subject A.J.

V_T (ml.)	Expired RQ	End-tidal RQ	$R_E - R_{ET}$
781	0.777	0.813	-0.036
891	0.784	0.801	-0.017
1171	0.825	0.837	-0.012
1423	0.830	0.804	+0.026
1464	0.854	0.837	+0.017
1565	0.882	0.874	+0.008
1573	0.849	0.857	-0.008
1674	0.830	0.824	+0.006
1849	0.893	0.878	+0.015
1861	0.861	0.847	+0.014
2170	0.883	0.868	+0.015
2356	0.859	0.832	+0.027
2389	0.880	0.858	+0.022
2483	0.901	0.880	+0.021

It may be that these somewhat unexpected results are due to mixing of successive portions of expired air during their passage through the respiratory valve and mouthpiece assembly. The RQ of the very first alveolar air to appear during the course of expiration tends towards infinity and

the inclusion of a small amount of gas from the S-shaped part of the gas concentration curve (Fig. 1) would have a disproportionate effect on the RQ of the sample.

The healthy students (excluding A.J.), J.G.T. and the old men provided 88 pairs of expired air and end-tidal air samples. The difference expired RQ minus end-tidal RQ was calculated for each pair. One difference (0.217) was rejected as probably erroneous. The mean of the remaining 87 differences was + 0.0024 and their standard deviation was 0.018. The differences ranged from -0.070 to +0.094. There are few data in the literature with which to compare these findings. Rahn's results (1949) have been mentioned, but these related only to resting conditions. Robinson (1938) published mean values for RQ in 10 numerically unequal age groups from 6 to 75 years. He used the Henderson-Haggard end-tidal sampling technique during the steady state of moderate exercise (5.6 Km/hr. at 8.6% gradient on a treadmill). The mean RQ difference for separate groups ranged from -0.01 to +0.06 with an "average mean" (weighted by unequal age-groups) of 0.027. This is ten times the mean difference in the present study, though the two figures are not quite comparable.

The seven patients with emphysema provided between them only 14 pairs of samples. The mean RQ difference for these was +0.0066 and the standard deviation 0.013. All patients were studied using the tambour switch; the levels of exercise performed by them were very low by comparison with the normal subjects. These differences may be partly responsible for the comparable RQ findings in the patients,

in whom one would expect bigger differences in RQ between expired and end-tidal air than in healthy people.

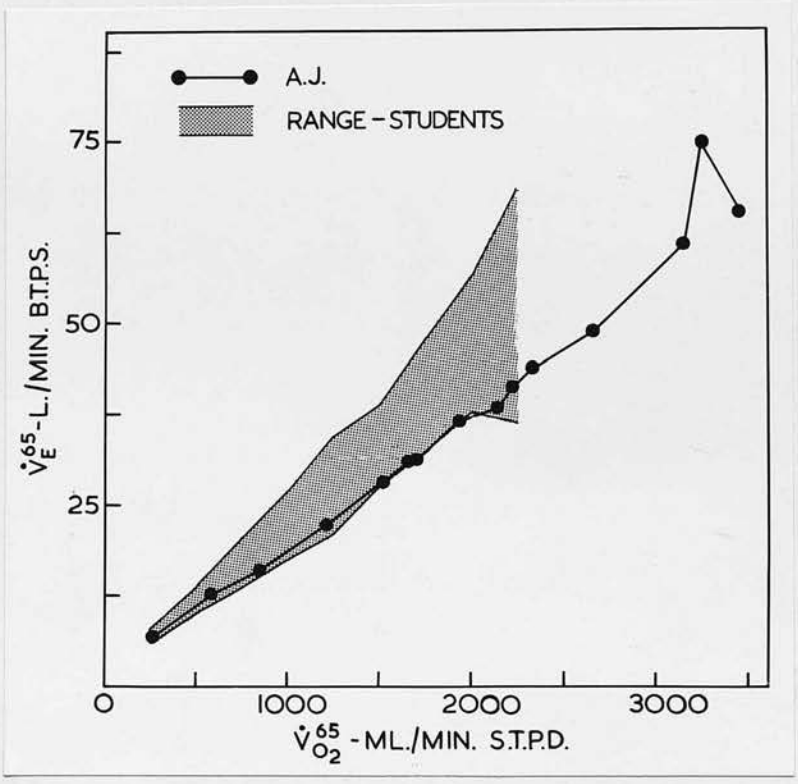

Fig. 12

Ventilation rate at different work rates: students and A.J. Values for students shown as 95% confidence limits.

CHAPTER X

VENTILATION

I. HEALTHY STUDENTS

Fig. 12 shows the relation between ventilation rate and oxygen consumption in the male and female students (excluding A.J.) and separately for A.J. In this and subsequent figures the results for the healthy students have been expressed in the form of 95% confidence limits. These were calculated in the following manner. For each individual, $\dot{V}_E^{65}$ was plotted against $\dot{V}_{O_2}^{65}$ and values of $\dot{V}_E^{65}$ were taken, by interpolation, corresponding to fixed $\dot{V}_{O_2}^{65}$ values at intervals of 250 ml./min. These interpolated figures were tabulated for all the students and their mean and standard deviation calculated for each $\dot{V}_{O_2}^{65}$ value. The range indicated in Fig. 12 represents two standard deviations on each side of the mean. 95% of the observed values may thus be expected to fall between these limits. The number of students falling in each $\dot{V}_{O_2}^{65}$ category was not constant and no limits were calculated if the number fell below six.

It is obvious from Fig. 12 that A.J.'s ventilation followed the lower limit of normal at all exercise levels studied. In Fig. 13 the same results are expressed in terms of oxygen extraction; male students are here separated from female and A.J. is again shown individually. There is little difference between male and female ranges of OE to an oxygen uptake of about 1250 ml./min./65 Kg. At this point the female upper limit falls while the male upper limit continues at its maximum level. Investigations were not extensive enough to show clearly the point at which the male

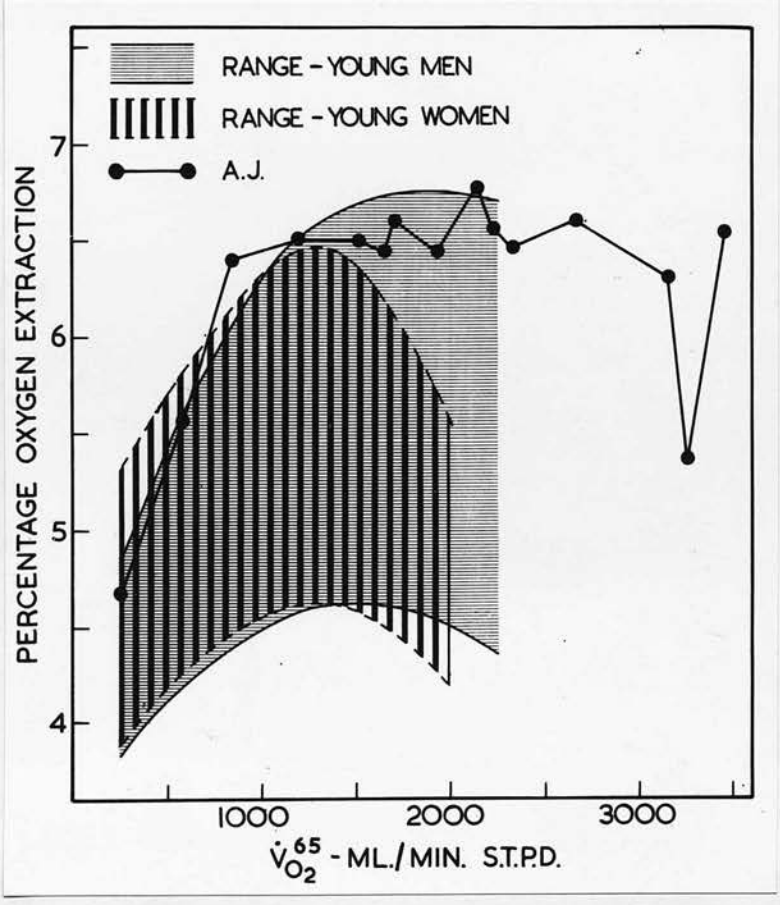

Fig. 13

Oxygen extraction at different work rates: male and female students and A.J. 95% confidence limits for students have been smoothed.

upper limit falls. A similar though less marked effect can be seen in the lower limit. As expected, A.J.'s OE follows the upper limit of normality.

The first part of these graphs may be misleading. The lowest exercise level studied in each case was usually about 1000 ml. O_2/min./65 Kg., and points between the resting value and this were obtained mostly by interpolation. Had they been experimentally determined the graphs might have risen more steeply. Since differences between males and females appear only at the higher levels of exercise this uncertainty about the first part of the graphs is not, in this connection, important. Further, as will be seen, it is during light exercise that ventilatory irregularities induced by the will are most likely to occur.

In these experiments the normal resting OE varied from 3.9% to 5.3% for young women and from 3.9% to 4.9% for young men. Maxima were reached at or just above a $\dot{V}^{65}_{O_2}$ of 1000 ml./min. and varied from 4.6% to 6.4% (women) and 6.8% (men). The OE of the women began to decline at 1250 ml./min. and at 2000 ml./min. varied from 4.2% to 5.6%, only a little above the resting range.

The majority of individuals showed a similar rise and fall in OE with increasing exercise, but there were exceptions. The most striking of these was M.P., the course of whose OE is shown in Fig. 14. During his first three exercises he was noticed to be overbreathing very obviously. His attention was drawn to this and he was asked to breathe more naturally. His response to this was to underbreathe, as indicated by the behaviour of his OE. At 1560 ml.

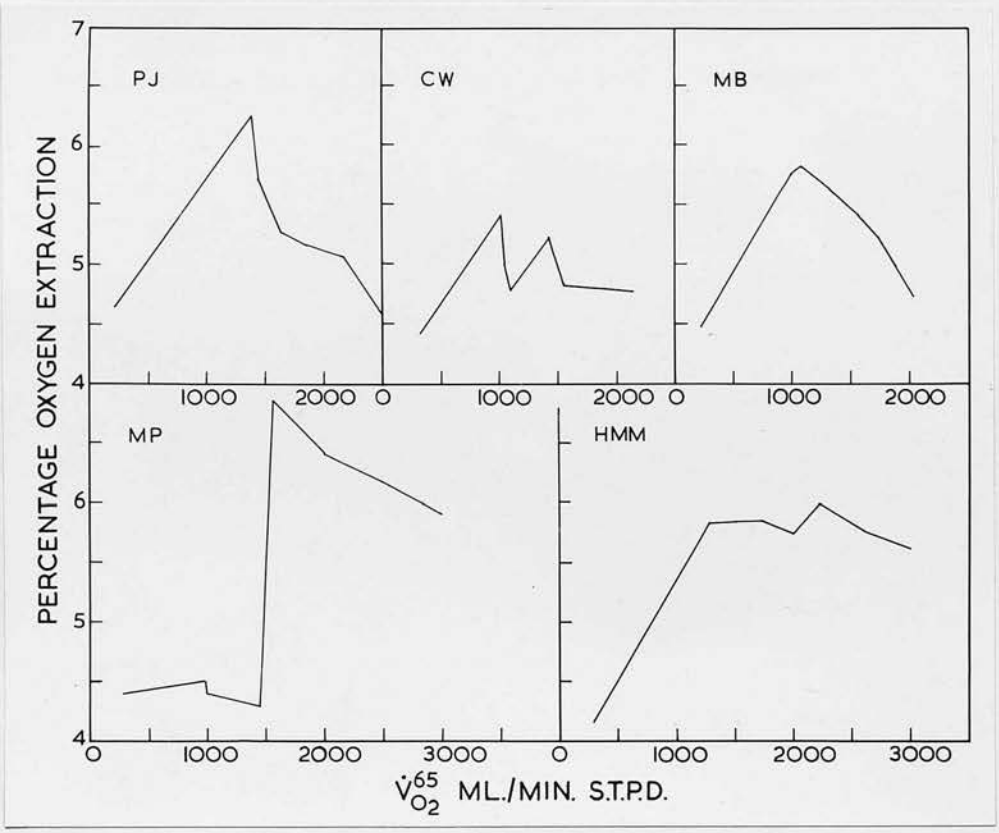

Fig. 14

Individual variations in oxygen extraction with increasing work.

O_2/min./65 Kg. his OE became 6.8%, the highest OE recorded in the entire study. The only part of the OE graph which fell well within the expected range was that above 2000 ml. O_2/min./65 Kg. It is doubtful whether he could have influenced this part much by voluntary means, since his reserves were being called upon to a considerable extent at the higher exercise levels. Similar observations, during light to moderate exercise, in some other subjects, suggested that voluntary factors were at play in determining OE.

Gross fluctuation of OE at the other end of the scale - the higher exercise intensities - was observed only once, and is illustrated in Figs. 12 and 13 by A.J.'s ventilation and O_2 extraction. $\dot{V}_E^{65}$ shows a marked rise, and OE a sharp fall, at 3260 ml.O_2/min./65 Kg. At 3460 ml. these changes are reversed. Reference to Figs. 16 and 17 indicates that alveolar clearance rose and P_{ACO_2} fell at 3260 ml., so that there must have been a true alveolar hyperventilation at this exercise intensity. A.J. did exercises 3260 ml./min. and 3460 ml./min. on the 3rd day of his study, and in that order. It might be argued that at 3260 ml. he had not fully adjusted himself to the experimental conditions and that his overbreathing was of nervous origin. Against this were the facts that he had already done two full programmes on the treadmill and that he was an intelligent and adaptable person. An alternative explanation may be found in the experimental conditions under which the two highest exercises were done. The first consisted of walking at 4 m.p.h. and a gradient of 18%. Since the treadmill could not be made steeper than this, further increases of exercise intensity

required a greater speed. A.J. was short and could not walk comfortably at 5 m.p.h. For the last exercise he was therefore asked to run at 10 m.p.h. with the treadmill level; this was the only exercise done running in the whole study. Now there is a big difference in ease of performance between walking up a very steep gradient and running level. A.J. found the uphill walk quite unpleasant, and experienced some tightness and pain in his calves. In contrast, the run - despite its higher O_2 uptake - was done in greater comfort. It seems probable that during the walk at 18%, in which the leg muscles relaxed for a shorter period between strides than in running, a substantial amount of work was done anaerobically. This would presumably result in the release of acid metabolites which would stimulate the respiratory centre, and a higher ventilation might thus ensue despite a lower P_{ACO_2} and P_{aCO_2}. In addition the local pain in the calf muscles (or accompanying stimuli) might have activated a reflex stimulation of respiration (Harrison et al., 1932; Asmussen et al., 1943 a & b, 1946; Gray, 1946; Bannister et al., 1954).

The observation of these fluctuations in OE, some occurring at low and others at high levels of exercise, is potentially important in connection with the use of the OE in clinical tests of exercise tolerance. At low work rates the OE may be influenced by voluntary control of breathing, and at high rates, near the aerobic capacity, the type of work done may decisively affect the OE. Viewed in this light, the decline of OE from peak values which was usually found in the student group represents, not a primary break-

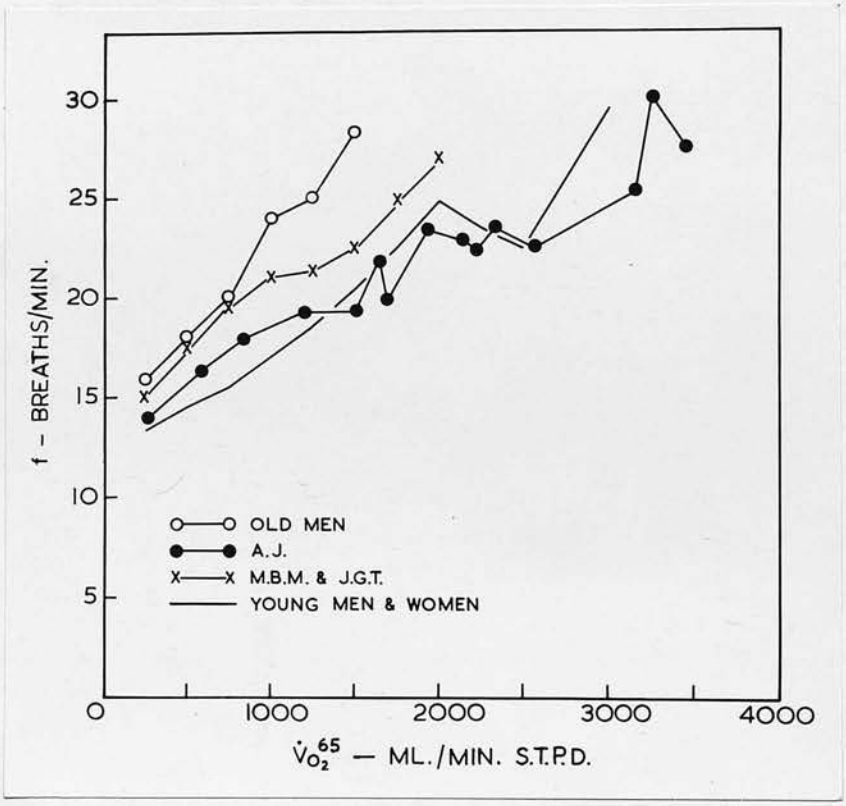

Fig. 15

Mean respiratory frequencies at different rates of work: healthy subjects.
Women fall out at 2000 ml./min.

down in ventilatory efficiency with increasing exercise, but the approach of the individual's aerobic capacity for that particular mode of exercise. It is thus a function, not of ventilatory factors, but of muscle blood flow and mechanical efficiency. It indicates, nevertheless, the approach of the maximum exercise, of a given type, of which the subject is capable, and the question arises as to whether it might be used as a measure of exercise tolerance.

It would, for instance, be reasonable to conclude from Fig. 13 that A.J.'s"tolerance" for grade walking at 4 m.p.h. was 3150 ml. O_2 per minute (corrected). Reference to Fig. 14 shows, however, that many subjects had no such clearly-defined limit. Some of the more irregular OE responses to increasing exercise are illustrated here; in none of them is there a definite ~~breaking~~ limiting point. In general, it was found that CO_2 discharge followed OE closely at a somewhat lower level.

Let us now return to the observation, illustrated in Fig. 12, that A.J.'s ventilation was, at each exercise level, at or near the lower limit of the normal range. One would expect A.J., as an athlete, to use his ventilation to the best advantage, and it appears that he did so. How was this brought about?

Fig. 12 shows that at 2000 ml. O_2/min./65 Kg. A.J.'s ventilation was about 10 l./min. lower than the mean value for the combined students. One way of conserving ventilation is to reduce the ventilation of the anatomical dead space, and this can be done mainly by reducing respiratory frequency. Fig. 15 shows that A.J.'s frequency at 2000 ml.

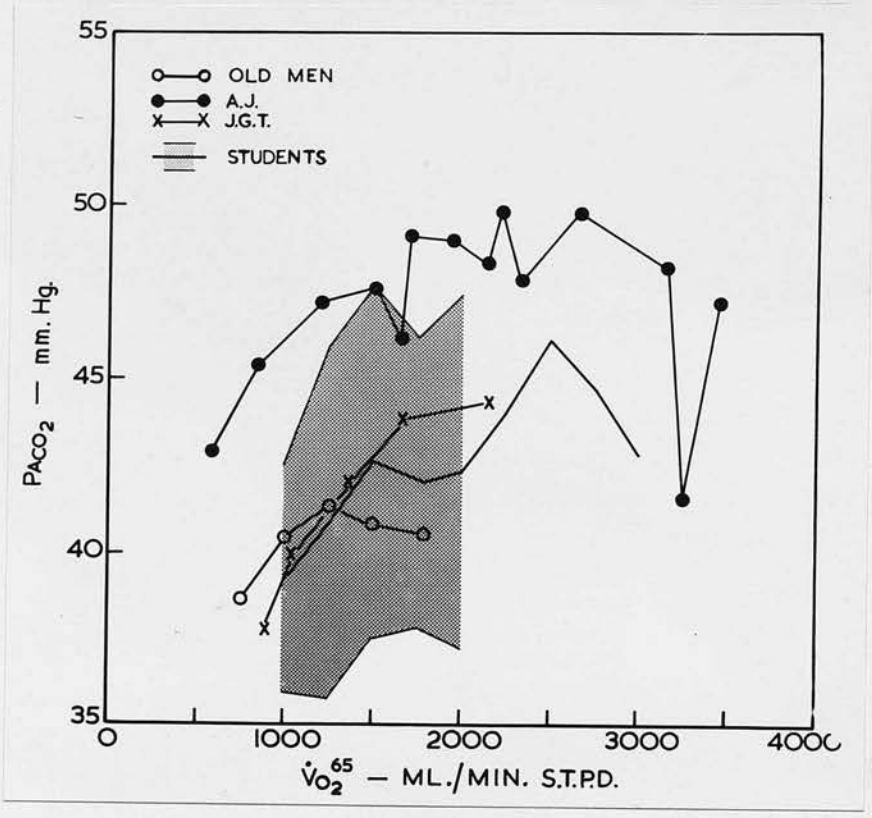

Fig. 16

Alveolar CO_2 pressures at different rates of work: healthy subjects. 95% confidence limits for students.

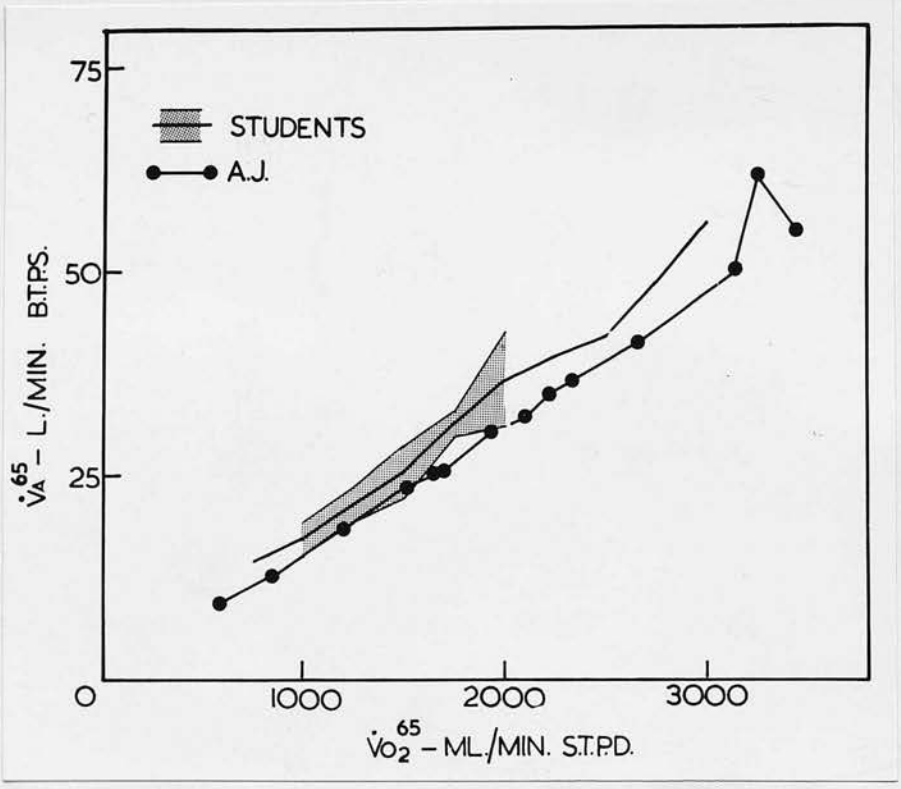

Fig. 17

Alveolar clearance at different rates of work: students and A.J. 95% confidence limits for students.

was rather less than 2 breaths per minute lower than the group mean. Allowing 200 ml. for V_D(An) - a generous estimate - this could represent a saving of only half a litre per minute. Nine and one-half litres per minute remain to be accounted for.

It is apparent from Fig. 16 that A.J. exercised throughout at an alveolar P_{CO_2} which was considerable higher than the group mean. At 2000 ml./min. the difference was about 6.4 mm. Hg. To eliminate the same amount of CO_2 per minute A.J. therefore needed to clear a smaller volume of alveolar air. As shown in Fig. 17 the saving in alveolar clearance corresponding to this P_{ACO_2} difference was 6 l./min. The ability to tolerate a high P_{ACO_2} (and therefore P_{aCO_2}) is evidently a major advantage in conserving ventilation. But of the original 10 litres saving in total ventilation, only $6\frac{1}{2}$ litres have been accounted for. The remaining $3\frac{1}{2}$ litres could have been conserved only in the ventilation of the alveolar component of the physiological dead space. Expressed in another way, a rise in the level of alveolar and arterial P_{CO_2} results, not merely in a reduction in the obligatory alveolar clearance, but in an even greater reduction in obligatory alveolar ventilation, using this term in its proper anatomical sense. Thus $9\frac{1}{2}$ litres out of the total saving in ventilation of 10 litres were conserved as a direct result of the higher alveolar and arterial P_{CO_2} levels at which A.J. operated during exercise.

It is of interest to see how A.J. conserved the 10 litres in terms of tidal volume and frequency. The total saving was 10 l. from 47 l., rather more than 20%. Tidal

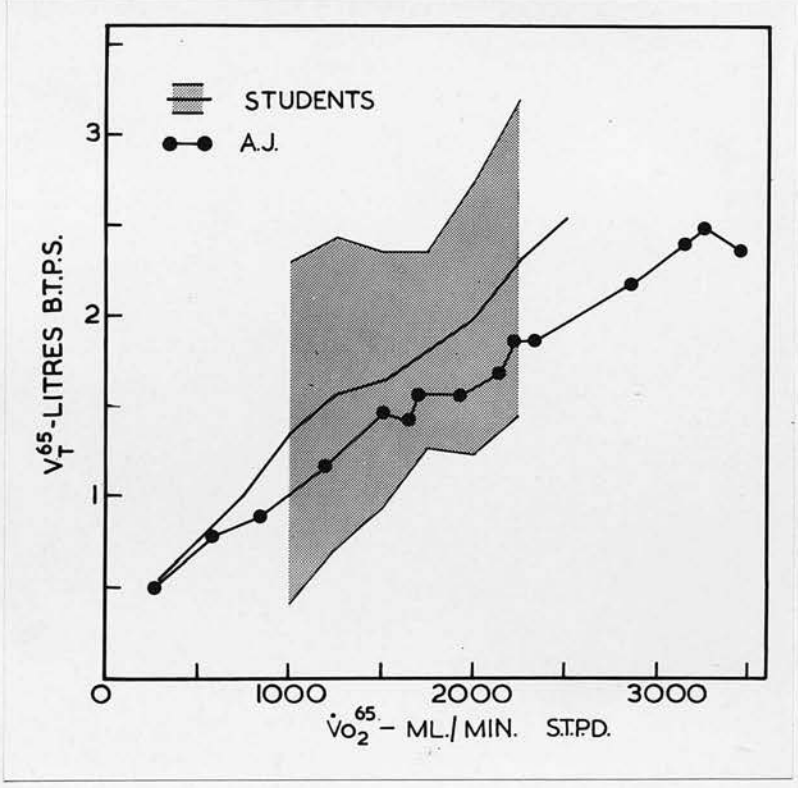

Fig. 18

Tidal volume at different rates of work: students and A.J. 95% confidence limits for students.

volume (Fig. 18) for A.J. at 2000 ml./min. was 19% less than the group mean. Frequency (Fig. 15) was about 6% less. The values for frequency obtained by interpolation are only approximate. But the fact emerges that some 80% of the reduction occurred at the expense of tidal volume, and only 20% at the expense of frequency. It may be surmised that this is the optimum distribution from the standpoint of ventilatory efficiency.

Fig. 19 indicates that A.J.'s physiological dead space was less at all exercise levels than the group mean. This follows from the results already discussed.

How was A.J. able to exercise at a higher P_{aCO_2} than less fit but healthy subjects? The answer to this question may lie partly in an increased tolerance of the respiratory centre to an increase of CO_2 tension and a fall of pH. It is known (Knehr et al., 1942) that physical training results in an increased tolerance to lactic acidosis, so that a greater amount of anaerobic work is possible. There may be a similar increase in tolerance to P_{CO_2}. In addition, training presumably results in a more rapid increase of cardiac output and muscle blood flow at the onset of exercise, and the initial anaerobic work is thereby reduced. The studies of Bang (1936) suggest that the early anaerobic work performed in a given exercise establishes a depot of lactate in the active muscles, which is then oxidised in the active and resting muscles and the liver even as exercise continues. The maximum lactate concentration in blood occurs between 5 and 10 minutes after the start of exercise. In the present experiments the ventilation rate was measured during the 5th

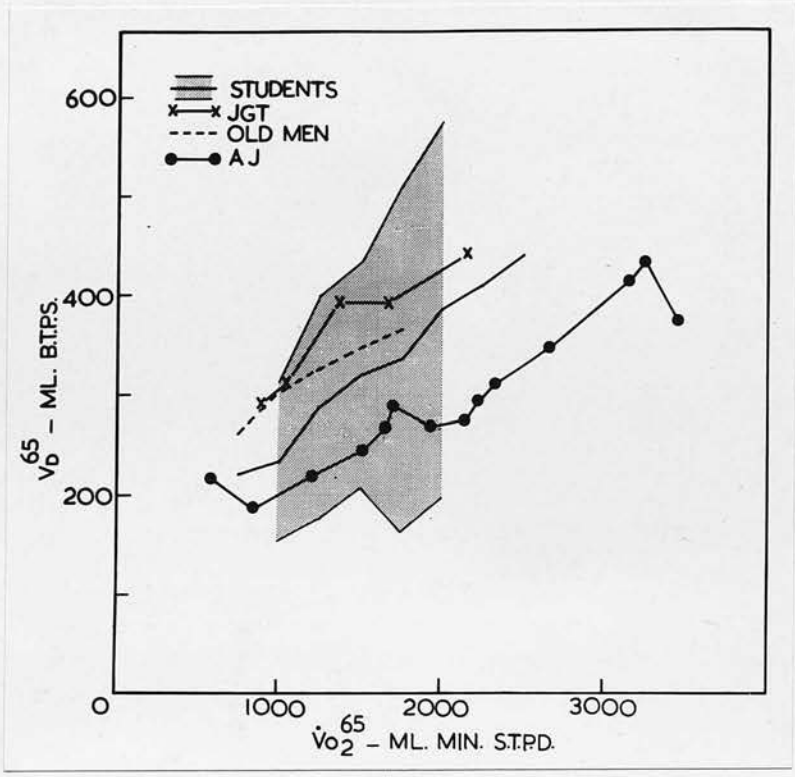

Fig. 19

Changes in physiological dead space with increasing exercise: healthy subjects. 95% confidence limits for students.

and 6th minutes of exercise at a time when lactate derived from early anaerobic work was presumably at its height, and its influence on pH and the respiratory centre likewise at a maximum. The shorter the initial phase of anaerobic work, therefore, the higher the arterial P_{CO_2} can rise in the 5th and 6th minutes for a given change of pH and ventilation.

In summary, the exercising ventilatory characteristics of a physically fit person shown by this study are a lower total ventilation, a larger relative reduction in tidal volume than in respiratory frequency, a higher alveolar and presumably arterial CO_2 tension, a small reduction in ventilation of the anatomical dead space and a large reduction in the alveolar ventilation. These features are found at all levels of exercise, not only the more severe.

II. THE EFFECT OF INCREASING AGE

The ventilatory responses to exercise of MBM (35) and JGT (47), together with the five old men, will now be considered. These seven cannot reasonably be grouped together because of the age difference, and it is unfortunate that neither group is big enough by itself to make statistical treatment useful. For purposes of comparison, therefore, only mean values, for MBM and JGT on the one hand and the five old men on the other, have been used. No data on alveolar air are available for MBM.

Fig. 20 shows that the ventilation rate in the older subjects fell well within the range of the younger ones. MBM and JGT occupy almost a mean position in this range. The old men lie roughly one standard deviation above the students' mean, which implies that only 15% of healthy

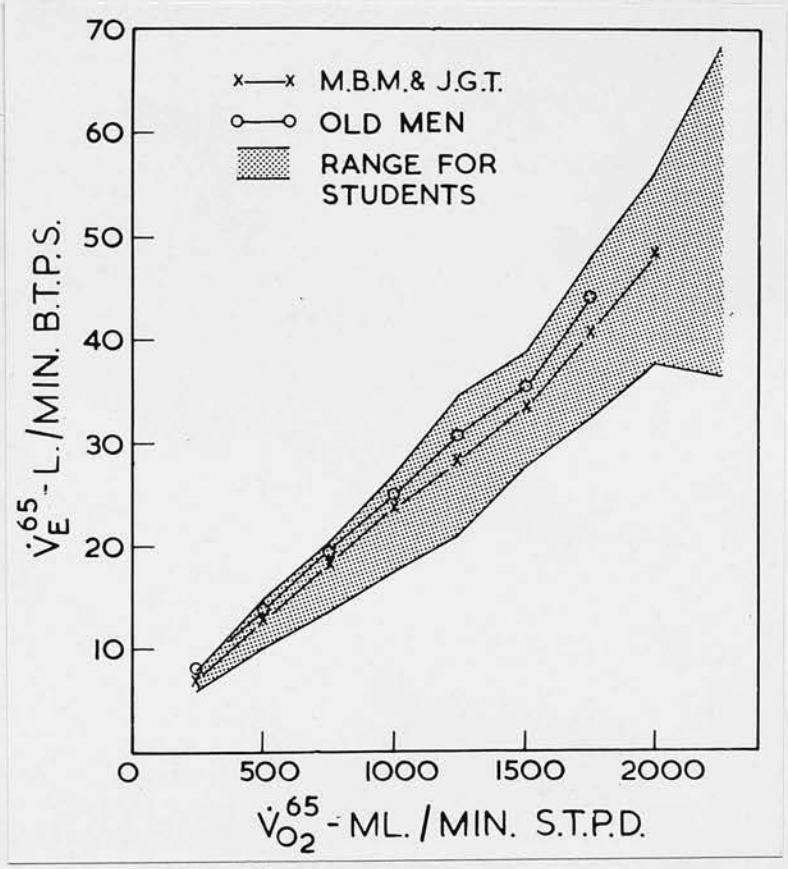

Fig. 20

Ventilation rate at different rates of work: students, MBM and JGT, and old men.

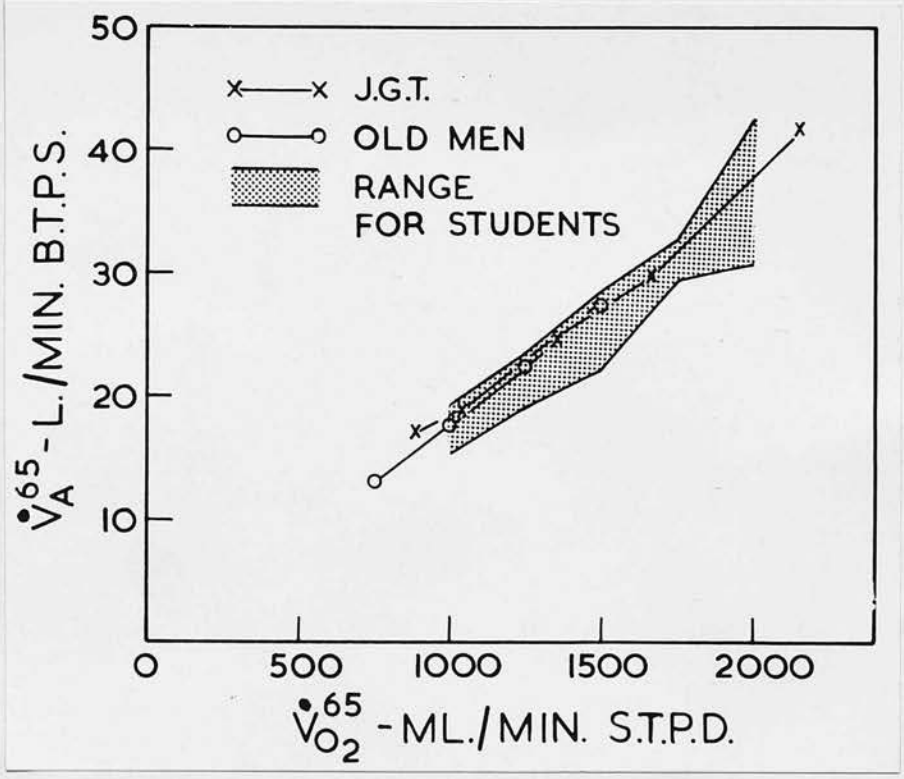

Fig. 21

Alveolar clearance in relation to O_2 uptake: students, JGT and old men

students ventilated at rates higher than the old men's mean. JGT's alveolar clearance and the mean alveolar clearance for the old men likewise lie in the upper half of the normal range (Fig. 21). The corresponding P_{ACO_2} levels are indicated in Fig. 16. JGT's follow the normal mean; the P_{ACO_2} of the old men tends to fall away at 1500 ml. O_2/min./65 Kg., though it remains well within the normal limits. Fig. 22 shows that tidal volume for JGT and MBM, and for the old men, was below the students' mean, as in the case of AJ. Their respiratory frequencies, however, unlike AJ's, were above the students' mean at all levels of exercise (Fig. 15). V_D for JGT and the old men was also above the mean values for the students (Fig. 19).

These findings in the two older age-groups must be interpreted with caution because of the small number of subjects studied. As far as they go, however, they seem to indicate that with increasing age there are certain modifications of the ventilatory response to exercise. Total ventilation, above middle age, is greater than the average for young people. Alveolar CO_2 pressure - and presumably arterial CO_2 pressure - is not significantly different, save for a slight fall of mean CO_2 pressure in the over-seventies beyond 1250 ml. O_2/min./65 Kg. when the students' mean is still rising. Consequently the alveolar clearance is little different from the mean values for young people. The increase of tidal volume with increasing work rate diminishes as age advances, and the increase of respiratory frequency becomes more pronounced.

The findings with regard to dead space are especially

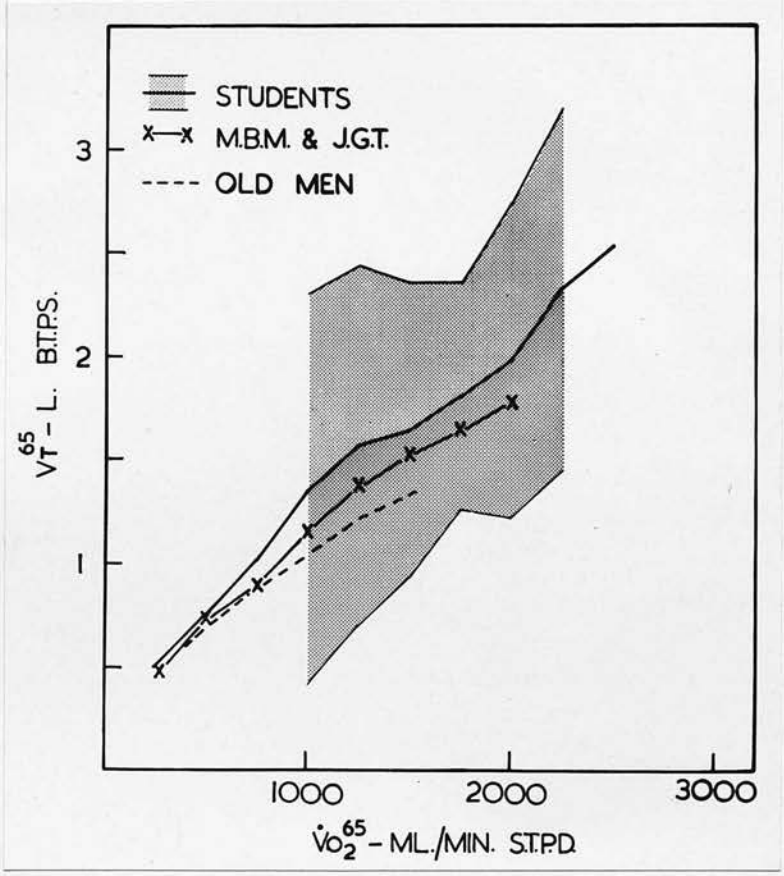

Fig. 22

Changes in tidal volume with increasing exercise at different ages: healthy subjects.

interesting. According to the classical view of dead space, relative diminution of tidal volume ought to result in a smaller V_D. Yet the older subjects, who exercised with a relatively lower V_T, had a higher V_D at each level of exercise than the students. On the other hand the older age-groups had a higher respiratory frequency than the young subjects, and we have seen that an increase of frequency, unless this results in a fall of P_{ACO_2}, must increase the alveolar component of V_D even though V_T remains unchanged. This is a possible explanation for the above observations. In addition one must consider the possibility of a higher respiratory level (FRC) in the older subjects than in the students, which must also have the effect of increasing physiological dead space just as it does in positive-pressure breathing at rest. Whether the FRC factor played a part in the present results must remain an open question, but it appears quite likely in view of the known increase in FRC at rest in healthy old people (Robinson, 1938; Greifenstein et al., 1952). Summarising, the relatively bigger V_D during exercise in the older subjects appears to be the resultant of at least three factors: the smaller tidal volume, tending to diminish it, and the higher respiratory frequency and FRC which both tend to increase it.

These observations confirm the results of Robinson (1938) who measured the responses to exercise of 84 subjects whose ages ranged from 6 to 91 years. He chose only two levels of exercise: moderate exercise at 1500 to 2000 l. O_2 per min. in the adult subjects, and exhausting exercise. Only the moderate exercise is suitable for comparison with

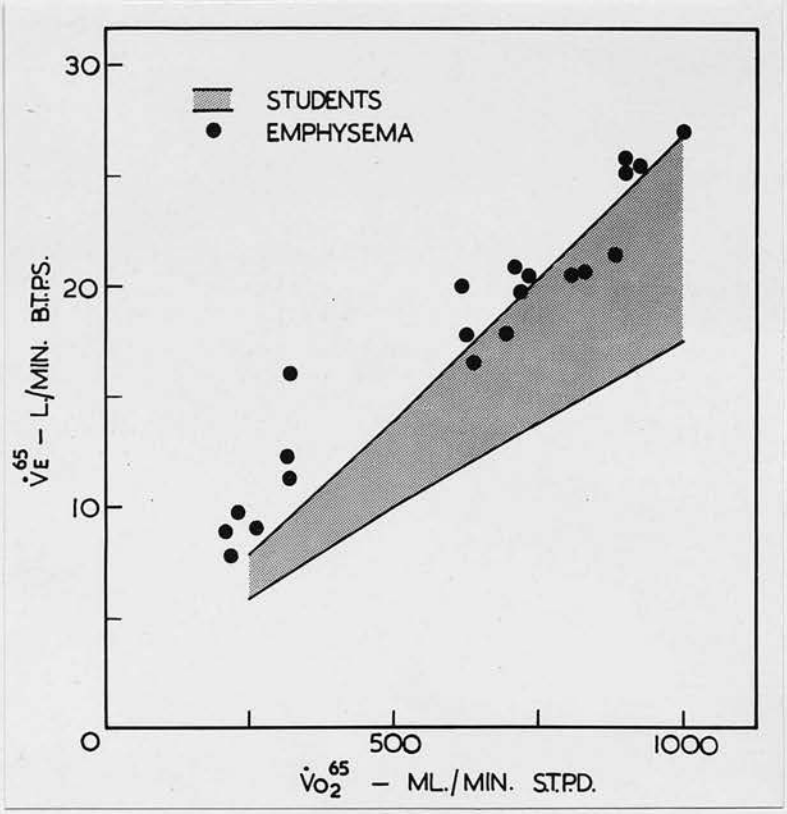

Fig. 23

Ventilation rate in emphysema at different rates of work

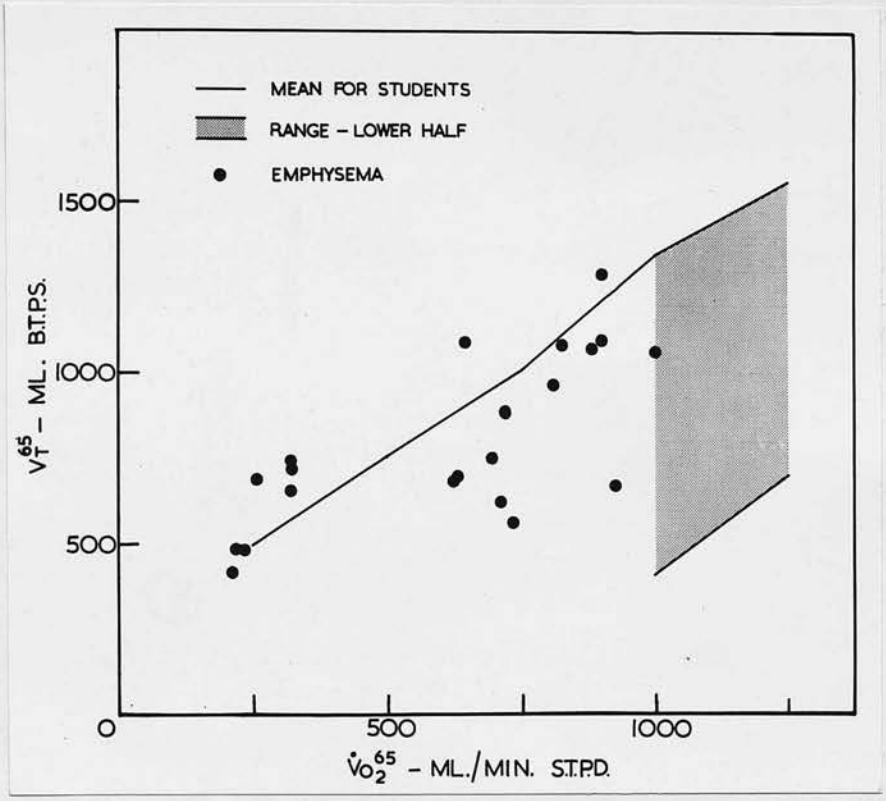

Fig. 24

Tidal volume in emphysema at different rates of work

the present results. His age groups averaging 24.5 and 75 years respectively are comparable with the student group and the old men in the present investigation. He found that mean exercise ventilation rose with increasing age, and that the increase was obtained by means of a bigger respiratory frequency; there was a slight relative fall in tidal volume. Alveolar CO_2 pressure was the same in young as in old. Dead space calculated from Robinson's mean figures gives a mean value of 465 ml. for young subjects and one of 485 ml. for old ones. These values are higher than those found in the present study; it will be recalled that Robinson's alveolar samples had an average RQ which was lower, in relation to expired air, than the present ones. This would mean that the CO_2 content of his samples, and therefore V_D, were rather higher than in this study. Though the difference is hardly significant his results do show the old people had a higher exercising V_D than the young ones, by about the same amount as the old men in this study.

III. VENTILATORY BEHAVIOUR IN EMPHYSEMA

In Figs. 23 to 27 are plotted values of $\dot{V}_E$, V_T, f, P_{ACO_2} and V_D obtained in the seven patients with emphysema. The corresponding values found in the healthy students are indicated for comparison.

Total ventilation in the emphysema patients was at or above the upper limit of the normal range, both at rest and at each level of exercise studied (Fig. 23). Tidal volume was actually within the lower half of the normal range (Fig. 24) and it follows that respiratory frequency (Fig. 25) was much higher than normal. The mean rate of increase of tidal

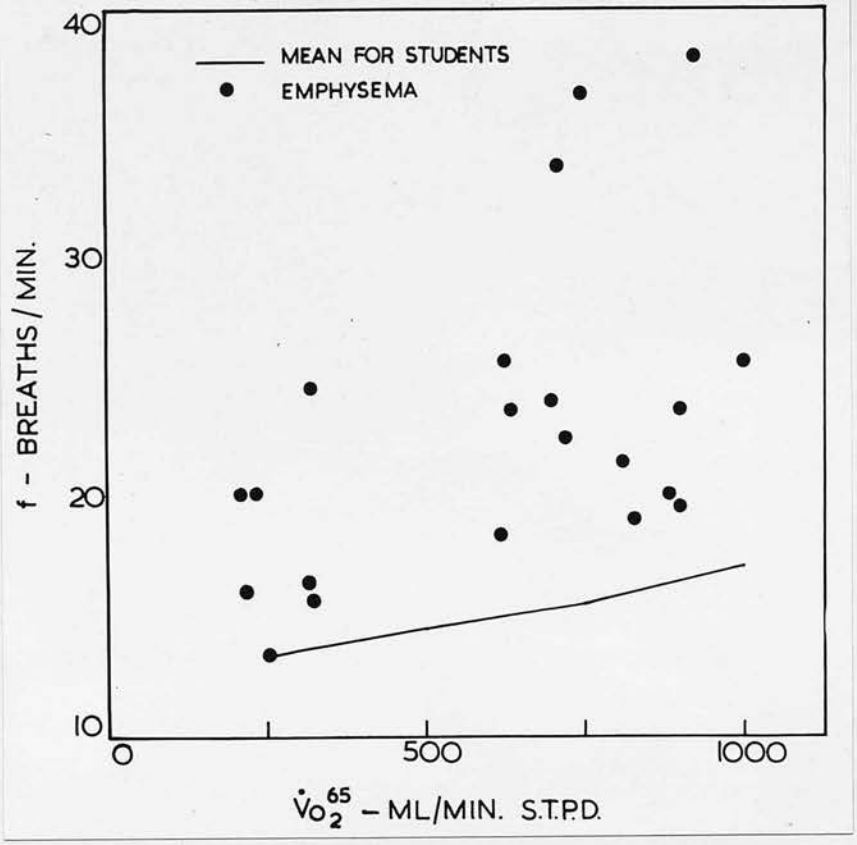

Fig. 25

Respiratory frequency in emphysema in relation to exercise intensity.

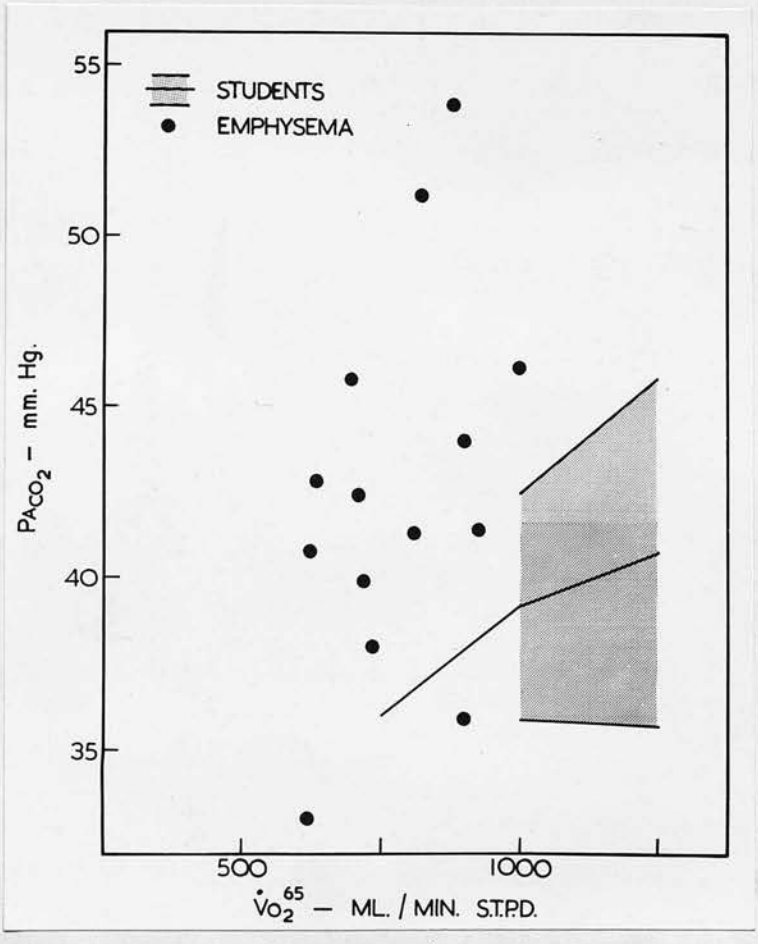

Fig. 26

Alveolar CO_2 pressure in emphysema at different rates of work.

volume with increasing exercise intensity was less in emphysema, corresponding with the reduced vital capacity. Respiratory frequency correspondingly increased more markedly with increasing exercise in emphysema than in health.

Alveolar P_{CO_2} during exercise showed a clear difference from the levels found in health (Fig. 26). 6 of the patients had alveolar pressures in excess of the normal mean value at a given exercise intensity, and most of them appear to be above the upper limit also. It is unfortunate that the exercise levels studied in the students were not low enough to allow adequate comparison with the emphysemas, who were all too disabled to exercise beyond 1000 ml. O_2 uptake per minute. Further, some of the emphysema patients had tidal volumes which barely met the requirements of direct alveolar sampling. Taking the results at their face value, however, and proceeding along the same lines as in the previous sections, it is clear that the requirement of these patients for an increased total ventilation did not arise because of an increase in the obligatory alveolar clearance, for this was actually less than normal. A substantial part of the excess ventilation was expended in the anatomical dead space. At 800 ml. O_2/min./65 Kg., for example, respiratory frequency in the patients was from 5 to 20 breaths per minute higher than the normal mean frequency. Allowing 200 ml. for V_D(An), this means an excess expenditure of 1 to 4 litres per minute out of a total ventilation of just over 20 litres per minute. Even with this taken into account, however, total ventilation was still a little higher in the emphysema patients, and as we have seen the alveolar clearance was

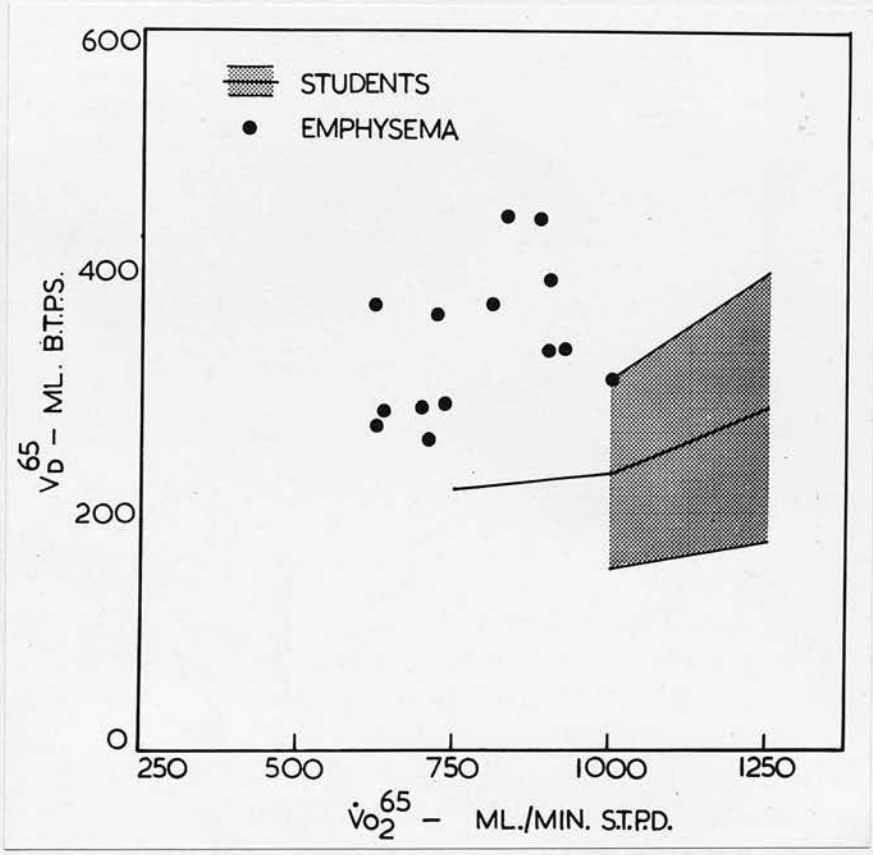

Fig. 27

Physiological dead space in emphysema at different exercise intensities.

actually lower. This might be the result of errors in sampling alveolar air, but it could also mean that for a given alveolar clearance, a larger alveolar ventilation is necessary in emphysema owing to defective mixing within the alveolar units. In conformity with these results are the abnormally high values for V_D found in the patients (Fig. 27).

Even if sampling errors are responsible for much of the difference observed, it seems that these errors are systematic ones which themselves arise from the abnormal ventilatory function of emphysema. If this is so the method, at worst, provides a consistent empirical means of distinguishing normal from abnormal function. For apart from respiratory frequency the values for dead space and P_{ACO_2} show the most marked deviation from the normal of all the measurements made. It would be of interest to see whether the same is true in cases of emphysema with less disability than the ones studied here. It may be noted that the two most severely disabled patients (as judged from their vital capacities and maximum breathing capacities), PC and WC, also had the highest alveolar CO_2 pressures and dead spaces during exercise. Their "mixing efficiencies" (which relate to distribution, rather than to intra-alveolar mixing) were, on the other hand, among the best in relation to the expected normal values (Table III). If the high P_{ACO_2} figures were predominantly a distribution effect one would expect the reverse. The fact that the RQ differences between the alveolar and expired air samples were not much greater in the patients than in the students and old men also suggests

that distribution effects on the alveolar samples were not marked.

IV. STANDARDISED VENTILATION - ALL GROUPS

Standardised ventilation (SV) was calculated from the experimental data for each exercise done by each subject. Usually it was a little higher than the exercise ventilation, but the difference seldom exceeded 4 l./min. and did not increase with increasing exercise. Proportionally, therefore, the SV - EV difference diminished as EV increased. There was no difference between the groups in the relation of SV to EV.

These results were expected in view of the findings of Hugh-Jones (1952) and Stock & Kennedy (1953) that SV appreciably exceeds EV only when the subject is forced to stop exercising in less than five minutes. In none of the present subjects, either healthy or emphysematous, was this the case.

DISCUSSION

The ventilatory features of the subjects studied are summarised in Table IV. The groups may be distinguished,

Table IV

Ventilatory characteristics during exercise in an athlete, a group of old men and a group of men with pulmonary emphysema; a group of healthy students form the standard of comparison.

	$\dot{V}_E$	V_T	f	$\dot{V}_D$(An)	$\dot{V}_A$	$\dot{V}_A$(An)
Athlete	-	-	- or N	N	-	-
Old men	+	-	+	sl. +	N	N or +
Emphysema	+	-	+	+	-	+

even at a qualitative level, by two characteristics, total ventilation and alveolar clearance. Knowledge of total ventilation alone might not differentiate between the effects of age on the one hand and emphysema on the other, since both result in an increase of total ventilation. These two groups differ, however, in alveolar clearance. The old men had a raised ventilation rate with a normal clearance, the emphysema patients a raised ventilation rate with a reduced clearance.

In order to express this difference quantitatively the ventilation rate may be corrected for the abnormality of the alveolar clearance. For example, patient WC, at a $\dot{V}_{O_2}^{65}$ of 1000 ml./min., had a total ventilation of 27.1 l./min. This was 22% in excess of the expected normal mean value. His alveolar clearance was 16.1 l./min., whereas the expected normal was 17.2 l./min. Assuming an anatomical dead space of 200 ml. his anatomical dead space ventilation was 200 x 25.5 = 5.1 l./min. and his alveolar ventilation therefore 27.1 - 5.1 = 22 l./min. If we assume that in order to reach the normal alveolar clearance he would have had to increase his alveolar ventilation proportionally, the latter would then have been 22.0 x 17.2/16.1 = 23.5 l./min. Adding the anatomical dead space ventilation, totalvventilation would have been 28.6 l./min., or 29% above the expected normal ventilation. The ventilation rate of the old men, on the other hand, would remain almost unaltered because their alveolar clearance was practically normal. The difference between the ventilation rates for the two groups would thus be

increased.

Total ventilation may be increased in the presence of a normal alveolar ventilation if anatomical dead space ventilation is increased. This may result chiefly from an increase of respiratory frequency. The old men in this investigation provide an example of this; their frequency at 1000 ml./min. was 7 breaths per minute higher than the students' mean. This difference might account, in terms of anatomical dead space ventilation, for most of the 2.5 l./min. difference in total ventilation. In the absence of exact knowledge of $V_D(An)$, precision is lacking; but any ventilation not accounted for in this way, and attributable to increased alveolar ventilation, must have been very small. In contrast the emphysema patients, who had an even higher frequency than the old men, had such a high total ventilation that their increased anatomical dead space ventilation probably could not have accounted for all the excess; it appears that they had a significantly higher alveolar ventilation also. Despite this, they made less use of it, for their alveolar clearance was actually less than that of the old men.

An increase of both $\dot{V}_D(An)$ and $\dot{V}_A(An)$ is also encountered in nervous hyperventilation, in which both f and V_T are commonly raised. Given normal distribution of inspired gas and normal intra-alveolar mixing, an increase of $\dot{V}_A(An)$ must result in a fall of alveolar P_{CO_2} and an increase of alveolar clearance. Nervous hyperventilation therefore stands in contrast to both emphysema and the effects of age. It is unfortunate that MP, who was the only subject in this

study who showed undoubted hyperventilation of this type during exercise, was studied before end-tidal samples could be taken, and cannot be used as an illustration of this pattern of response.

The importance of these distinctions lies in the fact that the three states, advancing age, emphysema and nervous or voluntary hyperventilation are frequently met in combination. Emphysematous patients are often elderly, and they are sometimes disposed, for various reasons, to make the most of their disability by exaggeration of their hyperpnoea. It is probable that by correcting their ventilation to a standard alveolar clearance, as already illustrated in the case of WC, a reasonably true measure of their ventilatory disability might be made. For just as a high ventilation becomes even higher when corrected for a low clearance, so it tends towards normal when corrected for a high clearance.

The theoretical objections to direct alveolar sampling in emphysema have been mentioned. From the practical point of view, however, the measurement of total ventilation and the collection of expired and end-tidal samples can be done simply and quickly. A detailed study of the composition of successive phases of expired air in emphysema, coupled with the estimation of arterial gas tensions, would show how consistent the errors of direct sampling are in this condition. A consistent error may be acceptable in a useful practical test.

SUMMARY AND CONCLUSIONS

The characteristics of the ventilatory responses to exercise of an athlete and of groups of young men, young

women, old men and patients with emphysema have been studied. In some subjects there is a more or less clearly defined "~~breaking~~ limiting point" at which ventilation increases more steeply with further increase of work, and which may be regarded as a measure of exercise tolerance. The exceptions are, however, too numerous to allow the point of decline of oxygen extraction or CO_2 discharge to be used as an index of working capacity.

The ventilatory response to a given level of exercise does, nevertheless, separate the groups in a way which would be expected on the basis of their differing fitness. Determination of alveolar air composition and alveolar clearance permits better definition, particularly between emphysema, old age and nervous hyperventilation - conditions which are often associated.

An attempt has been made to account for total ventilation in each group in terms of anatomical dead space ventilation and alveolar ventilation. Differences have also been noted in the way each group apportions total ventilation between tidal volume and respiratory frequency.

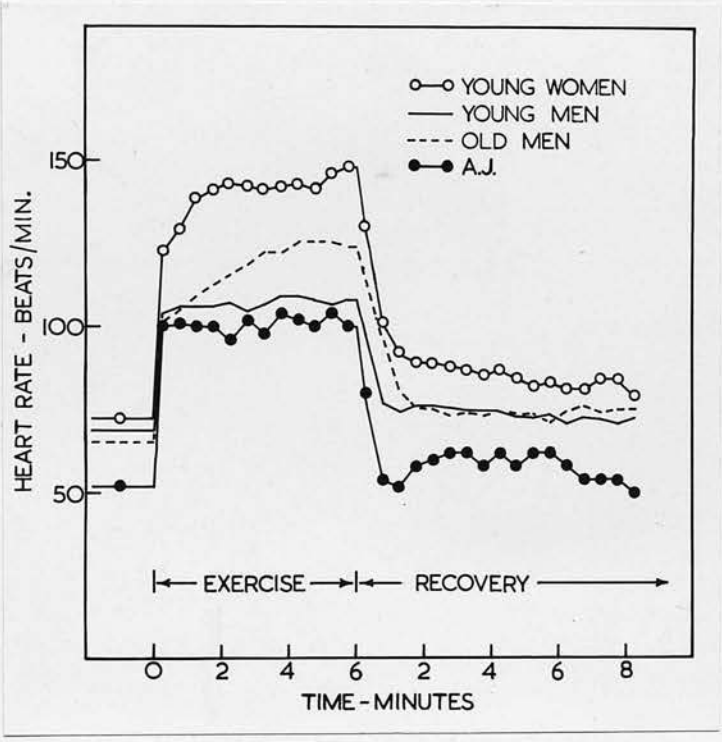

Fig. 28

Course of heart rate during exercise and recovery in relation to sex, age and athletic training. Exercise at 1500 ml. O_2 per minute.

CHAPTER XI

HEART RATE

I. THE COURSE OF THE HEART RATE DURING AND AFTER EXERCISE

Continuous records were available of the heart rate at half-minute intervals before, during and after exercises of several different intensities in each subject. In order to compare the groups with respect to the time-course of heart rate in response to exercise, it is necessary to select comparable exercises. This has been done at two levels. For each subject the exercises corresponding most closely to corrected O_2 uptakes of 1500 ml./min. and 2500 ml./min., respectively, were chosen, and successive half-minute counts were averaged for each group of subjects. Table V shows that the mean O_2 uptakes were comparable at each level. At the higher level only the young men and AJ could be compared.

Table V

SUBJECT GROUP	MEAN CORRECTED O_2 UPTAKE (ml./min.)	
	Level (1)	Level (2)
Young women	1538	-
Young men	1464	2502
Old men	1530	-
AJ	1513	2663

Figs. 28 and 29 show the mean half-minute heart rates for the different groups at these levels of exercise, and may be discussed under the following headings.

1) The rise from the resting heart rate At 1500 ml./min. the young men's and AJ's heart rates rose abruptly

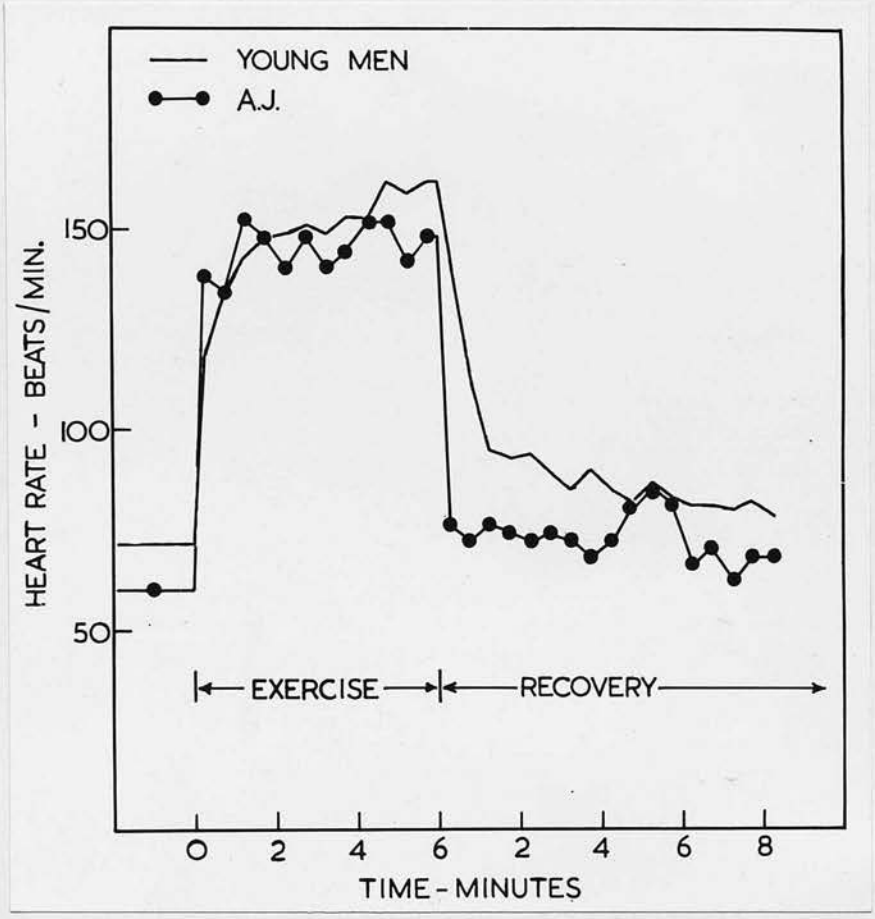

Fig. 29

Course of heart rate during exercise and recovery in male students and A.J. Exercise at 2500 ml. O_2 per minute.

at the beginning of exercise and after the first half-minute rose no further. In contrast, the young women achieved just over 70% of their total rise in heart rate in the first half-minute; the remaining 30% was accomplished by a further, slower rise lasting 1½ minutes. The half-minute rise in the old men was even less - under 60% - and the secondary rise lasted 3 minutes. At 2500 ml./min. the young men attained only about 50% of their total rise in the first half-minute, while AJ attained about 95% of his.

2) The "plateau" rate At 1500 ml./min. all groups reached an almost constant heart rate by the end of the 4th minute apart from a slight terminal rise in the young women of about 6 beats per min. The striking difference between the groups was the plateau rate reached. This was 142 beats per minute in the young women, 125 in the old men, 108 in the young men and just over 100 for AJ. At 2500 ml./min. the young men showed a tendency to plateau formation after 2 minutes, but there was a slight terminal rise in the last 1½ minutes similar to that seen in the young women at 1500 ml./min. AJ's heart rate fluctuated a little at 2500 ml./min. but there was no consistent rise in rate after the first 1½ minutes. His plateau lay 5-10 beats per min. lower than that of the young men.

3) The fall in heart rate after exercise At 1500 ml./min AJ's rate fell most rapidly and reached the resting level within 1½ minutes of stopping exercise. Thereafter his rate increased again by about 10 beats per minute, regaining the resting value only after 7 minutes' recovery. The young men, after 1½ minutes, had a rate still 6 beats per

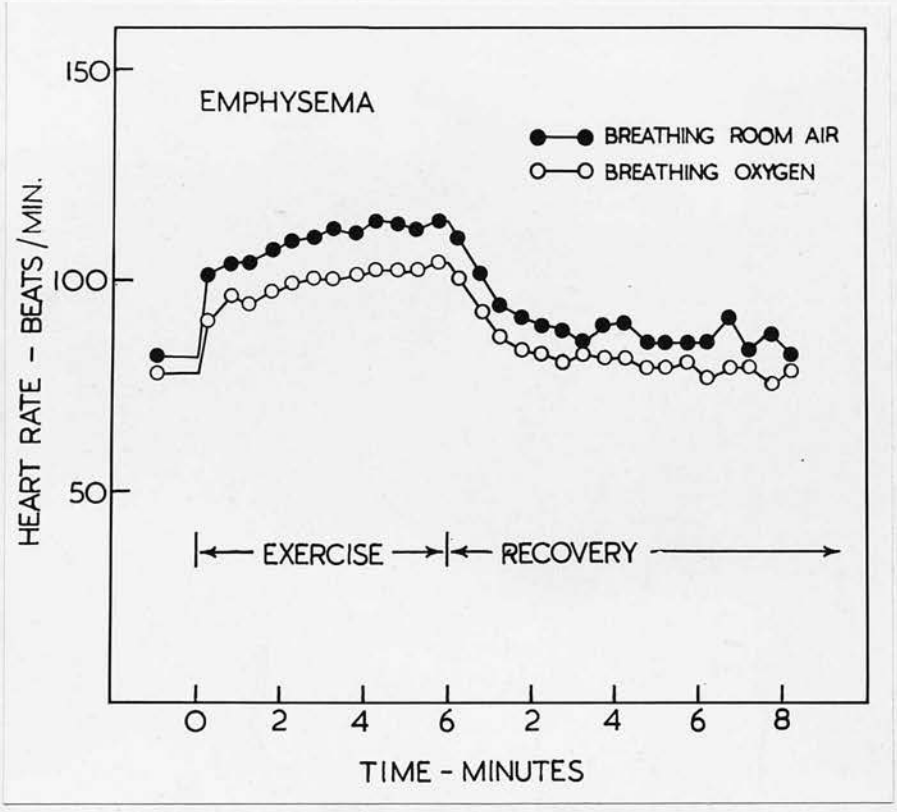

Fig. 30

Course of heart rate during exercise and recovery in emphysema: mean values.

minute above their resting level; after a very slight secondary rise their rate slowly fell and, like AJ's, had almost reached the resting level after 7 minutes' recovery. The young women showed no early "dip" in the recovery curve, though most of the fall was complete after 1½ minutes; after 8 minutes their rate was still 10 beats per minute above the resting level. The old men showed the slowest fall in rate during the early part of recovery (2 minutes), and no fall after that up to 8 minutes when the rate was still 10 beats above the resting level. Data were, of course, taken for longer periods of recovery than this. At 2500 ml./min. AJ's rate fell rapidly after exercise but did not show the "dip" seen at the lower intensity. After 1 minute it was 10 to 15 beats above his resting level and thereafter declined very slowly. The conspicuous rise at 5 minutes had no counterpart in the mean curves and may have been a random phenomenon of little significance. The recovery curve of the young men at 2500 ml./min. resembles that of the young women at 1500 ml./min.

None of the patients even approached 1500 ml. O_2 per minute, and cannot fairly be compared with the other subjects. However, their half-minute rates have been averaged at the highest rate of exercise they did - 1.375 m.p.h. at 5% gradient - at which the mean corrected O_2 uptake was 820 ml./min. (Fig. 30, upper curve). At this level their curve was not unlike that of the old men at 1500 ml./min. They reached 60% of their total rise in the first half-minute of exercise, their plateau was reached only after 4 minutes' exercise, and their fall was much delayed.

Many of the features described above, distinguishing those with good from those with bad exercise tolerance, are well known. The low resting heart rate, the relatively lower exercising rate and the relatively rapid recovery of the athlete have been reported many times (Schneider & Karpovich, 1949). The present results, however, show rather well that the differences are of degree only, and that a pattern of response seen in an unfit group of subjects at a given exercise intensity may be reproduced in a fit group at a higher intensity.

Two features merit comment. The "dip" in the recovery curve, shown by AJ at 1500 ml./min., was a fairly common finding in the fitter individuals, and often carried the heart rate to a level substantially below the resting level for a minute or two. This pattern was described by Bierring et al. (1936) as characteristic of ischaemic heart disease. Since the patency of AJ's coronary arteries may be presumed adequate, this conclusion cannot be correct.

The other, and chief, subject for comment is the contour of the heart rate curve during the exercise period. It is noteworthy that the essential features of this were described by Bowen in 1904. His opinions are worth quoting. He described the heart rate response under the following headings.

(1) An immediate rapid rise, attributable to reflexes from muscles and from cortical activity depressing the cardio-inhibitory centre. That cortical activity plays a part is clear from the anticipatory rise which usually precedes actual effort. The role of muscle afferents is more

debatable, but receives support from the recent work of Kao & Ray (1954a, 1954b, personal communication) in cross-circulation experiments in dogs.

(2) A continued rise, attributable to "heat and waste products formed in the heart and active muscles" and to increased coronary blood-flow. This is the rise seen in the young women and old men in the present study at 1500 ml./min. and in the young men at 2500 ml./min. That temperature plays a part in it seems doubtful. The rectal temperature, in treadmill walking at 1500 ml. O_2 per minute, rises rather less than 0.2°C in the first five minutes (Passmore & Harris, unpublished work) and it would be surprising if a rise of this order could account for an increase of 25 beats per minute in heart rate, which occurred in the old men. However, rectal temperature might not accurately reflect heart temperature. But the fact that the young men and AJ did not show this rise in heart rate at 1500 ml./min., while their deep temperature must have risen by much the same amount as the other groups, is another point against the temperature theory. Bowen, of course, was unaware of the Bainbridge reflex (Bainbridge, 1915), and it is possible that the speed at which the venous return increases after the onset of exercise has a major influence on the shape of this part of the pulse curve. Another possibility is that the delay in reaching the heart rate plateau reflects a delay in attaining the steady state cardiac output. Donald et al. (1955) have shown that in exercise at 500 ml./min. the cardiac output did not rise appreciably after the first minute in healthy but non-athletic subjects, whereas at 1500 to 2000 ml./min. it

continued to increase up to the end of the second or third minute. This again might be determined by the venous return. Finally, the delayed rise might appear because the anticipatory rise is inadequate to provide the whole of the increase in rate needed for a given exercise. Against this is the fact that AJ, perhaps the least nervous of all the subjects, succeeded in "hitting his target" in the first half-minute at rates of work well beyond anyone else.

(3) A plateau, due to the continuous action of (1) and (2) having reached equilibrium. But body temperature, at least, does not reach equilibrium at 1500 ml./min. in 5 minutes; it continues to rise for about 1 hour in ordinary surroundings. Venous return and cardiac output, of course, do reach a steady state within about 4 minutes.

(4) A secondary rise in heart rate, for which Bowen suggested no definite explanation. This is presumably the rise referred to by Müller (1950b) as the "Ermudungsansteig" ("fatigue rise") which occurs "very much more slowly than during the changeover from rest to work in the first minutes", and continues until work ceases. The terminal rise seen in the young women at 1500 ml./min. and the young men at 2500 ml./min. may have been the beginning of this rise; the exercise period in these experiments was too short to reach a firm conclusion. A slowly rising body temperature could well be one of the factors responsible for the "fatigue rise", and this possibility was adduced as an argument for limiting the exercise in the present study to six minutes.

II. THE HEART RATE DURING THE STEADY STATE

The curves described above indicate that the heart

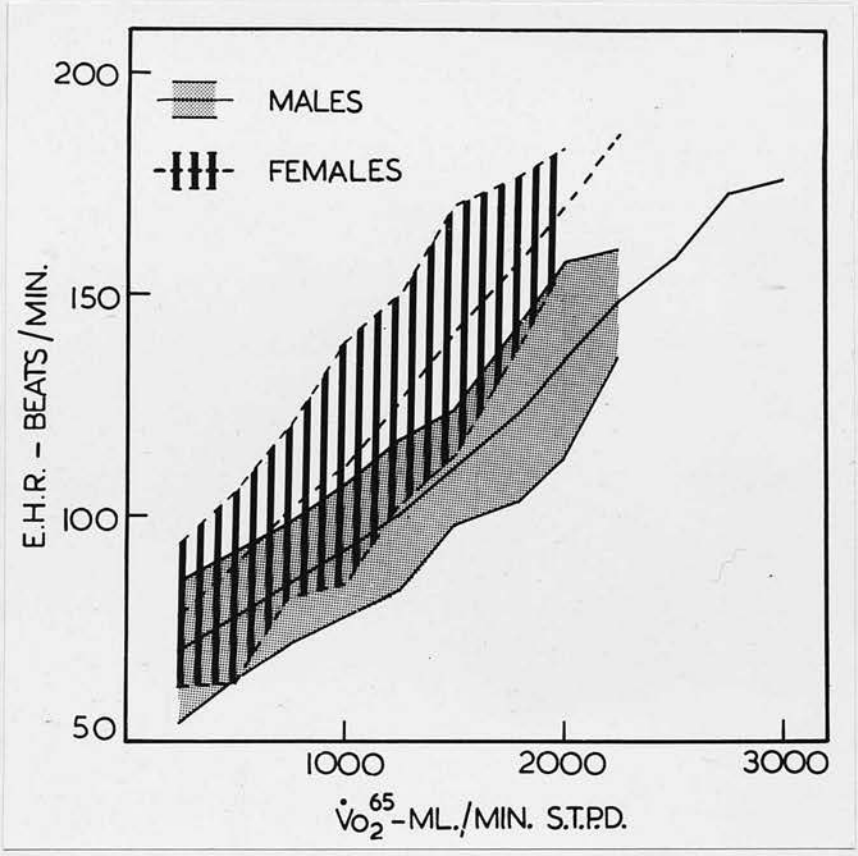

Fig. 31

Heart rate during the steady state
of exercise at different rates of work.
95% confidence limits for male
and female students.

rate during exercise reached an approximately steady state by the end of the 4th minute. This was true for individuals as well as for groups. The mean heart rate during the 5th and 6th minutes has been designated as the Exercise Heart Rate (EHR). The relation of the EHR to O_2 consumption is shown for the students in Fig. 31 in which mean values and 95% confidence limits are plotted separately for males and females.

It can be seen that the EHR bore an approximately linear relation to $\dot{V}^{65}_{O_2}$ but that the females had an appreciably higher EHR for a given $\dot{V}^{65}_{O_2}$. The rate of increase of EHR with work was greater in the females. There was considerable overlap between the two groups at the lower work rates, but above 1500 ml./min. this overlap diminished and at 2000 ml./min. it was negligible.

Values of EHR up to 1000 ml./min., from which Fig. 31 was constructed, were obtained mostly by interpolation. The slight bend in the mean EHR line (at 1000 ml./min. in the females and at 1250 ml./min. in the males) means only that average resting heart rates were a little above the EHR regression lines. Beyond these exercise intensities the mean EHR increased in almost perfect rectilinear fashion in both groups. This was true, in general, for individual subjects, though there was some random scatter. There was, in particular, no evidence of a "~~breaking~~ limiting point" at which EHR increased more rapidly at the higher exercise intensities.

Most of the subjects were studied once only, and their results do not allow an estimate of repeatability to be made.

AJ was studied on three separate days, and Fig. 33 shows his EHR for the first two of these days. There was a fairly consistent difference of 10 beats per minute at each value of $\dot{V}_{O_2}^{65}$. The reasons for this difference are not clear, but presumably do not include a difference in AJ's fitness on these days. The Astrand-Ryhming index would, nevertheless, have indicated such a difference; the upper line in Fig. 33 gives an "aerobic capacity" of 3840 ml./min., the lower line 4600 ml./min. - an increase of no less than 20%. On the other hand the slope of the lines is almost identical; the "Leistungspulsindex", which depends only upon the slope, would thus have given the same assessment of fitness on each day.

The lower line in Fig. 33 represents exercise at 3 m.p.h. with an almost uniform stride rate of 117 per minute. The upper line, apart from the lowest point, represents a speed of 4 m.p.h. at a stride rate of 133 per minute. If the rapidity of movement plays a part in the tachycardia of exercise, either by facilitating venous return or by setting up reflexes, or by some other mechanism, this might be significant. The work of Kao & Ray in this connection has been mentioned. According to Bowen (1904) "The rapidity of the pulse during work is much more dependent on the rapidity of the muscular movements than upon the amount of resistance that is overcome." This is, no doubt, an overstatement; but other workers have drawn attention to the dependence of the heart rate upon the type of exercise as well as upon its intensity. For instance, Collett & Liljestrand (1924) found that the heart rate at a given oxygen

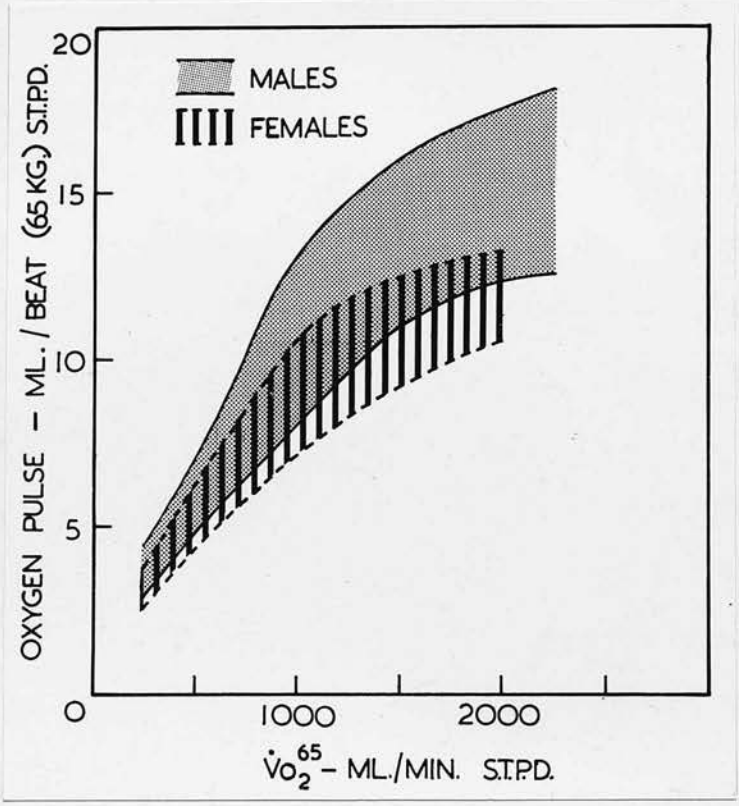

Fig. 32

Oxygen pulse at different rates of work: male and female students. 95% confidence limits have been smoothed.

uptake was higher when work was done by the arms on the ergometer pedals than when the legs were used, and higher during leg work on the ergometer than in exercise on the staircase treadmill. On the other hand Berggren & Christensen (1950) found the same relation between heart rate and oxygen uptake whether work was done on the bicycle ergometer or the treadmill, although arm work gave a different relationship. The effect of the rapidity of muscle movement, as distinct from the rate of work, on heart rate has not been adequately studied. Attention to this factor might lead to better repeatability of heart rate counts during exercise.

The relation between EHR and $\dot{V}_{O_2}^{65}$ may be expressed in terms of the oxygen pulse (OP) as shown in Fig. 32. The OP in both males and females continued to rise, though progressively more slowly, up to the highest exercise levels studied. As expected, the males had higher OPs than the females. It was argued in the introduction that a fall of OP with increasing work must mean a fall of stroke volume. This did not occur. Neither does the flattening of the OP curve at the higher exercise levels signify the arrival of a "~~breaking~~ limiting point". The asymptotic form of the OP curve follows from the relation between EHR and $\dot{V}_{O_2}^{65}$ which is of the type $y = ax + b$, where b has a positive value. The ratio x/y must increase at a diminishing rate as x increases. Henderson & Prince (1914) found that the OP behaved in a similar fashion with increasing exercise. It may well be, of course, that in neither their study nor the present one was exercise pushed hard enough to reach the point at which

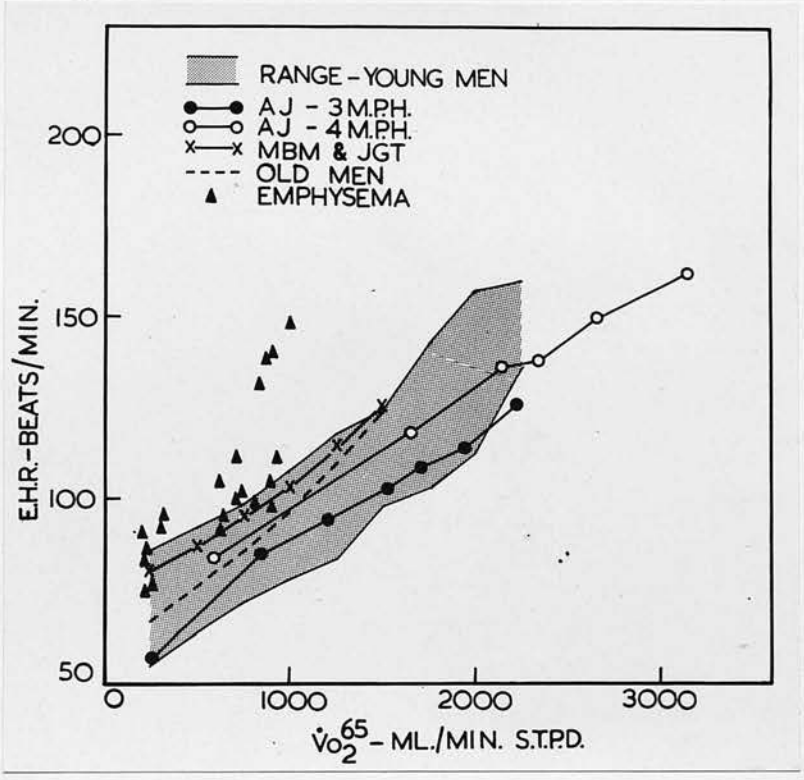

Fig. 33

Heart rate during the steady state of exercise at different rates of work. Healthy male subjects and patients with emphysema.

OP fell, and EHR increased more rapidly, with increasing exercise. If this point can be reached in healthy people it must be evident at only the very heaviest rates of work.

The EHRs of AJ, MBM and JGT, the old men and the patients with emphysema are shown in Fig. 33. The range for the male students is indicated for comparison. The data for AJ are plotted separately for each day of his study. Since most of the male students exercised at 4 m.p.h. the upper line for AJ is perhaps more strictly comparable with their range than the lower line.

There is little to distinguish AJ from the other young men up to an O_2 consumption of 2000 ml./min. At higher levels AJ's EHR became significantly lower than the rest. Similarly, the EHRs for MBM and JGT, for the old men, and even for some of the patients, were significantly higher than those for the young men only at exercise intensities approaching the upper limit for each group. These observations suggest that both the absolute EHR and its rate of rise with increasing exercise must be taken into account in "placing" an individual in the scale of fitness. Of these the rate of rise seems to be the more important. If absolute EHR be relied upon alone it is necessary to measure it at a rate of work near to the subject's maximum.

A search of the literature has failed to show any study of heart rate during treadmill exercise in which the data are properly comparable with the present ones. The most thorough study so far on the effects of exercise in relation to age is that of Robinson (1938), already mentioned in the chapter on ventilation. He studied two levels of exercise

only - moderate exercise at 1600 - 1700 ml. O_2 per minute (corrected to 65 Kg. body weight) and exhausting exercise which has no parallel in the present study. Only males were investigated. Robinson's Group V had a mean age of 24.5. In moderate exercise their mean steady state $\dot{V}_{O_2}^{65}$ was 1760 ml./min. During the 5th and 6th minutes of this exercise the mean heart rate was 128/min. with a range (not 95% limits) of 118 to 142/min. The corresponding values in Fig. 33 are: mean, 124/min.; range 104 to 144/min. The nearest age group in Robinson's study to the old men in the present study was Group X with a mean age of 75. It contained only 3 men and heart rate data were not detailed. The preceding group (mean age 63) had a mean EHR of 132 /min., and at a similar O_2 uptake the present old men had a mean EHR of 128/min.

The heart rate in emphysema

The heart rate during exercise in the patients with emphysema is of interest in relation to the development of heart failure in this condition. Baldwin et al. (1948) measured the heart rate during recovery from standard exercise in patients with pulmonary disease. They concluded: "Whether an increased pulse rate is of importance in detecting a circulatory factor in subjects with pulmonary disease still remains an open question." They were unable to correlate recovery heart rate with the presence or absence of other evidence of cor pulmonale.

None of the emphysema patients in the present study had ever shown evidence of heart failure, as judged by past or present oedema, jugular vein distension or right

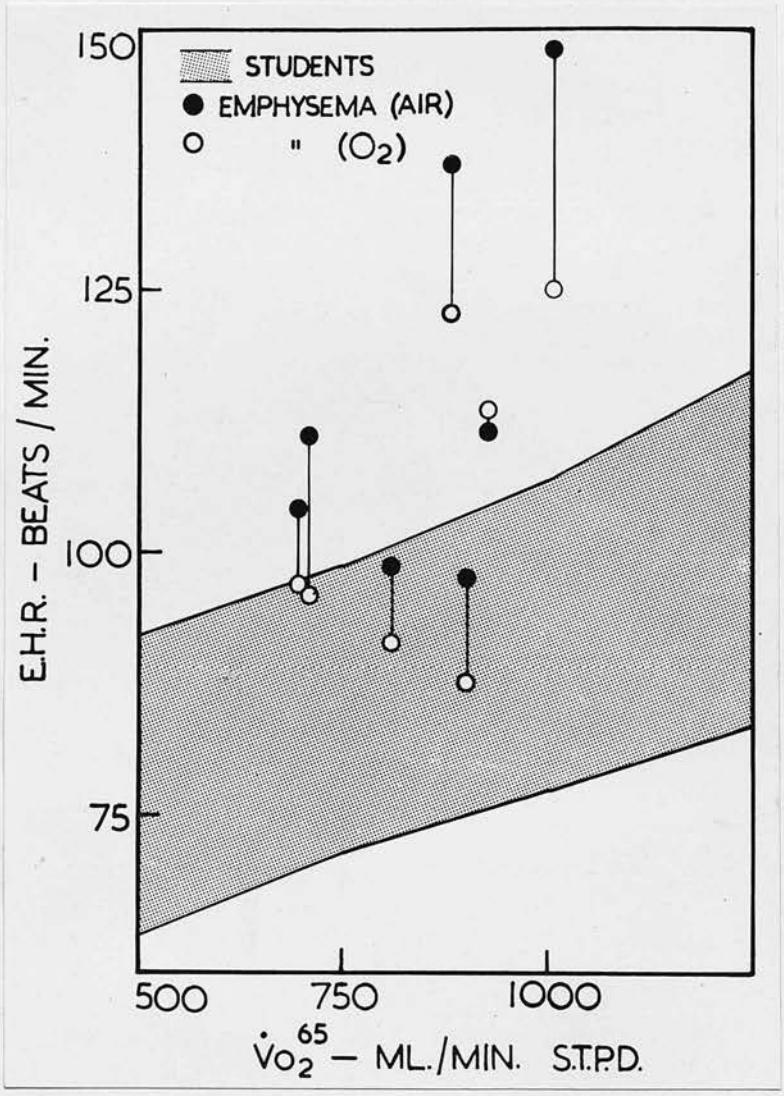

Fig. 34

Effect of breathing 100% O_2 on the steady state heart rate in emphysema. 95% confidence limits for male students.

auricular pressure on cardiac catheterisation. The mean exercise heart rate in the patients was, however, well above that for the healthy students. Fig. 34 shows that during the harder of their two exercises only two of the patients had an EHR within the normal range, but that when the same exercise was done breathing 100% oxygen all but one showed a fall of EHR, and four of the seven came within normal limits*. Fig. 30 contrasts the course of the heart rate during and after exercise when oxygen was breathed instead of room air. Oxygen breathing resulted in a uniform depression of the whole curve. It did not abolish the lag in the initial rise of the heart rate, nor the slow rise up to the end of the 4th minute. The rate of fall of the heart rate after exercise was the same with oxygen as without it. The resting rate was regained a little earlier with oxygen, but this would not have been so had the resting rate been 2 beats per minute lower - easily a matter of chance.

The walk at 5% on room air was the second, and on oxygen the third, exercise of the experimental session in every case. It might therefore be argued that the lower EHR on oxygen could have been the result simply of repetition, as suggested by the work of Schnebel & Elbel (1951) on the reaction of the pulse to successive periods of exercise. It would have been necessary to reverse the order of the exercises in order to meet this criticism, and this was

---

*Oxygen was given for 10 minutes before, and throughout exercise and recovery.

not done. However, these patients were so handicapped that exercise while breathing air probably caused substantial desaturation of their arterial blood, and it was striking to observe the relative comfort with which they exercised when breathing oxygen. It seems likely therefore that anoxia was partly responsible for the high EHR of these subjects, and that breathing oxygen prevented this anoxia. Anoxia is, of course, a potent cause of tachycardia in the healthy heart. Not all the patients had normal EHRs when anoxia was prevented, and one actually had a slightly higher EHR. Other factors must therefore be involved. Among these it is tempting to include lack of general fitness: these men had had very little exercise for years. In summary, it is clear that abnormally high heart rates may be found during exercise in emphysema, but that these may be due to causes other than heart failure.

III. INDICES OF PERFORMANCE BASED ON THE HEART RATE DURING EXERCISE

The present study provides data from which some of the proposed indices of working capacity can be calculated. The "aerobic capacity" (AC) of Astrand & Ryhming (1954), the "working capacity" (WC) of Wahlund (1948) and the "performance pulse index" (PPI) of Müller (1950b) have been worked out for each subject where possible. The AC proved straightforward when calculated as twice the $\dot{V}_{O_2}^{.65}$ corresponding to an EHR of 128 in males and 138 in females. For WC, extrapolation was sometimes necessary to find the $\dot{V}_{O_2}^{.65}$ corresponding to an EHR of 170, and when the necessary extrapolation was considerable it was thought best not to attempt

* It should be noted that Astrand & Ryhming did not study old people and they pointed out that different standards might apply to different age-groups. The point made on p. 108 about AJ's fitness indices on successive days does suggest, however, that the AC index may be fundamentally less reliable than the Leistungspulsindex.

it. The PPI was taken as the slope (rise in EHR per litre rise in $\dot{V}_{O_2}^{65}$) of the line giving by eye the best fit to the plotted points of EHR against $\dot{V}_{O_2}^{65}$. Confidence in the result was therefore inversely proportional to the scatter.

Table VI shows mean values of these indices for each

Table VI

SUBJECT	AC	%	WC	%	PPI
1.AJ	4320	100	3240	100	35
2.Young men	3767	87	2620	81	41
3.Young women	2855	66	1960	60	53
4.MBM and JGT	2970	69	2180	67	50
5.Old men	3340	77	-	-	55

group. On the basis of their athletic interests and pursuits the groups might be arranged in descending order of fitness as follows: first AJ, then the young men; next either the young women or MBM and JGT, and finally the old men; that is, either 12345 or 12435. AC gives 12543, WC gives 1243 and PPI 12435. AC and WC give the same order for the first four groups. At first sight this is not surprising, since these indices are very similar, differing only in the reference EHR. On the other hand, the AC makes allowance for the higher EHR of females, while the WC does not. Nevertheless they both place MBM and JGT above the young women. PPI gives the same order for the first four groups, but unlike the AC it places the old men last instead of third. Since the placing of the old men differs so markedly, either AC or PPI must be unreliable. Of the two, PPI accords more with common sense.*

Individual results are plotted in Fig. 35. This

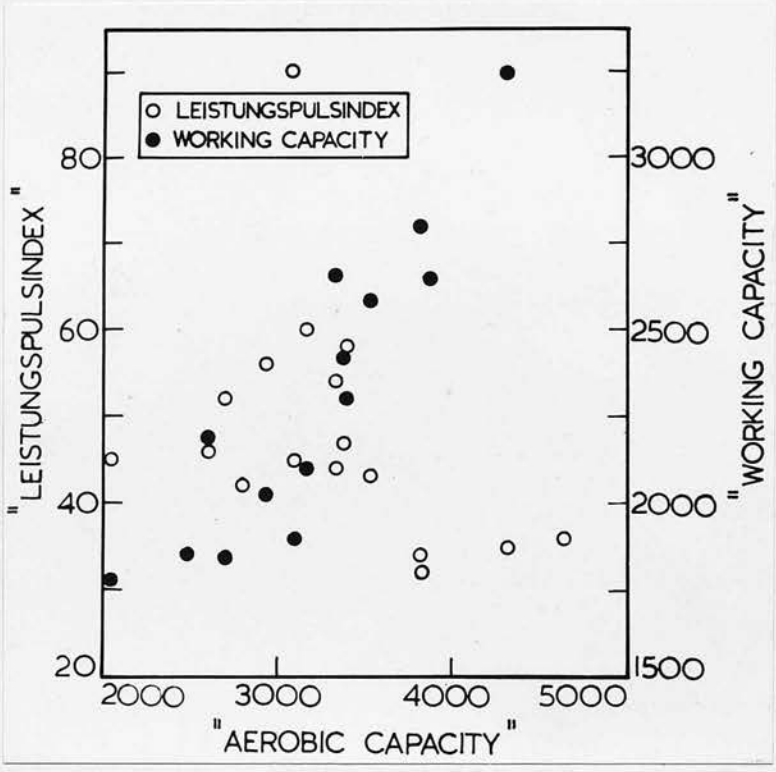

Fig. 35

See Text.

shows that WC does not bear a very close relation to AC, while PPI bears none.

In the absence of an independent criterion of fitness it is impossible to assess the reliability of the three indices discussed above. All that can be said is that they cannot all be reliable since they disagree with each other even in the placing of groups, which have less random scatter than individuals. Of the three, PPI seems to accord with expectation, and this is in keeping with the conclusion drawn from Fig. 33 regarding the best means of separating the groups on the basis of EHR. Whether the PPI is equally reliable in assessing individual subjects is a question which cannot be answered by the available information.

IV. THE RECOVERY HEART RATE

The analysis of the heart rate curves presented in the first section of this chapter showed that there were differences between the groups in the rate at which the heart rate returned to the resting level after exercise. This was a relative difference only, since a type of recovery curve shown by an unfit group at a low level of exercise could be found in a fit group at a higher level. It seemed worth while to examine this phenomenon a little more closely.

The difference between the SHR and the EHR at a given exercise intensity depends mainly upon the duration and height of the recovery curve. The mean difference between SHR and EHR for each group was calculated for different levels of exercise at fixed intervals of 250 ml./min. corrected O_2 consumption. The results are shown in Fig. 36. There was no appreciable difference between the groups up to

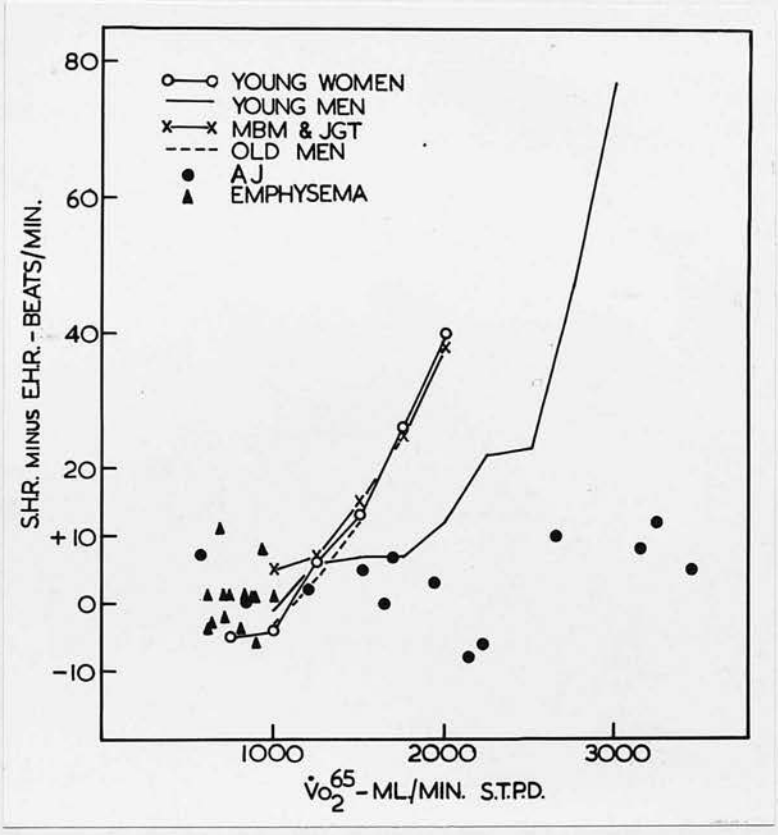

Fig. 36

Recovery heart rate index after different rates of work: all subjects. See text.

a $\dot{V}_{O_2}^{65}$ of 1500 ml./min. Beyond this rate of work there was no difference between the old men, the young women and MBM and JGT, but there was an increasing difference between these groups and the young men, and between AJ and the rest. AJ's results were noteworthy, since his SHR-EHR difference only once exceeded 10 beats per minute. He was the only subject who showed such a close correspondence between SHR and EHR.

The SHR is clearly of no value in distinguishing groups of unequal fitness except at very high work rates. This conclusion supports the views of Cureton et al. (1945) and Taylor (1944) that heart rate data taken during recovery do not provide a sensitive index of working capacity.

V. THE HEART RATE DURING EARLY EXERCISE

Most of the features of the heart rate curves during exercise and recovery have been considered. One remains - the course of the heart rate during the transition from rest to work. This was found to vary according to the group under consideration; the fit subjects tended to reach their exercise heart rate sooner after starting exercise than the less fit, but as the exercise intensity increased the same difference appeared between the fit subjects and the trained athlete. It seemed possible that this observation might be used as an indication of exercise tolerance.

The question was approached in two ways. First, the rise of heart rate in the first half-minute was calculated as a percentage of the difference between the initial resting rate and the EHR, for each exercise done by each subject. It was intended that if the percentage fell progressively

with increasing exercise, a "~~breaking~~ limiting point" might be defined as the work rate at which the percentage fell below some arbitrary value, say 70%. This proved impossible owing to the very irregular way in which the percentage fell with increasing work in the individual subject.

In order to avoid undue reliance on a single half-minute count, another method was tried. The total number of beats during the six minutes of exercise was calculated, and this figure was subtracted from the number which would have occurred had the heart rate risen at once to the EHR and remained there throughout exercise. The difference was plotted for each subject against oxygen uptake. As expected, it tended to increase with increasing work rate, but the individual irregularities were considerable. No useful estimate of a "~~breaking~~ limiting point" could be made.

SUMMARY AND CONCLUSIONS

We have seen that the heart rate response to exercise varies in several respects when groups of subjects of unequal working capacity are compared. These variations concern the transition from rest to work, the steady state of exercise and the recovery phase. The last two have been the subject of numerous reports in the literature and have stimulated efforts to measure "exercise tolerance" by means of heart rate measurements. To be of any value, a test of working capacity must be reliable in the individual case. This investigation suggests that heart rate measurements do not meet this requirement.

The claims of previous workers - Wahlund (1948), Astrand & Rhyming (1954) and Müller (1950b) - that the steady

state heart rate provides a reliable index of working capacity cannot be supported. The three indices proposed by these authors are contradictory even when applied to groups rather than individuals, and cannot therefore all be reliable. Of the three the Leistungspulsindex of Müller appears to give the best group assessment. Whether it is reliable in differentiating between individual subjects is a question which cannot be answered by the present data. The recovery heart rate gives satisfactory group definition at the higher rates of work; at low and moderate rates it appears to be unsuitable, and its value in the individual case is thus irrelevant. The behaviour of the heart rate during the early part of exercise, while showing apparent group differences, proved impossible to utilise as an individual index of performance.

It appears, therefore, that with the possible exception of the Leistungspulsindex the heart rate is at present of no practical value in assessing an individual's capacity for exercise. The heart rate is governed by a large number of variables, some of which - for example emotion - are beyond control or measurement; and while a better understanding of these variables might lead to improvements in existing tests it seems unlikely that adequate precision could be attained.

CHAPTER XII

CONCLUDING REMARKS

It was pointed out in the Introduction that there is no agreed definition of "exercise tolerance". Few, indeed, have attempted to define it, yet it is widely used in a loose way in clinical discussions. A priori, it might have a definite meaning in either of two senses. First, it could be used to mean the maximum performance in some particular type of exercise of which the subject is capable. One authority at least believes that a maximum performance is the best measure of working capacity (Taylor, 1944). We have seen, however, that it is unsuitable in clinical work because motivation, so important in maximum effort, cannot be relied upon and because maximum effort is not without danger in some types of cardiopulmonary disease. Alternatively, one might use the term "exercise tolerance" to mean the level of exercise at which the smooth integration of the various responses to exercise begins to break down; or, as Wahlund (1948) put it, the level at which the steady state can no longer be efficiently maintained. The clinical usefulness of this definition depends upon whether this breakdown (if it exists as a clear-cut point) begins to show itself at a level of exercise low enough to be safely determined in patients.

Wahlund (1948) placed the limit of efficiency (quite arbitrarily) at 170 heart beats per minute and 30 respirations per minute. Henderson et al. (1927) stated that 180 beats per minute is the ordinary limit of profitable tachy-

cardia, because stroke output declines beyond this rate. Their conclusions were based upon determinations of heart output by the ethyl iodide method, the accuracy of which it is permissible to question. The validity of these figures is thus open to doubt; and in any event they represent a level of exertion to which a sick person could not reasonably be taken. Concerning ventilatory efficiency, no corresponding standards have been laid down, as far as I am aware; but the oxygen extraction or CO_2 discharge might possibly be used to define the point of declining efficiency.

This investigation has shown, however, that the changes in neither heart rate nor ventilation, in relation to the rate of work, reveal anything in the nature of a "~~breaking~~ limiting point" in the majority of healthy subjects, up to moderately heavy exercise. The response of a subject to progressively increasing exercise forms a more or less continuous gradation from the very mildest work to the most severe. Nor does it appear possible to predict with any accuracy a person's maximum capacity from measurements made during submaximal effort. And although the patients studied were too few and too disabled to allow a firm statement to be made, it would be surprising if these conclusions did not apply also to states of disease. It may well be that in the last resort "exercise tolerance" is not measurable, in the senses defined above.

On the other hand, it is possible to obtain very useful information about a given subject's response to exercise by comparing his response to a particular test-exercise with the response expected of a normal person of the same age

and sex. This approach requires that a normal range of values be established for each variable over a big range of exercise intensities. The individual under test might then be exercised at perhaps three set intensities, according to his ability, and his ventilatory and other responses compared with the normal at the appropriate values of oxygen consumption. Ventilation, alveolar and expired air composition, respiratory frequency, oxygen debt and, perhaps, heart rate, together with their derivatives, could then be expressed as percentages of the expected values. Limitation of the number of exercises done would make duplicate or triplicate determinations feasible. Perhaps the chief contribution of the present study has been to show that all these variables may be measured simultaneously, and without much difficulty, during the most natural of all forms of exercise.

ACKNOWLEDGMENTS

This work was done during the tenure of a Fellowship in Clinical Research awarded by the Medical Research Council, to whom I am also indebted for a grant towards expenses.

I owe a particular debt to Professor D. Whitteridge, F.R.S. and to Dr. R. Passmore, F.R.S.E. Apart from affording me facilities and advice most generously, they provided the atmosphere in which a humble clinician could gain some insight into the methods of physiological research, and appreciate how difficult it is to produce results which mean anything.

For the help given me by the technical staff of the Physiology Department, Edinburgh University, I am most grateful. My instruction in Electronics by Mr. W. T. S. Austin was for the most part an uphill battle in which he concealed his despair and remained patient to the end. In Mr. D. Shirling I had a willing and critical helper during the experimental sessions.

Dr. J. G. Thompson, of the Public Health Department, kindly enabled me to study some members of the Sighthill Old People's Health Club. The patients were studied through the courtesy of Professor J. W. Crofton and Dr. I. W. B. Grant.

Mr. R. Mills, of the Department of Medicine, Birmingham University, gave valuable advice and help with the figures, and the photographs of these are the work of Mr. T. Dee.

APPENDIX I

CARDIOTACHOMETER

Reprinted from the QUARTERLY JOURNAL OF EXPERIMENTAL PHYSIOLOGY,
VOL. XLII, 1957.

MEASUREMENT OF HEART RATE IN EXERCISE.

By W. T. S. AUSTIN and E. A. HARRIS.[1] From the Department of Physiology, University of Edinburgh.

(*Received for publication* 14*th August* 1956)

DURING recent years there has been a revival of interest in the effect of exercise upon the heart rate. Measurements of heart rate are used for the assessment of physical fitness in the Harvard step test and other methods [Müller, 1950; Astrand and Ryhming, 1954]. In the industrial field pulse counts have been used to allocate rest-pauses on a rational basis [Müller, 1953]. In clinical medicine a test of working capacity based on heart rate measurements during exercise has been proposed [Wahlund, 1948; Bengtsson, 1956]. A feature common to all these studies has been the counting of high pulse rates and in most during exercise. Using conventional methods (palpation or auscultation) this is frequently difficult and always tedious, and there is a demand for an automatic pulse counter which is reliable under conditions of vigorous body movement.

A commercially produced, portable apparatus has been available since 1953. This is the "fotoelectrischer Pulszähler" of the Max Planck-Institut für Arbeitsphysiologie, Dortmund. Its operation depends on transillumination of the earlobe. Volume and colour changes, due to each pulse wave, are signalled by a photo-cell. The circuit employs positive feedback so that a small change of input is sufficient to trip the counter. As a result of this the instrument tends to self-oscillation, and we found it too unstable to be uniformly reliable.

We rebuilt the apparatus, using a miniature gas-filled photo-cell instead of the barrier-layer cell used in the Dortmund machine, eliminating feedback and increasing amplification. With these modifications we were able to record heart rate during mild exercise and to transmit the counts by radio over short distances. Disadvantages, however, soon appeared. The light source had to be bright, and readily burned the subject's ear. During really vigorous exertion artefacts were introduced, due presumably to the mass movement of blood to and from the ear, as suggested by Redfearn [1954]. With marked vasodilatation, dicrotic waves were often counted. Finally, in a study of a patient with moderately severe mitral stenosis, it was noticed that soon after the beginning of exercise counts were missed and that they stopped altogether within 60–90 seconds. We presumed that this resulted from

[1] Clinical Research Fellow, Medical Research Council.

extreme reduction in skin blood flow, as described in mitral stenosis by Donald *et al.* [1955]. It is clear that most of these criticisms apply to the use of any form of peripheral transducer, such as piezoelectric, capacitance or skin reflection systems. Limited attempts to use such systems showed also that proper fixation was very difficult.

Accordingly, some form of central signal, independent of pulse volume, seemed necessary. A small microphone passed down the œsophagus recorded waves from aorta and left auricle which could doubtless be used as the signal for a heart rate counter. No artefacts were produced by breathing or speech, but swallowing caused an extra wave to appear. It was, however, mainly because of the inconvenience of swallowing the microphone that we decided to explore further the possibility of utilizing the electrocardiogram (ECG) as a signal source.

Several methods using ECG amplification have been published, *e.g.* Boyd and Eadie [1952]. Most of these make use of critically tuned filters for suppression of interference from mains and muscle action potentials. While these are satisfactory for measurements at rest or during mild activity, the vast range of wave forms produced by muscle contractions in vigorous body movement contains components similar to the wave form of the ECG. These cannot be rejected by simple filtering without degradation of the wanted signal. It was therefore decided that critical filters should be avoided, and that interference should be as far as possible rejected at the input stage by means of a differential amplifier [Toennies, 1938; Dickinson, 1950].

Three copper gauze electrodes (10 × 7 cm.), enclosed in rayon lint bags soaked in saline, are firmly attached by adhesive tape to the right shoulder, the chest wall overlying the cardiac apex and the left arm (earth); the sites of application are well prepared by rubbing in electrode jelly containing powdered pumice.[1] These positions are chosen as giving the biggest QRS amplitude. Potentials are DC coupled into a pre-amplifier, consisting of two push-pull battery-operated stages with fairly short time constant RC coupling, which attenuates the P and T waves of the ECG, but leaves the shorter lasting QRS complex as a diphasic signal with a few random muscle spikes superimposed (fig. 1). This signal is fed into the main amplifier, comprising two stages of push-pull pentodes with reasonably long time-constant coupling but with some filtering to remove the shorter residual muscle potentials. No gain control is used; the main amplifier is working under conditions of voltage overload. A stabilized power-pack supplies this part of the apparatus. The output from one side of the amplifier is fed to a Schmitt trigger, the bias of which can be altered

[1]

Gum tragacanth	6·5 g.	Pumice powder	87 g.
Glycerine	17 g.	Phenol	1 ml.
Sodium chloride	64 g.	Methyl green	q.s.
Potassium bitartrate	3 g.	Water	100 ml.

by a variable cathode resistance. The square wave from this trigger is differentiated, and its positive component drives a variable pulse-width "flip-flop". Since several digital counters may be required, a Post Office relay with heavy-duty contacts is used with its own DC-coupled valve. The Schmitt trigger, "flip-flop" and P.O. relay stages have their own unstabilized power-pack. It was found essential to use two

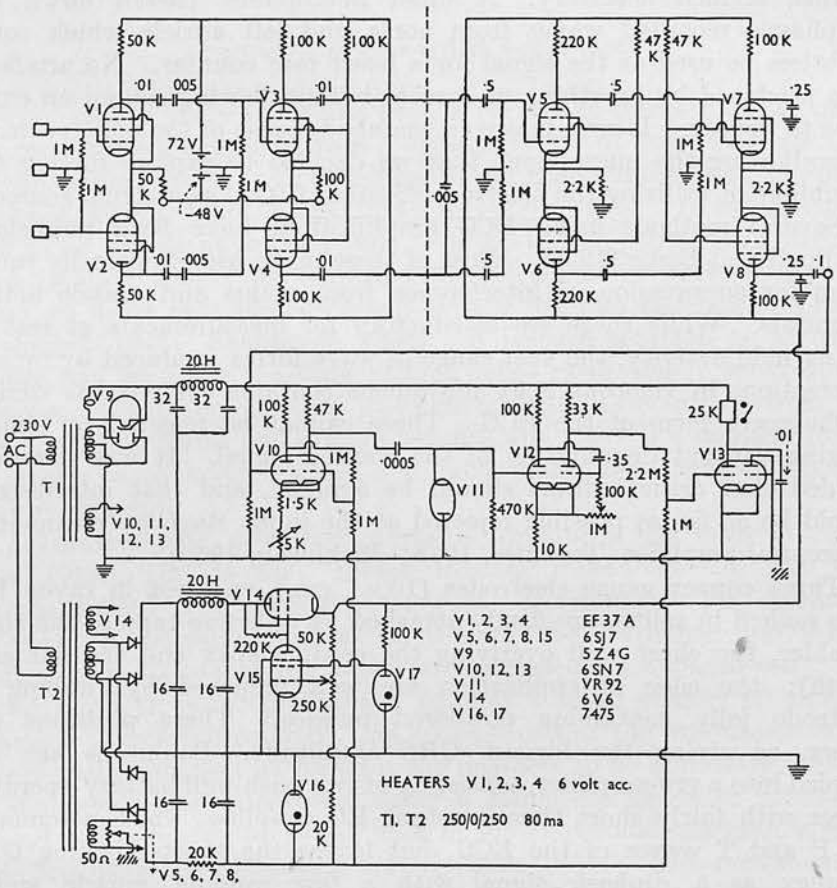

FIG. 1

separate power supplies, and these are both built on the main amplifier chassis, the pre-amplifier being at a distance from transformer fields. Common return paths at earth potential should be arranged so that magnetic loops are avoided.

For purposes of display electronic integrators were tried and considered too inaccurate. It is desirable, nevertheless, to have a permanent record of heart rate in addition to the more limited information available by reading digital counters. The simplest form of record is obtained by causing the P.O. relay to drive a ratchet and pawl mechanism to

which a paper drive is coupled. The paper thus moves forward a short distance with each heart beat, and the distance between time-marks on the paper is directly proportional to heart rate. It has been found possible to record ventilation and respiration on the same paper. Digital counters, from which "spot" counts can be read at any moment, are also operated.

The apparatus described is simple to operate, and works reliably in the presence of potential interference from the treadmill motor, several relays and violent muscular movement (running at 8 m.p.h. and 10 per cent uphill gradient), and in the absence of screening. Suppression of all switches and relays with 0·1 mfd. condensers across sparking points is necessary.

It is desirable that the pulse supplying the Schmitt trigger should have a positive-going leading edge, so the ECG leads should be applied to ensure this polarity. The bias of the trigger should then be adjusted, if necessary, to give reliable counts. The width of the "flip-flop" pulse must not be longer than the time between successive beats at the maximum rate to be counted. The rather large electrodes and the method of attaching them to the subject are undesirable features, but we have not found it possible to improve on them.

REFERENCES

Astrand, P.-O. and Ryhming, I. (1954). *J. appl. Physiol.* **7,** 218.
Bengtsson, E. (1956). *Acta med. scand.* **154,** 91.
Boyd, W. E. and Eadie, W. R. (1952). *Electronic Engng.* **24,** 102.
Dickinson, C. J. (1950). Electrophysiological Technique. London. Pp. 68–69.
Donald, K. W., Bishop, J. M. and Wade, O. L. (1955). *Clin. Sci.* **14,** 531.
Müller, E. A. (1950). *Arbeitsphysiologie,* **14,** 271.
Müller, E. A. (1953). *Quart. J. exp. Physiol.* **38,** 205.
Redfearn, J. W. T. (1954). *J. appl. Physiol.* **7,** 109.
Toennies, J. F. (1938). *Rev. sci. Instrum.* **9,** 95.
Wahlund, H. (1948). *Acta med. scand.*, Suppl. 215.

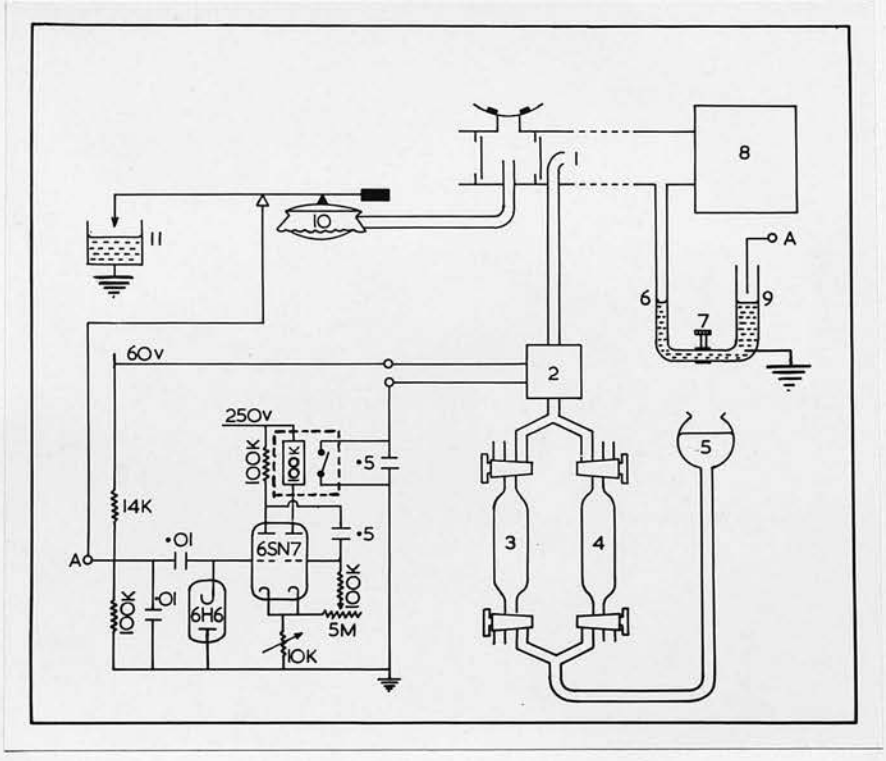

Fig. 37

Apparatus for collecting end-tidal air.
See text.

APPENDIX II

APPARATUS FOR COLLECTING END-TIDAL AIR SAMPLES

A narrow brass tube (1, Fig. 37) was sealed into the mouthpiece assembly just distal to the expiratory valve. From this, a length of thin rubber tubing (about $2\frac{1}{2}$ feet) passed through an electromagnetic valve (2) to two sampling tubes (3 and 4) to which suction could be applied by means of a mercury reservoir (5). Gas would pass from the expiratory tube to the sampling tubes only when valve (2) was open. In order to sample the last few ml. of each expiration valve (2) had to remain closed during expiration and to open for a brief interval at the beginning of each inspiration. This was achieved in the following way. A manometer (6) containing strong Na_2SO_4 and furnished with a damping clip (7) was used to detect pressure changes in the tube leading to the respirometer (8). The back-pressure of the respirometer during expiration was sufficient to make electrical contact between the solution and the platinum terminal at (9). When inspiration began, the pressure dropped and the contact was broken. This break was made to deliver a positive signal to the input grid of a variable pulse-width trigger circuit which, through a relay, caused the valve (2) to open for a brief interval which could be varied by adjusting the trigger time constant. The adjustment was made in such a way as to ensure that valve (2) closed before expiration began.

Before sampling, (3) and (4) were filled with mercury. End-tidal gas was first drawn into (3) in order to wash out the dead space contained in the tubing between (1) and the

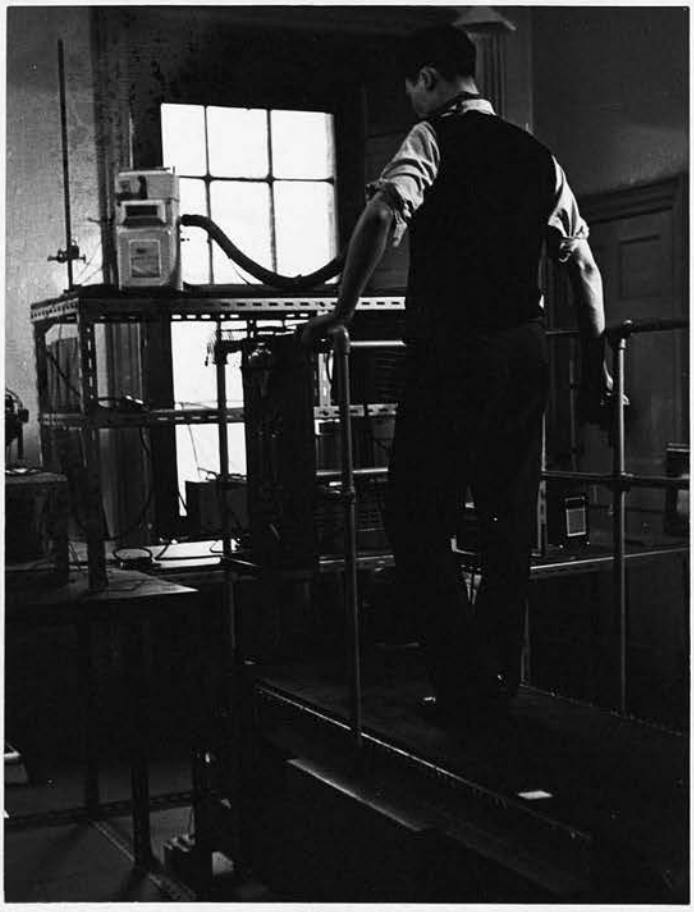

Fig. 38

A subject preparing to start exercise.
The general arrangement of apparatus is shown.

sampling tubes. When (3) was about half full the sampling was continued in tube (4), which was filled steadily, by lowering (5) appropriately, during the required period. Tube (4) was then replaced by an empty tube, and this and tube (3) were filled with mercury in readiness for the next sample.

This apparatus worked satisfactorily with healthy subjects, but it was found that the prolonged expiration of the emphysema patients often did not produce enough pressure to make contact at (9). An alternative signal-producing device was therefore used, in which a tambour (10) caused a balanced lever to break contact with electrolyte solution (11) when inspiration began. In this form the apparatus was similar to that of Clark-Kennedy & Owen (1927) except for the trigger circuit. The latter is a very desirable modification.

The use of mercury suction to draw gas into the sampling tube is open to criticism, since it is impossible to ensure that the same volume of gas is drawn from each expiration. In this study sampling was done only during the steady state and tube (4) was always filled as evenly as possible. For other purposes some form of constant suction might be preferable.

APPENDIX III

SYMBOLS

V = gas volume

$\dot{V}$ = gas volume/unit of time e.g. $\dot{V}_{O_2}$ = oxygen uptake

P = gas pressure e.g. P_{ACO_2} = alveolar CO_2 pressure

F = fractional concentration

f = respiratory frequency

R = exchange ratio (respiratory quotient)

An = anatomical (unofficial)

Subscriptions

I = inspired gas e.g. $F^{c}_{IO_2}$ = inspired O_2 content, corrected for R

E = expired gas

A = alveolar gas

T = tidal gas e.g. V_T = tidal volume

D = dead space gas e.g. $V_D(An)$ = anatomical dead space

a = arterial blood e.g. P_{aCO_2} = arterial CO_2 pressure

Superscriptions

c = corrected

alv = alveolar (unofficial)

65 = corrected to 65 Kg body weight (unofficial)

Table VII

Basic data for all subjects

Subject	Speed m.p.h.	Gradient %	EV l./min.	SV l./min.	OE %	$CO_2D\%$	$\dot{V}_{O_2}$ ml./min.	P_{AO_2} mm. Hg.	P_{ACO_2} mm Hg	f	EHR	SHR
AJ	0	0	6.5	-	4.67	3.77	250	-	-	14.0	57	-
	3	0	15.1	16.3	6.40	5.02	800	94.9	45.4	18.0	85	86
61.7 Kg.	3	4	21.3	21.8	6.51	5.37	1140	94.6	47.2	19.0	94	96
	3	8	26.8	27.0	6.50	5.55	1440	94.1	47.6	19.5	103	108
	3	10	29.6	29.9	6.61	5.61	1610	93.6	49.1	20.0	109	115
	3	12	34.6	33.4	6.44	5.68	1840	94.6	49.0	23.5	114	118
	3	15	39.1	37.9	6.56	5.86	2110	93.9	49.8	22.5	126	121
	1.375	0	11.9	13.1	5.57	4.33	550	98.8	42.9	16.5	84	77
	4	4	29.2	29.3	6.45	5.22	1550	94.6	46.1	22.0	118	118
	4	8	35.9	36.6	6.78	5.63	2010	93.1	48.3	23.0	136	128
	4	10	41.2	41.3	6.46	5.56	2200	94.8	47.8	23.5	138	128
	4	12	46.0	48.3	6.60	5.83	2510	93.8	49.8	22.5	150	161
	4	15	56.8	57.7	6.32	5.56	2970	95.0	48.2	25.5	162	170
	4	18	69.9	70.4	5.36	4.83	3060	101.7	41.5	30.0	175	186
	10	0	60.8	64.1	6.54	5.62	3240	92.9	47.2	27.5	175	180
PJ	0	0	9.1	-	4.65	3.52	340	-	-	-	73	-
	4	0	36.4	37.1	6.24	4.85	1830	-	-	18.0	98	118
86.0 Kg.	4	2	41.5	41.1	5.71	4.81	1910	-	-	19.0	114	130
	4	4	50.7	50.4	5.27	4.61	2150	-	-	22.0	125	132
	4	6	58.8	58.7	5.16	4.51	2440	-	-	22.0	139	144
	4	8	70.5	67.0	5.06	4.45	2870	-	-	23.5	147	166
	4	10	89.3	84.4	4.58	4.14	3290	-	-	28.5	163	197
MP	0	0	9.1	-	4.40	3.46	320	-	-	11.0	61	-
	3	0	32.2	33.3	4.40	3.86	1140	-	-	10.5	-	-
74.4 Kg.	3	0	30.7	33.7	4.55	3.82	1120	-	-	10.0	83	87
	4	0	48.2	50.5	4.29	3.68	1660	-	-	13.5	95	100
	4	2	32.5	33.2	6.86	4.94	1790	-	-	13.0	96	99
	4	6	44.5	47.7	6.41	5.39	2290	-	-	12.5	114	121
	4	10	57.6	59.5	6.17	5.56	2850	-	-	15.0	135	145
	4	13	72.1	74.1	5.91	5.43	3420	-	-	-	-	-
WGR	0	0	9.7	-	4.45	3.32	350	-	-	-	63	-
	3	0	30.3	31.0	5.32	4.06	1330	-	-	-	85	87
84.8 Kg.	4	0	42.4	40.0	5.35	4.29	1860	-	-	-	98	103
	4	2	44.6	44.1	5.44	4.45	2000	-	-	-	-	-
	4	4	51.4	52.5	5.17	4.34	2180	-	-	-	118	118
	4	6	62.4	59.1	5.05	4.30	2590	-	-	-	120	124
	4	9	63.3	68.7	4.64	4.31	2420	-	-	-	149	161
	4	13	89.5	91.5	4.60	4.27	3380	-	-	-	168	180
John G.	0	0	6.4	-	4.69	3.50	250	-	-	-	83	-
	3	0	15.5	17.3	6.15	4.37	800	-	-	15.0	98	100
58.0 Kg.	3	2	18.6	18.4	5.52	4.53	860	107.2	38.5	17.0	100	101
	3	4	20.1	21.2	5.69	4.67	960	99.9	44.3	18.0	102	107
	3	6	24.4	25.6	5.55	4.88	1140	101.3	45.2	17.5	111	119
	3	8	28.9	29.8	5.56	4.70	1350	101.2	44.0	18.5	118	125
	3	11	36.1	35.5	5.41	4.98	1640	103.2	45.2	18.5	136	147
	3	13	40.7	41.2	5.34	4.90	1820	102.8	44.3	21.0	147	163
	3	15	46.8	48.4	5.28	4.80	2070	103.9	44.8	21.0	164	219
HMM	0	0	9.8	-	4.16	3.43	340	-	-	-	78	-
	4	0	31.4	33.9	5.83	4.81	1530	101.6	43.4	17.0	108	110
77.5 Kg.	4	3	36.7	35.9	5.84	5.24	1800	100.7	47.9	17.5	118	121
	4	5	42.2	40.6	5.84	5.18	2070	102.2	45.0	19.0	125	124
	4	7	49.5	48.1	5.74	5.12	2380	101.1	46.2	22.5	130	136
	4	9	53.1	52.9	5.98	5.31	2660	99.0	47.8	23.0	140	152
	4	11	64.3	70.2	5.76	5.30	3110	98.8	48.9	24.0	170	184
	4	13	75.9	75.1	5.62	5.11	3580	101.9	46.1	28.5	173	231
WGP	0	0	7.4	-	3.80	3.27	230	-	-	12.5	67	-
	4	0	27.4	32.7	6.65	4.69	1480	97.8	37.7	15.0	110	119
76.8 Kg.	4	2	33.5	34.1	6.59	4.84	1450	102.7	41.7	18.5	115	122
	4	5	41.5	41.4	6.18	4.95	2090	100.5	39.4	20.0	128	150
	4	7	47.8	49.2	5.96	4.92	2320	98.8	42.0	25.0	146	171
	4	9	54.1	56.0	5.94	5.08	2620	97.3	43.0	24.0	156	183
	4	11	63.1	72.9	5.79	4.99	2970	97.6	43.6	23.0	169	211
	4	13	84.5	86.2	5.09	4.53	3500	103.8	39.1	30.5	181	273
RKT	0	0	7.2	-	4.21	3.07	250	-	-	-	81	-
	4	0	29.5	31.7	4.78	3.91	1150	-	-	24.0	119	119
64.7 Kg.	4	2	32.8	33.0	4.51	3.80	1210	-	-	24.0	137	138
	4	4	37.6	38.6	4.66	4.00	1430	-	-	26.5	155	174
	4	6	53.4	48.6	4.54	3.93	1980	-	-	30.0	175	192
	4	9	71.1	69.0	3.93	3.83	2280	-	-	33.0	188	223
Janet G.	0	0	4.5	-	5.29	3.63	200	-	-	-	64	-
	3	0	16.7	17.6	6.13	4.40	860	104.7	38.4	18.0	93	105
56.3 Kg.	3	3	19.6	19.7	6.21	4.70	1020	103.2	40.8	20.0	102	110
	3	5	21.0	22.2	6.06	4.59	1070	104.0	40.2	19.0	106	112
	3	7	24.3	24.5	5.92	4.66	1210	105.5	40.0	22.5	115	124
	3	9	27.0	27.7	5.81	4.90	1310	104.6	40.0	23.5	128	134
	3	11	30.7	31.9	5.65	4.88	1460	106.4	40.9	23.5	137	142
	3	15	41.1	43.4	5.57	4.87	1920	107.0	40.6	26.0	162	195
CW	0	0	6.3	-	4.42	3.37	230	-	-	-	81	-
	3	0	16.9	18.0	5.41	4.12	740	99.1	37.2	21.0	104	107
48.0 Kg.	3	2	18.8	18.9	5.00	4.01	770	103.2	37.5	22.5	106	112
	3	4	20.7	20.8	4.78	4.12	810	105.3	37.6	23.0	113	118
	3	7	24.6	24.2	5.22	4.45	1050	102.2	40.3	23.5	122	125
	3	10	29.1	28.9	4.82	4.34	1140	101.0	40.8	27.0	136	145
	3	15	40.5	38.7	4.77	4.26	1580	103.9	47.4	30.5	163	217
BH	0	0	6.8	-	4.45	3.27	240	-	-	16.0	66	-
	3	0	17.8	18.1	4.99	3.95	720	106.5	35.2	18.0	96	96
64.0 Kg.	3	3	20.4	20.2	5.69	4.35	950	95.5	41.4	17.5	101	97
	3	6	27.9	25.6	5.13	4.38	1160	101.4	40.6	22.0	115	114
	3	9	32.0	33.0	5.67	4.66	1470	95.7	43.3	23.5	133	142
	3	15	53.6	56.3	4.39	4.36	1910	101.3	42.0	31.5	174	276
JK	0	0	6.7	-	4.98	3.63	260	-	-	14.5	94	-
	3	0	25.6	26.1	5.30	4.21	1070	99.2	37.3	18.5	141	162
65.0 Kg.	3	3	28.2	29.1	5.91	4.54	1320	96.5	38.2	20.0	145	150
	3	6	32.4	33.8	5.32	4.51	1360	98.8	39.1	20.0	161	173
	3	8	35.1	37.0	6.03	4.85	1680	94.1	41.3	21.5	162	174

JK	0	0	6.7	-	4.98	3.63	260	-	-	14.5	94	-
	3	0	25.6	26.1	5.30	4.21	1070	99.2	37.3	18.5	141	162
65.0 Kg.	3	3	28.2	29.1	5.91	4.54	1320	96.5	38.2	20.0	145	150
	3	6	32.4	33.8	5.32	4.51	1360	98.8	39.1	20.0	161	173
	3	8	35.1	37.0	6.03	4.85	1680	94.1	41.3	21.5	162	174
	3	10	42.8	44.7	5.11	4.43	1730	99.9	38.2	26.0	174	209
	3	13	52.1	55.7	5.10	4.77	2100	99.1	40.1	22.0	184	261
FMcG	0	0	7.0	-	4.87	3.52	280	-	-	12.0	78	-
	3	0	21.9	23.8	5.92	4.38	1050	96.3	38.8	17.5	110	111
70.2 Kg.	3	3	26.0	27.3	5.76	4.56	1210	96.9	40.1	18.5	119	124
	3	6	29.6	33.5	6.43	5.00	1540	92.0	43.3	17.0	135	146
	3	9	43.8	43.1	5.33	4.53	1880	-	-	26.0	155	181
	3	13	60.0	59.6	4.86	4.51	2350	104.0	39.3	28.5	180	232
MB	0	0	6.9	-	4.48	3.35	260	-	-	13.0	-	-
	3	0	24.7	25.1	5.77	4.61	1180	101.2	41.2	18.5	-	-
77.8 Kg.	3	2	26.5	26.0	5.83	4.78	1280	99.0	43.5	17.0	-	-
	3	5	33.4	33.8	5.63	4.73	1560	98.2	44.4	18.0	-	-
	3	7	41.7	42.2	5.41	4.74	1870	100.5	43.8	20.5	-	-
	3	9	48.1	50.0	5.23	4.66	2090	100.3	43.8	22.5	-	-
	3	12	61.9	67.4	4.73	4.55	2430	104.1	43.5	27.0	-	-
RF	0	0	7.8	-	4.37	3.45	280	-	-	-	89	-
	3	0	22.6	25.0	5.48	4.06	1030	105.5	37.1	14.5	126	132
56.9 Kg.	3	4	24.4	27.3	5.62	4.49	1140	104.3	39.4	-	135	151
	3	8	33.3	34.5	5.29	4.47	1470	106.0	39.0	19.5	165.	189
	3	12	43.0	45.5	4.96	4.19	1780	107.9	37.8	27.0	177	225
MBM	0	0	8.9	-	4.26	3.63	310	-	-	16.0	71	-
	3	0	25.1	25.0	5.31	4.40	1080	-	-	23.0	87	92
77.7 Kg.	3	2	25.0	26.3	5.43	4.47	1100	-	-	22.0	88	89
	3	4	29.7	29.4	5.22	4.83	1250	-	-	23.5	95	97
	3	6	32.4	33.0	5.67	4.76	1480	-	-	24.0	102	106
	3	8	38.1	36.8	5.51	4.79	1690	-	-	25.0	109	109
	3	10	41.8	40.8	5.62	4.90	1900	-	-	25.0	114	117
	3	12	46.0	46.2	5.45	4.88	2020	-	-	26.5	133	133
	3	14	56.2	55.5	5.24	4.84	2380	-	-	28.5	141	153
JGT	0	0	8.5	-	4.14	3.13	290	-	-	13.5	87	-
	3	0	30.7	32.0	4.83	4.01	1210	103.9	37.7	19.5	111	124
88.7 Kg.	3	3	33.7	34.5	5.18	4.33	1420	101.2	39.9	18.5	116	121
	3	7	43.8	43.9	5.22	4.59	1860	100.2	42.0	18.5	132	145
	3	10	52.7	56.0	5.27	4.80	2260	98.1	43.8	22.0	146	192
	3	15	73.6	89.9	4.90	4.85	2940	102.3	44.3	27.5	169	225
JW	0	0	5.1	-	3.72	3.06	160	-	-	10.0	72	-
	3	0	30.8	34.7	5.08	4.28	1290	100.6	41.5	21.5	120	126
78.0 Kg.	3	2	32.1	33.2	5.06	4.35	1340	102.3	40.4	22.5	116	123
	3	4	33.8	34.4	5.00	4.40	1390	99.8	41.9	21.5	120	124
	3	6	38.6	37.8	5.43	4.54	1730	100.1	41.6	23.0	130	164
	3	8	51.1	50.5	4.87	4.35	2050	104.4	40.5	27.5	136	179
RE	0	0	8.4	-	4.03	3.25	280	-	-	15.0	75	-
	2.5	0	25.8	27.7	5.24	4.13	1110	99.0	39.8	22.0	98	104
74.5 Kg.	2.5	3	26.5	27.7	5.58	4.20	1210	96.9	41.5	21.5	98	103
	2.5	6	32.3	33.2	5.39	4.25	1420	98.0	41.5	24.0	105	113
	2.5	8	35.3	34.9	5.31	4.34	1530	97.9	42.2	23.5	111	116
	2.5	10	40.4	39.2	5.34	4.49	1760	99.6	42.0	23.5	116	125
TS	0	0	10.2	-	3.71	2.90	310	-	-	19.0	75	-
	2.5	0	22.0	-	4.87	3.92	890	102.8	40.8	20.5	96	98
81.5 Kg.	2.5	3	29.0	29.4	4.43	3.96	1070	104.9	41.4	23.0	101	100
	2.5	6	34.0	33.7	4.70	4.16	1330	103.2	42.4	24.0	106	108
	2.5	8	39.6	42.6	4.72	4.23	1550	103.5	42.4	26.0	112	116
	2.5	11	46.9	53.4	4.71	4.27	1840	104.4	43.9	31.0	131	144
AG	0	0	10.0	-	3.14	2.48	260	-	-	18.0	63	-
	2.5	0	24.8	25.7	4.54	3.73	930	104.7	39.4	23.0	80	81
72.6 Kg.	2.5	3	28.1	28.7	4.73	3.87	1100	104.5	40.0	25.0	86	93
	2.5	6	33.4	34.3	4.95	4.24	1370	103.7	41.4	25.0	100	105
	2.5	9	46.0	46.6	4.26	3.88	1630	110.1	37.5	32.0	120	133
HD	0	0	7.8	-	3.60	2.84	230	-	-	-	43	-
	2.5	0	24.1	25.5	3.98	3.35	790	108.2	35.8	30.5	65	62
63 Kg.	2.5	3	25.4	29.2	4.41	3.64	920	104.8	37.9	29.0	76	69
	2.5	6	30.7	33.1	4.48	3.87	1130	104.6	39.2	30.0	97	84
	2.5	8	32.9	34.3	4.65	4.12	1250	102.2	40.6	28.0	109	97
	2.5	10	39.1	39.3	4.42	3.98	1420	105.2	39.2	31.0	122	113
PC	0	0	9.8	-	3.48	2.97	280	-	-	15.5	96	-
	1.375	0	18.0	20.4	4.89	4.22	720	92.0	51.2	19.0	131	134
56 Kg.	1.375	5	18.7	22.4	5.01	4.43	770	90.2	53.9	20.0	137	138
SS	0	0	7.9	-	3.41	3.06	220	-	-	13.5	76	-
	1.375	0	14.2	16.6	4.68	3.57	550	96.1	42.8	23.5	95	93
56 Kg.	1.375	5	15.4	18.6	4.74	3.97	600	96.1	45.8	24.0	104	116
DC	0	0	11.8	-	3.14	2.62	300	-	-	16.5	92	-
	1.375	0	19.2	21.2	3.79	3.06	600	108.7	33.1	18.5	91	92
63 Kg.	1.375	5	24.3	26.1	4.37	3.50	870	104.4	35.9	19.5	98	92
JS	0	0	10.8	-	3.06	2.41	270	-	-	20.0	91	-
	1.375	0	26.8	29.1	4.35	3.21	960	101.1	38.0	36.5	101	102
85 Kg.	1.375	5	33.3	37.7	4.40	3.57	1210	99.3	41.4	38.0	112	120
AM	0	0	10.5	-	2.87	2.41	250	-	-	20.0	74	-
	1.375	0	21.5	22.7	4.42	3.43	770	100.6	39.9	22.5	100	98
69 Kg.	1.375	5	22.0	23.4	4.79	3.68	870	98.1	41.3	21.5	99	95
WC	0	0	11.5	-	2.46	2.18	230	-	-	24.5	87	-
	1.375	0	18.5	21.0	4.31	3.61	650	95.4	44.0	23.5	139	140
47 Kg.	1.375	5	19.5	21.7	4.58	3.90	720	92.8	46.1	25.5	148	149
GS*	0	0	7.9	-	3.38	2.91	220	-	-	16.0	83	-
	1.375	0	17.9	20.3	4.31	3.53	630	99.6	40.8	25.5	105	101
66 Kg.	1.375	5	21.1	22.0	4.18	3.51	720	97.9	42.4	33.5	111	112

*GS completed only 5 min. exercise at each intensity. The collection period was the 4th and 5th minutes instead of the 5th and 6th.

REFERENCES

Aitken, R. S. & Clark-Kennedy, A. E. (1928). On the fluctuation in the composition of the alveolar air during the respiratory cycle in muscular exercise. J. Physiol. 65, 389-411.

Altschule, M. D. (1954). Physiology in diseases of the heart and lungs. Harvard University Press: Cambridge, Mass.

Anthony, A. J. (1930). Untersuchungen über Lungenvolumen und Lungenventilation. Deutsch. Arch. klin. Med. 167, 129-176.

Anthony, A. J. (1937). Funktionsprüfung der Atmung. Barth: Leipzig.

Arsenijevic, M. S. & Knipping, H. W. (1930). Uber die Atmung beim Coma diabeticum. Z. ges. exp. Med. 74, 787-806.

Asmussen, E., Christensen, E. H. & Nielsen, M. (1943a). Humoral or nervous control of respiration during muscular work? Acta physiol. scand. 6, 160-167.

Asmussen, E., Nielsen, M. & Wieth-Pedersen, G. (1943b). Cortical or reflex control of respiration during muscular work? Acta physiol. scand. 6, 168-175.

Asmussen, E. & Nielsen, M. (1946). Studies on the regulation of respiration in heavy work. Acta physiol. scand. 12, 171-188.

Astrand, P. -O. & Ryhming, I. (1954). A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. J. appl. Physiol. 7, 218-221.

Austin, W. T. S. & Harris, E. A. (1957). Measurement of heart rate in exercise. Quart. J. exp. Physiol. 42, 126-129.

Bainbridge, F. A. (1915). The influence of diastolic filling upon the rate of the heart. J. Physiol. 49, xlv-xlvi.

Baldwin, E. de F., Cournand, A. & Richards, D. W. (1948). Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine (Baltimore) 27, 243-278.

Bang, O. (1936). The lactate content of the blood during and after muscular exercise in man. Skand. Arch. Physiol. 74, Suppl. 10, 51-82.

Bannister, R. G., Cunningham, D. J. C. & Douglas, C. G. (1954). The carbon dioxide stimulus to breathing in severe exercise. J. Physiol. 125, 90-117.

Barr, D. P., Himwich, H. E. & Green, R. P. (1923). Studies in the physiology of muscular exercise. I. Changes in acid-base equilibrium following short periods of vigorous muscular exercise. J. biol. Chem. 55, 495-523.

Barringer, T. B. (1916a). The circulatory reaction to graduated work as a test of the heart's functional capacity. Arch. intern. Med. 17, 363-381.

Barringer, T. B. (1916b). Studies of the heart's functional capacity as estimated by the circulatory reaction to graduated work. Arch. intern. Med. 17, 670-676.

Barringer, T. B. (1917). Studies of the heart's functional capacity. Arch. intern. Med. 20, 829-839.

Bartels, J., Severinghaus, J. W., Forster, R. E., Briscoe, W. A. & Bates, D. V. (1954). The respiratory dead space measured by single-breath analysis of oxygen, carbon dioxide, nitrogen or helium. J. clin. Invest. 33, 41-48.

Bates, D. V. & Christie, R. V. (1950). Intrapulmonary mixing of helium in health and in emphysema. Clin. Sci. 9, 17-29.

Beaumont, G. E. (1953). Medicine. Churchill: London.

Bengtsson, E. (1956). The working capacity in normal children, evaluated by submaximal exercise on the bicycle ergometer and compared with adults. Acta med. scand. 154, 91-109.

Benzinger, T. & Brauch, F. (1934). Fortlaufende Registrierung der Zusammensetzung der Alveolarluft mit dem Gaswechselschreiber von H. Rein. Klin. Wschr. 13, 1852-1854.

Berggren, G. & Christensen, E. H. (1950). Heart rate and body temperature as indices of metabolic rate during work. Arbeitsphysiologie 14, 255-260.

Bernstein, L., D'Silva, J. L. & Mendel, D. (1952). The effect of the rate of breathing on the maximum breathing capacity determined with a new spirometer. Thorax 7, 255-262.

Bierring, E., Larsen, K. & Nielson, E. (1936). Some cases of slow pulse associated with electrocardiographic changes in cardiac patients after maximal work on Krogh ergometer. Amer. Heart J. 11, 416-430.

Bishop, J. M., Donald, K. W. & Wade, O. L. (1955). Circulatory dynamics at rest and on exercise in the hyperkinetic states. Clin. Sci. 14, 329-360.

Bock, A. V., Dill, D. B., Hurxthal, L. M., Lawrence, J. S., Coolidge, T. C., Dailey, M. E. & Henderson, L. J. (1927). The composition and respiratory exchanges of normal human blood during work. J. biol. Chem. 73, 749-766.

Bock, A. V., van Caulaert, C., Dill, D. B., Fölling, A. & Hurxthal, L. M. (1928). Studies in muscular activity. J. Physiol. 66, 121-174.

Bohr, C. (1891). Ueber die Lungenathmung. Skand. Arch. Physiol. 2, 236-268.

Boothby, W. M. (1915). A determination of the circulation rate in man at rest and at work. Amer. J. Physiol. 37, 383-417.

Bowen, W. P. (1904). Changes in heart rate, blood pressure, and duration of systole, resulting from bicycling. Amer. J. Physiol. 11, 59-77.

Briggs, H. (1920). Physical exertion, fitness and breathing. J. Physiol. 54, 292-318.

Briscoe, W. A., Forster, R. E. & Comroe, J. H. (1954). Alveolar ventilation at very low tidal volumes. J. appl. Physiol. 7, 27-30.

Bruce, R. A., Lovejoy, F. W., Yu, P. N. G. & McDowall, M. E. (1951). Evaluation and significance of physical fitness for moderate work; study of patients with cardiovascular or pulmonary diseases. Arch. industr. Hyg. 4, 236-250.

Bruce, R. A. & Rodgers, D. L. (1953). Quantitative effects of medical and surgical treatment of mitral stenosis on exercise tolerance. Amer. J. Med. 15, 35-49.

Bruce, R. A., Merendino, K. A., Pampush, J. J., Bergy, G. G. & Brock, L. L. (1956). Functional evaluation of mitral valvulotomy. Amer. J. Med. 20, 745-755.

Campbell, M. (1934). Respiratory exchange during exercise in heart disease. Quart. J. Med. 27, 369-380.

Campbell, J. M. H. & Poulton, E. P. (1926a). The effect of exercise on the pulmonary ventilation and rate and depth of breathing in chronic bronchitis. Quart J. Med. 20, 27-48.

Campbell, J. M. H. & Poulton, E. P. (1926b). The effect of exercise on the respiratory exchange in chronic bronchitis. Quart. J. Med. 20, 49-68.

Campbell, J. M. H. & Sale, F. J. (1927). Effect of exercise on respiratory exchange in heart disease. Arch. intern Med. 40, 237-250.

Cecil, R. L. & Loeb, R. F. (1951). A textbook of medicine. Saunders: Philadelphia.

Chamberlain, E. M. (1951). A textbook of medicine. Wright: Bristol.

Christensen, E. H. & Högberg, P. (1950). The efficiency of anaerobical work. Arbeitsphysiologie 14, 249-250.

Christian, H. A. (1947). The principles and practice of medicine. Appleton-Century: New York.

Christiansen, J., Douglas, C. G. & Haldane, J. S. (1914). The absorption and dissociation of carbon dioxide by human blood. J. Physiol. 48, 244-271.

Clark-Kennedy, A. E. & Owen, T. (1927). The limitation of muscular effort and its relation to cardiac failure. Quart. J. Med. 20, 383-430.

Cogswell, R. C., Henderson, C. R. & Berryman, G. H. (1946). Some observations on effects of training on pulse rate, blood pressure and endurance, in humans, using step-test (Harvard), treadmill and electrodynamic brake bicycle ergometer. Amer. J. Physiol. 146, 422-430.

Collett, M. E. & Liljestrand, G. (1924). The minute volume of the heart in man during some different types of exercise. Skand. Arch. Physiol. 45, 29-42.

Comroe, J. H., Forster, R. E., Dubois, A. B., Briscoe, W. A. & Carlsen, E. (1955). The lung: clinical physiology and pulmonary function tests. The Year Book Publishers, Inc.: Chicago.

Conybeare, J. J. (1954). Textbook of medicine. Livingstone: Edinburgh.

Cooper, D. Y., Emmel, G. L., Kough, R. H. & Lambertsen, C. J. (1953). Effects of CO_2 induced hyperventilation upon the alveolar-arterial pO_2 difference and the functional respiratory dead space in normal men. Fed. Proc. 12, 281.

Cooper, E. A. (1955). Aerodynamic principles and their application to closed circuit respiratory apparatus. National Coal Board Physiology Panel Memorandum Ph.P/P (55)4.

Cotton, T. F., Rapport, D. L. & Lewis, T. (1917). After effects of exercise on pulse rate and systolic blood pressure in cases of "irritable heart". Heart 6, 269-284.

Cournand, A., Lequime, J. & Regniers, P. (1951). Analyse physiologique des facteurs et des symptomes de l'insuffisance circulatoire chronique. Acta cardiol. Brux. 6, 343-596.

Cureton, T. K. (1947). Physical fitness, appraisal and guidance. Henry Kimpton: London.

Cureton, T. K., Huffman, W. J., Welser, L., Kireilis, R. W. & Latham, D. E. (1945). Endurance of young men, Monographs of the society for research in child development, 10, 1-284.

Davidson, L. S. P. (1954). The principles and practice of medicine. Livingstone: Edinburgh.

Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. J., Gorlin, R. & Sawyer, C. G. (1951). Effect of exercise on circulatory dynamics of normal individuals. J. appl. Physiol. 3, 439-453.

Dill, D. B., Hurxthal, L. M., van Caulaert, C., Fölling, A. & Bock, A. V. (1927a). The carbon dioxide equilibrium in alveolar air and arterial blood. II. Resting subjects. J. biol. Chem. 74, 303-311.

Dill, D. B., Lawrence, J. S., Hurxthal, L. M. & Bock, A. V. (1927b). The carbon dioxide equilibrium in alveolar air and arterial blood. III. Exercising subjects. J. biol. Chem. 74, 313-320.

Donald, K. W. (1953). The definition and assessment of respiratory function. Brit. med. J. 1, 415-422, 473-478.

Donald, K. W. (1956). Personal communication.

Donald, K. W., Bishop, J. M. & Wade, O. L. (1954). A study of minute to minute changes of arteriovenous oxygen difference, oxygen uptake and cardiac output and rate of achievement of a steady state during exercise in rheumatic heart disease. J. clin. Invest. 33, 1146-1167.

Donald, K. W., Bishop, J. M., Cumming, G. & Wade, O. L. (1955). The effect of exercise on the cardiac output and circulatory dynamics of normal subjects. Clin. Sci. 14, 37-73.

Douglas, C. G. & Haldane, J. S. (1912). The capacity of the air passages under varying physiological conditions. J. Physiol. 45, 235-238.

DuBois, A. B., Fowler, R. C., Soffer, A. & Fenn, W. O. (1952). Alveolar CO_2 measured by expiration into the rapid infra red gas analyser. J. appl. Physiol. 4, 526-534.

Eliasch, H. (1952). The pulmonary circulation at rest and on effort in mitral stenosis. Scand. J. clin. lab. Invest. Suppl. 4.

Enghoff, H. (1938). Volumen Inefficax. Upsala Läkaref. förh. 44, 191. Cited by Birath, G. (1944). Lung volume and ventilation efficiency. Acta med. scand. Suppl. 154.

Erickson, L., Simonson, E., Taylor, H. L., Alexander, H. & Keys, A. (1946). The energy cost of horizontal and grade walking on the motor-driven treadmill. Amer. J. Physiol. 145, 391-401.

Eskildsen, P., Götzsche, H. & Tybjaerg Hansen, A. (1950). Measuring of the intra-arterial blood pressure during exercise. Acta med. scand. Suppl. 239, 245-250.

Evans, W. (1948). Cardiology. Butterworth: London.

Fishman, A. P., McClement, J., Himmelstein, A. & Cournand, A. (1952). Effects of acute anoxia on the circulation and respiration in patients with chronic pulmonary disease studied during the "steady state". J. clin. Invest. 31, 770-781.

Fishman, A. P. (1954). Studies in man of the volume of the respiratory dead space and the composition of the alveolar gas. J. clin. Invest. 33, 469-481.

Folkow, B. & Pappenheimer, J. R. (1955). Components of the respiratory dead space and their variation with pressure breathing and with bronchoactive drugs. J. appl. Physiol. 8, 102-110.

Forssander, C. A. (1950). Spontaneous equilibration of inspired CO_2 with mixed venous blood: some theoretical considerations. J. appl. Physiol. 3, 216-227.

Forssander, C. A. (1956). Alveolar air changes following inhalation of carbon dioxide during exercise, and calculation of cardiac output. J. appl. Physiol. 8, 509-512.

Fowler, W. S. (1948). Lung function studies. II. The respiratory dead space. Amer. J. Physiol. 154, 405-416.

Fowler, W. S. (1949). Lung function studies. III. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. J. appl. Physiol. 2, 283-298.

Fowler, W. S. (1952). Intrapulmonary distribution of inspired gas. Physiol. Rev. 32, 1-20.

Fraser, R. S. & Chapman, C. B. (1954). Studies on the effect of exercise on cardiovascular function. II. The blood pressure and pulse rate. Circulation 9, 193-198.

Friedberg, C. K. (1950). Diseases of the heart. Saunders: London.

Furusawa, K. (1926). The gaseous exchanges of restricted muscular exercise in man. Proc. roy. Soc. (B) 99, 155-166.

Garland, H. G. & Phillips, W. (1953). Medicine. Macmillan: London.

Gaubatz, E. (1938). In "Kollapstherapie der Lungentuberkulose" ed W. Schmidt. Thieme: Leipzig. Cited by Donald, 1953.

Gilchrist, A. R. (1934). The effects of bodily rest, muscular activity and induced pyrexia on the ventricular rate in complete heart-block. Quart. J. Med. 27, 381-399.

Gilson, J. C. & Hugh-Jones, P. (1949). The measurement of the total lung volume and breathing capacity. Clin. Sci. 7, 185-216.

Gray, J. S. (1946). The multiple factor theory of the control of respiratory ventilation. Science 103, 739-744.

Greifenstein, F. E., King, R. M., Latch, S. S. & Comroe, J. H. (1952). Pulmonary function studies in healthy men and women 50 years and older. J. appl. Physiol. 4, 641-648.

Grollman, A. (1932). The cardiac output of man in health and disease. Thomas: Springfield, Illinois.

Haldane, J. S. (1915). The variations in the effective dead space in breathing. Amer. J. Physiol. 38, 20-28.

Haldane, J. S. & Priestley, J. G. (1935). Respiration. Clarendon Press: Oxford.

Hamilton, W. F. (1945). Notes on the development of the physiology of cardiac output. Fed. Proc. 4, 183-195.

Hamilton, W. F., Moore, J. W., Kinsman, J. M. & Spurling, R. G. (1932). Studies on the circulation. IV. Further analysis of the injection method, and of changes in haemodynamics under physiological and pathological conditions. Amer. J. Physiol. 99, 534-554.

Harrison, T. R. (1954). The principles of internal medicine. Lewis: London.

Harrison, T. R., Harrison, W. G., Calhoun, J. A. & Marsh, J. P. (1932). Congestive heart failure. XVIII. The mechanism of dyspnoea on exertion. Arch. intern. Med. 50, 690-720.

Henderson, Y. & Prince, A. L. (1914). The oxygen pulse and the systolic discharge. Amer. J. Physiol. 35, 106-115.

Henderson, Y., Chillingworth, F. P. & Whitney, J. L. (1915). The respiratory dead space. Amer. J. Physiol. 38, 1-19.

Henderson, Y. & Haggard, H. W. (1925). The circulation and its measurement. Amer. J. Physiol. 73, 193-253.

Henderson, Y., Haggard, H. W. & Dolley, F. S. (1927). Efficiency of heart, and significance of rapid and slow pulse rates. Amer. J. Physiol. 82, 512-524.

Hermannsen, J. (1933). Untersuchungen über die maximale Ventilationsgrösse (Atemgrenzwert). Z. ges. exp. Med. 90, 130-137.

Hickam, J. B., Cargill, W. H. & Golden, A. (1948). Cardiovascular reactions to emotional stimuli. Effect on the cardiac output, arteriovenous oxygen difference, arterial pressure and peripheral resistance. J. clin. Invest. 27, 290-298.

Hill, A. V. & Lupton, H. (1922). Muscular exercise, lactic acid and the supply and utilisation of oxygen. Quart. J. Med. 16, 135-171.

Hill, A. V., Long, C. N. H. & Lupton, H. (1924). Muscular exercise, lactic acid and the supply and utilisation of oxygen. Proc. roy. Soc. (B) 96, 432-475; 97, 84-138, 155-176.

Hugh-Jones, P. (1952). A simple standard exercise test and its use for measuring exertion dyspnoea. Brit. med. J. 1, 65-71.

Huizinga, E. (1937). Uber die Physiologie des Bronchialbaumes. Pflüg. Arch. ges. Physiol. 238, 767-779.

Johnson, R. E. & Brouha, L. (1942). Pulse rate, blood lactate and duration of effort in relation to ability to perform strenuous exercise. Rev. canad. Biol. 1, 171-178.

Johnson, R. E., Brouha, L. & Darling, R. C. (1942). Test of physical fitness for strenuous exertion. Rev. canad. Biol. 1, 491-503.

Kao, F. F. & Ray, L. H. (1954a). Respiratory and circulatory responses of anaesthetised dogs to induced muscular work. Amer. J. Physiol. 179, 249-254.

Kao, F. F. & Ray, L. H. (1954b). Regulation of cardiac output in anaesthetised dogs during induced muscular work. Amer. J. Physiol. 179, 255-260.

Karrasch, K. & Müller, E. A. (1951). Das Verhalten der Pulsfrequenz in der Erholungsperiode nach korperliche Arbeit. Arbeitsphysiologie 14, 369-382.

Katz, L. N., Soskin, S., Schutz, W. J., Ackerman, W. & Plant, J. L. (1934). A "metabolic exercise tolerance test" for patients with cardiac disease. Arch. intern Med. 53, 710-723.

Kennedy, M. C. S. (1953). A practical measure of the maximum ventilatory capacity in health and disease. Thorax 8, 73-83.

Kleiber, M. (1950). Physiological meaning of regression equations. J. appl. Physiol. 2, 417-423.

Knehr, C. A., Dill, D. B. & Neufeld, W. (1942). Training and its effects on man at rest and at work. Amer. J. Physiol. 136, 148-156.

Knipping, H. W. & Moncrieff, A. (1932). The ventilation equivalent for oxygen. Quart. J. Med. 25, 17-30.

Kofranyi, E. & Michaelis, H. F. (1940). Ein tragbarer Apparat zur Bestimmung des Gasstoffwechsels. Arbeitsphysiologie 11, 148-150.

Krogh, A. & Lindhard, J. (1913). The volume of the "dead space" in breathing. J. Physiol. 47, 30-43.

Krogh, A. & Lindhard, J. (1914). On the average composition of the alveolar air and its variations during the respiratory cycle. J. Physiol. 47, 431-445.

Krogh, A. & Lindhard, J. (1917). The volume of the dead space in breathing and the mixing of gases in the lungs of man. J. Physiol. 51, 59-90.

Lawrence, J. H., Loomis, W. F., Tobias, C. A. & Turpin, F. H. (1946). Preliminary observations on the narcotic effect of xenon with a review of values for solubilities of gases in water and oils. J. Physiol. 105, 197-204.

Lehmann, G. (1953). Praktische Arbeitsphysiologie. Thieme: Stuttgart.

Levy, R. L. (1951). Disorders of the heart and circulation. Bailliere, Tindall & Cox: London.

Liljestrand, G., Lysholm, E. & Nylin, G. (1938). Immediate effects of muscular work on stroke and heart volume in man. Skand. Arch. Physiol. 80, 265-282.

Lindgren, A. (1953). Studies on oxygen consumption, pulmonary ventilation and ventilation equivalent for oxygen at rest and after work in healthy persons and in cases of heart disease. Cardiologia 23, 220-230.

Loeb, L. F. (1920). Die Kohlensäuretension in den Lungenalveolen. Z. ges. exp. Med. 11, 16. Cited by Henderson & Haggard, (1925).

Loeschke, H. H., Opitz, E. & Schoedel, W. (1939). Eine Methode zur fortlaufenden automatischen Registrierung des alveolaren sauerstoff- und Kohlensäuregehaltes. Pflüg. Arch. ges. Physiol. 243, 126-132.

Loewy, A. (1894). Uber die Bestimmung der Grösse des "schädlichen Luftraumes" im Thorax und der alveolaren Sauerstoffspannung. Pflüg. Arch. ges. Physiol. 58, 416-427.

Mahadeva, K., Passmore, R. & Woolf, B. (1953). Individual variations in the metabolic cost of standardised exercises: the effects of food, age, sex and race. J.

Marais, O. A. S. & McMichael, J. (1937). Theophylline-ethyleneiamine in Cheyne-Stokes respiration. Lancet 2, 437-440.

Master, A. M. (1935). The two-step test of myocardial function. Amer. Heart J. 10, 495-510.

Master, A. M. & Oppenheimer, E. T. (1929). A simple exercise tolerance test for circulatory efficiency with standardised tables for normal individuals. J. amer. med. Sci. 177, 223-243.

Matthews, M. B. (1954). Mitral valvotomy in rheumatic heart disease. M.D. Thesis, Cambridge.

McMichael, J. (1939). Hyperpnoea in heart failure. Clin. Sci. 4, 19-33.

Meakins, J. & Davies, H. W. (1925). Respiratory function in disease. Edinburgh: Oliver & Boyd.

Meakins, J. & Long, C. N. H. (1927). Oxygen consumption, oxygen debt and lactic acid in circulatory failure. J. clin. Invest. 4, 273-293.

Miller, W. S. (1947). The lung. Thomas: Springfield, Illinois.

Moncrieff, A. (1933). Tests for respiratory efficiency: the so-called dead space. Lancet 1, 956-961.

Moncrieff, A. (1934). Tests for respiratory efficiency. Spec. Rep. Ser. med. Res. Coun., Lond. No. 198.

Müller, E. A. (1950a). Der Wirkungsgrad des Gehens. Arbeitsphysiologie 14, 236-242.

Müller, E. A. (1950b). Ein Leistungs-Pulsindex als Mass der Leistungsfähigkeit. Arbeitsphysiology 14, 271-284.

Müller, E. A. & Reeh, J. J. (1950). Die fortlaufende Registrierung der Pulsfrequenz bei beruflicher Arbeit. Arbeitsphysiology 14, 137-146.

Musser, J. H. & Wohl, M. G. (1951). Internal medicine: its theory and practice. Lea & Febiger; Philadelphia.

Needham, C. D., Rogan, M. C. & McDonald, I. (1954). Normal standards for lung volumes, intrapulmonary gas-mixing, and maximum breathing capacity. Thorax 9, 313-325.

Nielsen, M. & Hansen, O. (1937). Maximale körperliche Arbeit bei Atmung O_2-reicher Luft. Skand. Arch. Physiol. 76, 37-59.

Nielsen, M. & Smith, H. (1952). Studies on the regulation of respiration in acute hypoxia. Acta physiol. scand. 24, 293-313.

Nylin, G. (1933). Clinical tests of the function of the heart. Acta med. scand. Suppl. 52, 1-92.

Nylin, G. (1938). The practical applicability of the cardiopulmonary function test. Acta med. scand. Suppl. 93, 1-24.

Otis, A. B., McKerrow, C. B., Bartlett, R. A., Mead, J., McIlroy, M. B., Selverstone, N. J. & Radford, E. P. (1956). Mechanical factors in distribution of pulmonary ventilation. J. appl. Physiol. 8, 427-443.

Pappenheimer, J. R. (Chairman) (1950). Standardisation of definitions and symbols in respiratory physiology. Fed. Proc. 9, 602-605.

Pappenheimer, J. R., Fishman, A. P. & Borrero, L. M. (1952). New experimental methods for determination of effective alveolar gas composition and respiratory dead space, in the anaesthetised dog and in man. J. appl. Physiol. 4, 855-867.

Passmore, R. & Durnin, J. V. G. A. (1955). Human energy expenditure. Physiol. Rev. 35, 801-840.

Peabody, F. W. & Sturgis, C. C. (1922). Clinical studies on the respiration. IX. The effect of exercise on the metabolism, heart rate and pulmonary ventilation of normal subjects and patients with heart disease. Arch. intern. Med. 29, 277-305.

Price, F. W. (1956). A textbook of the practice of medicine. Oxford Medical Publications.

Radloff, E. M. (1931). The oxygen pulse in athletic girls during rest and exercise. Amer. J. Physiol. 96, 126-131.

Rahn, H. (1949). A concept of mean alveolar air and the ventilation-bloodflow relationships during pulmonary gas exchange. Amer. J. Physiol. 158, 21-30.

Rahn, H., Mohney, J., Otis, A. B. & Fenn, W. O. (1946). A method for the continuous analysis of alveolar air. J. aviat. Med. 17, 173-178.

Rauwerda, P. E. (1946). Unequal ventilation of different parts of the lung and the determination of cardiac output. M.D. Thesis, Gröningen.

Riley, R. L. Lilienthal, J. L., Proemmel, D. D. & Franke, R. E. (1946). On the determination of the physiologically effective pressures of oxygen and carbon dioxide in alveolar air. Amer. J. Physiol. 147, 191-198.

Riley, R. L., Riley, M. C., & Hill, H. McD. (1952). Diffuse pulmonary sarcoidosis: diffusing capacity during exercise and other lung function studies in relation to ACTH therapy. Bull. Johns Hopk. Hosp. 91, 345-370.

Riley, R. L., Shepard, R. H., Cohn, J. E., Carroll, D. G. & Armstrong, B. W. (1954). Maximal diffusing capacity of the lungs. J. appl. Physiol. 6, 573-587.

Robinson, S. (1938). Experimental studies of physical fitness in relation to age. Arbeitsphysiologie 10, 251-323.

Robinson, S. & Harmon, P. M. (1941). The lactic acid mechanism and certain properties of the blood in relation to training. Amer. J. Physiol. 132, 757-769.

Roelsen, E. (1938). Fractional analysis of alveolar air after inspiration of hydrogen as a method for the determination of the distribution of inspired air in the lungs. Acta med. scand. 95, 452-482.

Rohrer, F. (1915). Der Strömungswiderstand in den menschlichen Atemwegen und der Einfluss der unregelmässigen Verzweigung des Bronchialsystems auf den Atmungsverlauf in verschiedenen Lungenbezirken. Pflüg. Arch. ges. Physiol. 162, 225-299.

Rossier, P. H. & Bühlmann, A. (1955). The respiratory dead space. Physiol. Rev. 35, 860-876.

Ryhming, I. (1954). A modified Harvard step test for the evaluation of physical fitness. Arbeitsphysiologie 15, 235-250.

Saha, H. (1956). Studies on respiratory metabolism during level walk and grade walk on a slow speed treadmill. Ph.D. Thesis, Birmingham.

Schall, L. (1921). Untersuchungen über die Methodik der Messung der Kohlensäurespannung in den Lungenalveolen. Z. ges. exp. Med. 14, 322. Cited by Henderson & Haggard (1925).

Scherf, D. & Boyd, L. J. (1948). Cardiovascular diseases, their diagnosis and treatment. Heinemann: London.

Schnebel, W. G. & Elbel, E. R. (1951). Reaction of pulse to successive periods of exercise. J. appl. Physiol. 4, 7-14.

Schneider, E. C. & Karpovich, P. V. (1949). Physiology of muscular activity. Saunders: Philadelphia.

Siebeck, R. (1911). Uber den gasaustausch zwischen Aussenluft und Alveolen. Zweite Mitteilung: Uber die Bedeutung und Bestimmung des "schädlichen Raumes" bei der Atmung. Skand. Arch. Physiol. 25, 81-95.

Simonson, E. & Gollwitzer-Meier, K. (1930). Zur pathologischen Physiologie des respiratorischen Stoffwechsels. V Mitteilung: Uber den Arbeitsumsatz in der Gripperekonvaleszenz. Z. ges. exp. Med. 75, 330-346.

Simonson, E. & Enzer, N. (1942). Physiology of muscular exercise and fatigue in disease. Medicine (Baltimore) 21, 345-419.

Starr, I. (1951). Units for the expression of both static and dynamic work in similar terms, and their application to weight-lifting experiments. J. appl. Physiol. 4, 21-29.

Stock, J. P. P. & Kennedy, M. C. S. (1953). The quantitative assessment of disability in mitral stenosis. Lancet 2, 5-10.

Tanner, J. M. (1949). Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation. J. appl. Physiol. 2, 1-15.

Taylor, C. (1944). Some properties of maximal and submaximal exercise with reference to physiological variation and the measurement of exercise tolerance. Amer. J. Physiol. 142, 200-212.

Trendelenburg, W. (1921). Zur Methodik der Gewinnung von Alveolarluft. Z. ges esp. Med. 14, 311. Cited by Henderson & Haggard (1925).

Versar, F. (1933). Die Regulation des Lungenvolumens. Pflüg. Arch. ges. Physiol. 232, 322-341.

Wade, O. L., Bishop, J. M. & Donald, K. W. (1954). The effect of mitral valvoltomy on cardio-respiratory function. Clin. Sci. 13, 511-533.

Wagener, H. P. & Keith, N. M. (1939). Diffuse arteriolar disease with hypertension and the associated retinal lesions. Medicine, Baltimore 18, 317-430.

Wahlund, H. (1948). Determination of the physical working capacity. Acta med. scand. Suppl. 215.

White, P. D. (1951). Heart disease. Macmillan: New York.

Williams, M. H. & Rayford, C. M. (1956). Effect of variation of tidal volume on size of physiological dead space in dogs. J. appl. Physiol. 9, 30-32.