EDUCATION

Logical limitations to the ''catastrophe'' models of fatigue during exercise in humans

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A central debate in the exercise sciences is the cause of fatigue, which develops especially during high intensity exercise of short duration. The most popular theory holds that this form of exercise is limited by a peripherally based, metabolite induced failure of skeletal muscle contractile function, independent of reduced muscle activation by the central nervous system; so-called peripheral fatigue. This theory arose originally from studies undertaken by Nobel Laureate Sir Archibald Vivian Hill and colleagues in Manchester, UK in the 1920s. In turn, their interpretations were crucially influenced by the earlier 1907 findings of Sir Frederick Gowland Hopkins, Nobel Laureate for his discovery of the vitamins, and Walter Morley Fletcher. They showed that the lactate concentrations of excised frog skeletal muscle, stimulated to contract to exhaustion in vivo, fell when incubated in an oxygen enriched environment, whereas concentrations rose when incubated in an oxygen free environment. Accordingly, they concluded that: ''Lactic acid is spontaneously developed, under anaerobic conditions, in excised muscle'' and that ''Fatigue due to contractions is accompanied by an increase of lactic acid''. Later, Hopkins wrote that: ''the accumulation of lactic acid in muscle occurs only in the conditions of anaerobiosis. With a proper oxygen supply it fails to accumulate at all'', and that the ''great importance of this work was that it started the study of muscle fermentation and its relation to muscular contraction …''. Hill acknowledged the dependence of his own theory on this interpretation: ''An isolated muscle stimulated in nitrogen soon fatigues and never recovers: an isolated muscle stimulated in oxygen may go on contracting for days. These observations of Fletcher's (sic) led to the lactic acid story''. Accordingly, Hill and colleagues proposed that performance during high intensity exercise is terminated by the development of skeletal muscle anaerobiosis as a result of a limiting skeletal muscle blood flow that followed the development of myocardial ischaemia. Such anaerobiosis ultimately prevented the neutralisation of the lactic acid that, Hill believed, initiated muscle contraction. As a result, lactic acid accumulation in maximally working anaerobic skeletal muscle impaired skeletal muscle relaxation, causing the (involuntary) termination of exercise. The natural evolutionary progression of this logic leads to the ''catastrophe theory'' of Edwards, which posits that exercise terminates as a result of the catastrophic consequences of physiological and biochemical events initiated when the safe biological limits of the body are exceeded with a resulting loss of intracellular homeostasis.

Previous publications by T D Noakes have addressed the historical evolution of Hill's cardiovascular/anaerobic/catastrophic model of exercise physiology. In this report we address six hallmark physiological requirements that must be correct if this model is the exclusive explanation for the fatigue that develops during maximum exercise to exhaustion. Furthermore the almost universal adoption of this (Hill) model as a prototype of ''peripheral fatigue'' has encouraged the belief that almost all forms of exercise fatigue result from a failure of homeostasis that develops only after human biological limits are surpassed. Accordingly, the critical predictions of additional models used to explain fatigue in other forms of exercise are also reviewed.

It is concluded that there is little published evidence supporting the theory that fatigue occurs only after physiological homeostasis fails; the catastrophe theory of Edwards. Rather, it is proposed that fatigue in any form of exercise may form part of a regulated, anticipatory response co-ordinated in the subconscious brain, the ultimate goal of which is to preserve homeostasis in all physiological systems during exercise.

A popular teaching in exercise physiology is that fatigue during most forms of exercise is due to a peripherally based, metabolite induced failure of skeletal muscle contractile function (peripheral fatigue),[1–6] independent of reduced skeletal muscle activation by efferent output from the motor cortex of the central nervous system (CNS); so-called central fatigue.

HISTORICAL DEVELOPMENT OF THIS MODEL OF PERIPHERAL FATIGUE

The origins of this belief can be traced to the pioneering studies of Fletcher and Hopkins,[1] and Hill[3 7–11] and colleagues[12–15] in the 1920s. The classical theory, since defined as the cardiovascular/anaerobic/catastrophic model of exercise physiology,[16 17] postulates that fatigue during high intensity exercise of short duration results from a skeletal muscle ''anaerobiosis'' (see Addendum) that develops when the oxygen requirement of the active skeletal muscles exceeds the heart's capacity to further augment oxygen delivery to exercising muscle by increasing the cardiac output. As a result, any additional increase in energy generation in the active muscles can come only from ''anaerobic'' metabolism, leading to fatigue because the ''maximum oxygen intake is inadequate, lactic acid accumulating, a continuously

Abbreviations: ATP, adenosine triphosphate; CNS, central nervous system; EMG, electromyographic; MR, magnetic resonance; MVC, maximal voluntary contraction; NIRS, near infrared spectroscopy; PCr, phosphocreatine; RPE, rating of perceived exertion

WHAT IS ALREADY KNOWN ON THIS TOPIC

Beginnning with the foundation studies of the British Nobel Laureates A V Hill and F G Hopkins in the early 1900s, the A V Hill cardiovascular/anaerobic/ catastrophic model of exercise physiology has evolved to dominate teaching and research in the exercise sciences. This model posits that exercise is regulated by metabolic changes in the peripheral muscles, independent of any regulation by the central nervous system (CNS).

WHAT THIS STUDY SHOWS

This review shows that the published literature does not support the six hallmark predictions of the Hill model of exercise physiology. In particular, there is no evidence that skeletal muscle recruitment is ever total during voluntary exercise to exhaustion in humans. The presence of skeletal muscle recruitment reserve at fatigue proves that exercise performance is regulated by the CNS, specifically to ensure that a catastrophic failure of homeostasis does not occur during voluntary exercise in humans.

increasing oxygen debt being incurred, fatigue and exhaustion setting in''.[12]

Hill[9] believed that the ''lactic acid'' generated by ''anaerobic'' conditions in skeletal muscle served two opposing functions. Its initial production stimulated muscle contraction; in the presence of an adequate oxygen supply, the oxidative removal of lactic acid produced the ''neutralisation'' necessary to allow muscle relaxation. However, at the higher exercise intensities at which skeletal muscle ''anaerobiosis'' developed, lactic acid could no longer be neutralised but accumulated progressively. This progressive accumulation of the chemical that, according to Hill, initiated muscle contraction would cause a progressive failure of skeletal muscle relaxation, leading ultimately to a sustained contraction—that is, skeletal muscle rigor, once skeletal muscle lactic acid concentrations exceeded some threshold value.

Thus, according to Hill's understanding, peripheral skeletal muscle fatigue caused by an ischaemia induced failure of myocardial pumping capacity triggered a skeletal muscle ''anaerobiosis'', which prevented the complete neutralisation of the lactic acid that, in physiological concentrations, was necessary for both muscle contraction and metabolism. This failure of neutralisation ultimately impaired skeletal muscle relaxation: ''This effect is very striking in short distance races, where slower muscular relaxation, commencing within seven or eight seconds from the start, causes a progressive diminution in the maximum speed long before exhaustion. The formation of lactic acid is the chemical reaction on which the whole of voluntary muscular activity depends''(p. 224[9]).

In retrospect, the pivotal function of the lactic acid generated by ''anaerobic'' metabolism in the Hill model is to act as a peripheral ''constrainer'', ''regulator'', or ''governor'' that directly impairs skeletal muscle function by slowing skeletal muscle relaxation, leading to fatigue and ultimately the involuntary termination of exercise.

Our more modern understanding would argue that a putative peripheral regulator is logically essential because, in its absence, adenosine triphosphate (ATP) concentrations within the exercising skeletal muscles, contracting anaerobically without restraint, would fall progressively as the rate of muscle ATP production by the anaerobic muscles fell inexorably behind their rate of ATP use. Ultimately, muscle ATP concentrations would be so low that muscle rigor would have to develop.[6 18] This explanation differs from Hill's, which was based on his incorrect understanding of the role of lactic acid as the initiator of muscle contraction, but the final outcome of either explanation is the same – the development of rigor in the exercising muscles. Of course, Hill[9] and colleagues[12] could not have surmised that ''fatigue and exhaustion'' was caused by a progressive failure of ATP generation in the active muscles, as Hill's model evolved in the period before the detailed metabolic pathways for ATP generation were described; indeed ATP itself was discovered in 1929,[19] 6 years after Hill's model was first proposed. In addition, the role of ATP and phosphocreatine in providing energy for muscle contraction had yet to be described.[20] Thus Hill could not have known that ATP depletion, rather than lactic acid accumulation, causes skeletal muscle rigor.

If correct, this classical theory in which lactic acid acts as the peripheral regulator or ''poison''[21] of muscle contraction would adequately explain why skeletal muscle rigor has never been reported during exercise in healthy persons. However, this mechanism is unable to explain why skeletal muscle rigor, as opposed to muscle cramps, has also never been observed in persons with those disorders of metabolism that prevent normal rates of skeletal muscle lactate and glycolytic ATP production because of defined enzymatic defects in either the glycogenolytic or glycolytic metabolic pathways, for example, patients with McArdle's syndrome.[18 22] Even more interesting is the finding, known for more than 38 years[23] and confirmed more recently,[24] that fatigue and abnormal skeletal muscle function during exercise in McArdle's syndrome occurs without significant reductions in skeletal muscle ATP concentrations,[23] as is also the case in other skeletal muscle glycolytic or glycogenolytic disorders.[18] As the defining characteristic of some of these disorders is the inability to generate lactate and hydrogen ions (lactic acid),[25] neither elevated muscle lactate concentrations nor increased intracellular acidosis can be the peripheral ''governor'' or ''poison'' that prevents the development of skeletal muscle rigor in these disorders. Hence, another theory[26] must be found that will also explain the protection of ATP homeostasis in muscles that lack a crucial pathway for ATP generation.

One possibility is the recent proposal of Shulman and Rothman[27] that muscle glycogenolysis makes the major contribution to the rapid ATP requirements during millisecond muscle contractions, and that glycogen resynthesis then occurs from metabolic intermediaries that contain carbon, including lactate, and from oxygen provided in the blood. Thus the lactate produced by rapid glycogenolysis during millisecond muscle contractions can then contribute to oxidative metabolism and the resynthesis of glycogen, hence the ''glycogen shunt''.[27] The absence of the glycogen shunt in some patients with McArdle's syndrome would then explain their reduced exercise capacity.[27]Furthermore, Vissing and Haller[28] have recently shown that the exercise performance of patients with McArdle's syndrome increases when they ingest 75 g of sucrose prior to exercise and that, following sucrose ingestion, they terminate exercise with higher blood lactate concentrations than when exercise follows the ingestion of a placebo. Thus, the inability to generate lactate, rather than the overproduction of this supposedly poisonous metabolite, limits the exercise capacity of some patients with this condition.

This interpretation that lactate is an essential muscle fuel rather than a muscle ''poison'' is supported by the intriguing recent finding of Nielsen and colleagues.[29] They have shown that lactic acid restores normal function to isolated rat soleus muscle, the function of which has been impaired by perfusion with a sufficiently elevated potassium concentration

considered also to impair skeletal muscle function during high intensity exercise.[29] The authors conclude that ''the accumulation of lactic acid protects against muscular fatigue'' so that ''in contrast to the often suggested role of acidosis as a cause of muscle fatigue, acidosis may protect against fatigue''. Therefore, if lactic acid is not the peripheral regulator predicted by Hill's cardiovascular/anaerobic/catastrophic model, then another mechanism must exist to ensure that muscles terminate exercise before they develop rigor.

Accordingly, this paper tracks the influence of the original studies of Hill and his colleagues on the evolution of what might collectively be called the oxygen and energy dependent ''limitations'' or ''catastrophe'' models of exercise physiology.[16] Thereafter, we discuss the ability of these different ''catastrophe'' models to explain the physiological and biochemical characteristics of those forms of fatigue that develop: (*a*) during exercise of progressively increasing intensity to exhaustion, usually used to determine the athlete's maximum rate of oxygen consumption (VO_{2max}); (*b*) during high intensity exercise of short duration (tens of seconds); and (*c*) during prolonged exercise (tens of minutes to hours), all of which terminate without evidence for substantive ATP or energy depletion in the active muscles.[6 30–34]

The question to be addressed is: how does a peripherally based, energy dependent, metabolite induced skeletal muscle fatigue develop without evidence for any measurable catastrophic disturbances in ATP homeostasis under any condition of exercise yet studied?[5 6 35 36] The conclusion has already been drawn that ''the rate of ATP utilisation falls before it reaches limiting levels.''[5] Thus, the question becomes: how does the body regulate the rate of ATP utilisation specifically to prevent a catastrophic fall in ATP concentrations in the active muscles, most especially during maximal exercise?

This review serves as the introduction to the two companion papers and to a concluding summary paper that unifies the arguments developed in these three papers. The focus of these papers is to propose a revolutionary solution that we have identified to this historical riddle.

HISTORICAL DEVELOPMENT OF THE OXYGEN AND ENERGY DEPENDENT ''LIMITATIONS'' OR ''CATASTROPHE'' MODELS OF EXERCISE FATIGUE

The role of ''anaerobiosis'' and ''lactic acidosis''

The real origins of the classical Hill cardiovascular/anaerobic/catastrophic model can be traced to the pivotal influence that the original study of Fletcher and Hopkins[1] at Cambridge University exerted on the thinking of Hill and colleagues in Manchester. Fletcher and Hopkins[1] wished to establish whether or not: ''within a muscle itself, means exist for an oxidative control of its own acid formation, or for the alteration or destruction of acid which has been formed, either there or by muscular activity elsewhere in the body.'' They were perplexed by the consistent finding at that time that lactic acid (lactate) concentrations in excised skeletal muscle preparations were always high, regardless of the experimental conditions, for example, whether the excised muscle came from rested, exercised, fresh, or preserved tissue. They wondered whether this unexpected finding resulted not from: ''the technical difficulties of lactic acid estimation, but that it is due to the difficulties inherent in the extractive treatment of an irritable muscle''.[2]

By rapidly immersing the excised hind limb muscles of frogs in ice cold alcohol, they were able to show that these muscles had low initial lactic acid concentrations and released little lactic acid during the first 24 hours when incubated in air at room temperature. Even less lactic acid was produced when the muscles were stored in oxygen enriched air also at room temperature. Lactic acid production was substantially increased when the muscles were stored in hydrogen; this effect was increased at higher temperatures. Next, prior to excision, the researchers electrically stimulated the hind limb muscles to contract until they no longer responded to stimulation. After prolonged stimulation, muscle lactic acid concentrations were elevated but were only about one half of the concentrations measured in muscles exposed acutely to chemical or heat induced damage.

Finally, previously stimulated muscles were left to recover for 18 or more hours, either in room temperature air, or in nitrogen or oxygen at different temperatures. In all cases, lactic acid concentrations were lowest in muscles exposed to oxygen at any temperature (fig 1).

Note that this in vitro muscle preparation was devoid of any neural connection to the CNS or of an intact blood supply, and is therefore more correctly described as as a model of no perfusion anoxia, rather than anaerobiosis. The absence of any neural connection also prevented the possibility of either feedforward or feedback control by the CNS.

On the basis of these findings, Fletcher and Hopkins concluded that: ''The lactic acid content of muscle is profoundly affected by the nature of the treatment received before or during the extraction. …The increase of acid is most rapid under anaerobic conditions, is slower in air, and it is not to be observed in an atmosphere of pure oxygen.''[1] Thus: ''the excised but undamaged muscle when exposed to a sufficient tension of oxygen has in itself the power of dealing in some way with the lactic acid which has accumulated during fatigue, and regaining irritability in an atmosphere of pure oxygen, their content of lactic acid is greatly reduced.''[1] As a result, they concluded that: ''Lactic acid is spontaneously developed, under anaerobic conditions in excised muscle''

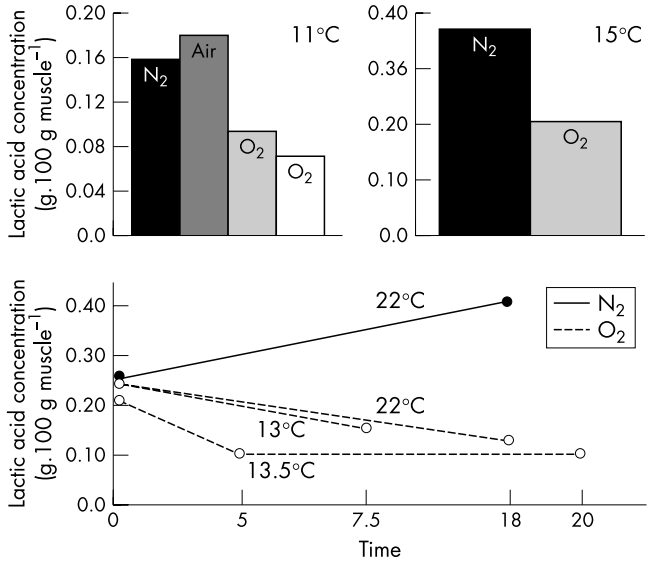

Figure 1 The study of Fletcher and Hopkins[1] showed that excised amphibian muscle that had been electrically stimulated to contract to exhaustion in vivo had an increased lactate concentration. When excised muscles were incubated in vitro in nitrogen at either 11, 15, or 22°C for up to 18 hours, muscle lactate concentrations either increased (upper right panel; lower panel) or did not decrease (upper right panel; lower panel) as much as when the muscles were incubated in an oxygen enriched environment. This led to the conclusion that: ''the accumulation of lactic acid in muscle occurs only in the conditions of anaerobiosis''.[2] Hill and colleagues based their cardiovascular/anaerobic/catastrophic theory on the assumption that this conclusion, drawn from studies of isolated, non-perfused and hence totally ischaemic, anoxic amphibian muscle studied in vitro, also applies to human skeletal muscle contracting in vivo in the presence of intact cardiovascular and CNS systems.

and that ''fatigue due to contractions is accompanied by an increase of lactic acid''.[1]

Fletcher and Hopkins did not conclude either that ''anaerobiosis'' or more correctly, no perfusion anoxia, was the sole reason for increased lactic acid production by amphibian muscle or that the ''increase of lactic acid'' caused fatigue. They merely described these separate phenomena whilst developing a novel technique (immediate immersion in ice cold alcohol) for the accurate measurement of lactic acid in biological samples. It is important to stress that their primary interest was not the effects of exercise on skeletal muscle metabolism.

However, these studies have historically been interpreted somewhat differently, ultimately establishing the classical interpretation that the absence of skeletal muscle aerobiosis, hence ''anaerobiosis'', is required for lactic acid production by skeletal muscle and that the accumulation of such lactic acid causes a peripherally located skeletal muscle fatigue. That Hopkins and Fletcher studied an in vitro model of no perfusion anoxia and not the effects of anaerobiosis in a blood perfused intact muscle under the control of the CNS has been emphasised.

As a result, when Hill and colleagues measured increased blood lactate concentrations during exercise in humans,[13] they were bound to conclude that the muscles were contracting in the absence of an adequate oxygen supply because: ''Lactic acid does not accumulate so long as the oxygen supply remains adequate''.[14] Thus arose the concept that oxygen deficiency limits maximum exercise performance,[16 17 38] specifically as a result of skeletal muscle ''anaerobiosis'' and a resulting lactic acidosis. The full details of the resulting Hill model have been described previously;[16 17 37–40] here we review only those specific issues that have yet to be resolved and that are especially relevant to this collection of papers.

The complete cardiovascular/anaerobic/catastrophic model of Hill, depicted in fig 2, postulates that exercise of high intensity and relatively short duration is limited by an inadequate oxygen supply to the exercising muscles, resulting from a limiting maximum cardiac output. Hill,[10] his colleagues,[13] and their associates in the United States[41 42] all believed that the maximum cardiac output was limited by the development of myocardial ischaemia.[16 17 38] As a result, the initiating cause of skeletal muscle anaerobiosis in the Hill model is myocardial failure, secondary to a limiting myocardial oxygen delivery that induces myocardial ischaemia (fig 2).

The role of a myocardial governor

As Hill and colleagues presumed that uncontrolled myocardial ischaemia would cause irreversible heart damage, they next proposed the existence of a ''governor'' in either the heart or brain,[15] the function of which is to protect the heart from ischaemic damage during maximal exercise.[40] Their theoretical governor would act to reduce the pumping capacity of the heart during this period of myocardial ischaemia, thereby reducing the risk of myocardial damage.

Mysteriously, this component of the Hill model appears to have disappeared from all subsequent generations of exercise physiology textbooks, perhaps since the demise of Bainbridge's *Textbook of Physiology*,[41] which records how Hill's ideas were embraced by David Dill and colleagues at the Harvard Fatigue Laboratory[43] in the early 1930s. However, in 1952, Astrand wrote that: ''It is common to consider the minute volume of the heart as the limiting factor for the oxygen intake during such types of exercise as cycling and running. *The working capacity of the heart should determine that of the muscles* (our emphasis)'' (p. 118[44]). He also observed, however, that: ''there was no sign of a decrease in stroke volume of the heart when the work became maximum, at least not in the older subjects. This would have been the case if the central circulation had failed'' (p. 120[44]) so that: ''during maximal running and cycling the heart probably works 'submaximally'.'' These statements would seem to be in conflict, as it is not clear how the working capacity of a heart that is working ''submaximally'' should determine that of the muscles unless it is part of an anticipatory process that terminates exercise before some maximally (limiting) capacity is reached.[40]

Nevertheless, an early consequence of the development of this Hill model was that series of highly influential studies[44–52] that sought to explain maximal exercise performance on the

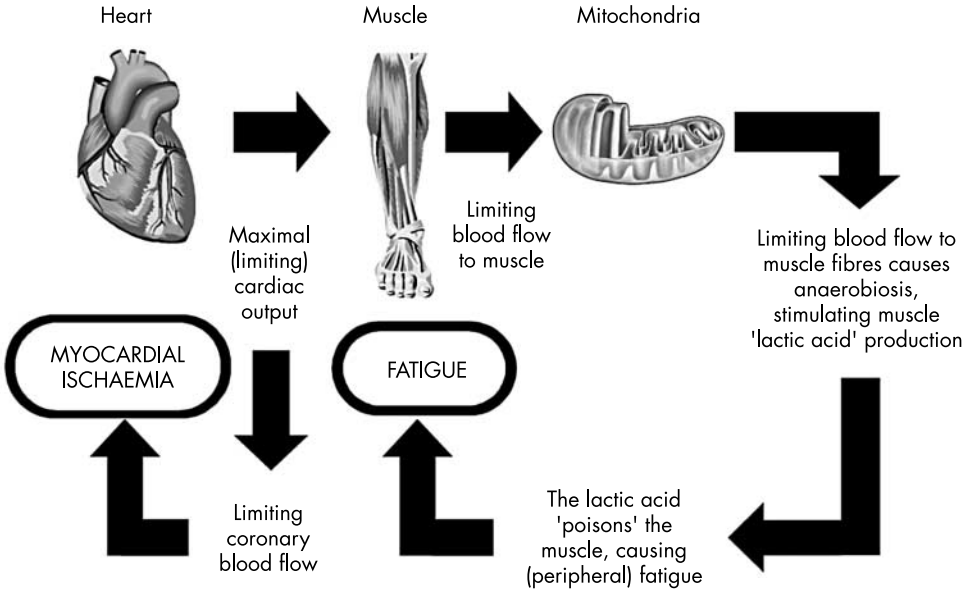

Figure 2 The original model of A V Hill and colleagues theorised that an inadequate supply of oxygen to the heart produced a myocardial ischaemia that limits the maximal cardiac output. Once this limitation was reached, skeletal muscle blood flow was inadequate to match the increasing skeletal muscle oxygen demands posed by a continuously increasing force output. The resulting skeletal muscle ''anaerobiosis'' caused a lactic acidosis that impaired skeletal muscle relaxation, ultimately terminating exercise. Hill and colleagues also proposed that the contractile force of the ischaemic heart would need to be regulated to ensure that severe ischaemia sufficient to produce irreversible myocardial damage did not occur. As a result, they proposed the existence of a ''governor'' either in the heart or in the brain, the function of which would be to protect the ischaemic heart from damage. Note that the figure includes mitochondria and their cristae. The function of these structures were first described[299] only after Hill had formulated his model and thus could not have been included in any theoretical diagrams drawn by Hill in 1923.

basis of the athlete's ability to delay the onset of an inevitable skeletal muscle ''anaerobiosis'', as the consequence of an unusually high maximum capacity for oxygen utilisation (VO_{2max}) during exhaustive exercise.

The pivotal event in the historical evolution of this model occurred in 1955, when Taylor *et al*[53] conferred a universal scientific acceptance of Hill's model by proposing that a ''plateau'' in oxygen consumption can be identified in most humans (94%) during repetitive laboratory testing. However, those researchers accepted, without due diligence,[17 38 54] Hill's core belief that an oxygen deficiency limits maximal exercise: ''The classical work of Hill[8] has demonstrated that there is an upper limit to the capacity of the combined respiratory and cardiovascular system to transport oxygen to the muscles. There is a linear relationship between oxygen intake and workload until the maximum oxygen intake is reached. Further increases in work load beyond this point merely result in an increase in oxygen debt and a shortening of the time in which the work can be performed''.[53] Yet, despite finding what they defined as a ''plateau'' in 108 of 115 subjects during treadmill running, they also reported that: ''increasing the working muscle mass by simultaneously running and arm work produced a definite increase in the *apparent* (our emphasis) maximal oxygen intake. It was concluded that the maximal oxygen intake is only maximal for specific working conditions'' (pp. 79–80[53]). Alternatively, in retrospect, it might be concluded that these data prove that the presence of the ''plateau'' phenomenon as defined by Taylor *et al*[53] does not guarantee that the athlete's highest VO_{2max} has been achieved. This is indeed paradoxical.

Influence of these ideas on the subsequent evolution of research in the exercise sciences

Notwithstanding the problems with this idea, the ''plateau phenomenon'' described by Taylor *et al* became entrenched as the virtual marker of a hypothetical intracellular event, namely the development of the skeletal muscle ''anaerobiosis'' that is the central pillar of the Hill model.[38] The universal and rapid acceptance of this uncontested theoretical model established a research direction in which the physiological basis for this limitation was intensively investigated by some of the most influential scientists in the history of the modern exercise sciences.[47 55–78]

Another research direction stimulated by this interpretation of Hill's model sought the nature of ''anaerobic'' metabolism during exercise and the possible role of lactic acid as the peripheral ''governor'' of exercise performance. Margaria *et al*,[79] among others, proposed that the post-exercise oxygen debt, originally conceived by Hill *et al*,[12–14] can be divided into a lactic acid and a non-lactic acid component, the latter contributed by energy derived from the breakdown of ATP and phosphocreatine (PCr). Concurrently, Hollmann[80] in West Germany and Wassermann's group in Los Angeles[81 82] coined the term ''anaerobic threshold'' to describe the work rate at which blood lactate concentrations begin to rise sharply during exercise. They proposed that this ''threshold'' could be used as a measure of physical fitness and a predictor of athletic ability. Their logic is that: ''lactate accumulation in the active muscle takes place when the muscle O_2 supply becomes critical'',[83] so that increasing skeletal muscle anaerobiosis, lactic acid accumulation, and rising acidosis will cause the termination of exercise at intensities above this ''anaerobic'' threshold.

Another eminent group of exercise scientists also studied the mechanisms by which this theoretical oxygen or energy limitation in the exercising muscles might cause a peripherally regulated fatigue consequent to metabolite accumulation or depletion. Presumably influenced by Hill's original model, the central assumption of all these models is that fatigue results from specific, metabolite induced changes in the active skeletal muscles. This research direction has been driven by the original work, especially of the Scandinavian researchers, beginning with Krogh and Lindhard[84] and Christensen and Hansen,[85 86] who pioneered research into dietary influences on exercise performance, culminating with the introduction of the muscle and liver biopsy techniques for the measurement of intracellular metabolite concentrations.[87]

Adoption of these novel techniques advanced the theory that fatigue, especially during prolonged exercise, is caused by the depletion of energy rich substrates, especially muscle glycogen,[88–91] but occasionally liver glycogen[92] stores, the latter causing hypoglycaemia. The studies of Coyle *et al*[93] established that the provision of carbohydrate during prolonged exercise of 3 or more hours' duration could enhance performance but could not entirely eliminate exhaustion, as subjects were unable to maintain their exercise performance indefinitely even when provided with exogenous carbohydrate at rates sufficient to prevent the development of hypoglycaemia.[94] Thus a factor other than total carbohydrate depletion explained the termination of exercise in those experiments.

Fig 3 charts a possible linkage of the most influential researchers who developed these different research directions and suggests how they may all, to a greater or lesser extent, have been dependent on the original assumptions, presumed first by Fletcher and Hopkins[1] and later by Hill and colleagues after 1923. The important point is that all these research paths are based on the presumption that it is a limitation in the provision of some substrate, be it oxygen, ATP, phosphocreatine, glucose, or glycogen, which causes fatigue during exercise.[16 17] Once this limitation is reached, there is a catastrophic breakdown of homeostasis with the development of skeletal muscle failure according to the ''catastrophe theory'' of Edwards.[4] An important component missing in this model is the role of sensory feedback to the CNS as an essential regulatory step in normal human physiology.[95]

An alternative proposal is that fatigue during exercise might be part of a regulated process in which, ''skeletal muscle contractile activity is regulated by a series of central, predominantly neural, and peripheral, predominantly chemical, regulators that act to prevent the development of organ damage or even death during exercise in both health and disease and under demanding environmental conditions''.[37]

In the next section, we begin to evaluate the ability of these different ''catastrophe'' models to explain what are some frequently reported findings in exercise physiology. We focus particularly on the precision of these models to explain how fatigue develops during the different forms of exercise, especially those commonly studied in the laboratory.

THE CARDIOVASCULAR/ANAEROBIC/CATASTROPHIC MODEL OF FATIGUE DURING EXERCISE OF INCREASING INTENSITY TO EXHAUSTION (TESTING FOR MAXIMUM OXYGEN CONSUMPTION (VO_{2MAX}))

Some of the theoretical limitations of this model, previously presented,[16 37 38] have elicited a vigorous response.[75 96–99] Here we extend that debate by itemising six hallmark requirements that must be correct if the original Hill cardiovascular/anaerobic/catastrophic model is the exclusive explanation for the fatigue that develops during progressive exercise to exhaustion. It is argued that if these absolute requirements are not met, then the cardiovascular/anaerobic/catastrophic model is unlikely to be the exclusive explanation for the fatigue that develops during maximum exercise testing to voluntary exhaustion. We base this argument on the concept, developed previously,[37] that a model unable to explain all the

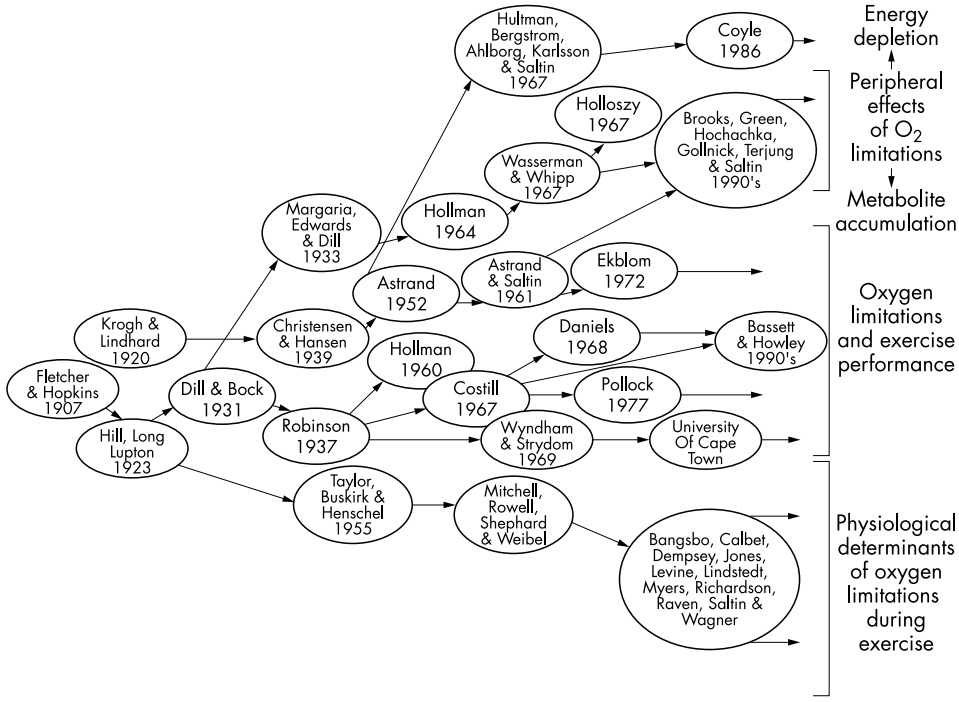

Figure 3 The family tree tracing the evolution of some of the different models in exercise physiology. Important contributors are listed either by the date of their significant publications referenced in this article or according to the period during which they are or were active. It is proposed that Hill's original research influenced the concept that exercise performance could be explained largely by changes in skeletal muscle metabolism (peripheral fatigue) either because of the accumulation of excessive amounts of inhibitory metabolites, especially during high intensity exercise of short duration, or because of the depletion of critical fuels, especially muscle glycogen, during more prolonged exercise. The fundamental assumption is that it is the rate of provision of ATP that regulates skeletal muscle contractile function, rather than the reverse. This follows from Hill's model, which theorises that skeletal muscle oxygen delivery determines skeletal muscle function and not the opposite—that is, that a third factor, the extent of skeletal muscle recruitment, controls the exercise performance, which in turn, determines the oxygen consumption.[188] In the latter CNS model, the critical chemical regulating exercise performance is calcium, not ATP, as it is the calcium released from the sarcoplasmic reticulum in response to the skeletal muscle action potentials generated by the CNS that initiates muscle contraction and hence, exercise performance.

observed phenomena is in dire need of revolutionary replacement rather than minor cosmetic adjustment.

The first hallmark requirement: if the development of oxygen deficiency in the active muscles is the exclusive factor limiting maximum exercise performance, and if the ''plateau phenomenon'' is the external marker of this skeletal muscle anaerobiosis, then the plateau phenomenon must occur in 100% of subjects at exhaustion during progressive exercise

Proof that the original studies of Hill and colleagues did not establish the existence of the ''plateau phenomenon'', provided the initial spur[54] motivating the proposition that Hill's cardiovascular/anaerobic/catastrophic model might be ''an ugly and creaking edifice''[37] in need of urgent revision.[16 17 38]

Table 1 reviews the details of 33 studies that have investigated the physiological criteria for determining the ''plateau phenomenon'' and the frequency with which such criteria are observed during maximal testing. A number of facts are immediately apparent.

Firstly, 10 different criteria (see footnote to table 1) have now been adopted in the attempt to identify the ''plateau'', despite the originally very precise description of Hill and Lupton that ''however much the speed by increased beyond this limit, *no* (our emphasis) further increase in oxygen intake can occur'',[12] and the seminal figure in the decisive early publication[61] in which the VO_2 ''plateau'' is depicted as a horizontal line despite increasing work rate beyond the ''maximum''. This is in keeping with the dictionary definition of a plateau, which is a ''*level* or stable state after an increase''.

Wyndham *et al*[52] were perhaps the first to draw attention to the fact that the traditional ''plateau'' as defined by A V Hill and Lupton is not usually found: ''Because of this slow approach to the asymptote of the true curve of O_2 intake plotted against work rate, it is clear that no simple criterion to define the level of maximum O_2 uptake will suffice, such as that proposed by Taylor *et al*[53]''. Accordingly Wyndham *et al*[52] developed an especially complex mathematical equation to calculate the VO_{2max} from the results of repeated (discontinuous) tests, yet their equation underpredicted the highest VO_2 values that they actually measured in these subjects.[52 54]

Similarly, Cumming and Friesen concluded as early as 1967 that: ''… whilst these criteria are useful indicators that oxygen uptake is starting to level off, their use will clearly underestimate truly maximal values of aerobic capacity. As long as working muscles are able to extract more oxygen from the circulation, *as long as a subject can recruit more muscles to perform the test exercise* (our emphasis), and as long as blood can be diverted from non-exercising to exercising areas, the arteriovenous oxygen difference will increase and so should oxygen uptake''.[104] This would mean that a true ''plateau'' in oxygen uptake may not exist for bicycle exercise in many subjects. The data of this report are in agreement with those of Wyndham *et al*, showing that: ''the curve of oxygen uptake plotted against the work load for bicycle exercise reaches a maximum asymptomatically, and in most subjects never completely levels off'' (p. 944[52]). Clearly it is surprising that such an apparently simple concept as the abrupt ''plateau'' as conceived by Hill and Lupton[12] has been so difficult to identify.

Secondly, of the approximately 1978 individual tests performed in the 33 studies listed in table 1, only 899 (45%) fulfilled these modified criteria for a gradual as

Table 1 Proportion (%) of subjects showing the ''plateau phenomenon'' in oxygen consumption during exercise testing to exhaustion

Author	Ref no.	% of subjects with ''plateau phenomenon''	Test protocol	Criteria	Subjects
Ansley	100	12	Ramp	1	84 tests in males
Ansley *et al*	101	14	Ramp	1	9 males
Armstrong *et al*	102	35,39	Continuous	2	18 girls; 17 boys
Astrand	44	50	Discontinuous	3	140 boys & girls
Cumming and Borsysk	103	42	Continuous	4	65 males
Cumming and Friesen	104	35	Discontinuous	5	20 boys ''tough enough to stand anything''
Cunningham *et al*	105	38	Continuous	2	66 boys × 2 tests
Day *et al*	106	17	Ramp	6	71 males
Doherty *et al*	107	25,39	Continuous	7	50 females & males
Draper *et al*	108	20,20,40,50,80	Continuous and discontinuous	1	10 males × 5 tests
Duncan *et al*	109	50,60	Continuous and discontinuous	1,2	10 males × 2 tests
Fielding *et al*	110	25	Bruce protocol	2	17 females
Foster *et al*	111	62,75,75	Continuous	7	8 Females × 3 tests
Freedson *et al*	112	<40	Discontinuous	2	301 males & females
Froelicher *et al*	113	7–33	Taylor, Balke and Bruce protocols	8	15 males × 3 tests
Hartling *et al*	114	0	Discontinuous Upper Body	3	5 males
Karila *et al*	115	68	Continuous	2	92 diseased children
Mitchell *et al*	63	72	Discontinuous	1	65 men
Myers *et al*	116	50,100	Ramp	9	5 males; 1 female × 2 tests
Myers *et al*	117	50	Ramp	9	6 males
Niemela *et al*	118	17	Continuous	1,2,	55 males; 44 females
Niemela *et al*	119	15	Continuous	10	33 males
Pollock *et al*	120	59,69,69,80	Balke, Bruce, Ellestad, Astrand protocols	1	51 males × 4 tests
Rowland	121	33	Continuous	1	6 boys; 3 girls
Rowland and Cunningham	122	33	Continuous	1	9 boys; 6 girls
Sargent *et al*	123	35	Continuous	2	33 patients with chronic fatigue; 33 controls
Sheehan *et al*	124	31,55,56,69	Continuous	1	16 boys × 4 tests
Sidney and Shephard	125	66–69	Continuous	2	26 males & females
Sloniger *et al*	126	100	Continuous	2	6 males; 2 females
St Clair Gibson *et al*	127	25	Continuous	2	20 males × 2 tests
Taylor	128	17	Continuous	3	12 males
Taylor *et al*	53	94	Discontinuous	1	115 males
Wyndham *et al*	52	100	Discontinuous	11	4 males

Criteria: (1) increase in VO_2 across two workloads was less than the mean increase in VO_2 minus 2SD; (2) increase in VO_2 across two workloads was less than 2.1 ml/kg/min; (3) VO_2 ''levelled off''; (4) VO_2 <90% of expected for load; (5) visual inspection of graph of VO_2 versus work rate; (6) deviation of VO_2 from linearity during last 3 minutes of exercise; (7) increase in VO_2 of less than 1.5 ml/kg/min; (8) not stated; (9) slope of the gradient of the VO_2 curve equal to zero; (10) VO_2 for three last workloads within 5%; and (11) asymptotic curve fitting from residual variances;.

opposed to the originally described abrupt (horizontal) ''plateau''. The incidence of the abrupt ''plateau'' as originally conceived by Hill and Lupton[12] was not reported, perhaps because it is so infrequently observed, but the incidence has to have been substantially less than 47% of all tests and might not even exist according to the logic of Cumming and Friesen.[104]

In the most recent edition of their textbook, Wasserman and colleagues[83] report that the ''plateau phenomenon'' occurs in ''about'' one half of tested subjects, a statement that, according to table 1, would appear to be correct only if a definition that differs substantially (*a*) from that originally proposed by Hill and Lupton[12] and (*b*) from the usual dictionary definition of a ''plateau'' is accepted. Nevertheless this conclusion represents a significant departure from the original doctrine that holds that performance in a progressive exercise test to exhaustion cannot be considered maximal—that is, oxygen limited, unless an appropriate ''plateau'' in oxygen consumption is observed.[53 61 63 106]

The third point from the studies reported in table 1 is that, when carefully sought, a true abrupt ''plateau'' also occurs repeatedly during submaximal exercise.[116 117 129] Accordingly the authors concluded that: ''a plateau … is not a reliable physiological marker for maximal effort''.[117]

Fourthly, the incidence of the gradual ''plateau'' appears to be even less (<20%) in tests in which a ramp protocol is used[100 106 130] and in the very best athletes,[107] the opposite of the prediction that only the best athletes are able to tax their cardiorespiratory function to its limit.[56 75] Furthermore, as more recently confirmed,[106 118 119 131 132] in a number of subjects there is a secondary increase in the rate of rise of VO_2 at exercise intensities above about 75% VO_{2max}, the precise opposite of the ''plateau phenomenon''. In the study of Day *et al*,[106] 27% of tested subjects showed this secondary increase; 56% showed a linear increase in VO_2 with increasing work rate until exhaustion, and only 17% showed evidence for the gradual ''plateau''.

This secondary increase in the rate of VO_2 increase in the study of Bearden and Moffatt[131] coincided with an increased neuromuscular activity in the vastus lateralis muscle, suggesting increased motor unit recruitment immediately prior to the onset of fatigue in a progressive exercise test. As the rise in oxygen consumption was appropriate for the increased neuromuscular activity, there was no reason to suspect the presence of ''anaerobiosis'' in that study.[131] Similarly, there is no logical reason to expect skeletal muscle ''anaerobiosis'' in the absence of an abrupt ''plateau''.

Fifthly, the study of Draper *et al*[108] measured higher VO_{2max} values in a ramp protocol than during the discontinuous test, even though the incidence of the ''plateau'' phenomenon was higher in the discontinuous test, analogous to the original finding of Taylor *et al*[53] that the ''plateau'' does not necessarily indicate that the absolutely highest VO_{2max} values has been achieved.

Finally, there is evidence that each individual does indeed have a single highest VO_{2max} value that can be measured by a variety of different exercise protocols lasting 60 or more seconds, whether or not the ''plateau'' phenomenon

occurs.[106 108 109 112 121 133 134] This could mean that a physiological factor, common to all forms of all out exercise lasting more than about 60 seconds, which is not necessarily skeletal muscle ''anaerobiosis'', may determine the highest work rate achieved within 1–5 minutes and hence the VO_{2max}.[101]

As a consequence of this clear difficulty in defining and identifying the elusive ''plateau'' phenomenon, more recently, ''modified'' criteria for a maximum effort have been proposed. These include (*a*) achievement of ± 11 beats/min of the age predicted maximum heart rate; (*b*) a respiratory exchange ratio in excess of 1.10; and (*c*) a post-exercise plasma lactate concentration $\geqslant 8$ mmol/l.[97 103 135] However, these modified criteria represent a scientific red herring because there is no evidence that any of these variables is a true virtual marker of the skeletal muscle ''anaerobiosis'' that first Hill and colleagues and later Taylor *et al*[53] believed was identified by what is clearly becoming an increasingly difficult to detect abrupt ''plateau phenomenon'' (table 1).

Certainly, there does not appear to be any independent verification that either the ''plateau phenomenon'' or any surrogate measures are real markers of skeletal muscle ''anaerobiosis''. Neither, as argued subsequently (second hallmark requirement), is there evidence that skeletal muscle ''anaerobiosis'' has ever been identified during voluntary exercise in healthy humans or even in those with established disease especially of the cardiac, respiratory, or peripheral vascular systems. Indeed, there seems to have been little appetite to determine to what extent these ''maximal'' metabolic criteria, purportedly identifying the development of skeletal muscle ''anaerobiosis'' in healthy young athletes, are present during maximal exercise in either the elderly or in patients with diseases that should impair skeletal muscle oxygenation, even though the prediction must be that skeletal muscle ''anaerobiosis'' is more easily developed in those whose exercise capacity is diminished by the presence of either age, cardiovascular or respiratory disease, or of all three. Rather, as discussed subsequently, the presence of the ''lactate paradox of disease'' in such patients proves the opposite. A similar pattern is observed in the elderly, as Dill reported when he compared the ''lactate paradox'' of high altitude to that present in older, healthier humans: ''This picture (the lactate paradox of high altitude), it seems to me, resembles that which is seen in the old man with a healthy cardiovascular system, but with limitations to which all persons of advanced age are subject. He, too, has a low maximal heart rate; he is unable to accumulate much lactic acid during exercise; he has a reduced capacity for supplying oxygen to his tissues; and he experiences shortness of breath on exertion'' (p. 450[136]).

Wasserman and colleagues explain how they consider a test may still be considered a maximum effort even without the ''plateau phenomenon'' and hence, presumably, without skeletal muscle ''anaerobiosis'': ''A plateau in VO_2 may also fail to occur during a progressively increasing work rate test when the subject stops exercising because of leg or chest pain, shortness of breath, mechanical limitation to breathing, or lack of motivation''.[83]

Similarly, Wagner proposes that those subjects who fail to show a ''plateau phenomenon'' during maximal exercise, do so because: ''the unpleasant symptoms of exhaustion, dyspnea and/or leg pain result in termination of exercise with no evidence of plateau'' (p.10[75]) so that the ''plateau phenomenon'' occurs only in human athletes ''with high pain and fatigue tolerance'' (p. 14[75]). Presumably, this means that skeletal muscle ''anaerobiosis'' also occurs only in athletes ''with high pain and fatigue tolerance'', but it is these very athletes who show one of the lowest prevalences of the ''plateau phenomenon'' yet measured[107] (table 1).

These suggestions are especially interesting as they now acknowledge that the termination of high intensity exercise may be under central (neural) command as originally concluded by Ikai and Steinhaus,[137] so that the subject's conscious motivation may determine whether or not skeletal muscle anaerobiosis develops during maximum exercise. As we argue subsequently, if the Hill cardiovascular/anaerobic/catastrophic model is physiologically valid, then complete (maximal) recruitment of all the motor units in the specific muscles involved in that activity is the single relevant criterion for a maximal exercise test, because if there is not a maximum skeletal muscle recruitment, then the conclusion of Ikai and Steinhaus remains valid, namely that: ''in every voluntarily executed, all out maximal effort, psychological rather than physiological factors determine the limits of performance. Because such psychological factors … are readily modified, the implications of this position gravely challenge all estimates of fitness and training effects based on testing programmes that involve measures of all out or maximal performance'' (p. 163[137]). The point is that metabolic criteria cannot be used to determine whether or not ''psychological'' factors limit the supposedly maximum performance; only the measurement of the full extent of skeletal muscle motor unit recruitment can determine whether or not there has been a maximal ''psychological'' effort.

Indeed, Gandevia has emphasised the obvious point that ''the decision to terminate'' any exercise undertaken without a fixed endpoint, as in progressive maximal exercise testing, ''is a voluntary act and can be influenced by cognitive processes''.[138] Thus, he concludes that the central nervous system must make the final decision to terminate a maximal exercise test, whether or not a ''plateau phenomenon'' occurs.

This point has been re-emphasised by Kayser who highlights the simple truth that: ''A conscious decision precedes a voluntary effort. The end of effort is again volitional and a forced conscious decision to stop precedes it, but it is not known what forces the off switch of recruitment at exhaustion although sensation of exertion certainly plays a role''.[139] Gandevia[138] and Kayser[139] really only reiterate the statement first made in 1939 by Lehmann *et al*,[140] who observed that the end point of any performance is never an absolute fixed point but rather occurs when the sum of all the negative factors, such as fatigue and muscle pain, are felt more strongly than the positive factors of motivation and willpower. Indeed, the finding that naloxone, an opiate antagonist, leads to significant reductions in VO_{2max} and exercise performance without any evidence for a confounding cardiovascular or metabolic effect, has led to the conclusion that ''in a laboratory setting peak working capacity was limited by the individual's perceived exertion, which can be attenuated by endogenous opioids, rather than by physiologic fatigue''.[141]

Notwithstanding this lucid logic, these recent modifications by Wagner[75] and Wasserman and colleagues[83] to an historical doctrine cleverly avoid two crucial points that cannot be indefinitely ignored.[38]

Firstly they ignore absolutely the fundamental point that the incontestable foundation for the cardiovascular/anaerobic/catastrophic model is the unambiguous conviction that the abrupt ''plateau phenomenon'' is the definitive proof that skeletal muscle ''anaerobiosis'' develops during maximum exercise[47 53 61–63] and that it is this ''anaerobiosis'' that leads directly to the termination of exercise. In other words, as acknowledged by Richardson *et al*: ''The classic concept that VO_2 demonstrates a distinct plateau as work rate is increased beyond that necessary to produce VO_{2max} was first recognised in 1923.[12] Since that time the *presumption* that this profile

measured at the mouth reflects the behaviour of actively exercising muscle VO_2 has been *implicitly accepted* (our emphasis)'' (p. H1456[65]). Hence, as here acknowledged by Richardson *et al*,[65] without the ''plateau phenomenon'', the cardiovascular/anaerobic/catastrophic model has no legitimacy. This point, emphasised in a previous article,[38] has been astutely ignored by all the respondents to that earlier challenge.[96–99]

Secondly, it leaves unanswered the dilemma identified in fig 3 of the previous article:[38] what causes fatigue and the termination of exercise in that 80% or more of subjects who do not show the traditionally defined abrupt ''plateau phenomenon'' during progressive ramp exercise to exhaustion (table 1)? How can exercise terminate when the exercising muscles of subjects who fail to show a ''plateau phenomenon'' cannot be ''anaerobic'', according to the corollary of Hill's original hypothesis?

Thirdly, how is possible to conceive of a defining human physiogical event such as a ''plateau phenomenon'' that apparently occurs purely as a feedforward phenomenon without any role for feedback to the CNS?[95]

Attempts to develop novel physiological criteria that define a maximum exercise test in the absence of the ''plateau phenomenon'' without addressing this fundamental intellectual challenge[96 97 106 135] strengthen the conviction that Hill's cardiovascular/anaerobic/catastrophic model has become ''a creaking and ugly edifice''[37] according to the ideas of Hawking.[142] Perhaps it is appropriate to recall that in their classic paper, Mitchell *et al*[63] come to essentially the same conclusion as did Taylor *et al*: ''The term *maximal oxygen intake* must, itself, be viewed sceptically….It is, therefore, maximal relative to a given set of conditions, which must be carefully selected, rather than in the absolute sense'' (p. 54[153]).

To which one might legitimately ask: if it is not what it is, then what is it?

The second hallmark requirement: skeletal muscle anaerobiosis must develop at exhaustion during maximum exercise

In contrast to coronary venous blood, which has an extremely low oxygen partial pressure (pO_2), perhaps as low as 5–10 mmHg,[143] the pO_2 of venous blood draining from maximally working skeletal muscle is substantially higher (~17–20 mmHg).[144 145] This information is central to the debate of whether or not convection (blood flow) or diffusion (transfer of oxygen from haemoglobin to mitochondria) limits oxygen delivery to skeletal muscle during maximal exercise and hence determines the VO_{2max}[146] according to the Hill cardiovascular/anaerobic/catastrophic model, yet the basis for this debate begins with the traditional presumption that oxygen limitation determines maximal exercise performance and hence the VO_{2max}.[47] However, there seems to be little enthusiasm for the alternate argument: how can skeletal muscle ischaemia, hypoxia, or ''anaerobiosis'' be present when the pO_2 of the venous blood draining from skeletal muscle is so much higher than that from the heart, which, as discussed subsequently, does not become ischaemic, hypoxic, or anaerobic during maximal exercise in healthy subjects?[147] Alternatively, what is the evidence that the skeletal muscle intracellular pO_2 falls below 2.9 mmHg or the intra-mitochondrial pO_2 below 0.05 mm Hg, the values at which an O_2 limitation alone would modulate mitochondrial respiration?[148 149]

Presently no study has yet established conclusively that skeletal muscle hypoxia or anaerobiosis develops during voluntary exercise in humans.[150–152] Rather the published evidence indicates that the calculated intracellular pO_2 of skeletal muscle does not reach critically low values despite large changes in the external work rate.[66 68 70 146] Thus Richardson *et al* have concluded that: ''…intracellular pO_2 remains constant during graded incremental exercise in humans (50–100% of muscle VO_{2max})'' so that: ''With respect to the concept of the ''anaerobic'' threshold, these data demonstrate that, during incremental exercise, skeletal muscle cells do not become anaerobic as lactate levels suddenly rise, as intracellular pO_2 is well preserved at a constant level, even at maximal exercise'' (p. 631[68]). They also conclude that: ''Net blood lactate efflux was unrelated to intracellular pO_2 across the range of incremental exercise to exhaustion'' but was ''linearly related to O_2 consumption'' (p. 627[68]). Another study confirmed these conclusions: ''…consequently these data again demonstrate that, as assessed by cytosolic oxygenation state (deoxy-Mb) during incremental exercise, skeletal muscle cells do not become ''anaerobic'' as lactate levels rise, because intracellular PO_2 is well preserved at a low but constant level even at maximal exercise'' (p. 2682[71]). These conclusions conflict with the interpretation of Wasserman *et al*[83] quoted earlier.

Even though Mole *et al* report a slightly different finding, namely, that skeletal muscle oxygenation falls linearly with increasing exercise intensity rather than staying constant at exercise above 60% VO_{2max}, they conclude that: ''…O_2 availability is not limiting VO_2 during exercise'' (p. R173[146]), as also concluded by Richardson *et al*, who state that: ''average intracellular pO_2 remains above pO_{2crit}, (the minimal effective pO_2 for mitochondrial oxidative phosphorylation) even at maximal exercise in hypoxia'' (p. 631[68]). Furthermore, Mole *et al* conclude that an increased respiration in the face of a falling pO_2: ''raises a provocative question which is not fully rationalised in the current model of bioenergetics'' (p. R179[146]). Nor is there any evidence that the intramyocardial pO_2 reaches critically low values[153] or that coronary blood flow is maximal during exercise in normoxia, as higher flows are measured in hypoxia indicating coronary flow reserve.[154 155] Predictably then, electrocardiograms show no evidence for myocardial ischaemia during maximal exercise in healthy humans.[147] Hence Hill's original idea that a skeletal muscle ''anaerobiosis'' occurs consequent to a developing myocardial ischaemia that prevents any further increase in the cardiac output (fig 2), cannot be correct.

Perhaps more unexpected is the finding that muscle deoxygenation measured with near infrared spectroscopy (NIRS) is much greater in the so-called ''anaerobic'' Wingate test than during maximal exercise (fig 4)[156 157] so that the level of deoxygenation during the Wingate test approaches levels reached during tourniquet induced total ischaemia.[156–158] Indeed, Szmedra *et al*[159] conclude that muscle deoxygenation is a function of the degree of static loading of the contracting muscles and is related to the impaired muscle blood flow that occurs when muscles contract at a higher percentage of their maximum voluntary contraction. More recently, Neary *et al*[160] have shown that muscle deoxygenation is about twice as great during a 20 km cycling time trial, in which athletes cycled at about 75% VO_{2max}, than it is during conventional VO_{2max} testing.

None of these findings is compatible with the traditional Hill interpretation that the VO_{2max} is limited by skeletal muscle ''anaerobiosis''.

What is even more surprising and which is not usually acknowledged, is that the work output during the Wingate test can be 3–4 times greater than the peak values measured during the traditional VO_{2max} test protocol.[157] This finding is not compatible with the theory that skeletal muscle work during the VO_{2max} test is limited by skeletal muscle hypoxia,[76] as much higher muscle work can be achieved during the Wingate test when the most profound levels of muscle deoxygenation yet measured in humans are present (fig 4).

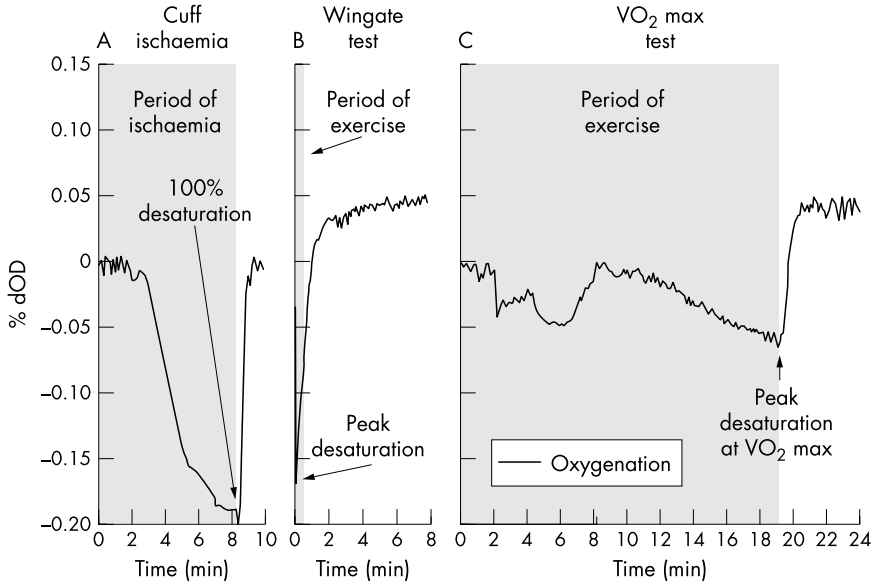

Figure 4 Haemoglobin/myoglobin desaturation measured with near infrared spectroscopy (NIRS) during (*a*) the application of a lower limb tourniquet cuff to induce total ischaemia (A; left panel); (*b*) a Wingate ''anaerobic'' exercise test (B; middle panel), and (*c*) during a progressive maximum exercise test to exhaustion for measurement of VO_{2max}[156 157] (C; right panel). Note that the application of a lower limb tourniquet produces complete desaturation within about 7 minutes, whereas almost the same level of desaturation is produced within seconds of the onset of the Wingate test. In contrast, a progressive maximal exercise test that lasted 19 minutes produced only a 33% level of desaturation. The finding (fig 4) that a much greater desaturation occurs in the ''anaerobic'' Wingate test shows (*a*) that there is a large aerobic component to this test[163] and (*b*) that muscles with a low oxygen content are able to produce more force during the Wingate test than are muscles with a higher oxygen content at the end of a VO_{2max} test. This argues against the theory that hypoxia directly impairs skeletal muscle function, which then explains the reduced exercise tolerance at extreme altitude.[164] Recall also the argument of Bigland-Ritchie *et al*[217] that the function of the respiratory muscles is clearly not impaired by hypoxia, suggesting that the reduced exercise tolerance in hypoxia is likely to be regulated centrally in the brain.

Further evidence that a limiting oxygen supply cannot explain all forms of maximal exercise performance is our finding[161] more than a decade ago that the VO_{2max} measured during downhill running is only 85% of the value measured during horizontal running. Similarly, blood lactate concentrations, maximum rates of ventilation and respiratory exchange ratios were all significantly lower at exhaustion during downhill running, but stride frequency was the same at exhaustion in both conditions. Stride frequency during a maximal exercise test and cadence during the Wingate test are likely to be regulated centrally in the CNS. If this is correct, then, as argued subsequently in more detail, central neural recruitment may regulate maximal exercise performance, at least during maximal downhill running as well as during the Wingate test.

Finally there is the intriguing recent finding that the opioid blocker, naloxone, reduces VO_{2max}, maximum work rate, and maximum heart rate, but not maximum perceived exertion.[141] The authors conclude that the peak work rate is determined by the perceived exertion rather than by physiological fatigue. This would be explained if the perception of effort regulates the number of motor units that are recruited during maximal exercise according to the central governor theory discussed subsequently.[40]

In summary, the acceptance that these is no firm evidence for the virtual event, skeletal muscle anaerobiosis, theoretically predicted[65] by the increasingly difficult to identify and understand ''plateau phenomenon''[75 106 116 117 129 130 162] is fundamental to any objective analysis of the authenticity of Hill's cardiovascular/anaerobic/catastrophic model, yet here the available evidence is strikingly clear – no study has yet established that skeletal muscle ''anaerobiosis'' develops during maximal exercise testing used to measure the VO_{2max} (fig 4). Indeed, fundamental consequences of endurance training are increased skeletal muscle oxygen extraction, increased capillary blood transit time and improved perfusion homogeneity,[165] all factors that would tend to reduce the probability that ''anaerobiosis'' would develop in the muscles of trained athletes.

Hence, maximal exercise performance must terminate for reasons other than the development of the skeletal muscle ''anaerobiosis'', or, as Froelicher and Lancaster[166] surmised when they discovered that exercise duration during a progressive treadmill exercise test could not predict the VO_{2max}: ''other factors than the maximum oxygen consumption must be operating in determining the treadmill performance''.

Furthermore, there is now a consensus that lactate production by muscle during exercise in humans occurs in the absence of skeletal muscle anaerobiosis.[27 68 70 95 167 174] Rather, according to the ''lactate shuttle'' hypothesis of Brooks[95 170–174] and the ''glycogen shunt'' hypothesis of Shulman and Rothman, lactate may accumulate when the rate of glycogen breakdown to produce the obligatory ATP for millisecond muscle contractions exceeds the rate at which the lactate so produced can be used: ''for oxidative energy production to restore glycogen and PCr levels during the intervals between contractions'' (p. 460[27]).

The third hallmark requirement: to maximise skeletal muscle blood flow and hence oxygen delivery, cardiac output must always be maximum at fatigue because, according to the cardiovascular/anaerobic/catastrophic model, the heart is merely the slave of the oxygen demands of the exercising muscles

A usually accepted dictum is that the oxygen demands of the active muscles determine skeletal muscle blood flow and hence the cardiac output during exercise.[175–178] Thus, if oxygen deficiency in the active skeletal muscles limits maximal exercise, as this model predicts, then it follows that the heart must always reach the same limiting maximum cardiac output at exhaustion regardless of the conditions in which

that maximum exercise is undertaken. This must be so if the heart acts simply as the mindless slave to the oxygen demands of the peripheral muscles, operating only to maximise oxygen delivery to all the muscles that are active during exercise. This is especially true if it is believed that oxygen delivery determines skeletal muscle function according to the Hill model.

Surprisingly there have been few attempts to show that the cardiac output does indeed plateau during maximum exercise. The early study of Mitchell *et al* (table VI, p. 543[63]) purportedly showed that the cardiac output at a work rate ''beyond the maximal oxygen intake level'' was indeed lower than that reached at the ''maximal oxygen intake level'', but as the peak oxygen uptake at this work rate was also less than the measured VO_{2max}, this suggests that the exercise terminated prematurely before a true maximum cardiac output could be achieved. The only other explanation would be that the lower cardiac output beyond the VO_{2max} resulted from myocardial ischaemia according to the Hill model (fig 2). However, it is known that myocardial ischaemia does not occur in maximal exercise in healthy athletes,[147] even during exercise in the marked hypoxia of simulated altitude,[164 179–181] and that coronary flow reserve exists at maximal exercise in healthy humans in normoxia.[154 155] Indeed, the latter finding that myocardial blood flow increases in hypoxia conflicts with the finding in exercising skeletal muscle in which the maximal cardiac output and skeletal muscle blood flow is reduced in hypoxia.[64–68 164 181] This discrepant finding must indicate that the maximal blood flow to the heart during whole body hypoxia must be regulated, as discussed subsequently, by vasodilatory factors in the coronary arterioles themselves, whereas factors external to the exercising skeletal muscle arterioles must regulate their maximum flow during exercise in hypoxia.

More contemporary studies show that cardiac output increases linearly with increasing work rate up to the VO_{2max}, with no evidence for any developing ''plateau''.[182–186] If anything, cardiac function appears to be enhanced at the work rate that elicits the VO_{2max}, especially in elite athletes,[183–186] who are presumably at greatest risk of developing a ''plateau'' in cardiac output and myocardial ischaemia according to the original Hill model (fig 2). Furthermore, the same VO_{2max} can be achieved at different maximum cardiac outputs.[187]

An especially important prediction of the Hill model is that the cardiac output must always be high under conditions of hypoxia or anaemia, when a high or increased cardiac output becomes the only factor that can maintain a maximum oxygen delivery to the exercising muscles.[188] Thus, if the heart is indeed the slave to the peripheral muscles, then the maximum cardiac output cannot ever be lower, for example, in hypoxia or anaemia than in normoxia or normocythaemia, unless the function of the heart is itself altered either directly or indirectly, by hypoxia or anaemia.

Furthermore, if the maximum cardiac output at sea level is limited by the diastolic filling characteristics of the heart,[189] rather than by the development of myocardial ischaemia as originally proposed in the Hill model (fig 2), then the cardiac output can never be higher than the maximum value measured during exercise at sea level. Nor, however, should it ever be lower, most especially not in hypoxia or anaemia, as a maximum cardiac output would be required to offset the effects of a reduced blood oxygen content in both those conditions.[188] Several studies are particularly relevant in this context.

The first example is the physiological response to maximum exercise in chronic hypoxia, which is characterised by what has been labelled the ''lactate paradox''. Less well recognised is the related ''cardiac output'' paradox. Fig 5 shows that exercise at increasingly higher altitudes terminates at progressively lower blood (and muscle) lactate concentrations,[190] as has been repeatedly shown.[191–194] Furthermore, as shown in the right panel of fig 5, maximum cardiac output and heart rate also fall as a function of

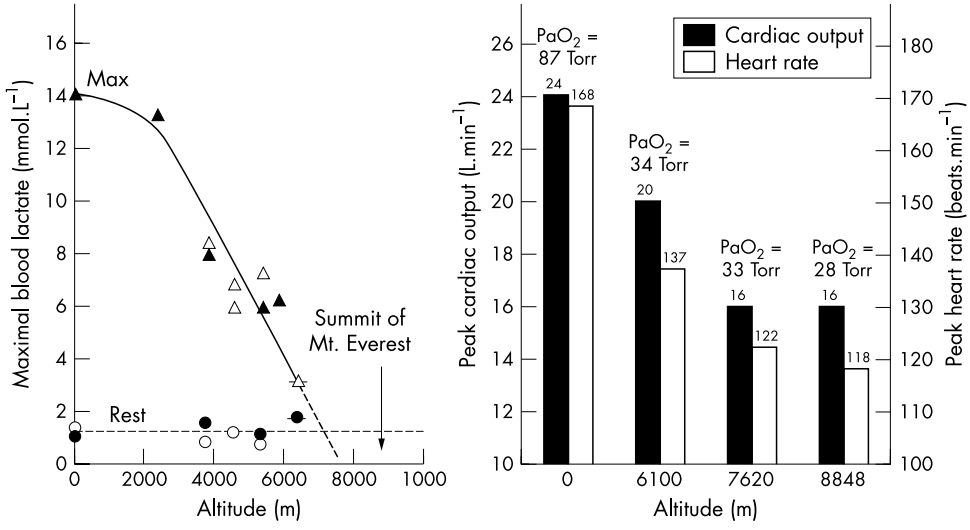

Figure 5 Maximal blood lactate concentrations (left panel)[190] and maximal cardiac output and heart rate (right panel)[179] are lower at exhaustion during maximal exercise at increasing simulated altitude. Thus, this form of fatigue cannot be explained by the Hill model, which requires that fatigue occurs only after muscle lactate concentrations have risen sufficiently to impair skeletal muscle function (fig 2). The lower cardiac output can also not be explained[188] by the direct effects of hypoxia on the myocardium,[76 164 181] as there is no evidence either that the heart is hypoxic in conditions of simulated altitude[154 155] or that myocardial function is impaired in any way during maximal exercise at altitude.[179 180] The lower cardiac output is also paradoxical if it is skeletal muscle ''anaerobiosis'' that limits maximal exercise performance at simulated altitude, as such hypoxia should elicit a maximum cardiac output to ensure a maximum oxygenation of the exercising muscle.[188] It is more likely that skeletal muscle recruitment is reduced at altitude[139 188 194] by the action of a ''central governor''[36] in order to ensure that cerebral hypoxia does not occur. According to this model, the maximum blood lactate concentrations, the maximum cardiac output, and the maximum heart rate measured during ''maximum'' exercise at altitude are entirely appropriate for the very low exercise intensities that are compatible with human survival under conditions of such extreme hypoxia and that are therefore ''allowed'' by the central governor. Thus according to the central governor model, it is the level of muscle work (determined by the number of motor units that are recruited by the CNS) that determines the VO_2, and not the converse.[188]

increasing altitude.[195] These findings are indeed paradoxical for a variety of reasons.

In the first place, muscle and blood lactate concentrations should, according to the cardiovascular/anaerobic/catastrophic model, be higher, not lower, during exercise at increasingly higher altitudes, when hypoxia becomes increasingly more severe. As West[190] has written: ''Above an altitude of about 7500 m, no blood lactate is predicted even for maximal exercise''. He concluded that: ''If this extrapolation held good, a well acclimatised climber who reached the summit of Mount Everest without supplementary oxygen would have no blood lactate. This is a paradox indeed, because such a climber is apparently more hypoxic during maximal exercise than in any other known situation.'' The unrecognised paradox, clearly incomprehensible according to any model requiring the peripheral regulation of exercise performance, is that these data clearly establish that the heart and the active skeletal muscles are at lesser risk of developing hypoxia during maximum exercise at extreme altitude than at sea level.

Subsequent research confirmed that West's prediction is indeed correct; muscle and blood lactate concentrations are lowest during maximal exercise at a simulated altitude equivalent to that of the summit of Mount Everest (8848 m).[192] Thus West's belief that: ''such a climber is apparently more hypoxic during maximal exercise than in any other known situation'' does not apply to the climber's heart or exercising muscles. Clearly, exercise at extreme altitude is regulated by the effects of a reduced arterial PO_2 on an organ or organs other than the heart and skeletal muscles. Hence the traditional metabolite induced model of peripheral fatigue is utterly unable to explain the extreme discomfort and profoundly impaired exercise capacity at extreme altitude. Thus the question remains: if exercise at altitude is not ''constrained'' by a peripherally based, metabolite induced fatigue consequent to the most severe skeletal muscle ''anaerobiosis'' predicted to occur at extreme altitude, then how is exercise performance regulated and muscle rigor prevented under these conditions of the most extreme hypoxia?

Therefore, the real paradox of the ''lactate and cardiac output paradox'' of high altitude is that the popular cardiovascular/anaerobic/catastrophic model (fig 2) cannot explain why fatigue develops at high altitude, as this form of fatigue clearly occurs without the development of a metabolite induced, specifically lactic acid inhibition of muscle contractile function. Biochemical explanations for this phenomenon[196] fastidiously avoid any discussion of this displeasing reality.

In addition, the ''lactate paradox'' is incompatible with the teaching that skeletal muscle anaerobiosis develops during exercise and must therefore be greatest during maximal exercise at extreme altitude.[38] Furthermore, the associated ''cardiac output paradox'' proves that the heart is not simply the ''slave of the periphery'', as the cardiac output is lowest when it should be highest[188]—that is, under those very conditions when oxygen delivery to the muscles is most threatened by the profoundly low arterial pO_2 that is reached during maximal exercise at extreme altitude.[197]

In a recent dissertation on this topic, Wagner[76] correctly concludes that the low cardiac output at altitude cannot be explained by any of the four factors known to be operative at altitude: increased blood viscosity, reduced cardiac filling pressures consequent to a reduced plasma volume, altered function of the autonomic nervous system, or hypoxic myocardial dysfunction. He therefore favours a simpler hypothesis, that the low cardiac output ''merely reflects the reduced requirement for muscle blood flow that results from the arterial hypoxemia of altitude (which reduces muscle O_2 availability and thus maximal muscle function)'' such that the ''likeliest cause of the diminished peak cardiac output is decreased demand caused by the hypoxic limitation of muscle metabolic rate''.[198] Hence, in effect, he proposes a novel modification to the Hill cardiovascular/anaerobic/catastrophic model in which, at extreme altitude, muscle hypoxia regulates skeletal muscle function directly, in the absence of elevated muscle lactic acid concentrations. This interpretation clearly conflicts with the conclusion of Richardson *et al*[68 71] and Mole *et al*[146] quoted earlier, that skeletal muscle hypoxia does not occur even in maximal exercise in hypoxia, and with the finding that muscle power production is greatest in the Wingate test when the most severe muscle deoxygenation is present (fig 4). Subsequently, as co-author of the paper by Calbet *et al*, Wagner offers an opposite suggestion, namely that: ''hypoxia first attenuates increases in cardiac output that limits muscle oxygen delivery and (skeletal muscle) power output and, in turn, the muscle pump and ventricular filling'' (p. R300[181]). Yet, as already argued,[188] there is no evidence that hypoxia directly affects the pumping capacity of the heart during exercise in subjects with an intact CNS.

However, Wagner's other new interpretation clearly conflicts with the traditional belief that hypoxic or ''anaerobic'' muscle has an increased, not a reduced rate of lactic acid production and that it is this increased rate of production that is causally related to fatigue.[83]

Thus, this novel interpretation begs answers to at least three further questions: If the skeletal muscles are unable to work because they are hypoxic, why is their rate of lactic acid production not increased? If the skeletal muscles are hypoxic, why is the cardiac output not increased in an attempt to offset that hypoxia? If the skeletal muscles are unable to function because they are hypoxic, why does the same not apply to the respiratory muscles and especially to the heart, which is at far greater risk of hypoxia when the arterial PO_2 falls as the heart can increase its oxygen consumption only by increasing coronary flow as oxygen extraction is near maximal even at sea level.[143] The answer would seem to be that, as predicted, maximal coronary blood flow is increased during exercise in hypoxia,[154 155] indicating that the heart has flow reserve[199] that is activated only under the added stress of hypoxia. The fact that skeletal muscle blood flow does not increase in hypoxia proves that, during maximal exercise in hypoxia, blood flow to the exercising skeletal muscles must be regulated by constraints that are external to the local skeletal muscle circulation.

Furthermore why is only the ''maximal muscle function'' affected when the clear evidence is that climbers who do not use supplemental oxygen at great altitude are barely able to stand upright,[197] let alone exercise at anything other than a profoundly submaximal effort? We return subsequently to these issues in order to show that this model of a metabolite induced, peripheral limitation of exercise performance suffers from one crucial limitation discussed under the fourth hallmark requirement. More importantly, there is a much simpler explanation for the mechanism of fatigue at altitude and one for which there is a solid body of published evidence.[40 139 188]

Thus, we must revisit the persistently recurring question that cannot be indefinitely ignored: what biological event terminates exercise at extreme altitude when there is no apparent metabolic basis for that fatigue according to the traditional cardiovascular/anaerobic/catastrophic model? The more obvious truth is that the low maximum cardiac output in acute or chronic hypoxia is entirely appropriate for the (low) work rate that is achieved,[65 69 76 164 179–181] indicating that the oxygen demands of the exercising muscles continue to determine the appropriate cardiac output, even at extreme altitude. Because leg blood flow and oxygen consumption are

appropriate, as is cardiac function,[179 180] neither the exercising skeletal muscles nor the heart can be hypoxic.[188] This disproves both the theory of Wagner[76] that exercise at altitude terminates because of a skeletal muscle hypoxia that directly regulates skeletal muscle contractile function in the absence of a lactic acidosis, and the explanation of Calbet *et al*[181] that a (non-existent) myocardial hypoxia limits the cardiac output and hence the exercise performance at altitude.

Other altitude related paradoxes that are seldom analysed include the finding (*a*) that adaptation to extreme altitude is associated with reduced skeletal muscle mitochondrial volume and enzyme content;[200 201] (*b*) that the skeletal muscle morphology of Nepalese Sherpas adapted to altitude is not different from that of acclimatised white climbers[202] except that (*c*) the volume density of skeletal muscle mitochondria is significantly smaller in Sherpas than in untrained sedentary subjects who are native to sea level.[202] All these findings suggest that superior exercise performance at altitude is unlikely to be determined primarily by a superior capacity to limit skeletal muscle hypoxia or ''anaerobiosis''.

The second set of provocative findings originate from studies of single legged exercise in which muscle performance and oxygen transport kinetics are studied under conditions of normoxia, hypoxia, and hyperoxia.[64 66] As is the case with whole body exercise at simulated altitude, these studies show that, without exception, oxygen consumption, leg blood flow, and cardiac output are always lower at peak exercise in hypoxia than in normoxia or in hyperoxia. The same has been found in two legged cycling exercise.[144 168 181]

The finding that skeletal muscle blood flow is lowest in hypoxia even when a small muscle mass is active during one legged exercise is especially surprising because, according to the predictions of the cardiovascular/anaerobic/catastrophic model, under these experimental conditions, exercise always terminates at a submaximal cardiac output. However, if oxygen delivery to muscle truly limits exercise performance with small muscle groups, then exercise should always terminate with the same maximal cardiac output, regardless of whether exercise is performed in hypoxia, normoxia, or hyperoxia,[188] but this does not occur when the exercise involves either small muscle groups and hence a submaximal cardiac output, or the large muscle groups that could theoretically elicit a maximal cardiac output. Indeed, as maximal exercise with small muscle groups always terminates at a submaximal cardiac output, then studies using this model must always conclude that the rate of oxygen delivery limits the maximal oxygen consumption of small muscle groups.[64 66] However, this interpretation fails to exclude the possibility that factors external to the cardiovascular system may determine performance both in this particular model and in whole body exercise.[188]

Studies of patient populations provide additional information to extend this interpretation further. Several studies have found that oxygen therapy increases the exercise performance of patients with chronic obstructive lung disease.[69 203] More importantly, leg blood flow, cardiac output, heart rate, and blood lactate concentrations were significantly increased at exhaustion with oxygen therapy (fig 6), as also occurs in altitude acclimatised subjects at the point of exhaustion when the inspired air is suddenly changed from hypoxia to hyperoxia.[164 181] Others have shown that patients with chronic respiratory disease terminate exercise at low cardiac outputs (5–6 l/min) and low blood lactate concentrations (2–3 mmol/l),[204] the opposite of the prediction that the cardiac output should be maximum in hypoxia and, if anything, reduced in hyperoxia. Hence, a limiting cardiac output and high muscle and blood lactate concentrations are unable to explain the fatigue that occurs when these respiratory patients exercise without oxygen therapy, another medical example of the ''lactate paradox'', the significance of which was emphasised in the J B Wolffe lecture of 1996.[37]

Findings in patients with chronic obstructive lung disease are counterintuitive, yet they prove that, in these patients, exercise without oxygen therapy terminates at lower cardiac outputs and blood lactate concentrations than does exercise in hyperoxia, but if, according to the Hill theory that exercise without oxygen therapy is indeed limited by either skeletal muscle ''anaerobiosis'' or hypoxia, then, as is the case at extreme altitude, it would be expected that cardiac output and blood lactate concentrations would be elevated under these supposedly more hypoxic conditions and would be reduced, not increased, in hyperoxia. This is especially relevant because, in response to a reduced arterial oxygen content, healthy subjects increase the cardiac output and limb blood flow so that tissue oxygen consumption remains unchanged at a constant work rate.[205] This again suggests that it is the amount of work that is performed that determines and ultimately regulates these responses,[188] and not the converse.

A third intriguing finding is that patients with peripheral vascular disease terminate exercise with lower blood lactate concentrations than do patients with other chronic diseases and substantially lower than in healthy age matched controls (table 2).[206] This is especially paradoxical if it is presumed that the poor exercise tolerance of these patients is determined by an excessive lactate production by their ischaemic muscles. Rather, this finding is compatible with the interpretation that exercise terminates before profound skeletal muscle ischaemia can develop—that is, before a catastrophic failure of homeostasis occurs.

The final perplexing finding is that the treatment of patients with chronic severe anaemia with erythropoietin also leads to higher blood lactate concentrations at the termination of maximum exercise,[207] again showing that maximum exercise in the untreated state cannot be limited purely by an impaired oxygen delivery to the exercising muscles. This is confirmed by the studies of Celsing *et al*[208] and Koskolou *et al*,[209] which show that acute anaemia, or conversely its correction with erythropoietin,[210 211] does not increase the peak blood flow or cardiac output at exhaustion even though exercise terminates at a submaximal cardiac output. Remarkably, Marrades *et al*[210] found that maximal leg blood flow actually decreased with erythropoietin therapy so that maximal leg VO_2 did not increase even though arterial oxygen content increased by 50%.

Thus Koskolou *et al*,[209] Roach *et al*,[205] and Wolfel *et al*[212] all conclude that O_2 delivery to muscle is tightly regulated. A more logical interpretation might be that the work rate determines the O_2 demand and that the work rate is, in turn, determined by factors other than the rate at which O_2 is delivered to the exercising muscles,[188] because the persistent problem remains: what mechanisms, other than a theoretical hypoxia that has never been shown to exist,[68 70] might ''constrain'' the maximum cardiac output under conditions of experimentally induced hypoxia or disease induced hypoxia in persons with chronic lung disease or in acute or chronic anaemia, when disinterested logic suggests that it should be increased?[188] Or, in the context of exercise at extreme altitude, what mechanisms prevent the muscles from exercising more vigorously as it is their low work rate that explains both the low cardiac output and the low muscle and blood lactate concentrations and not the converse?

As argued previously,[16 17 37–40] a reduced capacity to recruit voluntarily a larger muscle mass appears to explain the reduced exercise performance at altitude[139 194] and the same mechanism presumably explains the lower VO_{2max} in hypoxia than in normoxia or in hyperoxia.[164 181 213–217] This is

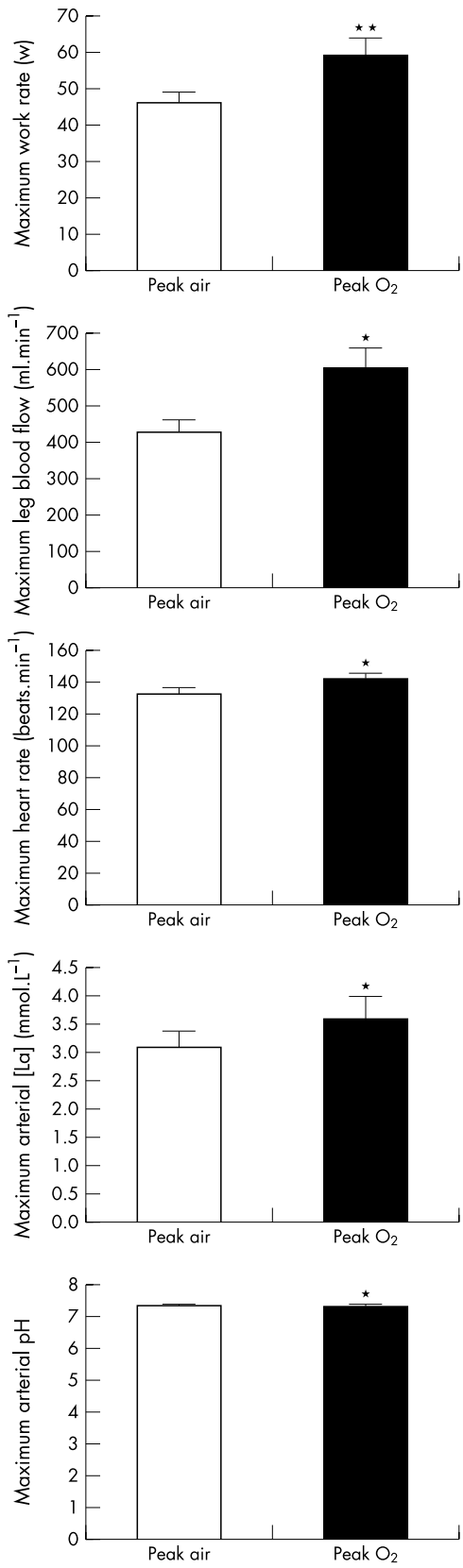

Figure 6 Oxygen therapy (peak O_2) allows patients with chronic obstructive lung disease (COPD) to reach higher maximum work rates, leg blood flows, heart rates, arterial lactate concentrations, and lower arterial pH than when they exercise in room air (peak air).[203] This is paradoxical because it shows that, as is the case at extreme simulated altitude in healthy subjects (fig 5), maximum exercise in room air in patients with COPD does not terminate at maximal cardiac outputs and maximum blood lactate concentrations, as required by the Hill model (fig 2). Rather, it seems probable that oxygen therapy allows the recruitment of a greater number of motor units in the exercising limbs, the converse of what happens during maximal exercise in hypoxia.[194] From data of Maltais *et al*[203]. *p<0.05; **p<0.001.

not a novel concept. Already in 1988, Bigland-Ritchie and Vollestad[216] hypothesised that a decreased central neural drive limits dynamic exercise with large muscle groups at altitude. This theory was sparked by their answer to their rhetorical question: ''Why should hypoxia have such a profound effect on limb muscle performance, while work capacity of respiratory muscles seemed unaffected when both muscle groups were performing similar types of dynamic exercise?'' (p. 375[217]). Recall that the highest sustained peak rates of ventilation are measured under conditions of the most extreme hypoxia.[195] Thus they concluded that: ''… it is essential for survival that somehow respiratory muscles must avoid the extremes of fatigue experienced by limb muscles. … This could be achieved if CNS strategy involves some kind of reciprocal inhibition between the motor drive to limb and respiratory muscles, with that from the respiratory system dominating. According to this scheme, the motor drive to limb muscles can achieve and retain maximal muscle activation, provided this does not increase the metabolic demand above that which the respiratory muscles can deliver. However, if either the muscle mass is too large or the exercise sufficiently demanding, such that metabolism exceeds the capacity of the oxygen delivery system, a balance between them is restored by an automatic reduction of motor drive to limb muscles. In this case, the limb muscles can no longer be fully activated and central fatigue ensures. … This may be brought about by reflex inhibition arising mainly from the fatigued diaphragm, but it could equally well be caused by reciprocal inhibition between the two systems acting centrally within the brainstem'' (p. 375[217]). Accordingly they concluded that: ''Thus, fatigue developed under these conditions may have been caused more by a reduced motor drive than by peripheral factors (so that) …taken together, these observations support the concept that the motor drive to limb muscles is reduced when the metabolic demand of skeletal muscle exceeds that which the respiratory muscles can supply'' (p. 375[217]). They even postulated that if this system works in severe hypoxia, ''it seems likely that similar interactions are also available under other stressful conditions which are more commonly encountered'' (p. 376[217]). Indeed, all the current evidence supports their hypothesis by showing that the central nervous system regulates exercise performance at altitude and presumably also in persons with chronic obstructive lung disease, by determining the number of motor units that are recruited.[40 139 194]

In summary, the studies described in this section are important because they establish, beyond reasonable argument, that while the heart may well act as if it is the slave to the demands of the periphery, those peripheral demands must be regulated by another, presumably neural, mechanism,[188] which acts to ensure that no organ in the body becomes hypoxic during the stress of maximal exercise[16 37 38 40] even in persons with advanced respiratory disease[204] and even at extreme altitude.[69 164 181] Furthermore, the finding that the cardiac output measured during maximum exercise at sea level may increase further in hyperoxia[213 215] challenges the belief that the cardiac output is constrained or limited during maximum exercise at sea level by a limiting capacity to fill during diastole[189] or by a limiting maximum heart rate.

These findings can be interpreted as proof that the ''maximum'' cardiac output, and by extension the VO_{2max}, is determined in response to the number of motor units that are recruited in the exercising muscles during voluntary

Table 2 Peak VO_2, respiratory exchange ratios (RER) and blood lactate concentrations during maximal exercise in patients with heart failure (HF), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD) and controls (CON)

	HF (n = 11)	COPD (n = 13)	PVD (n = 31)	CON (n = 13)
Age (years)	47 (5)	57 (5)	63 (13)	55 (7)
Peak VO_2 (ml O_2/kg/min)	12.5 (1.0)	17.0 (5.0)	17.0 (4.2)	26.0 (6.0)
Peak RER (units)	1.0 (0.1)	1.1 (0.2)	1.0 (0.1)	1.4 (0.2)
Peak ventilation (l/min)	36.1 (2.7)	41.3 (13.5)	43.0 (14.2)	87.5 (22.1)
Blood (lactate) (mmol/l)	4.6 (0.5)	5.1 (2.7)	3.3 (1.4)	9.7 (2.7)

Data of Parr[206] are expressed as mean (SD).

exercise and, as a consequence, by their oxygen requirements. The extent of this recruitment may, in turn, be regulated, at least in part during maximal exercise, by the rate of oxygen delivery to specific organs, or the partial pressure of oxygen in one or more tissues or organs,[40 164 181] or perhaps mechanical receptors in the active muscles, diaphragm, or respiratory muscles provide information on the maximum exercising workload that can be safely attempted.[100 101] This hypothesis will be developed more fully in other sections of this paper.

The fourth hallmark requirement: models of peripheral fatigue predict that there must always be complete recruitment of all motor units in the active limbs at fatigue

A popular graphic that is used to illustrate all the factors usually considered to limit the maximum oxygen consumption is reproduced in fig 7. The figure appears in a section of Rowell's book[176] entitled: ''What limits the ability to increase oxygen uptake?'' A similarly popular diagram can be found in the paper of Lindstedt *et al*.[218]

The answer for the humanoid depicted in both figures is clearly the absence of the central nervous system (CNS), as, in the absence of the CNS, there is no capacity to recruit any skeletal muscle motor units so that the VO_{2max} of the depicted humanoids would be the same as that of a quadriplegic human, which is the resting metabolic rate, or ~5 ml/kg/min. The crucial point is that while these figures provide a valid depiction of the predictions of the cardiovascular/anaerobic/catastrophic model, either is correct only if there is always complete recruitment of all the motor units in the exercising limbs that are being tested to measure the whole body VO_{2max} because, if fewer than 100% of the motor units are active at fatigue, then it is difficult to understand how a metabolite induced, peripheral fatigue mechanism can (*a*) regulate the function of muscle fibres that are not actively contracting or (*b*) prevent their subsequent recruitment by the CNS. More importantly, if motor unit recruitment is less than 100%, then a peripheral mechanism for fatigue cannot be assumed unless a limitation within the central nervous system has first been excluded, as, if the extent of motor unit recruitment is unknown, it cannot be excluded that the proximate ''limitation'' is the inability to recruit additional motor units, further to increase the oxygen demand in the periphery and hence the whole body VO_{2max}. Thus, the question becomes: what is the evidence that all available motor units are recruited during maximal exercise so that fig 7 can be interpreted as the true depiction of the exclusive factors that could limit the whole body VO_{2max}?

Several related studies show that fatigue during maximum exercise to exhaustion occurs when <100% of the motor units in the tested limbs have been recruited.

Firstly, studies of acute exposure to altitude show that electromyographic (EMG) activity and, by interpretation, the number of motor units that are recruited[219 220] is lower at exhaustion during maximum exercise at altitude than at sea

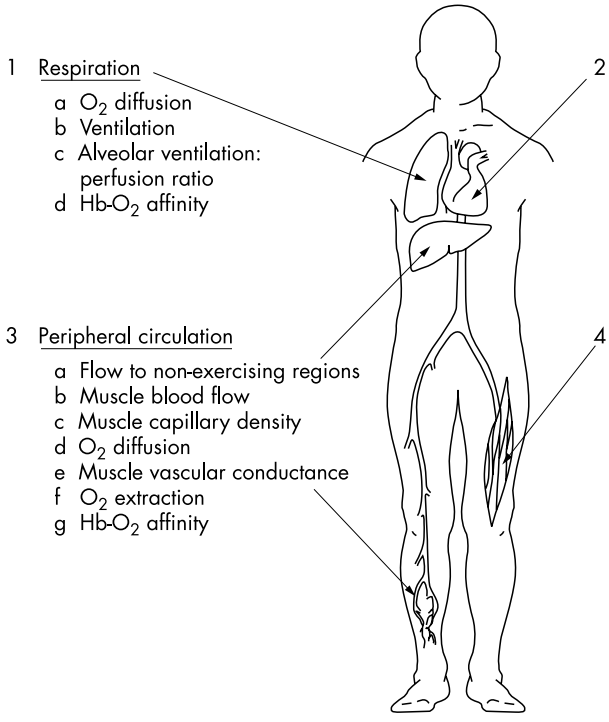

Figure 7 The classic diagram depicting the physiological factors that are believed to limit the VO_{2max}.[70 176 177] However, the (missing) factor in this diagram that clearly does ''limit the ability to increase oxygen uptake'' is the absence of the CNS, becauses, in its absence, no muscle work is possible. This model is the natural extension of the belief, implicit in Hill's original model, that it is the rate of provision of oxygen and hence of ATP that determines exercise performance. However, this diagram is valid only if all the motor units in the active limbs are active during maximum exercise. If this is not the case, then the recruitment of additional motor units might further increase the VO_{2max}, showing that skeletal muscle recruitment regulates the rate of ATP use and hence the VO_2 during maximal exercise in humans, in which case, the real regulator of skeletal muscle function during maximum exercise is not the rate of ATP production but rather the number of actin and myosin cross bridges that are formed in response to the calcium released into the myoplasm consequent to neural recruitment by the CNS. Respiration is in kg/min.

level.[194] Furthermore, increasing the oxygen content of the inspired air during exercise at altitude improves performance by increasing EMG activity in the exercising limbs.[194] As a result the authors conclude that: ''These results suggest that during chronic hypobaric hypoxia, the central nervous system may play a primary role in limiting exhaustive exercise and maximum accumulating of lactate in blood''.

However, the key finding is that fatigue during maximum exercise at altitude occurs in the absence of peak EMG activity and hence complete motor unit recruitment. Accordingly, as discussed in the previous section, this form of fatigue cannot result primarily from the factors shown in fig 7 except in the manner in which they might provide afferent sensory information to a postulated ''central governor'' in the brain.[40 139] This finding also allows a more probable interpretation of the studies of Calbet *et al*,[164 181] who showed that subjects terminated exercise at a lower maximal cardiac output in acute severe hypoxia than during exercise in normoxia. However, sudden exposure to hyperoxia at the point of exhaustion during maximal exercise in hypoxia rapidly reversed the fatigue, a finding originally described by Kayser *et al*.[194] Furthermore, a period of acclimatisation to altitude sufficient to increase blood haemoglobin content and hence arterial oxygen content did not influence exercise performance during acute hypoxia. In contrast, sudden exposure to hyperoxia at the point of exhaustion essentially normalised exercise performance in altitude acclimatised subjects, as was also the case prior to acclimatisation. Accordingly, the authors concluded that it was the reduction in arterial PO_2 and its rapid reversal on exposure to hyperoxia that regulated exercise performance in these experiments. As they did not measure skeletal muscle recruitment patterns with electromyography during exercise, they may have missed a logical explanation for these findings,[188] namely, that incipient brain hypoxia may reduce skeletal muscle motor unit recruitment, as found in the experiments of Kayser *et al*,[194] according to the concept of the central brain governor.[40 139 188]

In a second series of experiments, Peltonen *et al*[215] showed a strong correlation between the reductions in maximum workload and maximum cardiac output during maximal exercise in acute hypoxia, suggesting that a hypoxia induced reduction in the extent of motor unit recruitment would explain both the lowered maximum cardiac output and maximum oxygen consumption in acute hypoxia. They have also shown that EMG activity in the exercising muscles falls during repeated maximal strokes interposed in a simulated 2500 metre maximal rowing test, and that this fall is exaggerated in hypoxia but prevented in hyperoxia.[214] These data indicate that performance during maximum exercise in acute hypoxia is constrained owing to reduced motor unit recruitment but enhanced by an increased motor unit recruitment in hyperoxia,[213] in line with the findings of Kayser *et al*[194]

Thirdly, the detrimental effects of bed rest, which are traditionally described in terms of impaired cardiovascular function limiting skeletal muscle oxygen delivery,[221 222] or to skeletal muscle atrophy as a result of deconditioning,[223] may also result from an impaired capacity to recruit the same number of skeletal muscle motor units as before bed rest. Indeed, reduced muscular strength after bed rest is associated with reduced skeletal muscle EMG activity, suggesting that bed rest impairs motor unit recruitment.[224] This reduced EMG activity can be prevented by exercise training during bed rest. Others have also shown that untrained persons are unable to fully recruit all available motor units,[138 225] and that strength training increases the extent of skeletal muscle recruitment during a maximal voluntary contraction (MVC).[226]

Fourthly, contrast shifts in magnetic resonance (MR) images induced by exercise indicate that only between 40–90% of all the motor units in the different lower limb muscles are recruited during progressive horizontal or uphill running to exhaustion.[227 228] In contrast, the much higher rates of work achieved during the Wingate test are associated with EMG activity equivalent to that achieved in an MVC.[229]

Similarly, exhaustion during sustained contractions at 20% of a maximal voluntary contraction (MVC) occur when the neuromuscular activity in the exercising muscles is less than 30–50% of that measured during an MVC.[230] This suggests that less than 50% of the available motor units are active at exhaustion in this particular form of exercise. In addition, the classic studies of Ikai and Steinhaus[137] showed that a number of ''psychological'' interventions, including hypnosis, shouting, and loud and unexpected gunshots could substantially increase a ''maximum'' MVC effort. Consequenctly, they concluded that motor unit recruitment is submaximal even during a supposedly maximal MVC effort that would be expected to produce a greater EMG response than does progressive maximal exercise to exhaustion.

Finally, the common finding that the venous blood draining from maximally exercising muscle has a much higher PO_2 than does coronary sinus blood could be explained by incomplete muscle fibre recruitment in skeletal muscle but not in the myocardium, in which ''recruitment'' is always maximal.

In summary, there is no conclusive evidence that all the available motor units in the exercising limbs are recruited at the VO_{2max} during whole body exercise in normoxia or indeed during a supposedly maximal MVC when the muscle force output is likely to be substantially greater, but there is conclusive evidence that all available motor units are not recruited during maximum exercise in simulated hypoxia.[137 194 213]

Without evidence for maximum muscle recruitment at exhaustion during maximum exercise, it is not possible to conclude (*a*) that the central nervous system plays no part in determining the maximal exercise performance[138] and that (*b*) all the potential limitations can be defined exclusively in terms of those cardiovascular and metabolic factors depicted in fig 7 and without any possible contribution from the central nervous system.[137 139 141]

The fifth hallmark requirement: fatigue must always develop when a similar level of peripheral (inhibiting) metabolites has been reached

This prediction would seem to be disproved by (*a*) the lactate paradox of high altitude showing that fatigue occurs at different blood lactate concentrations during exercise at different altitudes above sea level (fig 5); (*b*) the finding that patients with chronic diseases also terminate exercise at low blood lactate concentrations[37 231–233] (table 2); and (*c*) the corollary finding that interventions such as exercise training,[232] glucose provision in McArdle's syndrome,[27] or oxygen therapy in chronic obstructive pulmonary disease[203] (fig 6) allow higher blood lactate concentrations and higher work rates, and hence a greater skeletal muscle motor unit recruitment after the intervention. Similarly Calbet *et al*[181] found that subjects acclimatised to altitude terminated exercise at significantly higher blood lactate concentrations during exhaustive exercise when the inspired air was suddenly switched from a hypoxic to a hyperoxic mixture at the point of exhaustion in hypoxia. Conversely, acute anaemia[209 234] causes exercise to terminate at lower blood lactate concentrations than was the case before the intervention. Hence, all these studies dissociate a specific blood or muscle lactate concentration and the onset of fatigue.

Studies of high intensity exercise also show that different interventions produce fatigue at different blood lactate concentrations in the same subjects,[235 236] such that ''considerable inter-individual differences must exist in the pH sensitivities of the various processes involved'', thus ''if acidosis makes any contribution to the fatigue during performance of this (high intensity) type of exercise, it is an indirect one…..''.[236] Elevated blood lactate concentrations also do not contribute to the slow component of the rise in oxygen consumption during high intensity exercise and hence to any possible effect that this may have on the fatigue process.[237] More significantly, the study of Nielsen *et al*[29 238] would seem to show that lactic acid enhances rather than inhibits skeletal muscle contractile function when the extracellular potassium concentrations are also high. This would be most probable if lactate is one of the preferred fuels for skeletal muscle metabolism[239] as it is for cardiac muscle when extracellular lactate concentrations are elevated, for example during high intensity exercise.[143] It seems paradoxical that the same substrate that is the preferred fuel for the maximally working (lactophilic) heart is supposedly toxic to the maximally working (lactophobic) skeletal and respiratory muscles (fig 2).

The sixth hallmark requirement: fatigue must always be absolute

If it is the accumulation of metabolites in the active muscles that causes fatigue, then their progressive accumulation must lead to the onset of an absolute fatigue, which requires a period of recovery and metabolite removal before exercise can again begin.[240] This forms the basis for studies evaluating the effects of different recovery periods on metabolism and exercise performance because it is presumed that the two are causally linked.[241–244] However, all these studies clearly show that fatigue is not absolute as, regardless of the level of exhaustion, exercise can always be continued in a subsequent bout, albeit at a lower exercise intensity, regardless of how soon after the initial bout that exercise is performed. Indeed, the study of Hargreaves *et al*[244] found that performance was the same in the first and final bouts of exercise, regardless of the amount of exercise undertaken in between, suggesting the presence of an anticipatory pacing strategy[100 245–249] that regulated the exercise intensity throughout the entire exercise bout or, indeed, over many consecutive bouts of exercise.[250] In fact, it is a common observation that even the most exhausted marathon runner can, at any time, choose to walk rather than to continue running. Hence, those metabolites that are believed to cause peripheral fatigue must have only a partial effect. To our knowledge, no one has yet chosen to explain how such ''constrainers'' act only partially.

Furthermore, as discussed subsequently, the absolute fatigue requirement is clearly at variance with what actually happens during competitive sport, in which athletes adopt a pacing strategy such that they usually speed up in the last 10% of the race;[17] the ''end spurt'' phenomenon.[251] The metabolite based, absolute fatigue theory is completely at variance with this common observation of an end spurt in all forms of exercise in which the duration or distance of the activity is already known prior to the onset of exercise.

Summary

It is clear that the six hallmark requirements of the cardiovascular/anaerobic/catastrophic model are at variance with both the published evidence and some common observations. This indicates that this particular model cannot be considered the sole explanation for fatigue during this form of exercise, thus additional or alternate explanations need to be considered. In particular, the evidence that skeletal muscle recruitment is submaximal at the point of fatigue during maximal exercise both at sea level[227 228] and to an even greater extent in extreme hypoxia;[139 194] the absence of any evidence for skeletal muscle ''anaerobiosis'' during maximal exercise under any conditions yet studied;[68 146 156 157] the absence of evidence that metabolites, especially lactate, regulate skeletal muscle function through their peripheral effects;[29 238] the absence of any evidence for a catastrophic failure of homeostasis during maximum exercise in profound hypoxia[164 181 190 197] (fig 5); and the finding that the VO_{2max} can be reduced by a drug that increases the perception of effort during exercise without altering blood lactate concentrations[141] all indicate that there is no longer any sustainable scientific foundation for Hill's original cardiovascular/anaerobic/catastrophic model of exercise physiology (fig 2).

Rather, all the current evidence is explicable according to a model in which the CNS, through a system of feedforward control modifiable by afferent sensory feedback from a variety of organs in the body, regulates the number of motor units that are active at any time: the central governor model.[40] The goal of such regulation then becomes the maintenance of homeostasis,[37] the opposite of the ''catastrophe'' model of Edwards.[4] Furthermore, the finding that non-circulatory factors contribute to the symptoms of heart failure[252] has led to the theory that morphological abnormalities in skeletal muscle may contribute to the impaired performance and exercise related symptoms in cardiac and other chronic diseases,[230 231 253] but it is more probable that, as is the case in healthy subjects at extreme altitude, a reduced skeletal muscle recruitment, consequent perhaps to the physiological effects caused by these morphological changes, explains the lactate paradox of disease.

To strengthen these arguments and further to explain the predictions of this novel model, we next evaluate the logical limitations to the currently popular ''catastrophe'' explanations for fatigue that occurs in exercises of other durations and intensities.

THE ''LIMITATIONS'' OR ''CATASTROPHE'' MODEL OF FATIGUE DURING MAXIMAL ''ANAEROBIC'' EXERCISE LASTING 10–90 SECONDS

Maximum exercise lasting 10–90 seconds is usually used to measure the ''anaerobic'' exercise capacity, according to the unproven theory that this capacity determines performance under these conditions. In particular, it is believed that fatigue results from the inability to generate ATP sufficiently rapidly to sustain a high power output for the duration of the activity. The assumptions that define this model have allowed the construction of a popular diagram indicating the maximum rates of ATP generation from the different metabolic pathways during exercise of different intensities and durations (fig 8).

Thus fig 8[254] is constructed according to a model that proposes that the high initial rates of power output during ''anaerobic'' exercise are sustainable only because the rates of ATP production from phosphagen breakdown are sufficiently rapid to sustain the very high energy requirements of the explosive power released during the initial seconds of such exercise. Thereafter, the contribution of glycolytically produced ATP become increasingly important, until oxidative metabolism becomes the most important source of ATP generation in exercise lasting more than 2 minutes. Thus, the basis for this diagram is the theory that a progressive reduction in the rate at which the different metabolic pathways can generate ATP explains the inexorable reduction in the power output that occurs after the first few seconds of such all out ''anaerobic'' exercise.[255]

However, there is no independent proof that the high rates of power output achieved during ''anaerobic'' exercise are determined exclusively by the limiting rates at which ATP can

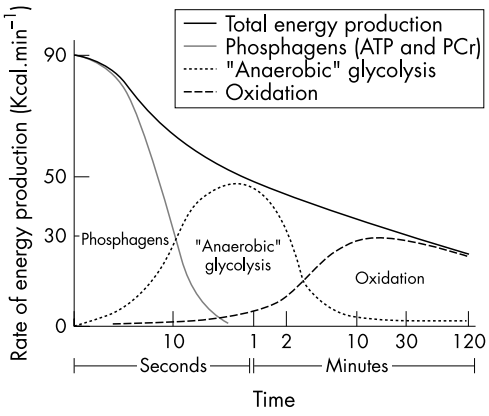

Figure 8 As it is implicitly believed that the rate of ATP delivery regulates maximal skeletal muscle function (fig 7), the energy supply/energy depletion model predicts that the decline in the power output with increasing duration of maximal exercise is determined by (and can therefore be used to predict) the rate of ATP generation from the different metabolic pathways. Thus it is believed that the highest rate of work achieved in the first seconds of exercise is the result of the high capacity for ATP generation from the phosphagens. There is now good evidence that oxidative metabolism can reach a maximum within as little as 50 seconds[257] and that ''anaerobic'' glycolysis also reaches peak values within a much shorter period than depicted in this diagram. There is no independent verification that rates of ATP production directly regulate skeletal muscle performance in the manner that this model predicts, however, a method for homeostatic regulation of muscle ATP concentrations must exist. The central governor model predicts that the extent of motor unit recruitment by the CNS must be regulated specificially to ensure that muscle ATP depletion and muscle rigor does not occur in any form of exercise. Based on figure of Howald *et al*.[254]

be generated from the different metabolic pathways. Indeed this theory would appear implausible for two reasons. Firstly, skeletal muscle rigor, not fatigue, should be the final outcome of any process in which the rate of ATP production is less than the rate of ATP use. Secondly, there is clearly a major aerobic component to this form of exercise as skeletal muscle deoxygenation occurs to a much greater extent in the Wingate test than in a maximal exercise test used to measure VO_{2max} (fig 4). It is perhaps therefore not surprising that three recent studies essentially disprove the hypothesis that exercise performance in the Wingate test is determined solely by the rate of ''anaerobic'' energy production.

Weyand *et al* found that all out sprint running performance lasting 15–60 seconds was unimpaired in hypoxia (13% O_2) and that rates of ''anaerobic'' energy production were increased in hypoxia to compensate for the reduced aerobic ATP production. They concluded that: ''Our results also pose a challenge to metabolic explanations for the decreases in maximal running speed that occur with increases in the duration of all out runs…. Our results indicate that rates of anaerobic ATP resynthesis are not truly maximal during normoxic sprint running. Therefore, decreases in maximal running speeds that occur with increases in sprint time cannot be explained simply by concomitant decreases in maximal rates of anaerobic metabolism'' (p. 2063[256]).

Calbet *et al*[163] studied high quality sprint and endurance cyclists who also performed the Wingate test in normoxia and hypoxia. They made four crucial findings: (*a*) that the rate of oxygen consumption (VO_2) increased rapidly, reaching ~60 ml O_2/kg/min or approximately 83% of the VO_{2max} within the first 25 seconds of ''anaerobic'' exercise, a result that clearly conflicts with the predictions of fig 8; (*b*) the performance of endurance cyclist was the same in hypoxia and normoxia, indicating that total ATP production was not reduced in hypoxia; (*c*) the rate of ''anaerobic'' ATP production was increased to compensate for the reduced rate of oxidative ATP production in hypoxia, as also found by Weyand *et al*[256]; and (*d*) the performance of sprint cyclists was impaired in hypoxia; remarkably, this impairment was present within 2 seconds of the onset of exercise[163] (fig 1; p 671) and must therefore have occurred before a significant metabolic error signal had developed.

This study leads to the following conclusions:

1. The Wingate ''Anaerobic'' test is not purely an ''anaerobic'' test, as at least 20–30% of the energy utilised during the test comes from aerobic sources. An unmeasured amount must also come from oxygen stored within the muscle, which is rapidly depleted in this type of test[156 157] (fig 4). Indeed, Bangsbo *et al*[257] have shown that oxygen uptake can reach maximum values within 50 seconds of the onset of intense dynamic exercise. Astrand and Saltin[45] were perhaps the first to appreciate this when they showed in 1961 that exercise at 2700 kpm/min elicited the same VO_{2max} as did exercise at 1800 kpm/min but within 1 minute compared with the 5 minutes required at the lower work rate. Indeed, a recent study found that a 60 second Wingate test produces the same VO_{2max} as does the conventional method of testing.[133] This is clearly paradoxical. How can an extended ''anaerobic'' test be used to measure the maximum aerobic capacity? Perhaps this finding suggests that aerobic and oxygen independent glycolytic (anaerobic) metabolism are inextricably linked as a consequence of the CNS determined skeletal muscle fibre recruitment and the action of the ''glycogen shunt''[28] and the ''lactate shuttle''.[174] Perhaps this capacity for oxygen independent energy production represents that vestigial reptilian metabolism needed for rapid energy production during the flight response.[258]
2. Performance during the ''anaerobic'' Wingate test cannot be limited by the rate of ''anaerobic'' ATP production in normoxia, as higher rates can be achieved during hypoxic exercise. Thus a reserve capacity for ''anaerobic'' ATP production exists that is not fully activated during exercise in normoxia, as also shown by Weyand *et al*[256]
3. As a consequence, the rate of total ATP production also cannot limit performance in this test because there is clearly reserve capacity for ATP generation during maximal testing in normoxia.
4. As the reduced exercise performance of sprint cyclists in hypoxia is present within the first 2–3 seconds of exercise, this cannot have resulted from metabolites acting directly within the exercising muscles. Rather it must result from some form of anticipatory process,[100 245 251] analogous to that present during exercise in the heat.[259 260]

More importantly, the study of Calbet *et al*[163] provides the crucial evidence that disproves the fundamental basis for the model, depicted in fig 8, and which holds that the exponential fall in power output during the Wingate test occurs because the rate of ATP production is always less than the rate of ATP use. Instead, the clear evidence is that control mechanism(s) exist to ensure that there is metabolic reserve in this model and it is this reserve that ensures that muscle ATP concentrations do not fall progressively, leading ultimately to muscle rigor. In particular, there must be an anticipatory mechanism to ensure that the work output and hence the rate of ATP use equals but does not exceed that which can be sustained by the maximal rate of aerobic ATP production within 50–60 seconds of the onset of maximal exercise.[133 257] This anticipatory component to this test[245] would explain how exposure to acute hypoxia might impair

the exercise performance of sprint cyclists, essentially from the onset of the Wingate test.[163]

Although unrecognised by them, the study of Calbet *et al*[163] also clearly establishes the nature of that anticipatory control process, as the regulation of power output in this model is expressed through a change in pedalling cadence (revolutions/min), which determines the change in power output in the Wingate test and which begins to decline after the first 7–8 seconds of exercise (fig 9). There are two broad mechanisms that might explain this progressive fall in power output resulting from this progressive fall in cadence; either there is a reduced rate of motor unit recruitment by the central nervous system (the concept of muscle wisdom[261 262]), or the rate of recruitment stays the same but the peripheral nervous system, including excitation/contraction coupling within the active skeletal muscles, becomes increasingly refractory to such constant stimulation. To our knowledge, no one has yet offered a possible mechanism for this latter effect, which would have to be extremely effective, as cadence drops by about 50% during the Wingate test (fig 9).

Rather, as cadence falls rapidly, beginning within the first 5 seconds of exercise and in a clearly regulated as opposed to a random effect, it seems logical to assume that the regulation of cycling cadence can only be regulated centrally in the motor cortex, particularly as the reduction in cadence requires a co-ordinated reduction in the actions of the vastus lateralis and biceps femoris muscles,[263] which are not likely to be performing identical amounts of physical work. Thus, performance in the Wingate test seems to be another example of central regulation of motor unit recruitment in order to maintain homeostasis and to prevent peripheral organ damage, in this case the development of skeletal muscle rigor consequent to ATP depletion in the maximally exercising muscles.

The finding of Hunter *et al*[229] that the total EMG activity during consecutive 5 second bouts approaches values measured during an MVC and does not fall during the 30 second Wingate test, despite the close to 50% reduction in power production and in pedalling cadence, would, at first sight, seem to suggest that central neural drive remains unchanged

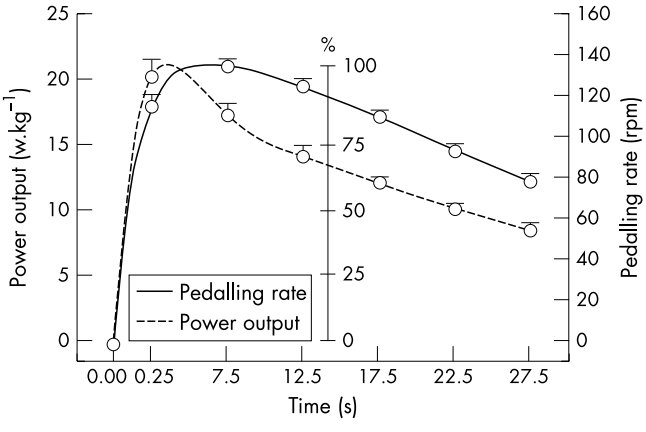

Figure 9 It is believed that power production in the Wingate ''anaerobic'' test is limited by the rate of ATP production in the active muscles according to the logic of fig 8. However, the fall in power production in this testing procedure is determined by the 43% reduction in pedalling cadence from 140 to 80 cycles/second. This 43% reduction in cadence can occur only because of either (*a*) a progressive and regulated reduction in the rate of motor unit recruitment by the CNS, or (*b*) a progressive failure of skeletal muscle excitation/contraction coupling so that the same rate of CNS motor unit recruitment produces a progressive decline in the rate at which the same or fewer motor units are actively recruited in the exercising muscles. The original Hill model (fig 2) does not provide for this latter possibility. Figure from data of Calbet *et al*[163]

and that peripheral mechanisms must explain the reduction in power output.[263] However, the ~50% reduction in cadence would indicate that the active limbs were generating force for ~50% less time at the end than at the start of the test. If EMG activity were the same, then substantially more motor units must be recruited at the end than at the beginning of the Wingate test. Thus, this finding implicates a central regulation of motor unit recruitment with the initial recruitment of a smaller number of fast contracting fibres contracting more frequently at the outset of the Wingate test, with their progressive replacement by a larger number of slower contracting fibres contracting less frequently as the test progresses and the power production and cadence falls. The study of Vandewalle *et al*[263] found that EMG activity particularly fell after 30 sec of a 40 sec Wingate test, compatible with the adoption of a pacing strategy once the exercise duration exceeds ~30 seconds.[245]

The study of Ansley *et al*[245] most clearly establishes the role of the CNS regulation of power output during the Wingate test. They showed that subjects who were misinformed that the duration of the Wingate test was actually 36 seconds and not the 30 they had been told developed a significant reduction in power output between 33 and 36 seconds. This effect was not present when subjects were honestly informed that the true duration of a subsequent test was indeed 36 seconds. Hence this effect could only have resulted from an error message generated in the CNS when it became aware after about 33 seconds that the real exercise duration exceeded the anticipated exercise duration. As the subjects were observing a clock that, unbeknown to them, was running 20% slower in the 36 second deception trial, this error signal was generated even though their conscious brains were receiving information that agreed with what they had been told but that must have conflicted with internally generated sensory feedback.

Finally, one of the concerns with the Wingate test is that the curve of a rapid and progressive fall in power after the first 5 seconds of exercise (fig 9) is clearly specific for only one form of exercise–that is, exercise in which the body is not supporting its own body weight, as when humans must carry their own weight, for example in running, they do not show this dramatic (>50%) and progressive fall in power output during the first 20–30 seconds of exercise, as is clearly shown by observing the running speeds of athletes completing sprint races of 100–400 m.[264] Because humans have the same capacity for power output, whether they sprint on a bicycle or sprint on a running track, this fundamentally different exercise response must indicate that some variable other than the rate of ATP production alone regulates sprinting speed in weightbearing activities and that this regulation is not present, at least initially, in non-weightbearing activities such as the Wingate test. One possibility is that weightbearing activities provide additional afferent sensory information to the CNS that is not present in non-weightbearing activities, and that this information influences the nature of the muscle recruitment patterns that are produced during the different forms of exercise.

In summary, there is now good evidence that the Wingate test is not an exclusively ''anaerobic'' test that is limited by the capacity to generate ATP by the different metabolic pathways. Rather, the clear evidence is that the rates of ATP generation are submaximal,[163 256] indicating the presence of metabolic reserve even though muscles achieve much higher levels of deoxygenation during the Wingate test than during a progressive maximal exercise test to exhaustion, levels usually found only in complete ischaemia (fig 4). Despite severe hypoxia, muscle power output is higher during a Wingate test than during other forms of maximal exercise testing that do not produce such hypoxia, thus, as argued in

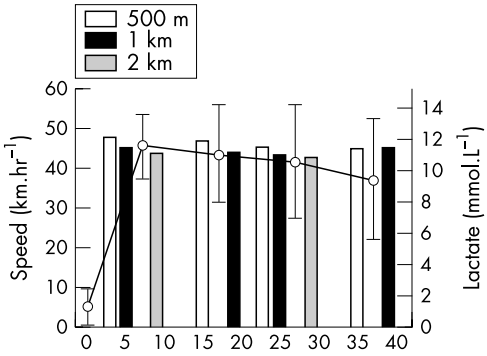

Figure 10 Some theorise that the adopted pace during selfregulated exercise, for example, cycling time trials, is chosen specifically to maintain constant blood and muscle lactate concentrations and a consistent blood pH. The study of Schabort *et al*[265] showed that blood lactate concentrations (solid line) peaked within the first 7 km of a 40 km laboratory cycling time trial and fell thereafter with blood pH showing the opposite response (data not shown). Cycling speed at a series of interposed 0.5, 1, and 2 km sprints (columns) fell progressively during the first 35 km of the time trial despite falling blood lactate concentrations, but increased in the final 1 km sprint at 39 km, the end spurt phenomenon[251] (see also figure 11). The ingestion of a buffering agent, sodium citrate, before exercise altered the blood lactate concentrations and pH during exercise without altering the pacing strategy or overall cycling performance (data not shown). From data of Schabort *et al*[265] for subjects who ingested 0.2 g/kg sodium citrate before exercise.

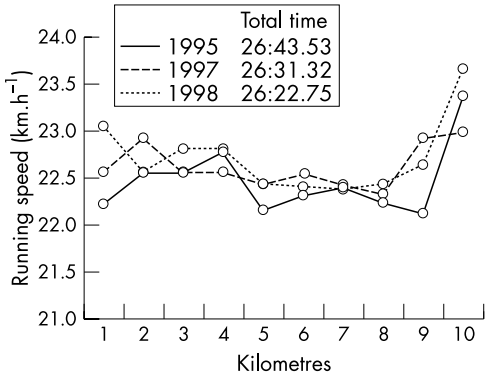

Figure 11 Running pace (km/h) at each kilometre of the world 10 000 m record holder in three world record performances. Note that the chosen pace is adopted early, within the first kilometre, and that the speed is greatest in the last two and especially in the final kilometre of the race, the end spurt phenomenon, as is also apparent in fig 10. As a result, speed in the last 2 km is the factor that distinguishes the progressively improving records from 1995 to 1998. The Hill model is unable to explain this end spurt phenomenon[251] as, in the example of a world record performance at this distance, the athlete should be running continuously at a speed above his ''anaerobic threshold''.[273] This should cause a progressive increase in the blood lactate concentration and hence, according to the Hill model, a progressive fall in running speed, the opposite of what is observed. The more likely explanation is that changes in pace result from changes in the number of motor units that are recruited; more when the pace is faster, fewer when the pace falls.[274]

detail here, the marked fall in cadence that characterises this form of exercise testing (fig 9) is not likely to be the result of peripheral skeletal muscle regulation but of an altered anticipatory skeletal muscle recruitment by the CNS.[245]

THE ''LIMITATIONS'' MODEL OF FATIGUE DURING EXERCISE LASTING 20–60 MINUTES

Fatigue during exercise of this duration is difficult to explain according to any peripheral model of exercise regulation because rates of ATP production are lower than during high intensity exercise of short duration; blood (fig 10) and presumably muscle lactate concentrations rise early in this form of exercise before falling progressively thereafter despite increasing perceptions of fatigue.[265] Furthermore the activity terminates before absolute muscle glycogen depletion occurs.[28 32–34 266] Especially interesting is the clear observation that the best athletes are able to increase their energy expenditure for the last ~10% of this type of exercise, the end spurt[251] phenomenon that exists in all forms of human endeavour in which the duration of exercise is known before the activity commences so that a pacing strategy can be adopted.[246] Indeed, the study of Rauch *et al*[267] showed that subjects were able to produce their highest power outputs during the last minute of a 60 minute cycling performance trial that followed 150 minutes of exercise at 75% VO_{2max}. This proves that glycogen depleted muscle retains the capacity to increase its power output at the end of very prolonged exercise that is sufficient to produce severe symptoms of fatigue. This effectively dissociates muscle glycogen depletion as a cause of ''peripheral fatigue'' and emphasises the emotional construct of fatigue.[226 240 268]

For example, fig 11 shows the speeds (km/h) achieved during each consecutive kilometre of world 10 000 m record holder, Haile Gebrselassie, during his three world record performances in 1995, 1997, and 1998. There are two crucial observations. Firstly, his pacing strategy is clearly apparent within the first kilometre of each race and varies only slightly from kilometres 1−9. Secondly, in all events his fastest pace is always achieved in the final 2 kilometres of each race. Importantly, this end spurt is also clearly evident in laboratory trials in which athletes selfselect their own paces for the duration of the exercise,[247 249 260 265 267 269 270] showing that it is a universal phenomenon.[251] However, neither of these overt phenomena – the early adoption of the pacing strategy and the end spurt – can be explained according to the traditional cardiovascular/anaerobic/catastrophic (peripheral) model of fatigue. For example, a popular biological explanation for the pacing strategy adopted during running is the following: ''Your marathon pace is very close to your lactate threshold pace, which is determined by your oxygen consumption at your lactate threshold and your running economy. If you run faster than your lactate threshold pace, then lactate accumulates in your muscles and blood; this occurrence deactivates the enzymes for energy production and makes you slow down''.[271]

Similarly, medical biologist, Arctic explorer, and marathon runner Michael Stroud, echoing the words of Webster[21] six decades earlier, has written: ''But if high levels of work are sustained for more than a few second, the lactic acid formed from this process begins to accumulate. This poisons several enzyme systems, including the one splitting glucose from glycogen. Within a 100 metre race, such lactic acid effects hardly matter, but go on for more than 200 metres and even top class sprinters begin to falter. It is lactic acid buildup that explains why world records for 100 metres are well under ten seconds, for 200 metres are less than twenty, but for 400 metres are around 43 seconds and for 800 metres close to 100 seconds'' (p. 42[272]). Furthermore: ''When most of us run hard, even for a few seconds, we rapidly feel our legs turning to jelly as the lactic acid builds up'' (p. 43[272]).

However, peripheral metabolite accumulation cannot explain an early choice of pace, as that pace is well established within the first kilometre of each race (~150 seconds after the onset of vigorous exercise) and perhaps within the first few hundred metres, and therefore too soon for the presumed pacing metabolites in muscle and blood to have reached a steady state. Rather, the rapidity with which any pacing strategy is adopted and subsequently modified suggests the presence of a CNS control.

Then there is the remarkable observation that this world record holder runs the fastest when he should be the most tired—that is, in the last kilometre of all his world record performances. Furthermore, as Gebrsellasie is likely to be running at intensities of close to 95%VO_{2max},[273] almost certainly in excess of his ''anaerobic threshold'', there should be a progressive accumulation of muscle and blood lactate concentrations through the 10 000 m, yet when muscle and blood lactate concentrations are presumably at their highest concentrations in the final 2000 m of the race, Gebrsellasie runs his fastest. Indeed, as Gebrsellasie increases his pace during the last 2000 m of the race, clearly he runs with ''metabolic reserve'' in the first 8000 m of these races, indicating that his speed during the first 8000 m must be ''constrained'' by something other than metabolite accumulation in his active muscles. As he must recruit fewer than all his lower limb motor units during this submaximal exercise (see fourth hallmark prediction), the logical explanation is that the changes in his pace are due to a constantly changing number of motor units that are recruited during the race with the greatest (but still submaximal) recruitment when he runs the fastest in the last 2000 m of these races.[274] Conversely, the trailing athletes may be unable to increase skeletal muscle recruitment, thereby increasing their pace, as the homeostatic challenge posed by any increase in work rate may induce symptoms of fatigue that are not ''worth the effort''.[137 140 217]

Indeed, any model of peripheral metabolite regulation of the pacing strategy cannot be correct because it predicts that: (*a*) the average pace would be the same – one single universal pace – in all events regardless of distance, as there would be only one pace that does not cause muscle lactate concentrations to rise sufficiently to cause a ''deactivation'' of energy systems; but (*b*) that that pace would alternately speed up and slow down as the work rate continuously increased and then fell, in order to maintain blood lactate concentrations at the concentration immediately below that causing enzyme ''deactivation''; and (*c*) that the concentration of the metabolites causing ''deactivation'' of energy systems must be highest when the running speed is lowest, and lowest when the athlete is running their fastest. Of course, it is well known that the opposite applies, namely that blood lactate concentrations increase as a function of increasing work rate,[83 171] which essentially disproves the role of peripheral metabolites as the direct regulators of the pacing strategy.

More recently, attention has focused on the possible role of changes in neuromuscular function on changes in performance during running events lasting up to 60 minutes. Thus Paavloninen *et al*[275] found that EMG activity immediately preceding footstrike, so called muscle pre-activation, falls during a 10 km running time trial. Pre-activation influences skeletal muscle function by determining the stiffness of the muscles immediately prior to heelstrike. The authors also found that reduced muscle pre-activation was associated with longer foot contact times and slower running velocities. Furthermore, higher calibre runners showed greater muscle pre-activation but lesser EMG activity during the propulsive phase of the running stride. Subsequently these authors have shown that foot contact time is an important predictor of running ability,[276] and that a neuromuscular intervention programme emphasising explosive strength training and reduced foot contact time increased running performance without altering the traditional measures of aerobic capacity.[277] The authors concluded that neuromuscular factors under the control of the CNS, modifiable with a neuromuscular training programme, influence distance running performance.

Using the same techniques, Sharwood *et al*[278] confirmed that muscle preactivation is reduced in five lower limb muscle groups during a 5 km running time trial. This reduction was associated with a reduced stride length and a linear fall in running speed. Hence, these authors argue that a reduced CNS directed neural input to the leg muscles during running causes a reduced muscle preactivation that results in an increased transition time between the eccentric and concentric phases of the running stride. As a consequence, ground contact time is increased and the ability to store and use elastic energy is reduced, causing stride length, running speed, and running economy[277] to fall.

As pre-activation is under the exclusive control of the CNS, this finding alone indicates a previously unrecognised role of the CNS in determining running performance, independent of the extent to which the motor units in the active skeletal muscles are activated.

In summary, the presence of a pacing strategy that is established early in exercise and that varies during exercise, increasing near the end of exercise so that the highest work rate is achieved immediately prior to the termination of exercise (the end spurt) is incompatible with any exclusively peripheral model of exercise regulation. Furthermore, the finding that some of the world's best athletes improve their best performances by as much as 3% during the last 21 days leading up to and including the finals of the Olympic Games[279] suggests that all exercise testing outside of the Olympic finals may be submaximal, as perhaps anticipated by the early findings and conclusions of Ikai and Steinhaus.[137] In 1968, Wilmore[280] already showed that subjects performed significantly better (~21%) in a maximum exercise test when they competed against others of matched ability than when they exercised alone. There was no measurable physiological explanation for this difference. Similarly, exercise testing performed out of doors may elicit higher VO_{2max} values than those measured in laboratory testing.[281]

These findings can best be explained by a model in which the opportunity of setting a world record or of winning an Olympic gold medal increases the ''maximum'' work rate that can be sustained as a result of an increased motor unit recruitment by the CNS.[217 274]

As originally proposed by Lehmann *et al*,[140] it seems more probable that performance is never a fixed maximum but is rather the outcome of a psychological skirmish within the CNS between the sum of all the negative factors such as fatigue and muscle pain, and the positive factors of motivation and will power. Or as Bigland-Ritchie *et al* have written: ''The sense of effort is a major factor influencing motivation. As fatigue ensues, the increased sense of effort tends to make subjects think they can no longer drive their muscles maximally or continue to exercise at all. The ability to activate a muscle during high force contractions or to prolong endurance time is clearly improved by practice. While this process is attributed mainly to peripheral events, the greater willingness of subjects to put up with discomfort and to push themselves harder is important. This willingness is clearly enhanced if the event takes place in a competitive environment. Hence, sports records are more often broken in competitions, in which participants make a greater effort to get *psyched up*, than in practice sessions'' (p. 373[217]). The authors then discuss ways in which this atmosphere of competition can be mimicked in the laboratory in order to produce a ''maximal effort''. However as we stress in the companion paper,[240] it is not immediately apparent how, if fatigue is a purely peripheral phenomenon caused by ''poisoning'' of the exercising muscles, motivation alone can sustain the force output of those ''poisoned'' muscles.

Nevertheless, it is clearly the outcome of this conscious skirmish identified by Lehmann *et al*[140] and Bigland-Ritchie *et al*[217] between fatigue and pain on the one hand and motivation and willpower on the other that determines the

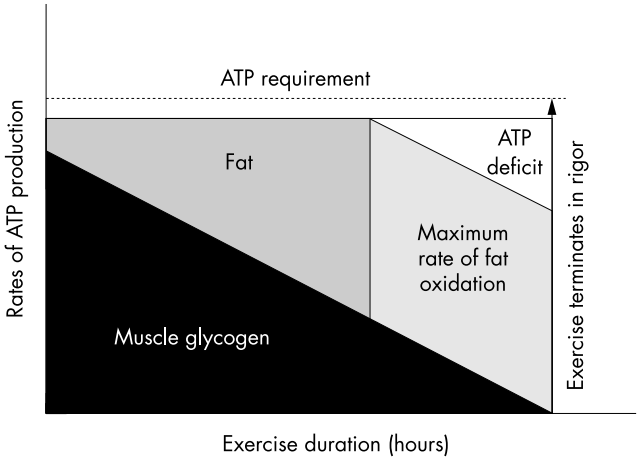

Figure 12 The energy depletion model of exercise physiology predicts that the progressive fall in muscle glycogen content during prolonged exercise reduces the capacity for ATP generation from glycogenolysis. Initially, the required rate of ATP production is appropriate for that exercise intensity and can be provided by ATP derived from the oxidation of intramuscular and circulating fat. However, once the limiting (maximum) rate of fat oxidation has been reached, a deficit in the rate of ATP generation must occur. While some argue that this reduced rate of ATP generation must cause ''fatigue'', the precise biochemical mechanism by which this occurs has not been proposed. The more logical conclusion is that, if the rate of ATP generation falls below the rate of ATP use, then the final outcome must be muscle rigor. As muscle rigor has never been described as a final outcome in mammalian exercise, this explanation is improbable. The more likely explanation is that the central governor in the CNS regulates the number of motor units that are recruited, specifically to match rates of ATP production and use, so that skeletal muscle ATP depletion and rigor do not occur (fig 13). One theoretical explanation[268] of how the central governor might pre-set the anticipated endpoint of prolonged exercise to ensure that muscle energy depletion does not occur is presented in fig 14.

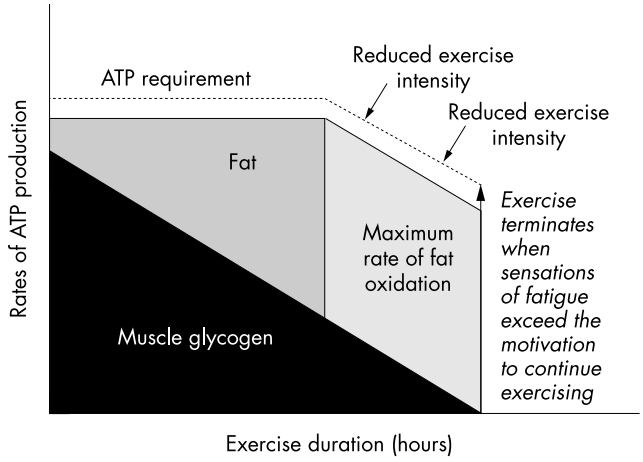

Figure 13 A progressive reduction in the exercise intensity in anticipation of muscle glycogen depletion would explain why prolonged exercise terminates without the development of either skeletal muscle rigor or glycogen or ATP depletion (figs 15 and 16). The termination of exercise might then occur when the sensations of fatigue exceed the athlete's motivation either to continue at that exercise intensity or indeed at any intensity, according to the original suggestion of Lehmann *et al*[140] that exercise may terminate ''when the sum of all negative factors such as fatigue and muscle pain are felt more strongly than the positive factors of motivation and will power''.

extent of motor unit recruitment by the CNS during a ''peak'' effort. Accordingly it is the brain that regulates the performance within the constraints of the athlete's ultimate physiological capacity.[137]

THE ''LIMITATIONS'' OR ''CATASTROPHE'' MODEL OF FATIGUE DURING PROLONGED ENDURANCE EXERCISE LASTING MORE THAN 120 MINUTES AND UP TO 8 OR MORE HOURS

The original studies of fatigue during prolonged exercise identified a role for carbohydrate metabolism, as carbohydrate ingestion either improved performance[282 283] or reversed fatigue[85 86] during prolonged exercise. In addition, performance was apparently improved during exercise that followed a high carbohydrate diet.[84 283] The common conclusion from those early studies was that carbohydrates acted by reversing or preventing the development of a premature hypoglycaemia, caused by liver glycogen depletion. However, the introduction of the transcutaneous muscle biopsy technique in the early 1960s and the classical studies of pre-exercise ''carbohydrate loading'' dramatically reversed this traditional interpretation. Thus the early studies of carbohydrate loading[87–89 91 284 285] were interpreted as evidence that it was specifically muscle and not liver glycogen depletion that was the proximate cause of fatigue during prolonged exercise. For example, a recorded interaction between Drs Hultman and Asmussen[284] identifies the logic that led to this altered interpretation:

> Dr Erling Asmussen: As I remember in the old experiments of Christensen and co-workers, working capacity was helped quite considerably by increasing the blood sugar; but apparently you put all the emphasis on the low muscle glycogen. What role, then, does the blood sugar play?
> Dr Hultman: It helps cerebral tissues, of course, but I don't think it plays any important role in the working muscle.
> Dr Asmussen: The working capacity was not restored by glucose itself?
> Dr Hultman: No, the working capacity is strictly connected to (muscle) glycogen. You can use glucose instead of free fatty acids, but you cannot use it instead of glycogen.

Note that in this discourse, Asmussen refers to a possible role for glucose in reversing a central (brain) component of fatigue, whereas Hultman's argument is that because muscle glycogen, not bloodborne glucose, is the primary fuel for muscle contraction, only an increase in muscle glycogen concentrations can reverse a peripheral, skeletal muscle fatigue. This indicates that Hultman, but not Asmussen, whose work has included studies of the central (brain) contribution to fatigue,[286] believed that fatigue occurred exclusively as the result of peripherally based phenomena. The alternative theory that glucose derived from the bloodstream might delay the onset of fatigue by acting centrally in the brain[287] was discounted and subsequently lost, despite the historic evidence from the early Scandinavian and North American scientists. As a result, the theory soon became established that muscle glycogen depletion is the most important determinant of fatigue during very prolonged exercise, an idea that continues to dominate modern teaching and research.[6 28 288] Whether or not this theory is correct, it invites speculation of the exact biological mechanism by which this effect is achieved. The currently popular explanation holds that when the concentration of glycogen in the exercising muscles falls below some ''critical''[6] concentration, the maximum rate of oxidative ATP production from the alternate fuel, fat, is insufficient to sustain the rate of ATP generation required for that exercise intensity, hence the work rate must fall to one at which the rates of ATP production and use are again in balance. Alternatively, according to the ''glycogen shunt'' theory,[27] it has been proposed that low muscle glycogen concentrations may be

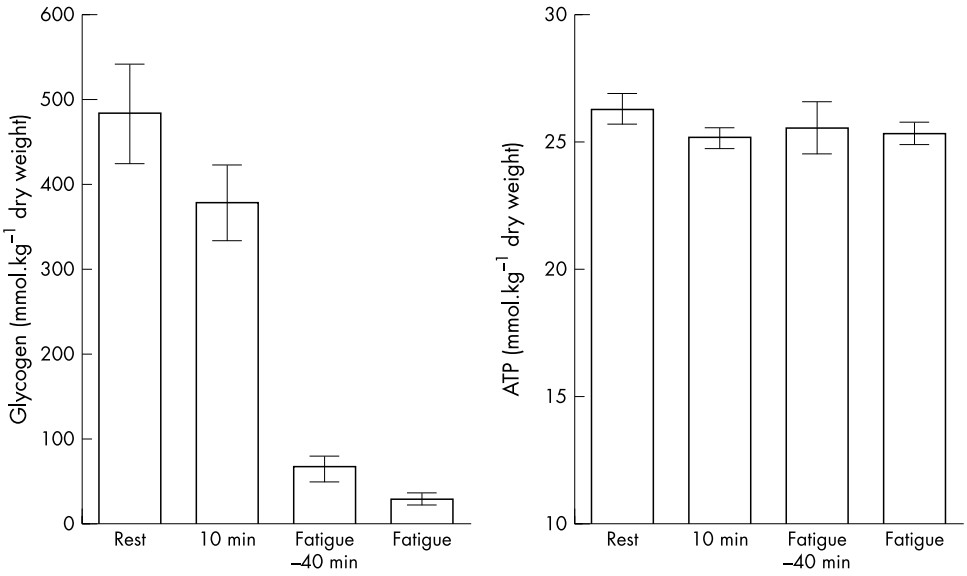

Figure 14 The study of Febbraio and Dancey[289] confirms that muscle ATP concentration (right panel) is not reduced at fatigue during prolonged exercise even though muscle glycogen concentrations fall substantially (left panel). This indicates that the muscle defends the ATP concentration even when glycogen depleted (fig 13). Note also that absolute muscle glycogen depletion does not occur. Both these findings conflict with the predictions of the ''catastrophe'' model of Edwards.[4] From study of Febbraio and Dancey.[289]

unable to provide the rapid burst of glycogenolysis necessary to produce high muscle power outputs.

In his review published to mark the 20th anniversary of these original studies, Conlee[288] wrote: ''When glycogen runs out… the muscle fails from lack of aerobic adenosine triphosphate (ATP) production. However plausible and attractive this theory is, it is unproven. …what is clear is that, in glycogen depleted muscle, ATP is being used up faster than it can be manufactured, and so force output is diminished''. In fact, what is most clear is that this explanation cannot be correct. Firstly, there is no evidence that muscle glycogen ever completely ''runs out'', rather exercise always terminates when there is still some glycogen remaining in the muscle.[28 30 32–34 289 290] Secondly, in the absence of any other influence, if the rate of ATP production during prolonged exercise falls below the rate of ATP use, then the muscle ATP concentrations must fall progressively, terminating ultimately not in fatigue but in muscle rigor (figs 12, 13), exactly as would occur in ''anaerobic'' exercise if the rate of ATP production limited such exercise in the absence of a ''constrainer'' or ''governor'' that ensures ATP homeostasis.

Indeed, numerous studies show that muscle ATP concentrations are not abnormally reduced at exhaustion during prolonged exercise[28 30 33 289 290] (figs 14, 15). Rather, they are clearly homeostatically regulated at concentrations that are appropriate for the exercise intensity. Similarly, Baldwin *et al*[30] could find no evidence that glycogen depleted muscle is metabolically ''run down'', as the total concentration of muscle tricarboxylic acid cycle intermediates at the end of prolonged exercise was not lower than concentrations measured in glycogen replete muscle, again suggesting a perfect match between the muscle power output and the rate

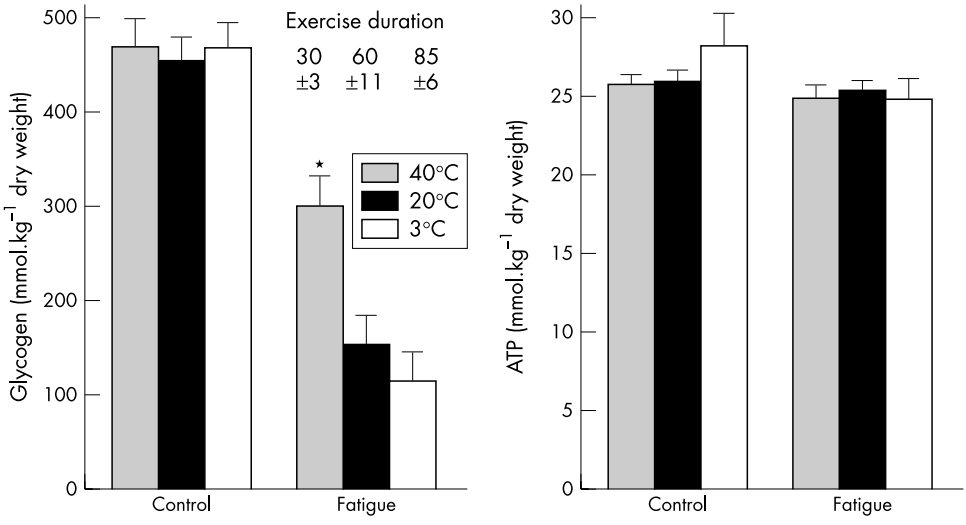

Figure 15 When prolonged submaximal exercise is undertaken in different environmental conditions (3, 20, and 40˚C), exercise terminates after different durations (85, 60, and 30 minutes respectively) and at different muscle glycogen concentrations (left panel), but at the same muscle ATP concentrations (right panel) that are not different from values measured at rest.[30] This indicates that (*a*) prolonged exercise in the heat does not terminate as a result of depletion of either muscle glycogen or ATP stores and (*b*) conversely, that muscle ATP concentrations are regulated such that fatigue always occurs without a substantive change in their concentration. The probable explanation is that exercise in the heat is regulated by the CNS to ensure that a dangerous elevation in the core body temperature does not occur.[259 260 292] From study of Parkin *et al*[30]

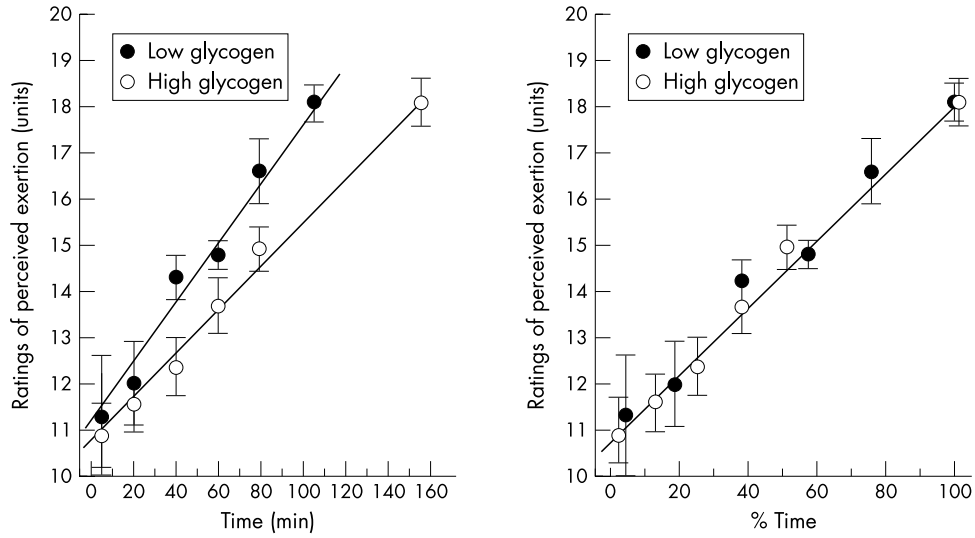

Figure 16 Left panel: the plot of rating of perceived exertion (RPE) against absolute exercise duration (minutes) shows that regardless of whether exercise begins with low or high muscle glycogen content, there is a linear increase in RPE with exercise duration. However, the rate of rise of RPE is faster during exercise that begins with low muscle glycogen content (carbohydrate depleted exercise). Note also that exercise terminates at the same RPE in both exercise conditions (right panel). When the RPEs for both exercise conditions are plotted against the percentage of total exercise time, the data fall along the same line.[268] These data suggest[268] that (*a*) the maximal RPE that can be sustained determines the time at which the decision[138 139] is made to terminate exercise, and (*b*) the rate at which the RPE increases may determine the duration of exercise specifically to ensure that total energy depletion does not occur in the active muscles during more prolonged exercise. This implies that the duration of prolonged exercise is set (by the subconscious brain) and hence is known at, or shortly after the onset of exercise. Data plotted from the relevant information in table 1 of Baldwin *et al*,[30] reproduced with the permission of *Journal of Applied Physiology*.

of energy production. Similar findings have been reported by Gibala *et al*.[32 290] These findings support the earlier conclusion of Green that: ''Although it has been popular to implicate a compromised energy status, occurring as a result of the depletion of glycogen in the muscle fiber, such a proposition is not supported by present experimental evidence'' (p. 295[34]).

Conversely, others have shown that the superior performance of high intensity exercise after carbohydrate loading cannot be explained by changes in carbohydrate metabolism in the muscle so that ''other unmeasured factors must explain differential fatigue development when the carbohydrate content of the diet is manipulated''.[290] One such ''unmeasured factor'' might be the capacity to recruit a larger number of motor units in the active muscles in anticipation of their being greater energy reserves for the upcoming exercise.[267] The study of Parkin *et al*[33] is especially interesting, as fatigue developed after different durations of exercise as a result of the different environmental conditions imposed during the different trials. Most importantly, during exercise in the hottest environmental conditions, fatigue developed in the absence of either muscle glycogen depletion or a reduction in muscle ATP concentrations (fig 16). The conclusion has to be that under those conditions, exercise terminated as the result of the actions of a central (brain) regulator as originally predicted in the JB Wolffe lecture,[37] and since confirmed experimentally.[260 292]

Thus, if there is indeed a limiting rate of ATP production from the oxidation of fat in glycogen depleted muscle (fig 13), some other mechanism must still exist to match the rates of ATP production and use so that the maximum (limiting) rate of ATP production from fat oxidation (if indeed such a physiologically relevant limit does indeed exist), is never exceeded and the muscle does not become metabolically derelict. Hence, just as A V Hill recognised the need for a central governor to protect the heart from myocardial damage when the cardiac output reached its ''plateau'' value, so another governor or governors must exist to match the rates of ATP production and use under all exercise conditions. According to this theory, what appears to be a limiting rate of fat oxidation during prolonged exercise may instead result from the actions of central or peripheral governors or both, the function of which is to reduce progressively the sustainable work rate during prolonged exercise, specifically to ensure that the rate of ATP use never exceeds its peak rate of production. This contrasts with explanations based on the traditional ''limitations'' or ''catastrophe'' models, which hold that the rate of ATP production limits its rate of use and hence determines the power output of the active muscles (fig 8).

Accordingly, the point is that, as muscle rigor does not develop during prolonged exercise, so the rate of ATP production cannot be less than the rate of ATP use. Rather, both rates must be matched by either a centrally controlled, anticipatory neural mechanism that modifies the number of motor units that are recruited, or as the result of a direct peripheral effect of the falling muscle glycogen concentrations; a peripheral ''governor''. The ''glycogen shunt'' mechanism[27] would indeed provide a direct link between the available muscle glycogen stores and the rate of ATP production, hence acting as a ''peripheral governor'' or ''glycostat''.[267]

The result of either mechanism would be a reduction in muscle force production and hence in the rate of ATP use. Presently there is good evidence for a central determination of muscle force output as a consequence of the number of motor units that are recruited during prolonged exercise.[293–298] This mechanism ensures that the achievable work falls progressively as the exercise is prolonged and muscle energy depletion threatens (fig 13).

Hence the findings of all these studies are also compatible with the interpretation that a ''governor'' or ''controller'', situated principally but not exclusively in the CNS, must exist to reduce the number of motor units that are recruited during prolonged exercise, thereby matching the rate of ATP use by the exercising muscles to the rate of ATP supply. This mechanism becomes especially important as muscle glycogen concentrations fall during prolonged exercise. If the rate of oxidative ATP production from fat is indeed unable to substitute for any shortfall in total ATP production in

glycogen depleted muscle, then this mechanism of central regulation would explain why neither muscle rigor, muscle ATP depletion, nor total muscle glycogen depletion (figs 14 and 15) has ever been recorded in exercising humans even though this is the sole logical prediction of the ''catastrophe'' models of exercise physiology.

The recent observations:[268] (*a*) that the rating of perceived exertion (RPE) rises as a linear function of exercise duration at a fixed work rate (fig 16); (*b*) that exercise terminates at the same peak RPE (fig 16); and (*c*) that the rate of rise of RPE is a function of the starting muscle glycogen concentration (fig 16) raises the interesting possibility that, at the onset of prolonged exercise, on the basis of some carbohydrate signal that is increased after a carbohydrate rich diet, the subconscious brain calculates the anticipated duration of the exercise that can be safely sustained without causing absolute, whole body energy depletion. Anticipating the maximal RPE that it will tolerate, the brain centre responsible for the generation of the RPE then increases the RPE as a function of the percentage of that total exercise time that has been compeleted (or the percentage of time that remains). As a result, the final tolerable RPE is reached just prior to complete muscle glycogen depletion. If this is in fact so, then the brain ''knows'' either before, or shortly after the exercise begins, for exactly how long it is prepared to allow the body to work.

This evidence for changes in RPE induced by differences in starting muscle glycogen concentrations, combined with an RPE induced termination of voluntary exercise prior to the loss of cellular homeostasis, provides the biological explanation for the conjecture of Bigland-Ritchie *et al*[217] that: ''As fatigue ensures, the increased sense of effort tends to make subjects think they can no longer drive their muscles maximally or continue to exercise at all''. However, it is the subconscious,[240] not the conscious mind that ultimately determines the duration of each exercise bout; perhaps the conscious mind merely chooses the exact moment that the bout will terminate.[138 139]

SUMMARY

This paper has reviewed the influence that the cardiovascular/anaerobic/catastrophic model of exercise physiology has had on the popular adoption of an exclusively peripheral model of fatigue during all forms of exercise. It is clear that this model of peripheral fatigue is unable to explain a wide range of common observations from both laboratory studies and from the real world of competitive sport (fig 11). Perhaps the single most telling disproof of the cardiovascular/anaerobic/catastrophic model is the finding that fatigue develops in all forms of voluntary exercise without evidence for complete motor unit recruitment in all muscles involved in the activity, as the key assumption of any peripheral model of physiological regulation is that fatigue always develops when there is complete recruitment of all the motor units in the active limbs (fourth hallmark requirement of the cardiovascular/anaerobic/catastrophic model) so that any possible contribution of the CNS can be ignored and the brain excluded from the model (fig 7). It is difficult to understand how a metabolically derived, peripherally based fatigue can develop in all muscle fibres, only some of which are actively recruited at the point of fatigue, yet there is clear evidence presented here and in the companion paper,[240] that skeletal muscle is never fully recruited during voluntary exercise in humans, so that the central nervous system must be the ultimate controller of exercise performance.[138 139] Accordingly, instead of continuing to attempt to shore up the cardiovascular/anaerobic/catastrophic model of exercise physiology with increasingly more convoluted and unintelligible arguments, none of which have yet refuted the six hallmark requirements presented here, it is perhaps time to consider retiring the old model and replacing it with an updated version, better able to explain all the currently observed and measured phenomena. To repeat[37] the words of astrophysicist Stephen Hawking: ''In practice, people are very reluctant to give up a theory in which they have invested a lot of time. They usually start by questioning the accuracy of the observations. If that fails, they try to modify the theory in an ad hoc manner. Eventually the theory becomes a creaking and ugly edifice. Then someone suggests a new theory in which all the awkward observations are explained in an elegant and natural manner'' (p. 36[142]).

The two companion papers that follow present our logical development of this new model, better to explain a number of observed physiological phenomena in a consistent and, in the future judgement of history, hopefully in a somewhat elegant manner.

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ADDENDUM

In the context in which it is currently used in the exercise sciences, it appears that Fletcher and Hopkins[1] may have been the first to use the term ''anaerobiosis'' to describe the nature of the metabolism occurring in the isolated frog muscle that they studied in vitro. However, as it lacked an intact blood supply, their model is more correctly described as a model of total ischaemic (no blood perfusion) anoxia (without oxygen). Any effect of oxygen incubation on the subsequent production or removal of lactate in that model must have occurred as a result of oxygen diffusion into the more superficial muscle fibres, thereby partially relieving the state of complete ischaemic anoxia present in those fibres. Hill and colleagues then adopted the term ''anaerobiosis'' to describe the metabolic processes necessary to cause the increase in blood lactate concentrations that they measured in humans during voluntary exercise. Their assumption was that a state of ischaemic anoxia, identical to that present in the frog muscles studied by Fletcher and Hopkins, must also be present in human skeletal muscles during voluntary exercise (fig 2). However, human skeletal muscles are neither ischaemic nor anoxic[68 146 156 157 167 168] during voluntary exercise. Hence, when applied to conditions in human skeletal muscle during exercise, the terms ''anaerobiosis'' or ''anaerobic metabolism'' are incorrect because they are scientifically imprecise. More correct terms would include ''hypoxia'', indicating a relative, yet still homeostatically regulated reduction[168] in the partial pressure of oxygen (PO_2) in exercising skeletal muscle cells below the PO_2 present at rest, and ''dysoxia'', indicating those conditions in which O_2 limits cytochrome turnover.[168] The term ''oxygen independent'' metabolism could be used to indicate metabolic processes that can occur whether or not the cells are normoxic, hypoxic, or anoxic. The ''glycogen shunt'' mechanism,[27] for example, must occur irrespective of the exact intracellular PO_2.

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