Medicine & Science in Sports & Exercise: Volume 29(5) May 1997 pp 571-590

Challenging beliefs: *ex Africa semper aliquid novi*

NOAKES, TIMOTHY DAVID

Liberty Life Chair of Exercise and Sports Science and Director MRC/UCT Bioenergetics of Exercise Research Unit, University of Cape Town, Sports Science Institute of South Africa, Newlands, 7925, SOUTH AFRICA

Submitted for publication December 1996.

Accepted for publication December 1996.

Besides those already acknowledged, persons too numerous to identify individually have influenced my career. To all who have participated in developing the sports sciences at the southern tip of Africa, including many international colleagues from the ACSM, there is a special debt of gratitude. My tutors at the Medical School of the University of Cape Town inspired a desire for excellence; my colleagues and our students in the Department of Physiology and the Sports Science Institute of South Africa provide the daily incentive to continue in that quest. The dedicated financial support of the University of Cape Town, the Medical Research Council of South Africa, the Liberty Life Insurance Company, the Founding Donors of the Sports Science Institute of South Africa, and a host of nutritional and pharmaceutical companies dedicated to the furtherance of scientific study have provided the material sustenance to sustain a dream. Most importantly, my wife, Marilyn Anne, and our children, Travis and Candice, have played pivotal roles by sharing life's joys and its tribulations with equanimity, love, friendship, and support.

Address for correspondence: Professor T. D. Noakes, Sports Science Institute of South Africa, Boundary Road, Newlands, 7925, South Africa. E-mail: TDNOAKES@SPORTS.UCT.AC.ZA.

ABSTRACT TOP

The basis of the scientific method is the development of intellectual models, the predictions of which are then subjected to scientific evaluation. The more robust test of any such model is one that aims to refute or falsify its predictions. Successful refutation forces revision of the model; the revised model persists as the truth until its predictions are, in turn, refuted. Thus, any scientific model should persist only as long as it resists refutation. An unusual feature of the exercise sciences is that certain core beliefs are based on an historical physiological model that, it will be argued, has somehow escaped modern, disinterested intellectual scrutiny. This particular model holds that the cardiovascular system has a limited capacity to supply oxygen to the active muscles, especially during maximal exercise. As a result, skeletal muscle oxygen demand outstrips supply causing the development of skeletal muscle hypoxia or even anaerobiosis during vigorous exercise. This hypoxia stimulates the onset of lactate production at the anaerobic, lactate, or ventilation thresholds and initiates biochemical processes that terminate maximal exercise. The model further predicts that the important effect of training is to increase oxygen delivery to and oxygen utilization by the active muscles during exercise. Thus, adaptations that reduce skeletal muscle anaerobiosis during exercise explain all the physiological, biochemical, and functional changes that develop with training. The historical basis for this model is the original research of Nobel Laureate A. V. Hill which was interpreted as evidence that oxygen consumption plateaus during progressive exercise to exhaustion, indicating the development of skeletal muscle anaerobiosis. This review confirms that Hill's research failed to establish the existence of theplateau phenomenon during exercise and argues that this core component of the historical model remains unproven. Furthermore, definitive evidence that skeletal muscle anaerobiosis develops during submaximal exercise at the anaerobic threshold initiating lactate production by muscle and its accumulation in blood is not currently available. The finding that exercise performance can improve and metabolism alter before there are measurable skeletal muscle mitochondrial adaptations could indicate that variables unrelated to oxygen use by muscle might explain some, if not all, training-induced changes. To accommodate these uncertainties, an alternate physiological model is proposed 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. During maximal exercise, the peripheral regulation of skeletal muscle function and hence of oxygen use by skeletal muscle, perhaps by variables related to blood flow, would prevent the development of muscle rigor, especially in persons with an impaired capacity to produce ATP by mitochondrial or glycolytic pathways. Regulation of skeletal muscle contractile function by central mechanisms would prevent the development of hypotension and

myocardial ischemia during exercise in persons with heart failure, of hyperthermia during exercise in the heat, and of cerebral hypoxia during exercise at extreme altitude. The challenge for future generations of exercise physiologists is to identify how the body anticipates the possibility of organ damage and evokes the appropriate control mechanism(s) at the appropriate instant.

The invitation to present the J. B. Wolffe Memorial Lecture is one of the greatest honors to which an exercise scientist can aspire. I am very mindful of the unique nature and real significance of this lecture. I am also acutely aware that among those who have presented this lecture are the intellectual giants of our discipline-the gods who have inspired me and many others to greater effort. Not once in my most extravagant dreams did I ever expect to share this moment with such illustrious names, and I am humbled by that association.

But with this great honor comes an important responsibility: to fashion a message that will be relevant to the diverse interests of all members of the College. How can one possibly say anything that will be an inspiration to such a broad community of scientists?

My colleague, Dr. Randy Eichner, has called me a gentle iconoclast. The less-guarded assessment of a fellow scientist from the Antipodes, is that loose cannon might be a more appropriate epitaph. In keeping with those labels, I wish to review some contentious beliefs in exercise physiology to illustrate my understanding of the nature of scientific inquiry. Although the focus will be on exercise physiology, I hope there will be a broader message for all exercise scientists, regardless of their specialization.

WHY ME? TOP

When invited to deliver this lecture, my immediate response was to wonder why I had been so honored. My conclusion is that my selection resulted from the pivotal influences of (i) having been born and trained in Africa; (ii) the impact of North America on my life and its scientists on my career; (iii) the nature of my training in medicine; and (iv) perhaps somewhat surprisingly, by my lack of formal training in the exercise sciences, especially in biochemistry and research methodology.

THE INFLUENCE OF AFRICA TOP

Two facts about the continent of my birth, Africa, are not widely appreciated. The first is that one of the oldest known medical texts, the Papyrus Ebers dated 1550 BC (40, p. 21), comes from Egypt. Indeed, the first correct description of the pulmonary circulation may have been made by the Egyptian physician, Ibn Al-Nafis(55, p. 264), four centuries before William Harvey provided what is usually accepted as the definitive initial description of the systemic and pulmonary circulations.

The second fact is that the ancestral humanoids probably evolved on the plains of South and East Africa and not in the far East as originally supposed.

The initial discovery underpinning the African origin of Man was made by Professor Raymond Dart (26,27), formerly Dean of the Medical School of the University of the Witwatersrand in Johannesburg. The lesson of his discovery is twofold. First, Dart drew his conviction from a single observation that the foramen magnum of the skull unearthed in Taung, Botswana, and later named by him, Australopithecus Africanus (Southern Ape), was situated directly over the vertebral column. Dart concluded that this could only occur if Australopithecus walked upright. Second, Dart's postulate that Australopithecus was an early hominid was initially ridiculed, perhaps because of twin prejudices that little of value comes from Africa and that humans must have evolved in some more exotic location, probably in the East, perhaps in Java. However, Dart persisted in his certitude, and additional findings in both South and East Africa confirmed his faith in what has been acknowledged as one of the 20 most significant discoveries of the 20th century. Professor Dart epitomized the scientist's need to follow his or her intuition even if based on a single, but conclusive, observation. Dart was also one of the first African scientists to show that our continent does perhaps have something to offer the international scientific community.

Perhaps either of these could justify Pliny's statement to the effect that there is always something new from Africa. But for the purpose of this paper, the title expresses the pride that I and my fellow scientists in the developing world have for our respective nations and their scientific and other achievements.

Another unusual benefit of living in South Africa for the past four decades has been the opportunity to participate in an extraordinary social and political change. My fortune was to have been prepared, at least in part, by a short period of study in the United States at the time of that nation's own greatest recent social upheaval.

THE EARLY AND CONTINUING INFLUENCE OF THE UNITED STATES OF AMERICA TOP

My first direct contact with the United States occurred as a high school exchange student studying at Huntington Park High School in Los Angeles for the 1967/68 academic year. For one who had studied at a racially segregated school fashioned on the privileged British public school model, the abrupt exposure to the more open and egalitarian society that I encountered in Los Angeles had a profound and lasting effect. It introduced me to the idea that two nations could operate at polar ends of the social structure. Perhaps that experience made me wonder what exactly is the truth.

Later described as the year which shaped a generation and which like a knife blade,.....severed past from future(75), 1968 taught me about the rapidity with which change can occur-a feature that is perhaps less surprising to citizens of the United States than to a young South African, at least in the 1960's. It was also during that period that the event occurred that would have the single greatest influence on my future career; an event to which the United States made a crucial contribution.

THE INFLUENCE OF THE WORLD'S FIRST SUCCESSFUL HUMAN HEART TRANSPLANT TOP

On Sunday, December 3, 1967, the world's first successful human heart transplant was performed at what would become my alma mater, Groote Schuur Hospital, in Cape Town by a South African team led by Professor Christiaan Barnard (5). I shared the wonderment of my host nation that such an historic achievement had occurred outside the United States. In fact, this event, which stimulated my decision to follow a medical career, was possible only because of the brilliant tutelage that Barnard received at the University of Minneapolis under cardiac surgeon and scientist, Professor Owen Wangenstein (7). Wangenstein arranged that when he returned to South Africa after completing his training, Barnard was accompanied by a special gift from President Lyndon Johnson and the United States government-the first heart-lung machine ever brought to the African continent (22). Without the generosity of that gift from the United States, perhaps I would not have followed my career in the exercise sciences.

Two features were crucial for Barnard's success. First, he required inordinate courage for he knew that two consecutive failed cardiac transplantations would terminate his surgical career. In fact, the early results of Barnard's team were the best of any group then performing that operation (6).

Barnard's courage is a feature of his Afrikaner (Dutch) heritage and was strengthened by a capacity to think differently, an attitude epitomized by his statement that: Most of us think along straight lines, like a bus or a train or a tram. If the destination isn't up on the board, few of us would know where we are going-and that applies even to scientific researchers who should know better. We tend to let tradition lead us by the nose. It takes an effort of will to break out of the mold (22, p. 65).

So my choice of career was strongly influenced, albeit indirectly, by the rich and outward-looking academic culture that is perhaps the finest of the many astonishing achievements of the United Stated of America and one of its great gifts to the international scientific community. That intellectual inspiration has only increased with time, not least through my more than twenty-year membership of the American College of Sports Medicine and through contact with the exceptional scientists who ensure the continued excellence of our discipline.

THE INFLUENCE OF MY MEDICAL TRAINING TOP

As a result of the influence of Professor Barnard's achievement, I entered medical school at the University of Cape Town in early 1969. During my medical training I acquired other insights that I now consider valuable. The first is the need to understand the whole body. In medicine this insight is imperative because disease, like health, invades all the body's organs. Similarly, no medical or biological problem exists in an isolated section of the body. There are advantages, even for exercise scientists, to appreciate the broader picture and to avoid intemperate specialization in a small region or tissue of the body.

The second lesson that one immediately learns when first exposed to patients is one's high level of personal stupidity. Indeed, there is a collective level of medical ignorance, so brilliantly described by Dr. Lewis Thomas (108, p. 10): The greatest single achievement of science in this most scientifically productive of centuries is the discovery that we are profoundly ignorant... I wish there were some formal courses in medical school on medical ignorance; textbooks as well, although they would have to be very heavy volumes. We have a long way to go. Indeed, the beauty of the textbooks of ignorance would be their accuracy. I am reminded of these quotations whenever a scientist expresses the ignorance of absolute certainty. Regardless of any appearance of individual brilliance, we are each profoundly ignorant. And never more so than when we are absolutely certain of our conviction.

A third lesson is the crucial importance of challenging the truth. The single characteristic that distinguishes medicine from otheralternative practices is the controlled clinical trial in which the merit of a particular medical intervention is compared either with doing nothing or with the established practice(s). The results of such trials cause medical truths to be recycled very rapidly. Indeed, medicaltruths change with the weekly appearance of the *New England Journal of Medicine* and many other influential medical publications. Thus, the emphasis of medical research is specifically to disprove and thereby to improve current practice. It is this ethos which distinguishes medicine from those professions that are based on fixed beliefs that are hallowed, changeless, and beyond question. My Professor of Medical Biochemistry, Wieland Gevers, encouraged the heresy that the active skeletal muscles may not become anaerobic during exercise and that separate biochemical processes explain the production of lactate and protons by the active muscles during exercise (38).

This distinctive characteristic of medicine to challenge the truth(88) explains the intellectual paradox captured in the quotation attributed to a former Dean of Harvard, Dr. Sydney Burwell by G. W. Pickering (92), himself formerly Professor of Medicine at the University of London: My students are dismayed when I say to them,`Half of what you are taught as medical students will in 10 years have been shown to be wrong. And the trouble is, none of your teachers know which half.'

WHAT MY MEDICAL TRAINING FAILED TO TEACH ME TOP

Like most medical doctors who have experienced a traditional clinical training, I have very real gaps in my understanding of the tools of science, including statistics and research methodology. My undergraduate training also occurred before the modern explosion of knowledge in both biochemistry and the exercise sciences. As a result, much of my knowledge is self acquired; my tutors have been the writers of what I consider to be some of the classic texts in my field of interest(3,17,23,80,98).

Learning in this way has important disadvantages, but one unique advantage is the avoidance of indoctrination, which is the tendency towards a stubborn, if subconscious, acceptance of a specific scientific mindset or prejudice that we may acquire from our venerated tutors whom we may assume to be intellectually infallible (62). For a crucial outcome of our scientific training is that it conditions us to accept only a limited sample of all the possible truths.

Ignorance can be a formidable attribute if it provides the freedom to consider any intellectual possibility. For it is such ignorance that can encourage the development of novel scientific insights.

WHAT SCIENCE HAS TAUGHT ME TOP

The concept of refutability and the burden of disproof. In his influential text, Viennese philosopher Sir Karl Popper(93), posed the fundamental question: What identifies empirical science and therefore distinguishes it from pseudoscience? He concluded that: A statement (a theory, a conjecture) has the status of belonging to the empirical sciences if and only if it is falsifiable(93). According to this criterion, a statement or theory is falsifiable, that is, able to be refuted, if and only if there exists at least one potential falsifier-at least one basic statement that conflicts with it logically. He continues that the falsifier does not itself have to be known to be true, only that it logically refutes the conjecture.

In Popper's view, an important aim of science is therefore to generate theories that are able to be refuted (falsified). Successful refutation(falsification) of successive conjectures leads to new and occasionally revolutionary theories, each of which is likely to be somewhat closer to the truth than its predecessors. Victor Katch (59) was one of the first to bring this to the attention of modern exercise scientists.

Popper also concludes that we will never know whether a specific conjecture is the final truth because our scientific methods and our logic are too imprecise ever to be certain that we have subjected a particular theory to every possible test of falsification. Thus, a theory that has yet to be refuted is the nearest we ever approach the truth. In this analysis, even Einstein's theory of relativity is simply a conjecture which has, for the most part, escaped refutation (116). Einstein understood this for he wrote: No fairer destiny could be allowed to any physical theory than that it should itself point out the way to introducing a more comprehensive theory in which it lives on as a limiting case(35, p. 131).

These are lofty goals, but they do not always reflect reality. For the surprising nature of much scientific endeavor is a profound resistance to those new ideas that threaten to refute favored dogmas.

The development of intellectual mind-sets (paradigms). A characteristic of the scientific mind is the development of intellectual mind-sets or frameworks within which we interpret all new information(62). Popper described this subconscious process accordingly: Thinking people tend to develop some framework into which they try to fit whatever new idea they may come across; as a rule, they even translate any new idea which they meet into a language appropriate to their own framework. One of the most characteristic tasks of philosophy is to attack, if necessary, the framework itself(93).

The value of these intellectual frameworks is that, when accepted by the entire community, they facilitate communication. The basis for this common understanding does not need to be reviewed endlessly as all the experts in that field accepts the truth of the model and its predictions. Frameworks or paradigms represent those scientific areas in which an intellectual truce has been declared, the intellectual battles have been fought, the arguments have been exhausted, and a common consensus has been achieved. There is a common acceptance that no further advantage can be gained by arguing the intellectual basis of the paradigm. Rather, the accepted framework makes predictions which scientists are then able to evaluate. Kuhn (62) refers to this as normal science. As elegantly described in the analogy of Friedman (37), the danger of such frameworks is that, like clothes, these ideas become comfortable and are not easily discarded.Accepting a new paradigm is like acquiring a new wardrobe. Initially, the garments fit well, look stylish, and are suitable for almost all occasions. However, with the passage of time, the clothes become too loose or too tight, frayed and tattered, and the wearer begins to feel unsuitably dressed for certain events. At this point, he or she can either alter the outfits or purchase a new wardrobe. But the older clothes are not so easily cast aside. They are more comfortable in some ways, they served long and well, they are like old friends; a certain attachment has set in. Indeed the wearer may decide to keep the old wardrobe and restrict his or her activities accordingly, passing up occasions at which the clothes seem out of place. The activities that are dropped become defined as unimportant and eventually no longer belong to the wearer's `real' world. Choosing a new wardrobe, on the other hand, is comparable to what Kuhn terms a `paradigm revolution': the basic framework that defines activity is altered, and `normal' science is replaced with a new range of possibilities. We may call this a `new reality' (37).

Paradigms and model-dependent reality. The eminent mathematician Stephen Hawking has written a remarkably successful popular book on astrophysics (42). His book describes models from which we can attempt to understand how the universe is (currently) believed to work. The models make predictions that can be tested, but these are not guaranteed to be either true or real. As Hawking explains: We cannot distinguish what is real about the universe without a theory...(But)...it makes no sense to ask if a theory corresponds to

reality, because we do not know what reality is independent of a theory....How can we know what is real, independent of a theory or model with which to interpret it? ((43), p. 38).

Exercise scientists spend their academic lives developing models of how the body works. We need to remember that these models do not necessarily reflect reality or absolute truth.

The nature of truth in scientific endeavor. Consideration of these views allows one to propose that scientific truth is subject to change which often occurs with rude suddenness; that truth is model-dependent; and that truth reveals itself through refutation of the less-true.

If truth is constantly in flux, it follows that one measure of the vigor of any scientific discipline is the frequency with which its major hypotheses are refuted and reformulated. On this basis, a science like astrophysics might be considered vigorous as the ideas and theories in the discipline are always in flux. So one might ask, how do my particular areas of interests, exercise physiology and sports medicine, measure up?

This analysis begins by considering two hypotheses, the refutations of which have been readily accepted. Then follows an analysis of five topics which, in my opinion, provide evidence for substantial resistance to novel interpretations, suggesting that the concept of refutability is not always eagerly accepted in all areas of our discipline.

ACCEPTED REFUTATIONS IN THE EXERCISE SCIENCES TOP

My introduction to more serious science started with an attempt to refute the statement which claimed that: A search of the literature has failed to document a single death due to coronary atherosclerosis among marathoners of any age. Marathoners were defined as those completing 42.2 km in under 4 hours and only autopsied cases were considered (8). This statement formed the basis for a conjecture which soon became known as the Bassler hypothesis: As no cases of fatal atherosclerosis have been documented in marathon finishers of any age, it follows that such activity confers virtual immunity from fatal heart attacks(102). To this was added the rider: ...it is biologically impossible for atherosclerosis to progress in anyone capable of even walking the 42-km distance! Indeed reversal of the disease is seen(10). Insurance against heart attack could also be achieved with a relatively small investment: For the nonsmoker who trains at distances over 6 miles for a total of 100 miles, protection starts here and continues as long as he continues running(9). The dramatic growth of marathon running at that time helped to popularize Bassler's thesis.

This conjecture has the characteristic of a scientific theory as it is open to refutation, which was provided by a single report detailing the deaths of marathon runners from coronary atherosclerosis (87). This refutation was readily accepted (95), perhaps because it does not impact on the more important hypothesis, also the subject of a previous Wolffe lecture and for which there is no contradictory evidence: that persons who are vigorously active may live longer and suffer less from heart attacks, hypertension, diabetes mellitus, and certain cancers than their less active peers (89).

Seldom is a single case report sufficient to refute an hypothesis; more commonly, a more detailed experiment is required. The study of Coyle et al.(24) provides a fine example of work that resolved a controversy that had raged for at least 50 years and that had important practical implications for athletes competing in endurance events. Those authors evaluated the popular conjecture that held that only water should be ingested during exercise. This hypothesis stems from the intellectual model that holds that carbohydrate ingestion during exercise delays the rate of gastric emptying, slowing the rate at which fluid is delivered to the small intestine, thereby promoting the development of dehydration and the probability that heat injury will develop especially during prolonged exercise(84,85). The hypothesis drew strength from a study, published in the *New England Journal of Medicine* in 1981(36), which concluded that: ...correction of hypoglycemia by glucose ingestion (during prolonged exercise) does not consistently delay exhaustion or alter the subjective sensation of exertion during the exercise. These findings thus do not support a role for glucose ingestion in improving performance during prolonged exercise, and they may have relevance to endurance sports such as marathon running.

What is particularly remarkable is that these conjectures were universally accepted despite the presence of a number of refutations, published half a century earlier, that clearly showed that carbohydrate ingestion either

reversed or delayed the onset of fatigue during prolonged exercise, including marathon running (21,33,66). Indeed, on the basis of the evidence available in 1936, Grace Eggleton(34, p. 153) had written that: When they (long distance runners) have run to exhaustion, the level of blood sugar is found to be abnormally low...If the eating of sugar candy during a race was encouraged...it seems possible that new records might be achieved in long-distance running. As Popper has warned, it is usually unwise to accept a conjecture for which there is a single logical refutation already present in the literature. Yet, in this example, besides the three published refutations, there was a substantial volume of anecdotal evidence favoring the ergogenic benefits of carbohydrate ingested during prolonged exercise(83,86).

Coyle et al. (24) confirmed the validity of these historic refutations by showing that, when they ingested a concentrated carbohydrate beverage, trained endurance cyclists who had not eaten for 12 h, were able to exercise for up to 33% longer than when they ingested a sweetened placebo.

The above example should teach us two important lessons. One is that any hypothesis can be immunized from all attempts at refutation once it becomes the established mind-set supported by influential scientists. As Miller(73, p. 10) has exhorted: It is the perpetuation of errors that interferes with our understanding; and it is this, rather than their perpetration, that we must exert ourselves determinedly to avert. Influential scientists can harm their discipline if they lose the desire to challenge the dogmas they have created.

The second important lesson of this example was the rapidity with which its results were accepted by the scientific community; how swiftly its conclusions were integrated into a new intellectual model, and how decisively this new information altered the eating and drinking habits of athletes competing in endurance events. Usually novel ideas that refute the existing mind-set are accepted only by the next generation of scientists.

Another refutation that has been less readily accepted deals with the popular prejudice that people collapse during or after prolonged exercise, especially marathon and ultramarathon running, because they develop dehydration-induced hyperthermia (85). This theory can be questioned on two grounds. The first is the finding that the vast majority of athletes who collapse during or after exercise, or with the experimental condition termed heat strain (100), do not have abnormally elevated rectal temperatures(53,96,97,100) and are therefore not suffering from hyperthermia. If the theory linking hyperthermia to dehydration(118) is correct, then the athletes with the condition are probably not excessively dehydrated. Similarly, collapse from heat strain is not prevented by adequate fluid ingestion(100), indicating that dehydration is not an etiological factor for collapse from this condition. But adequate fluid ingestion during exercise especially in the heat does confer significant physiological benefits and does increase substantially the duration of exercise that can be sustained before the onset of collapse from heat strain(100).

More to the point, the finding that 85% of such collapses in competitive athletes occur after the athlete has already completed such distance races(53), suggests that severe dehydration is not the primary determinant of collapse. For if severe dehydration caused collapse by reducing the circulating blood volume and hence the cardiac output, one would expect dehydration-induced collapse to occur during exercise when the cardiovascular system is under the greatest stress. Instead, the majority of such collapses occur at the end of exercise when the cardiovascular system is reverting to the resting state and the athlete may be experiencing postural hypotension(54).

Attempts to promote this line of argument (85) continue to be ignored because of the entrenched mind-set that dehydration alone explains the majority of the medical problems that develop during exercise. The historical origin of this prejudice has been described(85).

Why are novel ideas accepted with reluctance by the scientific community? Popper (93, p. 14) has described why scientists find it so difficult to discard their intellectual wardrobes:Most of us... hold a great number of theories consciously.. and we may be prepared both to defend these by argument and to give them up when good arguments are brought against them. *But we also hold theories that we take for granted more or less unconsciously and therefore uncritically; and these uncritically held theories often contain the strongest reason for continuing to hold those other theories consciously* (author's emphasis).....it may become necessary to attack beliefs which, whether or not they are consciously held, are taken so much for granted that

any criticism of them is felt to be perverse or insincere. Whenever the framework itself is attacked, its defenders will as a rule interpret, and attempt to refute, the attack within their own adopted framework.

Hawking has described the same phenomenon (43, p. 36):The theory always came first, put forward from the desire to have an elegant and consistent mathematical model. The theory then makes predictions, which can be tested by observation. If the observations agree with the predictions, that doesn't prove the theory; but the theory survives to make further predictions, which again are tested against observation. If the observations don't agree with the predictions, one abandons the theory. Or rather, that is what is supposed to happen. In practice, people are very reluctant to give up a theory in which they have invested a lot of time and effort. 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.

Hawking also identifies a popular method that is used to delay the acceptance of a new conjecture. In this technique labeled refutation by denigration, the scientific credibility of the person who questions the accepted model is brought into doubt and his or her professional standing is subtly undermined. It is the classic technique of shooting the messenger so that the message may be conveniently ignored. This method is unfortunately still quite popular in the exercise sciences. It has no part in mature science and must be exposed whenever and wherever it reveals its ugly presence.

It would seem that even the intellectually brilliant are not immune from this reluctance to accept a new intellectual model. Both Newton and Einstein, two of the most revolutionary scientists, could not accept predictions of their own theories that were in conflict with a religious dogma. Newton refused to accept that the absolute position in a space of a large object could not be defined as this conflicted with his belief in an absolute God. Similarly, Einstein would not believe that the position of the very small was also indeterminate (the Heissenberg Uncertainty Principle) because it also conflicted with his religious belief. God, Einstein wrote,does not play dice (43, p. 91). His prediction of the existence of astronomical black holes lead Hawking to suggest that: God not only plays dice but also sometimes throws them where they cannot be seen (43, p. 103).

I have encountered five intellectual frameworks in the exercise sciences that, in my opinion, have to a lesser or greater extent, become ugly and creaking edifices. A feature of the majority is that they share a common origin in the hypothesis that the active skeletal muscles contract anaerobically during high intensity exercise. What are these conjectures and what evidence or logic might seem to refute them?

SOME UGLY AND CREAKING EDIFICES TOP

1. The maximum oxygen consumption of Hill(˙VO2max·hill). The work of Nobel Laureate Archibald Vivian Hill et al. (47-51) forms the basis for the popular conjecture that an oxygen limitation develops during maximal exercise causing skeletal muscle hypoxia to terminate exercise. The critical flaw in logic perpetuated in those studies has been described in two previous tutorial lectures to our College and in one publication in this journal (82). These refutations of Hill's conjecture and its potential implications for some crucial areas of the exercise sciences have, with a few notable exceptions(2,77,78,99), been essentially ignored. Perhaps this fourth attempt to challenge an entrenched mindset will be more successful!

In their experimental series, Hill et al. measured oxygen consumption($\dot{V}O_2$) every 30 s in subjects who ran for 3 min at different speeds on a circular grass track 85 m in circumference. Their relevant findings are reproduced (again) in Figure 1. The authors' interpretation of their data was the following (49):

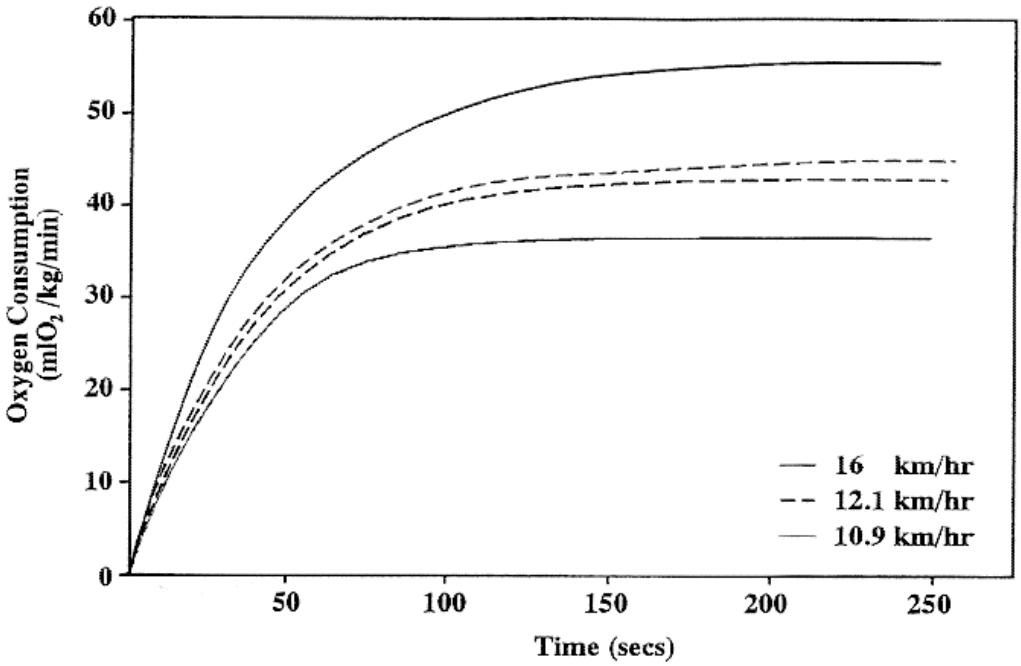

Figure 1-Oxygen consumption of A. V. Hill when he ran at three different speeds for up to 4 min. Data redrawn from Hill and Lupton (49) as previously published in reference 82 . Noakes, T. D. Implications of exercise testing for prediction of athletic performance: a contemporary perspective. *Med. Sci. Sports Exerc.* 20:319-330, 1988.

When muscular exercise is taken in man at a constant speed, the lactic content of his active muscles increases gradually from its resting minimum at the start. The rise in lactic acid content increases the rate of oxidation, so that finally if the oxygen supply is adequate, a `steady state' is reached in which the rate of lactic acid production is balanced by the rate of its oxidative removal, and its concentration remains constant in the muscle as long as exercise at that speed is maintained. The lower three curves represent a genuine steady state and the uppermost curve only an apparent steady state in which the oxygen intake is at its maximum and the oxygen debt is rapidly increasing.

Hill and Lupton concluded that the constant $\dot{V}O_2$ they measured at the fastest running speed (16 $km \cdot h^{-1}$ in Fig. 1) represented an apparent, not a true, steady state. The basis for this conclusion was a circular argument based on Hill's subconscious model explaining fatigue during exercise (Fig. 2). For Hill began with the subliminal premise that fatigue during exercise is caused by an oxygen deficiency; he naturally interpreted his findings within that conceptual framework.

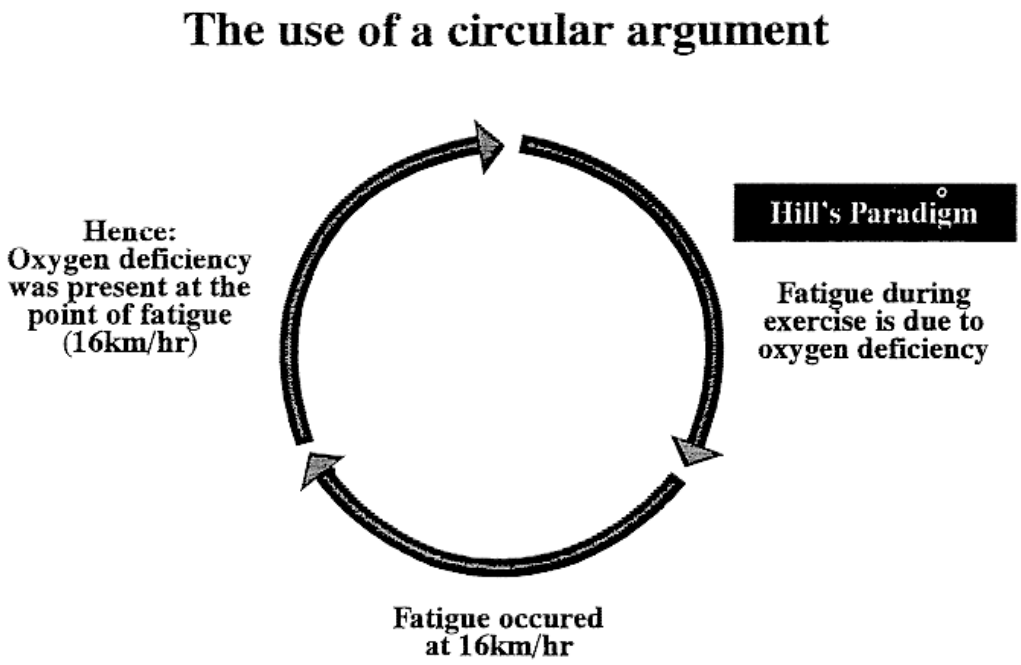

Figure 2-Hill's conclusion that his oxygen consumption was less than his requirement when running at 16 km·h-1 (Fig. 1) **, was based on a circular argument. His subconscious assumption was that fatigue during exercise is owing to oxygen deficiency in the active muscles.**

From the subjective feelings of the fatigue that he experienced when he ran at 16 km·h^{-1}, Hill drew the equally subjective conclusion that he must have developed an oxygen deficiency. As a result he concluded that his real $\dot{V}O_2$ must have been higher than that which was objectively measured at 16 km·h^{-1}. Thus, Hill et al.(50) speculated: Considering the case of running...there is clearly some critical speed for each individual... above which, the maximum oxygen intake is inadequate, lactic acid accumulating, a continuously increasing oxygen debt being incurred, fatigue and exhaustion setting in. Hill (47) further concluded that:The oxygen intake may attain its maximum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory systems.

Not only did Hill et al. (50) fail to measure concurrently either the oxygen debt or muscle or blood lactate levels during these or subsequent studies, they also failed to subject their hypothesis to the accepted process of refutation. For the next logical study would have been to measure Hill's $\dot{V}O_2$ when he ran at a speed faster than 16 km·h^{-1}. Their hypothesis would have been supported if the$\dot{V}O_2$ at that higher speed was either the same or lower than that measured at 16 km·h^{-1}.

However, as that experiment was not performed, Hill et al. could not conclude that Hill's $\dot{V}O_2$ had plateaued and was indeed maximal at 16 km·h^{-1}. Thus, their major conclusion that$\dot{V}O_2$ reaches a plateau during exercise of progressively increasing intensity was not proven because this test of refutation was not conducted. Fortunately, it is possible to submit their conclusion to retrospective refutation.

The data shown in Figure 3 confirm that Hill did not reach some critical speed...above which the maximum oxygen intake is inadequate. For the data clearly show a linear relationship between Hill's mean $\dot{V}O_2$ at three different speeds. Hence, there is no evidence in these data for the plateau phenomenon, indicating that any postulated $\dot{V}O_{2max\cdot Hill}$ had not occurred. The implications of this refutation of Hill's conjecture are two-fold. First, it raises the question of whether the plateau phenomenon indicating $\dot{V}O_{2max}$ really exists (82). Second, by logical extension, it questions the hallowed notion than anaerobiosis develops during exercise and that it is this anaerobiosis that induces specific physiological and biochemical changes that terminate high intensity exercise.

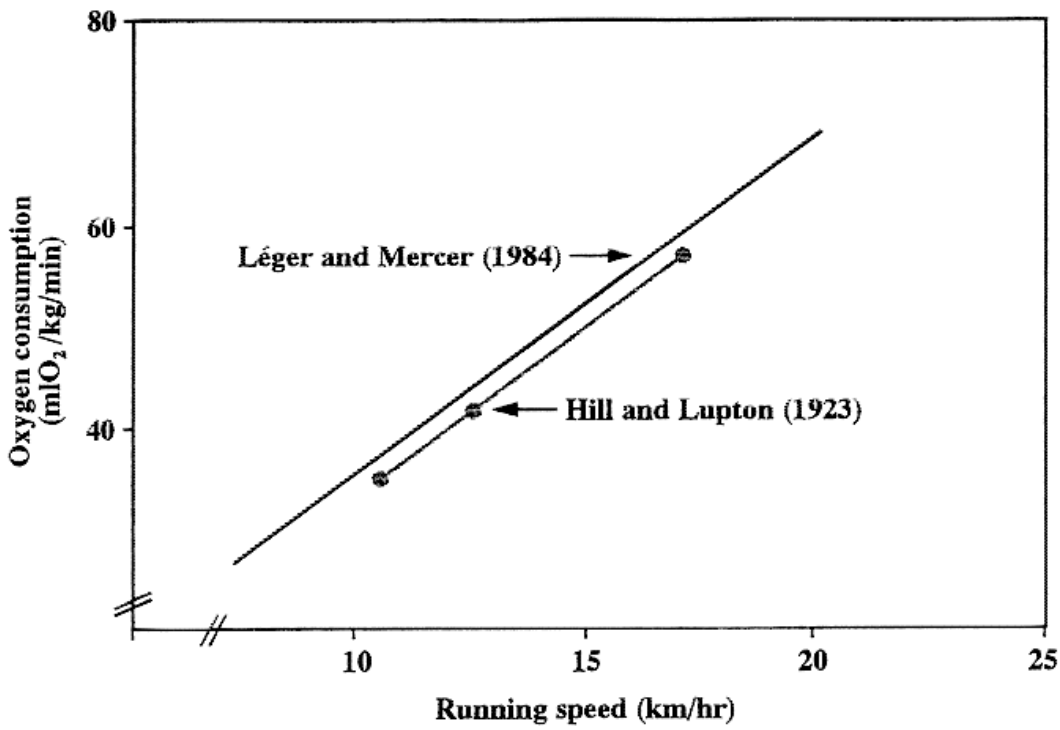

Figure 3-There is a linear relationship between running speed and the average ˙VO2 measured at the different running speeds shown in Figure 2 . The relationship is similar to that reported in the literature. Data redrawn from Hill and Lupton (49) as previously published in reference 82 . Noakes, T. D. Implications of exercise testing for prediction of athletic performance: a contemporary perspective. *Med. Sci. Sports Exerc.* 20:319-330, 1988.

Hill and Lupton (49) were silent on the mechanisms causing fatigue during exercise at or above their postulated $\dot{V}O_{2max\cdot Hill}$. They proposed only that lactic acid was involved but evaded the issue of how elevated lactic acid concentrations either in muscle or blood cause fatigue(49).

If Hill and Lupton's work offers no basis for the hypothesis that $\dot{V}O_2$ plateaus during maximal exercise, what other evidence is there to sustain this particular conjecture?

After Hill and Lupton's work, the next classical study usually considered as additional definitive proof of the plateau phenomenon is that of Mitchell et al. (74). However, that study was not designed to test the $\dot{V}O_{2max\cdot Hill}$ hypothesis for it began by echoing Hill's assumption that, during progressive exercise, there is a workload at whichmaximal oxygen intake per unit of time is reached; beyond this point the workload can usually be increased still further but, ordinarily, oxygen intake levels off or declines (74, p. 538). Rather, the aim of that study was not, however, merely to re-examine previously established characteristics of maximal oxygen intake but, rather, to inquire into its physiological meaning (74, p. 543). Hence, they determined the cardiorespiratory changes, in particular in cardiac output and in arterial and venous oxygen tensions including the arteriovenous (AV)oxygen difference, that occurred during steady state exercise of short duration at near maximal exercise intensities. During those experiments, $\dot{V}O_2$ was calculated from expired gas samples collected during the last minute of consecutive, but interrupted, exercise bouts that lasted 2.5 min.

Their principal finding was that increases in both cardiac output and in the AV oxygen difference contributed to the maximal oxygen consumption, with the rise in cardiac output being the more important. They concluded thatthe maximal oxygen intake is a measure of cardiac capacity and the ability to increase the AV oxygen difference, not of the ability of the vascular bed to accommodate left ventricular output(74, p. 545). As an aside, they also reported that 72% of subjects showed a plateau phenomenon defined as an increase in $\dot{V}O_2$ of less than 54 ml at the highest exercise workload. But that finding had no bearing on their conclusion. Based on

Hill's conclusions, the authors had already assumed that there is a $\dot{V}O_{2\ max\cdot Hill}$ which is determined by limitations in the cardiovascular system.

But does that study also provide any definitive information about theplateau phenomenon? The only physiological model, which allows conclusions to be drawn from the testing protocol used by Mitchell et al.(74) in which the interrupted exercise bouts last less than 3 min, is one in which $\dot{V}O_2$ rises very rapidly at the onset of exercise, reaching its maximum within 90 s of the onset of exercise. If that model is incorrect, then conclusions about the plateau phenomenon cannot be drawn from that testing protocol. For example, an apparent plateau phenomenon would occur with the testing protocol of Mitchell et al. (74) if the initial rate of increase in $\dot{V}O_2$ were the same for all the high work rates that they studied. Proof that their interrupted testing protocol identifies a real plateau in $\dot{V}O_2$ would require that additional samples be taken at later time points to ensure that there had been no further increase in$\dot{V}O_2$ after the first 2.5 min of exercise.

Subsequent searches have found the plateau phenomenon to be elusive (2,25,82). An early attempt to identify this phenomenon in adult men concluded that: The plateau is theoretically exact, in practice it is much less so(25). The most recent review published in September 1995(56) concluded that: there is no general agreement on the use of specific criteria for establishing that $\dot{V}O_{2max}$ has, in fact, been achieved.

Only one study has attempted directly to determine whether oxygen consumption during progressive, ramp exercise reaches a maximum beyond which no effort can drive it (47). Myers et al.(78) summed $\dot{V}O_2$ over one or more breaths during both steady-state and progressive (ramp) exercise. Using a rolling average, they continuously calculated the rate and direction of change in$\dot{V}O_2$ throughout exercise. They showed that there is considerable variability in $\dot{V}O_2$ measured breath-to-breath or averaged over short intervals and that this variability is a result of changes, predominantly in tidal volume. The result is that instantaneous$\dot{V}O_2$ does not rise as an exactly linear function of a progressively increasing (ramp) work rate but in a rather more irregular pattern. This variability is reduced when longer sampling times are used so that$\dot{V}O_2$ rises as a linear function of work rate when sampling times of 60 s or more are used.

Myers et al. (78) concluded that the rate of change in$\dot{V}O_2$ during ramp exercise is erratic and frequently transiently negative indicating a plateau phenomenon even during submaximal exercise. They proposed that: ... considerable variability exists in the slope of the change in VO_2 with a consistent change in external work... suggesting that a plateau (defined as the slope of a VO_2 sample at peak exercise that does not differ significantly from a slope of zero) in VO_2 is not a reliable physiological marker for maximal effort(78).

This finding has implications for the duration of the sampling period used to establish whether the plateau phenomenon exists; the shorter the sampling period, the less likely it is that a definitive plateau phenomenon will be identified. One might suggest that a phenomenon that can be identified only with some difficulty and under certain specific experimental conditions is unlikely to be a fundamental biological truth.

In summary, Hill's original interpretation of his own data is in error. This error has been perpetuated for 70 years with the result that Hill's theory of the plateau phenomenon, although unproven, persists as a fiercely protected paradigm in the exercise sciences. It is important that we appreciate the uncertain status of the plateau phenomenon so that we are not unwitting agents of its continued perpetuation.

2. Progressive muscle hypoxia limits maximal exercise performance. The second creaking and ugly edifice follows directly from the first. It holds that hypoxia develops in the active muscles during exercise and that this hypoxia causes fatigue and therefore limits maximal exercise performance under all conditions. This model holds that the hypoxia results from an inability of the heart to increase its cardiac output sufficiently to match the maximum demands of the active skeletal muscles(98).

The first issue of concern with the theory of muscle hypoxia is that there is no logical reason why exercise should terminate shortly after the development of the plateau phenomenon as is usually described. This ignores the known capacity of skeletal muscle to generate energy by oxygen-independent metabolism.

Figure 4 is a usual textbook figure showing the rates of ATP production that can be sustained for varying durations of exercise. The diagram indicates the large capacity for oxygen-independent ATP production that can be activated during high intensity exercise of short duration (less than 10-30 s). But if the plateau

phenomenon is correct, it requires that progressive ramp exercise, which starts at a low work rate, does not activate fully the oxygen-independent metabolic pathways. For the plateau phenomenon predicts that exercise terminates immediately or shortly after the maximum skeletal muscle oxidative capacity has been reached and without full activation of the oxygen-independent metabolic pathways.

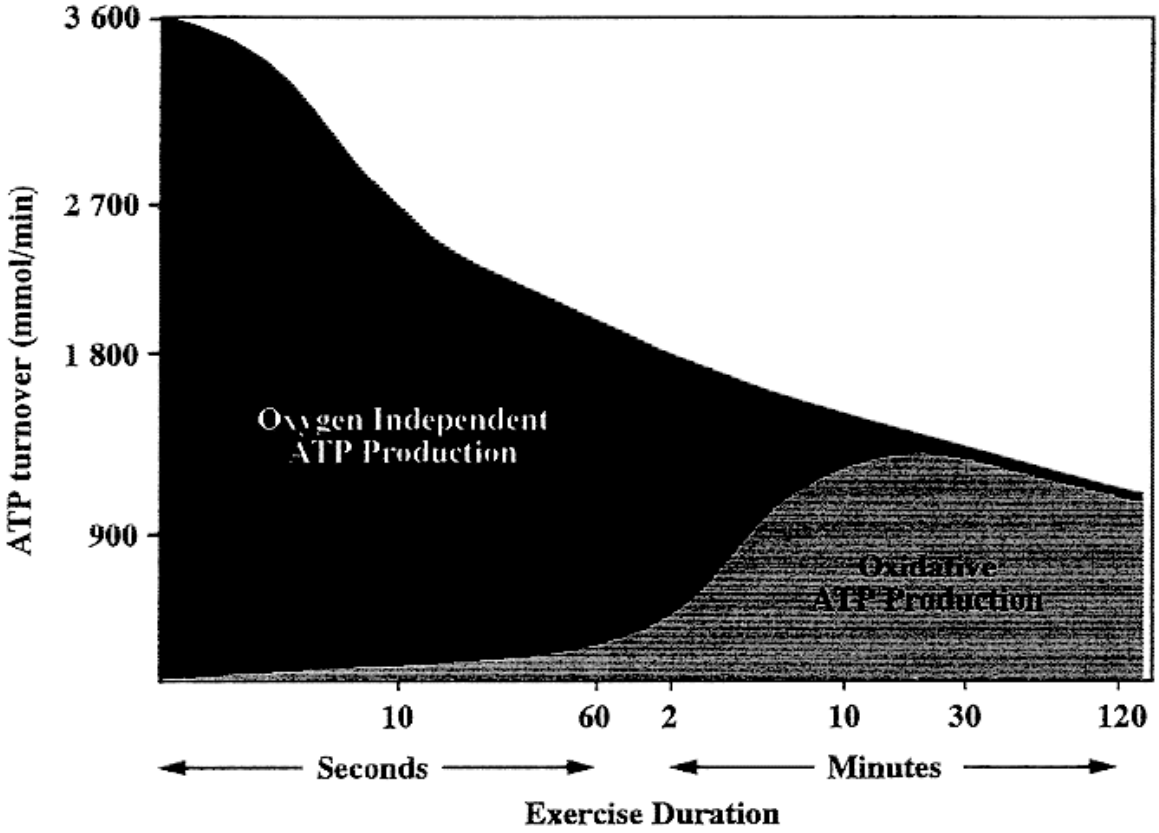

Figure 4-The maximum rate of sustainable ATP turnover falls sharply with the increasing duration of activity. ATP production during high intensity exercise of short duration (<30 s) is provided by oxygen-independent pathways.

Figure 5 presents the argument more directly. It shows that adding the maximum ATP-generating capacity of only the oxygen-independent glycolytic pathway (≈ 500 mmole·min^{-1})(105) to the maximum skeletal muscle oxidative capacity, measured as the $VO_{2max.Hill}$, should allow the athlete to continue exercising to a work rate equivalent to an additional $\dot{V}O_2$ of 1.7 L·min^{-1} after the development of the plateau phenomenon. No proponent of the plateau phenomenon has yet described this phenomenon.

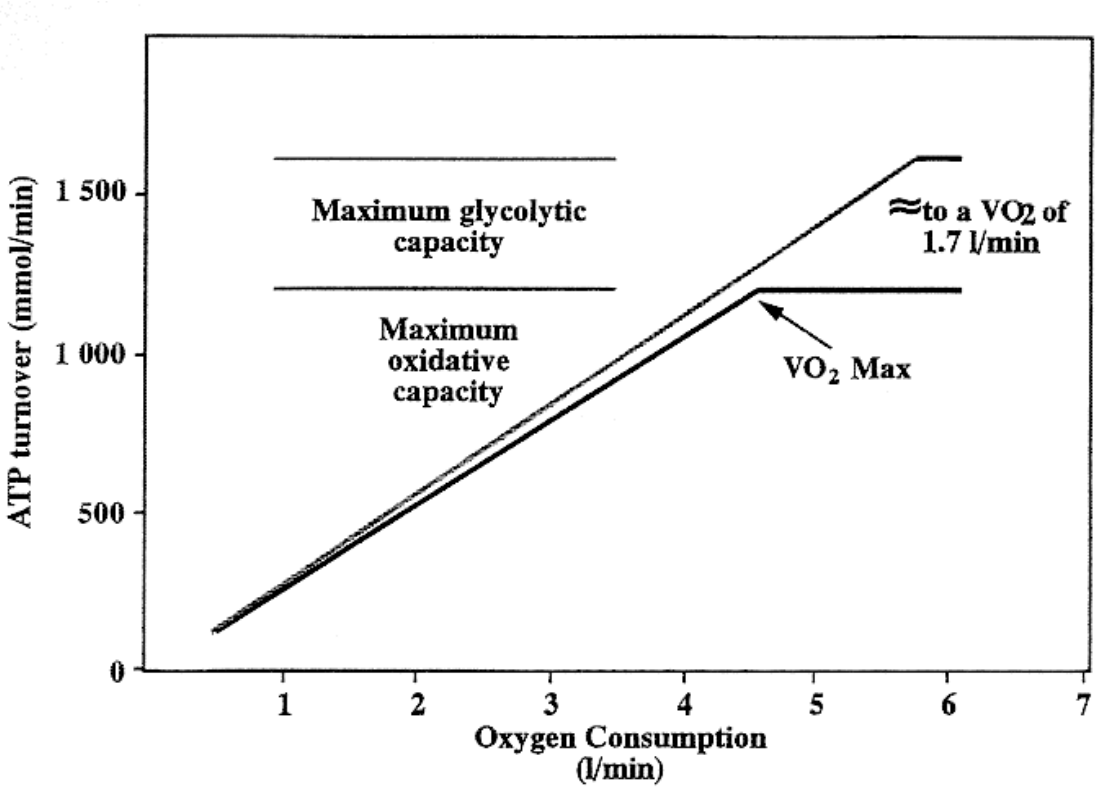

Figure 5-The additional energy provided by the maximum rate of oxygen-independent glycolytic ATP production should allow exercise to continue to a work rate 1.7 L·min-1 above that at the theoreticalplateau phenomenon which, it is assumed, corresponds to the maximum achieveable skeletal muscle oxidative capacity.

Accordingly, one might hypothesize that progressive exercise to exhaustion in which exercise starts at submaximal work rates must terminate before the maximum rates of oxygen-independent ATP production are reached. If this is correct, it suggests that contraction of the exercising muscles ceases before their maximum metabolic capacity-in particular their maximum capacity for oxygen-independent ATP production-is used. Specific findings in both healthy and diseased subjects support this interpretation.

First, the novel study of Spriet et al. (104) was designed specifically to determine whether skeletal muscle forced to exercise under ischemic and ultimately anaerobic conditions would continue to contract until ATP depletion and rigor developed. To test this theory, the quadriceps muscle group of human subjects was rendered ischemic by the application of a pressure tourniquet to the upper thigh and forced to contract repetitively by electrical stimulation.

The key findings were (i) that skeletal muscle ATP concentrations fell to 57% of the resting values and (ii) that skeletal muscle contractile function fell progressively. More importantly, rates of muscle ATP production fell coincident with falling rates of muscle ATP use. Thus, the likely conclusion is that under ischaemic conditions and, by extension, presumably also under hypoxic conditions, skeletal muscle contractile function and hence rates of muscle ATP use are regulated to prevent any large variance in the protected variable skeletal muscle ATP concentrations. If correct, this model represents a substantial change from the traditional model of Hill(47) which postulates that energy demand outstrips supply during high intensity exercise. The new model proposes that energy demand is regulated by the rate of energy supply specifically so that demand can never outstrip supply.

In diseases of skeletal muscle metabolism including muscle phosphorylase deficiency and the mitochondrial myopathies in which capacity to produce ATP by either oxidative or glycolytic pathways is reduced, exercise does not cause an abnormally large reduction in skeletal muscle ATP concentrations(67). This provides further

evidence for the hypothesis that skeletal muscle contractile function and its rate of ATP use is regulated by the rate of muscle ATP supply so that muscle ATP concentrations are protected.

Perhaps the most striking example of this phenomenon occurs during exercise at extreme altitude, for example, at or near the summit of Mount Everest (8848 m). Maximum oxygen consumption falls with the reduction in barometric pressure so that at altitudes in excess of 8000 m the $\dot{V}O_{2max}$ is elicited even by the most gentle exercise. Indeed, even in climbers using supplemental oxygen, maximum effort near the summit of Mount Everest consists of prolonged periods of rest interspersed with very brief bouts of exercise. The experience is perhaps best described by the first man to reach the summit of Mount Everest without the use of supplemental oxygen, Reinhold Meisner(107): We can no longer keep on our feet to rest.... Every 10-15 steps we collapse into the snow to rest, then crawl on again.

On first principles, one would predict that Meissner's symptoms were caused by a severe metabolic acidosis resulting from profound muscle hypoxia causing very high circulating blood lactate concentrations. This postulate was tested by Howard Green et al. (39) in the landmark Operation Everest II study which was made possible largely through the tenacity of Dr. John Sutton.

They showed that peak blood lactate concentrations during maximal exercise ***fell*** rather than increased as a function of increasing altitude(39). This observation, now known as the lactate paradox, is not novel. David Dill (32, p. 173) first described the phenomenon in 1938 and proposed that: The inability to accumulate much lactic acid in great heights or to disturb the internal economy of the organism so profoundly as at sea level may be looked upon as useful safeguards against overexertion. It is as though the body, realizing the delicacy of its situation with regard to oxygen supply, sets up an automatic control over anaerobic work which renders impossible the severe acid-base disturbances which can be voluntarily induced at sea level. Notice Dill's profoundly novel suggestion that an automatic internal control may act as a safeguard to regulate skeletal muscle contraction. A recent study has confirmed that his explanation for the lactate paradox is correct.

Kayser et al. (60) exposed the same group of subjects to exercise at 122 and 5 050 m above sea level. During exercise, integrated electromyographic (IEMG) activity of the vastus lateralis muscle was measured. IEMG activity increased progressively during exercise at sea level but not at altitude. Furthermore, IEMG activity was substantially higher at exhaustion at sea level than at altitude. But IEMG activity increased in subjects exercising at altitude when they inhaled 100% oxygen and were able to exercise to higher work rates.

The interpretation of these findings is that skeletal muscle recruitment is reduced during exercise at altitude. Hence the authors concluded that:These results suggest that during chronic hypobaric hypoxia, the central nervous system may play a primary role in limiting exhaustive exercise and maximum accumulation of lactate in blood(60).

The lactate paradox is also observed in patients with certain chronic medical conditions including chronic renal (61) and cardiac disease (31). The logical assumption is that patients with renal failure are unable to exercise because of an anemia that reduces oxygen transport capacity to the active muscles during exercise; in heart failure, there is a reduced capacity to increase blood flow to the active skeletal muscles during exercise. As a result, the muscles of both groups of patients should develop a premature hypoxia during exercise, leading to the production of high and limiting concentrations of lactate in muscle and blood. But this does not occur.

For example, a recent study (31) of the physiological responses to maximal exercise in patients with heart failure showed that blood lactate concentrations and rates of pulmonary ventilation were substantially lower in patients than in age-matched controls at any% $\dot{V}O_{2max}$ (Fig. 6). Furthermore, patients showed severe morphological abnormalities in skeletal muscle. The probable conclusion is that the impaired exercise tolerance of these patients results either from a reduced capacity to recruit skeletal muscle during exercise or from impaired skeletal muscle contractile function.

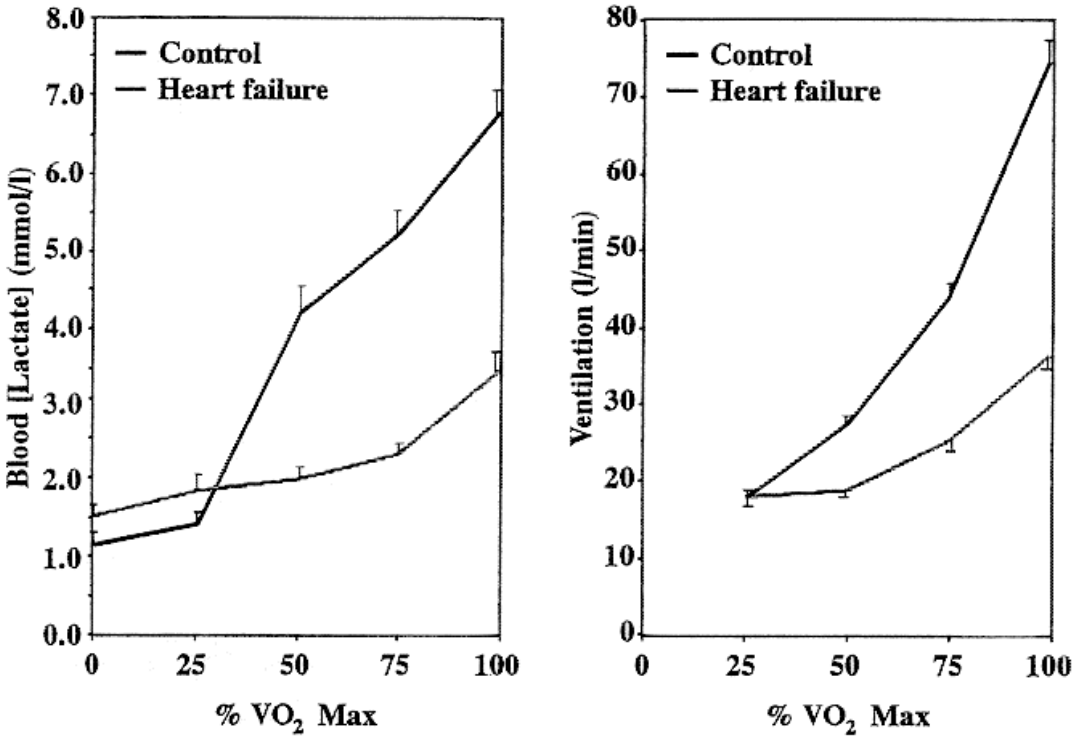

Figure 6-Blood lactate concentrations (*left panel*) and ventilation rates (*right panel*) during progressive exercise to exhaustion in patients with heart failure and in controls. Values are substantially lower in heart failure patients at all exercise intensities in excess of 25% ˙VO2max. Data of reference 31 **. Derman, K. L. Exercise tolerance and skeletal muscle structure and function in patients with severe chronic heart failure. MSc thesis, University of Cape Town, 1995.**

Indeed, the peripheral nature of the lactate paradox can be shown in persons with heart failure who have undergone cardiac transplantation. Derman(31) has also compared the exercise capacity of patients before and after cardiac transplantation with that of controls. She showed that there were small but insignificant increases in peak workload and˙VO_{2max} 2 months after cardiac transplantation, but peak venous blood lactate concentrations remained low and abnormal skeletal muscle histology scores were not improved (Table 1). All values were significantly different from those measured in controls. Subsequent studies suggest that, in the absence of exercise training, skeletal muscle histological abnormalities persist for at least 12 months after cardiac transplantation.

	Controls	Heart Failure Patients	Following Cardiac Transplantation
Peak workload (W)	190 ± 30	65 ± 20	80 ± 20
$VO_{2\ max}$ (mL·kg^{-1}·min)	30 ± 3	12 ± 2	17 ± 2
Peak lactate (mmol·l)	6.9 ± 0.7	3.4 ± 0.4	4.0 ± 0.4
Skeletal muscle histology score (units)	2 ± 1	12 ± 3	11 ± 2

Unpublished data of E. W. Derman, University of Cape Town.

TABLE 1. Changes in exercise tolerance and $VO_{2\ max}$ after cardiac transplantation.

Another study (72) confirms that peak $\dot{V}O_2$ remained very low (≈ 16 mL·kg^{-1}·min^{-1}) and did not increase during the first 12 months after cardiac transplantation, confirming that replacing the heart does not normalize the impaired exercise tolerance and low peak $\dot{V}O_2$ values of patients with chronic heart failure.

In summary, these studies indicate that progressive skeletal muscle anaerobiosis is an unlikely mechanism limiting or impairing exercise performance in a variety of experimental and clinical settings. Rather, these findings invite the hypothesis that skeletal muscle contractile function is regulated during exercise in both health and disease by a hierarchy of central and peripheral mechanisms, the goal of which is likely to prevent organ damage, including death. The evidence for this grand hypothesis is the following:

Skeletal muscle function during exercise appears to be regulated by different mechanisms (i) to prevent the development of muscle ATP depletion causing irreversible skeletal muscle rigor during high intensity exercise(67,104); (ii) to prevent cerebral hypoxia during exercise at altitude (32,39,60); (iii) to prevent a catastrophic fall in blood pressure (98) that would reduce perfusion of the diseased coronary arteries in chronic heart failure; (iv) to prevent catastrophic hyperthermia (heatstroke) during prolonged exercise in the heat (81); and (v) to prevent glucopenic brain damage during prolonged exercise when hypoglycemia results from liver glycogen depletion (13).

Perhaps the tantalizing challenge for exercise scientists is to define the control mechanisms that provide these safeguards. Central control mechanisms may include brain receptors for hypoxia to limit exercise at altitude, for blood glucose concentrations to limit exercise during hypoglycemia, and for temperature to prevent heatstroke. Peripherally-based receptors would need to link metabolic and cardiovascular signals. The intriguing finding that blood flow may regulate skeletal muscle contractile function independent of oxygen delivery (106) raises the possibility that a peripherally-located flow signal may also regulate skeletal muscle contractile function. Indeed, the possible role of the vascular endothelium needs to be considered.

A credible hypothesis can be advanced to explain why skeletal muscle contractile function should be controlled by its blood flow. Rowell(98) has concluded that overall cardiovascular function is regulated during imposed stresses including exercise to maintain the arterial blood pressure. A major determinant of this control is regulation of blood flow to, and blood volume distribution in, the different arterial and venous beds. During exercise, skeletal muscle contractile activity is the major determinant of the overall blood flow and blood volume distribution with the result that the greater percentage of the cardiac output is directed to the active skeletal muscles.

Thus, it makes sense that the variable, skeletal muscle contractile activity, which can most effect whole body blood flow distribution during exercise and therefore the maintenance of an adequate blood pressure, should itself be regulated by the blood flow it receives. If blood flow does regulate skeletal muscle contractile function, then the maximum cardiac output would indeed limit peak exercise performance as traditionally argued(3,74,98). However, this limitation would not be determined by a limiting rate of oxygen delivery to the working muscles, but rather by a limiting cardiac output that is unable to counter the blood pressure lowering effects of any additional fall in total peripheral resistance that would occur if further skeletal muscle recruitment were to induce additional vasodilation in an attempt to increase skeletal muscle blood flow further.

In summary, the testable hypothesis is proposed that exercise under different conditions is limited in both health and disease by a regulated process of skeletal muscle mechanical arrest. During high intensity exercise, this control would prevent the development of irreversible damage (rigor) in the active skeletal muscles. This control could be provided by blood flow regulation of skeletal muscle contractile function and could result from the accumulation of metabolites which reduce skeletal muscle contractile activity and hence the blood flow requirement. On theoretical grounds, control of overall skeletal muscle contractile function by blood flow is an attractive hypothesis as it provides the link for the simultaneous regulation of overall cardiovascular function with skeletal muscle metabolism and contractile activity.

Perhaps the challenge for exercise scientists is better to understand the effectors that might regulate this elegant, albeit still hypothetical, model.

3. Anaerobiosis explains the onset of lactate production by skeletal muscle at the anaerobic threshold. The third creaking and ugly edifice holds that oxygen delivery to the active muscles becomes inadequate, not

at the $\dot{V}O_{2max\cdot Hill}$, but at a lower work rate. This hypothesis stems from another central component of Hill and Lupton's belief that lactic acid accumulates in muscles that contract anaerobically, thereby developing an oxygen debt. The modern confirmation that blood and muscle lactate concentrations increase during submaximal exercise has fortified this belief that anaerobiosis develops in muscle before the plateau in $\dot{V}O_2$ at a submaximal exercise intensity since identified as the anaerobic threshold(109-111,114). Extension of this hypothesis holds that the resulting metabolic acidosis which develops at, and accelerates above, the anaerobic threshold leads to bicarbonate buffering of the excess hydrogen ions released in this process causing an increased CO_2 production. This, in turn, stimulates ventilation leading to simultaneous anaerobic and ventilation thresholds(eqs. 1 and 2).

$$\text{Glucose} \rightarrow 2 \text{ lactate} + 2H^+ \qquad [1]$$

Equation 1

$$H^+ + HCO_3^- \rightarrow H_2O + CO_2 \qquad [2]$$

Equation 2

There are four potential sources of refutation of this specific model.

First, the terminology is inexact. Anaerobic means in the absence of oxygen. But as every manufacturer of expensive equipment for the measurement of $\dot{V}O_2$ during exercise will be quick to assert, whole body $\dot{V}O_2$ is not zero during submaximal exercise. Hence, the muscles are not contracting anaerobically during submaximal exercise. An important discipline of science is to use words according to their exact meanings. When applied to submaximal exercise, the use of the term anaerobic is clearly incorrect. Perhaps the intended meaning is that the active muscles becomes hypoxic during exercise in which case the more correct term should be the hypoxic threshold. If so, the existence of an hypoxic threshold should be identifiable during progressive exercise.

If such a threshold exists, then at some submaximal work rate below the $VO_{2max.Hill}$, $\dot{V}O_2$ must begin to lag behind demand, rendering the active muscles increasingly hypoxic. At that point, $\dot{V}O_2$ will no longer increase linearly with increasing work rate. Thus, the hypoxic threshold should be identifiable as a submaximal work rate well below the $\dot{V}O_{2max\cdot Hill}$ at which $\dot{V}O_2$ no longer increases as a linear function of increasing work rate (Fig. 7).

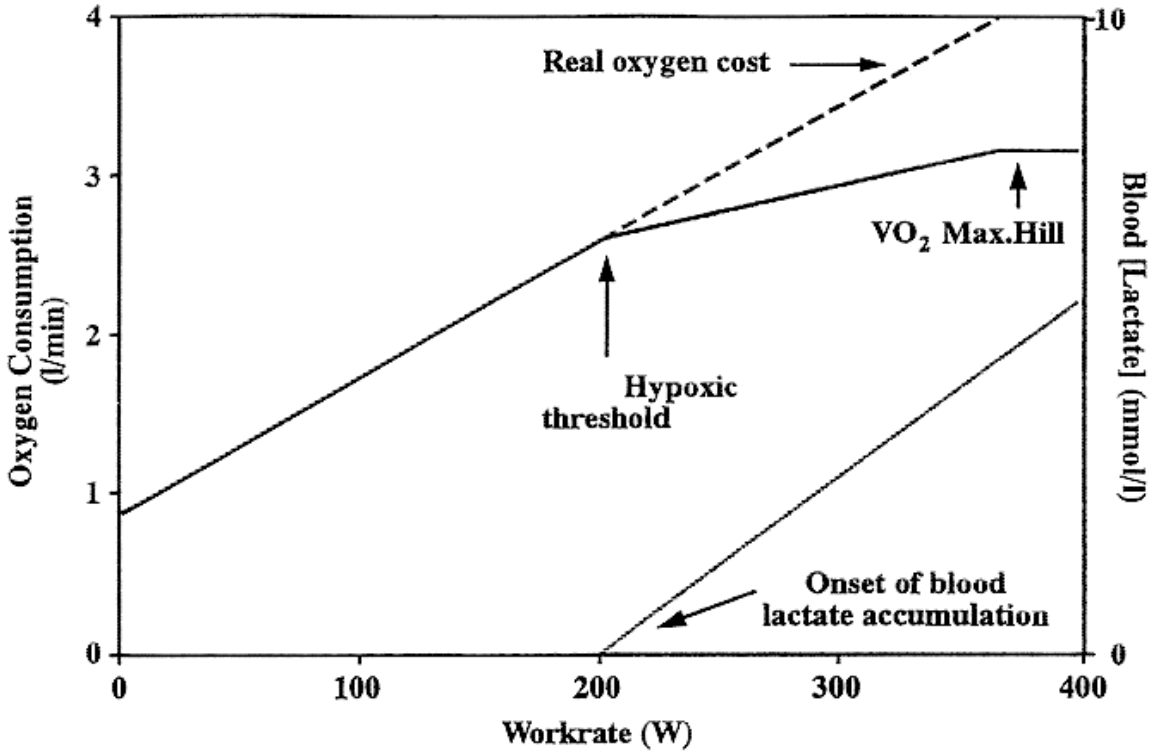

Figure 7-The hypoxic or anaerobic threshold should be identifiable as the submaximal work rate above which (i) the rise in ˙VO2 with increasing work rate deviates from linearity and (ii) lactate first appears in the blood. Neither phenomenon occurs.

But this too does not occur. For if the average sampling time is sufficiently long (30-60 s), so that the breath-to-breath variation in $\dot{V}O_2$ (77) is smoothed, $\dot{V}O_2$ rises as a linear function of increasing work rate even to exhaustion with no evidence of a plateau at the hypoxic threshold (30) (Fig. 8). Thus, the absence of this theoretical hypoxic threshold during the submaximal component of the maximal exercise test is the second potential refutation of this creaking and ugly hypothesis.

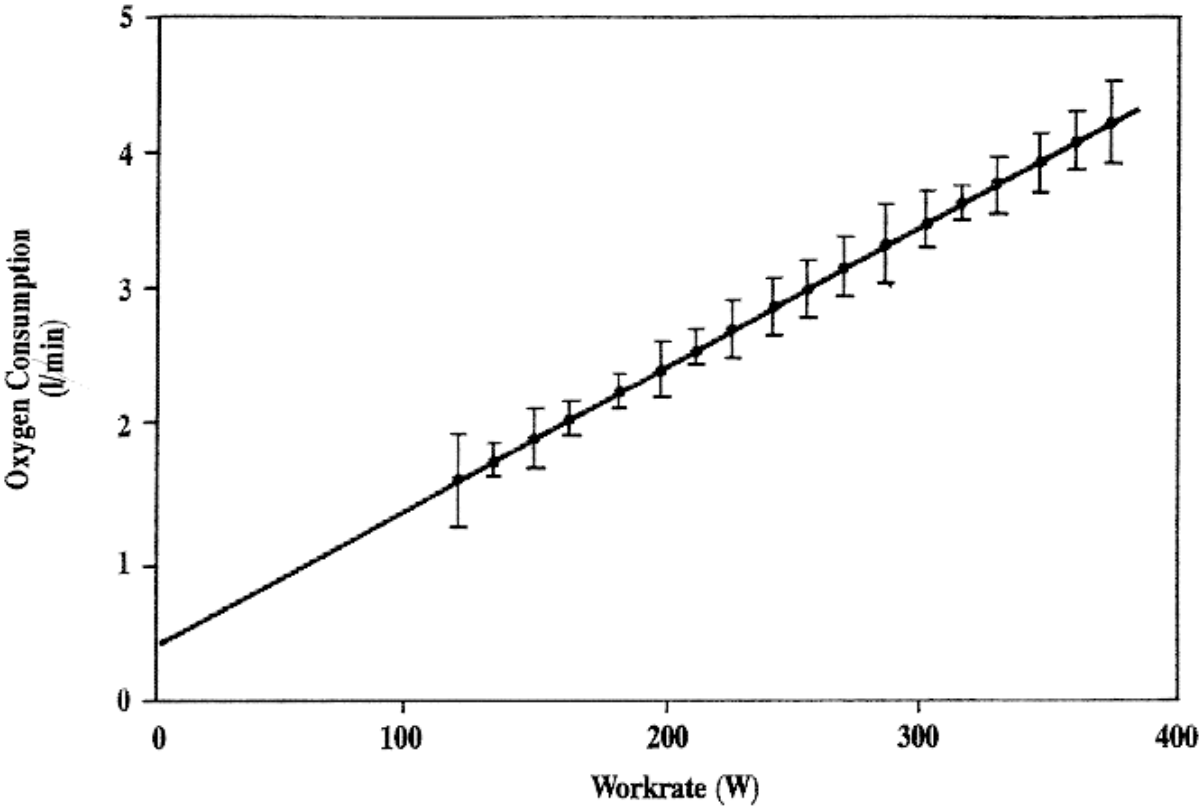

Figure 8-Whole body ˙VO2 rises as a linear function of increasing work rate without evidence for an hypoxic threshold at submaximal work rates or, in this series of a plateau phenomenon. Data from reference 30 . Dennis, S.C., T. D. Noakes, and A. N. Bosch. Ventilation and blood lactate increase exponentially during incremental exercise. *J. Sports Sci.* 10:437-449, 1992.

The third potential refutation of this hypothesis has been provided by new studies of lactate kinetics during submaximal exercise. The question addressed by these studies is: What stimulates muscles to increase their production of lactate, thereby causing blood and muscle lactate concentrations to rise during exercise?

The popular explanation for the increase in the blood lactate concentrations during exercise is probably not greatly different from that described in the classic textbook (4): The production of lactic acid, which culminates in a muscular contraction, is a non-oxidative process and can take place in the absence of oxygen: its subsequent removal is an oxidative process and demands an adequate supply of oxygen. Fletcher and Hopkins consider that the appearance of lactic acid precedes, and is intimately bound up with, the mechanical shortening of the muscle whereas its oxidation is effected after the contraction is over, and brings about the return of the muscle to its former resting condition.

Their explanation includes two ideas: first, that lactic acid is produced exclusively by non-oxidative or anaerobic processes, and second, that lactic acid is the messenger that induces the muscle to contract. The latter postulate is now known to be incorrect; calcium, not lactic acid, is the chemical that initiates muscle contraction. Furthermore, if blood lactate concentrations rise only as the result of hypoxic conditions in muscle, then this model predicts that blood lactate concentrations should be zero at all exercise intensities below the hypoxic threshold.

The first major advance in the understanding of factors determining the rise in blood lactate concentrations during exercise was provided by George Brooks et al. (14-17). Their work has established that the blood lactate concentration is the result of two processes, the production of lactate (appearance, Ra) and its removal(disappearance, Rd) and that these processes can be studied with the use of radiolabeled tracers. This

technique is still not widely used, and this may perhaps explain why these fundamental concepts have yet to receive more universal acceptance.

Using this technique, Dr. Holden MacRae, currently of Pepperdine University in Malibu, together with Professor Steven Dennis and Dr. Andrew Bosch in our laboratory, completed a series of experiments determining the effects of endurance training on lactate metabolism measured with C^{14} lactate tracers (68-70). Figure 9 shows changes in blood lactate concentrations, $\dot{V}O_2$, lactate Ra and Rd, and carbohydrate oxidation during exercise at different work rates. It shows that even at low work rates of 60 W equivalent in these subjects to about 30% $\dot{V}O_{2max}$, there was an appreciable lactate Ra. Clearly lactate production at low work rates cannot be a result of skeletal muscle hypoxia. As rates of lactate disappearance (Rd) matched lactate Ra, blood lactate concentrations remained constant at those low work rates, but were not zero.

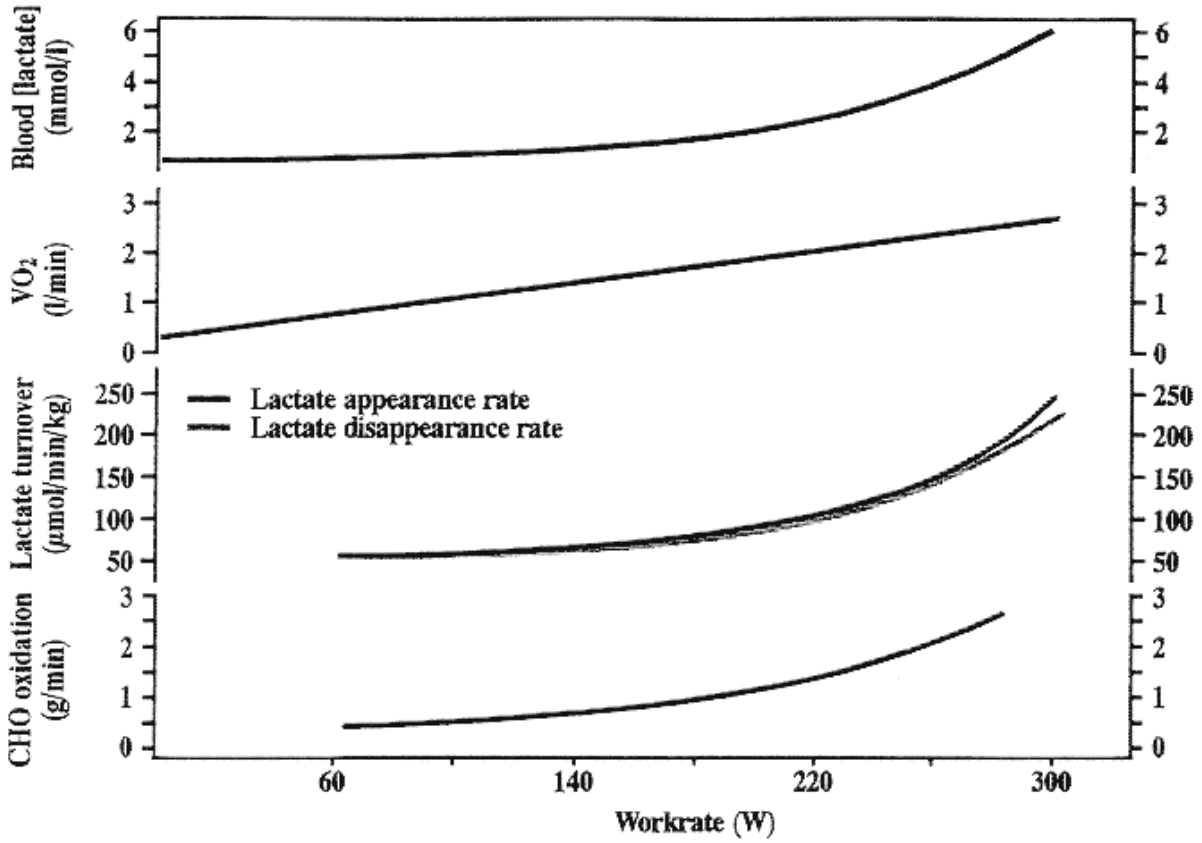

Figure 9-Changes in blood lactate concentrations, ˙VO2, lactate Ra, lactate Rd, and rates of carbohydrate oxidation with increasing work rate during progressive exercise to exhaustion. Note that blood lactate concentrations, lactate Ra, lactate Rd, and rates of carbohydrate oxidation all increase as curvilinear functions of increasing work rate and that lactate Ra, lactate Rd, and blood lactate concentrations are not zero at low exercise intensities. ˙VO2 also increases linearly with increasing work rate without evidence for an hypoxic threshold.

Both lactate Ra and Rd rose as curvilinear functions of increasing work rate. But at higher work rates, lactate Ra exceeded lactate Rd so that the blood lactate concentration began to rise. At those work rates, $\dot{V}O_2$ continued to rise as a linear function of work rate without any evidence for an hypoxic threshold coincident with this increasing rate of lactate production and rising blood lactate concentrations.

The figure also shows that the curvilinear rises in lactate Ra and Rd and in the blood lactate concentrations are matched by a curvilinear increase in the rate of carbohydrate oxidation measured under steady state conditions at the different work rates.

Hence these studies confirm (i) that blood lactate concentrations are not zero at rest; (ii) that there is a measurable lactate Ra at rest and at low exercise intensities; (iii) that lactate Ra and Rd both rise with increasing work rate until a submaximal $\dot{V}O_2$ is reached, at which Ra exceeds Rd causing blood lactate concentrations to rise; (iv) that the work rate at which lactate Ra exceeds Rd corresponds to a $\dot{V}O_2$ that is rising as a linear function of increasing work rate without evidence for anhypoxic threshold; and (v) that lactate Ra, Rd, blood lactate concentrations, and rates of carbohydrate oxidation and of ventilation(30) all increase as curvilinear functions of work rate suggesting perhaps that a common metabolic sequence links these phenomena.

Indeed the fourth source of refutation of the traditional model is a more reasoned explanation for the metabolic sequence that might explain these curvilinear relationships. It is based on the more modern understanding of how protons are generated with increasing rates of carbohydrate oxidation during exercise. Central to this theory is the contention that proton production during exercise is a continuous and not a threshold phenomenon.

Equations 1 and 2 show the original interpretation of how anaerobiosis induces the conversion of glucose to lactic acid with the production of two protons that are buffered in the blood by bicarbonate ions with the release of CO_2, which then stimulates ventilation at the hypothetical ventilation threshold. This interesting hypothesis is threatened by its inaccuracies.

For the critical point ignored in equation 1 is that the conversion of glucose to lactate generates ATP. When the ionic charges associated with this conversion are added to the original equation, it is clear that there is no net proton production when glucose is converted to lactate (29,38,71) (eq. 3). Hence the question arises: From where might the protons arise during accelerated glycolysis? eq. 3

$$\text{Glucose} + 2\text{Mg ADP}^{-} + 2\text{Pi}^{2-} \rightarrow 2\ \text{lactate}^{-} + 2\ \text{MgATP}^{2-} \qquad [3]$$

Equation 3

One argument (29,38) holds that protons accumulate during high intensity exercise because such exercise must be fueled almost exclusively by carbohydrate metabolism. The conversion of glucose or glycogen to lactate or pyruvate generates ATP; the protons required for that ATP synthesis are generated by the steps of the glycolytic pathway. Subsequent hydrolysis of glycolytically-produced ATP releases protons that are not needed for the resynthesis of ATP by that pathway (eq. 4). This contrasts with the resynthesis of ATP via either oxidative phosphorylation or net creatine phosphate breakdown. In those pathways the H^+ ions arising from ATP hydrolysis are re-consumed in ATP resynthesis: eq. 4

$$\begin{array}{lcl} & \text{MgATP}^{2-} \rightarrow \text{MgADP}^{-} + \text{P}_\text{i}^{2-} \rightarrow & \text{H}^{+} \\ \text{pyruvate}^{-} & \vert \qquad\qquad \vert \qquad\qquad \vert & \text{glucose} \\ \text{or} & \text{---------------------------------} & \text{or} \\ \text{lactate}^{-} & & \text{glycogen} \end{array} \qquad [4]$$

Equation 4

At first, the protons generated by high rates of glycolytic ATP breakdown are (i) taken into the mitochondria with pyruvate, (ii) used in the reduction of pyruvate to lactate via the cytosolic pyruvate$^-$ + NADH + $H^+ \leftarrow \rightarrow$ lactate + NAD^+ equilibrium, and (iii) buffered by intracellular histidine residues and by inorganic phosphate. However, unbuffered intracellular protons leave the cell via the sarcolemmal Na^+/H^+ exchangers and the H^+ + lactate$^-$ symport. As a result, this model predicts (i) that muscles dump lactate to remove H^+ into the bloodstream whenever carbohydrate utilization is increased to provide energy for exercise of very high

intensity and (ii) that the respiratory compensations for lactic acidosis are notthreshold responses to muscle hypoxia as has been proposed(109-111,113).

Indirect evidence for this postulate has been provided by MacRae et al.(70) who studied the effects of training on blood lactate concentrations, lactate Ra and Rd, and the ventilatory responses to exercise in previously untrained cyclists.

Figure 10 (*left panel*) shows that this training program greatly reduced the blood lactate concentrations at any submaximal work rate. However, the effect of training on the ventilatory response to exercise was relatively modest. Thus, training dissociated the relationship between changes in blood lactate concentrations and in ventilation predicted by the anaerobic threshold hypothesis. A number of other interventions have also dissociated these two variables(41,45,57,118). Perhaps the most telling such finding is that patients with McArdle's syndrome who lack the enzyme, glycogen phosphorylase, and whose skeletal muscles are therefore unable to produce lactate during exercise nevertheless show aventilation threshold (41), perhaps resulting from some residual capacity to generate glycolytic ATP. Interestingly, a linear relationship between ventilation and the rate of carbohydrate oxidation was unchanged after training (Fig. 10, *left panel*). Figure 10 (*right panel*) shows that training reduces the blood lactate concentration at any rate of carbohydrate oxidation because lactate Ra is reduced whereas lactate Rd is unchanged (68).

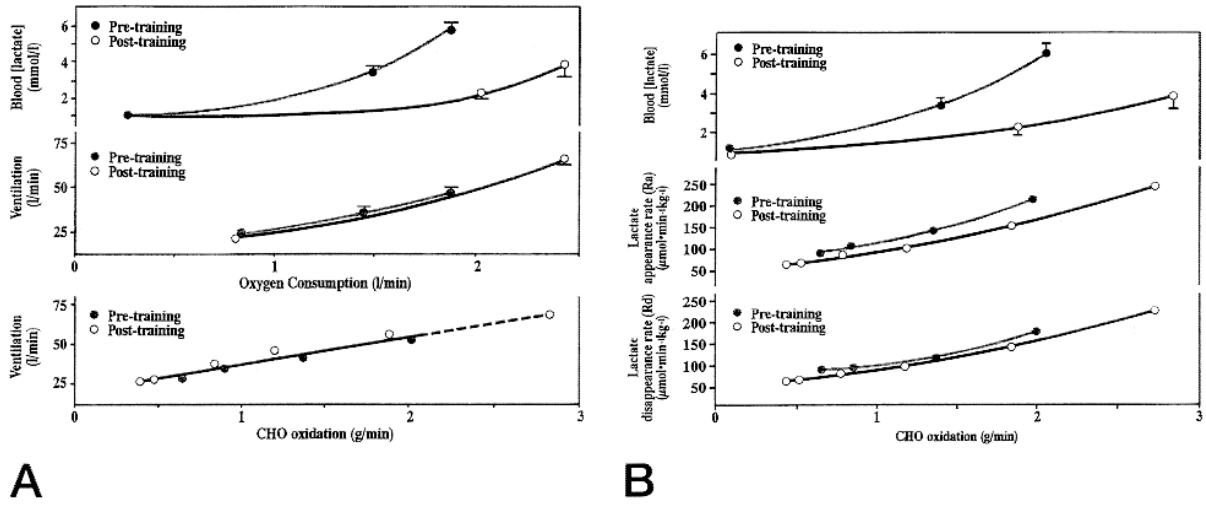

Figure 10-Effects of training on blood lactate concentrations and rates of ventilation with increasing ˙VO2, as well as the relationship between the rates of ventilation and carbohydrate oxidation(*left panel*). Note that the linear relationship between the rates of ventilation and of carbohydrate oxidation is unaltered by training. *Right panel* shows the effects of exercise training on blood lactate concentrations and on lactate Ra and lactate Rd at increasing rates of carbohydrate oxidation. Data from reference 70 . MacRae, H. S-H., T. D. Noakes, and S. C. Dennis. Role of decreased carbohydrate oxidation on slower rises in ventilation with increasing exercise intensity after training. *Eur. J. Appl. Physiol.* 71:523-529, 1995.

The finding that the rates of ventilation and of carbohydrate oxidation are linearly related both before and after training can be explained by a physiological model in which the progressive curvilinear increase in carbohydrate oxidation during ramp exercise causes a progressive increase in the rate of H^+ production according to equation 4. In turn, this continual increase in proton production causes the exponential increase in ventilation with increasing work rate, a relationship that was unaffected by exercise training.

In summary, there are four crucial sources of refutation for the anaerobic threshold hypothesis. In particular, the terminology is incorrect; there is no identifiable hypoxic threshold during progressive exercise; studies of lactate kinetics show that blood lactate concentrations rise during exercise when lactate Ra exceeds lactate Rd; and, finally, the conversion of glucose or glycogen to lactate does not produce H^+. Rather, utilization of glycolytically-produced ATP releases the H^+ which are reconsumed only if the ATP is regenerated via the oxidative mitochondrial pathways. Hence H^+ production by muscle is not a threshold phenomenon but

increases progressively with increasing rates of carbohydrate and glycolytic ATP use. Thus, all the phenomena traditionally described on the basis of ananaerobic threshold, might be better explained by the progressively increasing rate of carbohydrate oxidation that occurs during ramp exercise of increasing intensity.

Therefore, one might argue that the lactate anaerobic threshold is a theoretical concept for which, like the Bassler hypothesis and the $\dot{V}O_{2max\cdot Hill}$, there is currently no firm experimental support. Furthermore, no logical argument can be presented to support this specific conjecture. Rather, an alternate hypothesis is compatible with all the present observations.

4. Mitochondrial adaptations and exercise performance. If oxygen delivery to muscle determines exercise performance, then it has been logical to assume that any training adaptations that improve exercise performance, must also enhance oxygen delivery to, and utilization by, the active muscles during exercise. The universal finding that the $\dot{V}O_{2max}$ increases with training (3,98), is compatible with this interpretation.

Furthermore, since the earliest study showing that chronic exercise produces mitochondrial adaptations in those skeletal muscles that are active during the training program (28,52), it has been assumed that these changes also explain the training-induced adaptations in skeletal muscle metabolism and performance. But such cross-sectional studies are unable to prove this assumption. To verify that skeletal muscle mitochondrial adaptations cause the training-induced changes in metabolism and performance, it is necessary to show that mitochondrial changes, metabolism, and performance all change in the same temporal sequence and to a similar degree during longitudinal training studies. But such longitudinal studies have shown that training-induced changes in exercise performance or metabolism can occur without or before there are measurable skeletal muscle mitochondrial adaptations.

For example, in one study (64) rats were trained for either 4, 8, or 12 wk and sequential changes in their run time to exhaustion during maximum and submaximum exercise, and in their skeletal muscle oxidative capacity were measured. The unexpected finding was that run time to exhaustion increased before skeletal muscle oxidative capacity altered.

Similarly, a study in humans showed that the addition of six to eight sessions of very high intensity training to their usual endurance-type training program substantially improved the performance of cyclists during a simulated 40-km time trial in the laboratory (112). That training effect occurs without measurable changes in the activities of key skeletal muscle mitochondrial and glycolytic enzymes(113).

Similarly, training-induced changes in metabolism during exercise can occur before skeletal muscle mitochondrial enzyme activities increase. This has been shown most clearly by Phillips et al. (90,91). Their studies show that five consecutive daily training sessions, each of 2 h duration at 60% of $\dot{V}O_{2max}$, altered the metabolic response to exercise in previously untrained humans. These adaptations occurred before there were measurable changes in skeletal muscle mitochondrial enzyme activities. These metabolic adaptations were more marked after 30 d of training, by which time the first changes in the activities of the mitochondrial enzymes, SDH, MDH, and B-HAD, were measured.

Thus, the conclusion from these studies must be that factors other than increased skeletal muscle mitochondrial enzyme activities explain the early changes in exercise performance and metabolism that result from aerobic endurance training. The point is that skeletal muscle adapts in many ways to exercise training and the intellectual challenge is to determine (i) which of those changes explain the training-induced alterations in metabolism and performance and (ii) what are the real physiological and biochemical effects of the increased skeletal muscle mitochondrial enzyme activities. For example, studies showing that weight training can increase aerobic endurance performance and $\dot{V}O_{2max}$ suggest that skeletal muscle strength may be a factor influencing endurance capacity (82).

5. A high carbohydrate diet maximizes performance during training. The belief that a high carbohydrate diet is essential for the maintenance of optimal daily training loads stems from the original research that followed the introduction of the skeletal muscle biopsy technique in Sweden in the 1960's (1,11,46). This research established that the higher the carbohydrate content of the diet during the last few days before an exhausting exercise bout, the higher the initial muscle (and liver) glycogen content and the longer the duration of exercise that could be sustained until fatigue (Fig. 11). More modern studies confirm that a high

carbohydrate diet can also increase performance during a set exercise task in which the speed of completion, rather than the duration of exercise, is the measure of performance(94). The logical assumption is that the ideal diet for a single exercise bout to exhaustion would also be optimum for repeated daily bouts of exercise, that is, for daily training. Thus, the consensus opinion is that a diet rich in carbohydrate (>70% of total energy intake) should be ingested by all endurance athletes during training(1,11,18,23,44,79,83).

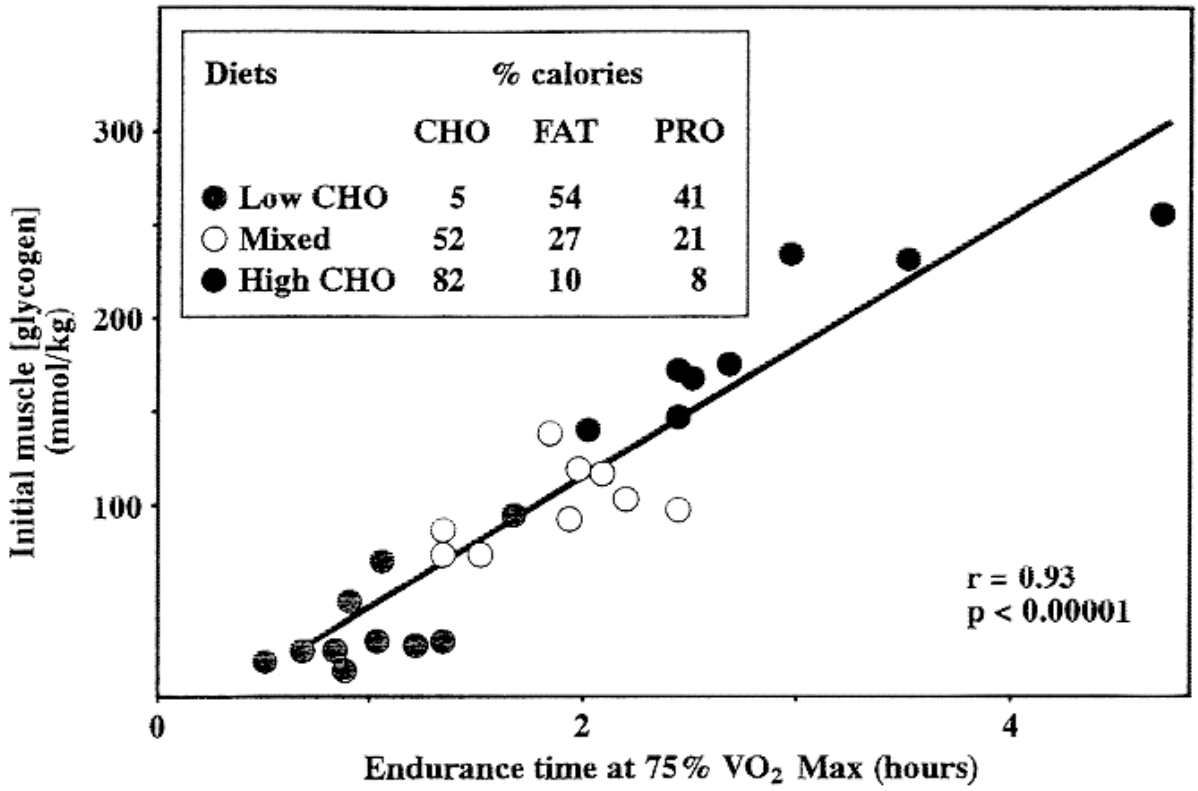

Figure 11-There is a linear relationship between the starting muscle glycogen content and the duration for which a subsequent bout of endurance exercise can be sustained. From data of reference 11 . Bergstrom, J., L. Hermansen, E. Hultman, and B. Saltin. Diet, muscle glycogen, and physical performance. *Acta. Physiol. Scand.* 71:140-150, 1967.

Three potential sources refute this consensus.

First, athletes do not eat such rich carbohydrate diets during training. In a review of the literature, Hawley et al. (44) show that the percentage of the energy intake provided by carbohydrate in the habitual diets of athletes has not changed materially over the past 50 years. This is despite the recent intrusion of sports nutritionists dedicated to the promotion of high carbohydrate diets for all endurance athletes. Thus, the diets of some marathon runners in the 1948 Olympics contained 44% carbohydrate(12); a more recent study found that carbohydrate contributed only 52% of the dietary energy intake of a group of marathoners(19). Figure 12 shows that these findings are representative of all the reported studies. This information is important because it conflicts so absolutely with what athletes are told. It is important that we should discover whether our scientific advice is incorrect.

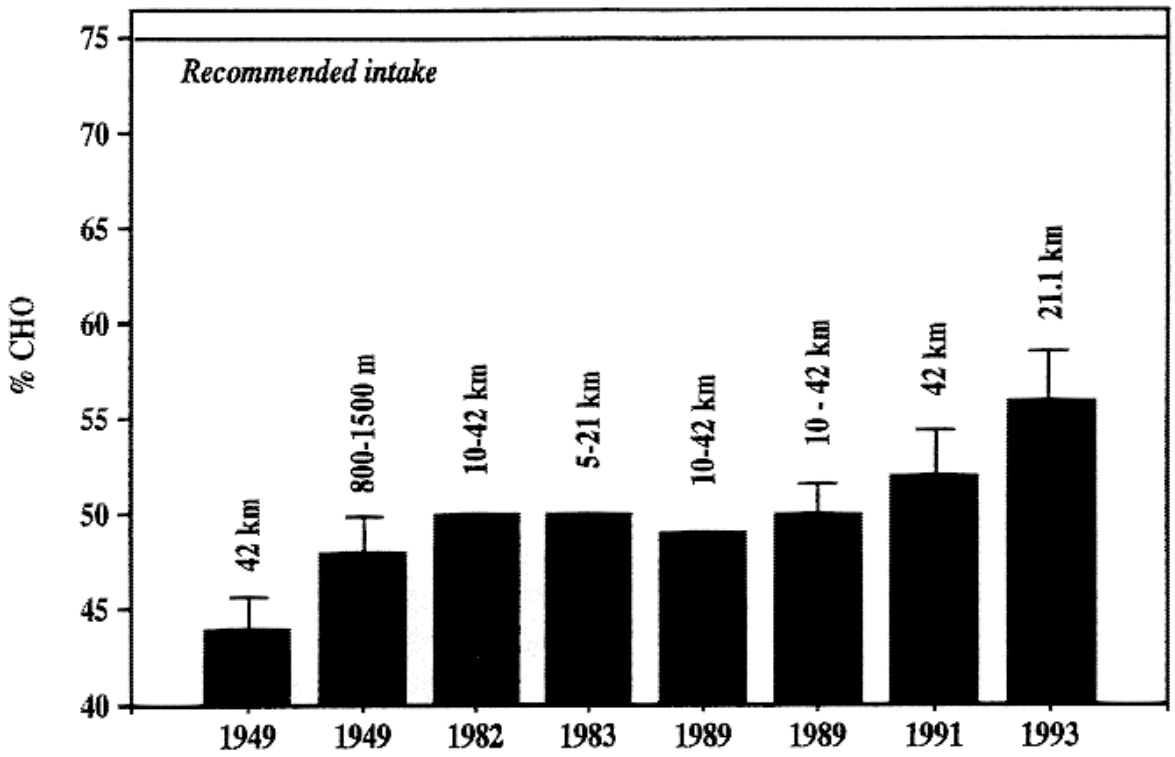

Figure 12-Actual vs recommended dietary carbohydrate intakes reported in studies of endurance athletes from 1949-1993. Note that the percentage contribution of carbohydrate to the daily dietary energy intake has not changed materially in the last half century and is substantially less than is currently recommended. Complete references to each individual study can be found in reference 44 **. Hawley, J.A.,S.C. Dennis, F. H. Lindsay, and T. D. Noakes. Nutritional practices of athletes: are they sub-optimal? *J. Sports Sci.* 13:S75-S87, 1995.**

The second source of refutation are interventional studies that have measured the effects of alterations in dietary carbohydrate content on performance during training. Two such studies(63,103) have shown that performance during training was not materially different in athletes eating diets with either high or low carbohydrate contents. Sherman and Wimer(101) have concluded that: The hypothesis that insufficient dietary carbohydrate during training causes low muscle glycogen concentrations that, in turn, cause diminished training or performance capabilities and overreaching or staleness, is not strongly supported by the literature.

The third potential source of refutation are studies showing that a period of adaptation to a low carbohydrate diet may improve subsequent performance during prolonged exercise. An early study in our laboratory showed that subjects who adapted to a low (7%) carbohydrate diet for 2 wk were able to exercise for longer during an exercise bout at 60% $\dot{V}O_{2max}$ that was preceded by bouts of high intensity exercise (65). Similarly, Muoio et al. (76) showed that endurance time at 70-85% $\dot{V}O_{2max}$ was increased in athletes who had pre-adapted to a high (40%) fat diet.

Pre-adaptation to a high fat diet may enhance performance by inducing specific adaptations in the skeletal muscle mitochondrial enzymes that increase the capacity to oxidize fat during exercise(20). This adaptation may explain why subjects who have adapted to a high fat diet continue exercising with muscle glycogen concentrations that are lower than those causing exhaustion in subjects who habitually ingest high carbohydrate diets (65).

Therefore, the conclusion must be that the ergogenic effects of a high carbohydrate diet are established only for acute ingestion during the last 3 or more days before a single bout of prolonged endurance exercise. There is a need to study the ergogenic effects of dietary manipulations other than a high carbohydrate diet, especially

in activities that last more than 3-4 h and in which a greater capacity for fat oxidation might enhance performance, especially when muscle glycogen concentrations are low.

CONCLUSION TOP

The English scientist of the last century, Thomas Huxley(58, p. 3), wrote that: The known is finite, the unknown is infinite; intellectually we stand on an island in the middle of an illimitable ocean of inexplicability. Our business in every generation is to reclaim a little more land.

I come from the city of Cape Town, which is situated on a small peninsula surrounded by two great oceans at the very base of Africa. From that isolated peninsula so far away from the intellectual capitals of the world, I have fashioned a challenge for exercise scientists to reclaim some more land in our young discipline. I have indicated the debt that I owe to the United States and to this College and its members. I have tried to repay some of that debt by challenging especially the young members of our College to be true to the aims and methods of scientific endeavor as I understand them. The core challenge is always to question the very beliefs that we hold most dear.

The central conjecture that I have questioned originates from the statement by Hill et al. in the 1920's to the effect that: The oxygen intake(during maximal exercise) may attain its maximum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory systems. This conjecture has exerted a profound influence on the teaching of exercise physiology for the past 70 years. It predicts a physiological model in which exercise, especially of high intensity, causes the oxygen demand of the active muscles to outstrip the available oxygen supply, requiring the muscles to contract in the face of a developing anaerobiosis. This physiological model also predicts: that anaerobic conditions in muscle terminate maximal exercise; that the onset of anaerobiosis occurs at the anaerobic or lactate threshold, causing blood lactate concentrations to rise during submaximal exercise; and that the principal effect of exercise training must be to induce skeletal muscle mitochondrial and capillary adaptations that increase the capacity of those muscles to use a limiting oxygen supply during exercise.

Yet the contradictory evidence is absolute. Hill's original conclusions were not supported by his own findings. Therefore, the original basis for this physiological model is without substance. If the basis for the model is in doubt, then it behooves us to question vigorously the further predictions of that original model.

The alternate model proposes that skeletal muscle contractile function is regulated by a hierarchy of controls specifically to prevent damage to any of a number of different organs. Severe anaerobiosis is one specific endpoint that must be thwarted so that irreversible rigor and necrosis in the active muscles is prevented. The challenge for exercise scientists is to understand how the body anticipates the potential for organ damage and how skeletal muscle contractile function is regulated specifically to preclude any such calamities.

No doubt many will be tempted to reject this new conjecture as the rantings of an irreverent and ill-educated foreigner. But that would be the most simple response because it does not require that one question personal dogmas. Former United States President William Taft, who was himself raised in Cincinnati, the city hosting this year's J. B. Wolffe Memorial lecture, warned against this approach: We cannot meet new questions nor build the future if we confine ourselves to the dogmas of the past.

This capacity to embrace new ideas and to challenge the dogmas of the past is perhaps the greatest treasure bequeathed to the world by the United States and Western culture. Columnist Jeff Wise (117) captured the importance of this influence: If the West means anything at all, it is not a specific set of values, but a meta-value, an idea about ideas. It is about throwing open the gates to the richness of world culture and daring to embrace the best of what you find. The prospect can be intimidating; it promises wholesale cultural changes, possibly radical ones.

Perhaps the dare for our young exercise scientists is to be open to these ideas from Africa, regardless of the wholesale, perhaps intimidating intellectual challenges that they may pose. We will best serve our science if we continuously question all our beliefs, regardless of their origin or how hallowed they have become.

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$\dot{V}O_{2max}$; ANAEROBIOSIS; ANAEROBIC THRESHOLD; LACTATE; MITOCHONDRIA; CARBOHYDRATE; SCIENTIFIC METHODS; POPPER