CONCLUSION

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DESIGN AND PERFORMANCE OF MUSCULAR SYSTEMS: AN OVERVIEW

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For a general physiologist, A.V. Hill's definition that 'muscle is a machine that converts chemical to mechanical energy at constant temperature' is still a valid concept. But it is clearly not sufficient to tell us how muscles are used to perform a variety of different functions, such as locomotion, pumping blood through the circulation or air into the lung, or even catching prey and ingesting food. Muscles must be organized in a proper way, they must be operated in a well controlled fashion, and they need fuel which must be supplied according to needs. The 'muscular system' (Fig. 1) can thus be defined as the concerted action of molecular events permitting the generation of mechanical force, with the biochemical and physiological functions of energy supply under the control of the nervous system. Because of the dependence of all parts of the system on all others, any part can in principle limit the performance of the entire system. One important question is therefore to see how the various parts react when the demands on the system are altered, in other words, to see how malleable the system is.

THE BASIC UNIT

In all striated muscles, the basic unit of muscle function is the sarcomere of a myofibril (Fig. 2). This unit generates force by the interaction of myosin and actin, a force which is in effect directional, as it is exerted on the actin filaments which are anchored in the Z-disks. This force can only be generated if ATP is immediately available; the basic unit is therefore associated with enzyme complexes that generate ATP from various substrates, be it enzymes of the glycolytic sequence, mitochondria for oxidative ATP formation, or creatine phosphokinase for drawing on the cell's high energy phosphate reserves. On the control side, the unit is associated with elements of the sarcoplasmic reticulum which regulate the flux of calcium ions under the control of the cell membrane that extends, through the system of T-tubules, into the immediate vicinity of the sarcomere. The basic unit therefore assembles, at the organelle level, all components of the muscular system: mechanical force generator, control and fuel supply.

It is interesting to note that the sarcomere has the same basic design in all vertebrates, and in many invertebrates as well. The fundamental invariant in the functional features of the sarcomere is that maximal stress, that is the maximal force

generated per unit cross-sectional area, is a constant. This is related to the fact that all sarcomeres have equal length in all muscles throughout the animal kingdom. In cross-section, actin and myosin are highly ordered in a hexagonal para-crystalline lattice, allowing all myosin heads to become attached to an actin filament. All myosin heads in one half-sarcomere pull on the actin filaments of that half-sarcomere and therefore act in parallel. The invariant nature of maximal stress is said to be related to the strength of the actin filaments. In this respect it is interesting to note that the actin molecule is a highly conserved protein which appears to be genetically invariant. On the other hand, myosin is a variant component of the sarcomere; up to 13 genes have been identified which make myosin isoforms that differ mostly with respect to the time constants of crossbridge cycling. Fast-twitch and slow-twitch muscles differ essentially with respect to the myosin isoforms of their sarcomeres. The myosin composition of sarcomeres becomes modified during development, and even in adult muscles the nature of the myosin isoforms can be modified if altered performance is required.

On the energy supply side it appears that mitochondria with their complex of Krebs cycle enzymes and respiratory chain are highly conserved units; this seems to hold for the enzyme composition as well as for the surface density of inner mitochondrial membrane, the design element that allows coupling between oxidation and

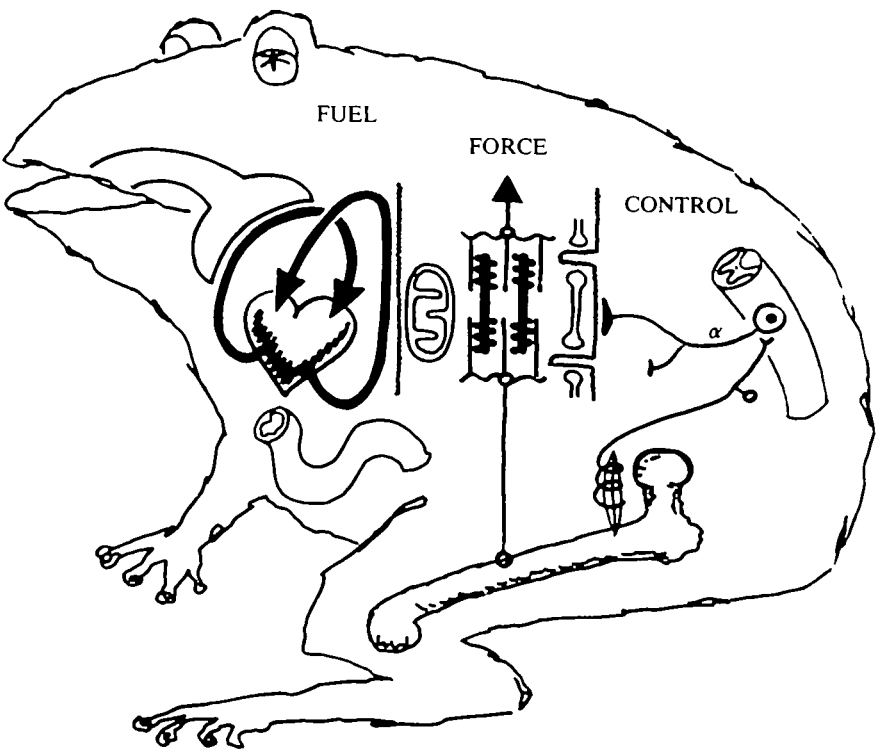


Fig. 1. The muscular system.

phosphorylation. The enzyme system of glycolysis is also highly conserved, at least as far as the activity levels of the various enzymes is concerned. The energy supply unit to the muscle is, however, modulated to match the metabolic requirements of the sarcomere; this is achieved particularly by modifying the quantitative balance between the different enzymes.

On the control side it appears that the membrane of the sarcoplasmic reticulum is also invariant with respect to its capacity to release and absorb Ca^{2+} ions. The need for different Ca^{2+}fluxes imposed by the capabilities of the myosin molecules is met by modifying the density of sarcoplasmic reticulum tubules.

MAKING A MUSCULAR SYSTEM

The muscular system results from assembling basic units of different characteristics according to an ordered design, and by connecting them in a hierarchic fashion to the energy supply and the nervous control systems (Fig. 1). The musculoskeletal system represents a complex assembly of muscle fibres of different characteristics so as to allow for both rapid force generation and sustained muscle activity. Some of the design principles of connections of muscles with the nervous system allow an ordered recruitment of motor units in relation to different patterns of locomotion. The muscles can be subdivided into task groups which become activated during different parts of limb movement. The interaction of different muscle fibre groups in making for well-balanced movements begins to be understood, but this is evidently a field where much new insight can still be gained. The same is true for the problem of mechanical efficiency of muscles and the contribution made by the arrangement of fibres or the pattern of connection to tendons and bones.

The energy supply to the muscle cells receives a great deal of attention because the cost of locomotion, and of muscle activity in general, is reflected in the amount of

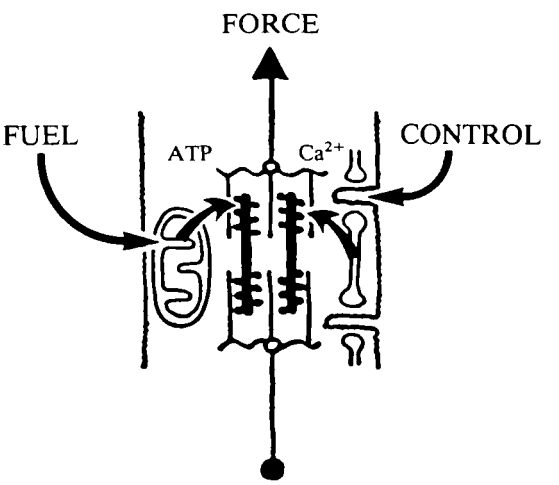


Fig. 2. The basic unit.

energy consumed. One is usually equating energy supply to the muscles with oxygen supply through the respiratory system for the good reasons that (1) in oxidative phosphorylation the amount of ATP produced is stoichiometrically related to the amount of O_2 consumed, and that (2) O_2 must be supplied continuously through blood and lung and is therefore a potential limiting factor of muscle energetics. On the other hand it appears that some of the design properties of the energy supply system, particularly of the microvasculature, cannot be accounted for solely on the basis of O_2 supply; the supply of substrates, the redistribution of lactate, the removal of heat and wastes are additional factors to be taken into account.

The question of whether muscle mitochondria are more closely related to maximal oxygen consumption or to endurance capacity is not settled. In some studies on the adaptability of muscles to increased demand it appears that the amounts of mitochondrial enzymes correlate more closely with endurance capacity, whereas comparative studies demonstrate a close proportionality between maximal oxygen consumption and mitochondrial content of muscles. Maybe these arguments can be resolved by considering what happens in the mitochondria. Between the mitochondria and the myofibrils energy is carried in the form of high energy phosphates (ATP). The energy carried *to* the mitochondria is however contained in substrates and oxygen. One can therefore look at the energy pathway as a sequence of two very distinct steps, with the mitochondria as a link (Fig. 3). In a well designed system we would expect the mitochondria to respond to the ATP demands of the myofibrils, and the respiratory system to the oxygen demands of the mitochondria. Indeed, in a recent comparative study on the mitochondrial content of heart muscle it was found that the quantity of mitochondria was related to the work output of the heart (Fig. 4), that is to the ATP demand. The work output of the heart is, however, not matched to maximal oxygen consumption but rather to the work required to pump the blood through the vascular system at about the same blood pressure in all mammals, irrespective of size. It must also be considered that oxygen consumption measured in the lung reflects the energetic demands on the system by *all* working organs. Adaptations achieved in one muscle group by specific training should therefore lead to an increase in mitochondrial mass proportional to energy demand in that muscle group; but the effect on the overall demand for oxygen expected from such local adaptations would necessarily be smaller. On the other hand, local and overall changes may well be similar when considering the effects of body size on energetics.

WHAT CAN BE LEARNED FROM COMPARATIVE PHYSIOLOGY?

One of the most remarkable features of the muscular systems is that the basic mechanisms are so universal; this appears to indicate that an optimal solution may have been found early on in the course of evolution. New methods, such as nuclear magnetic resonance, provide new insights into parts of these mechanisms, for example the role played by phosphocreatine as a buffer for high energy phosphate supply to myosin. Technical progress also allows old methods, such as low angle X-ray diffraction, to be further exploited in order to unravel the details of molecular

interaction within the sarcomere in the course of contraction. Computer analysis of the activity of motor units provides an explanation of how movements of the limbs can be smooth in spite of the twitch-like contraction of muscle fibres.

However, many observations remain difficult to explain and further progress cannot be expected to come merely from descriptions of processes. It is also possible that one may be led astray by concentrating too much on convenient 'laboratory models', such as the frog sartorius, the rat extensor digitorum longus, or the human vastus lateralis, muscles often chosen for study because of their easy accessibility. Some enigmas may be solved by taking a broader view.

This is where comparative physiology can play an important role in that it offers 'experiments of nature' where the system has been disturbed in one way or another in order to cope with special requirements. Comparative physiology can also reveal the coincidence of identical muscle properties occurring in vastly different evolutionary states. One example is that of an astonishingly low efficiency of locomotion in small mammals as compared to larger species, a low efficiency similar to that observed in insects.

An apparent paradox is also found in animals of different size. The time constants of contraction are determined by myosin isoforms. It has been shown that the molecular structures of slow and fast myosin are very similar throughout mammalian muscles.

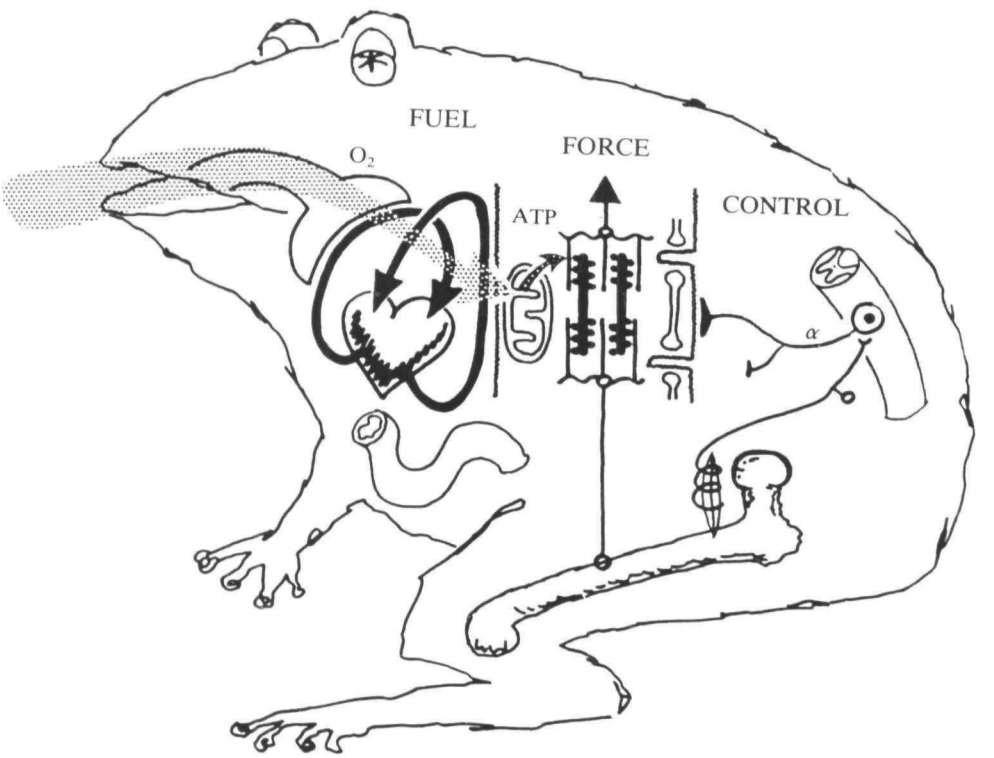


Fig. 3. The energy flow in the sarcomeres is broken into two steps, with the mitochondria as a link.

The time constants are, however, also affected by body size such that they decrease as body mass increases, in proportion to $M_b^{-0.25}$. This leads to the paradox that slow muscles of the mouse are actually faster than fast muscles of the cat – and still the cat catches the mouse! Such paradoxes could perhaps be resolved if the variation occurring in the animal kingdom were systematically exploited, combining physiological, biochemical, morphological and genetic methods.

In this respect it appears particularly worthwhile to look at limiting cases where special solutions are needed to make the system work. It is interesting that some muscles in molluscs are capable of generating a greater maximal force per unit area than usual, and that these muscles contain a particularly high amount of actin. The hypothesis that maximal stress is limited by the strength of actin could be tested by looking at such cases. Insect flight muscles are required to develop contraction rates which cannot be achieved by synchronous stimulation of muscle contraction from the nervous system; in some insects the principle of asynchronous control has therefore evolved.

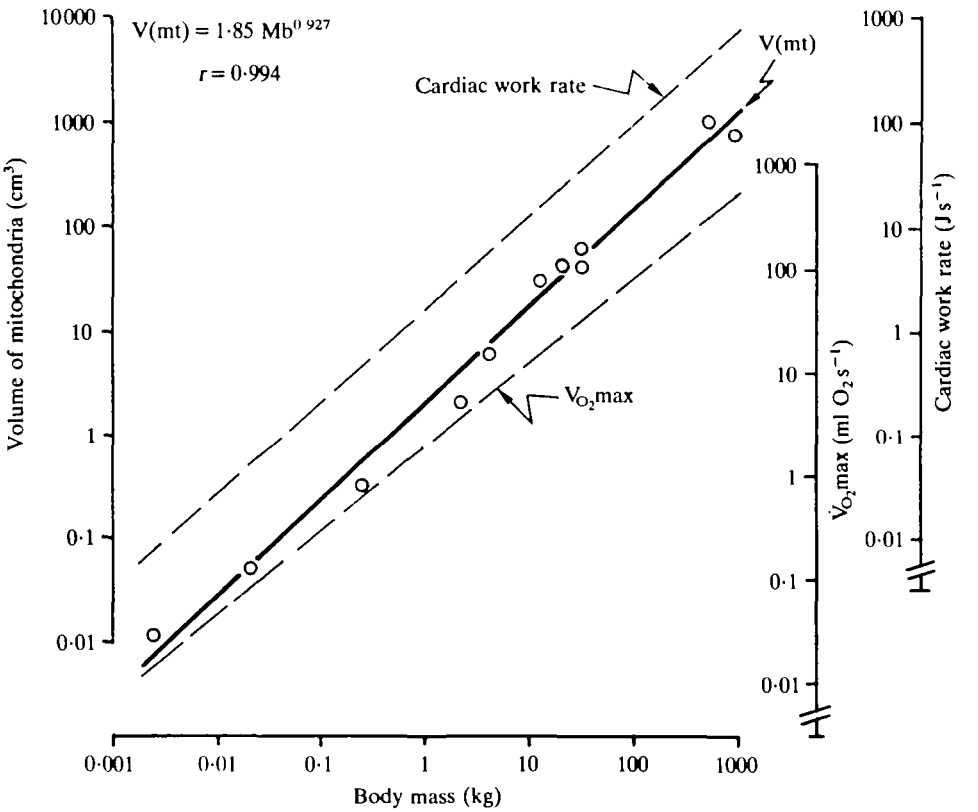


Fig. 4. The volume of mitochondria in the heart for 11 species correlates more closely with cardiac work (ATP needs) than with $\dot{V}_{O_2}max$. [Reproduced with permission from H. Hoppeler, S. L. Lindstedt, H. Claassen, C. R. Taylor, O. Mathieu & E. R. Weibel (1984). *Respir. Physiol.* **55**, 131–137.]

One interesting limiting case is the smallest mammal hitherto known, the Etruscan shrew, *Suncus etruscus*, whose adult body weight is 2–2·5 g. Recently, a bat weighing only 2 g has been discovered in caves in Thailand, but this animal has not yet been studied physiologically. Why is there no mammal smaller than 2 g in body mass? One reason may perhaps be found in the heart muscle of these animals. Fig. 5 shows that the heart of the Etruscan shrew must beat at a frequency of over 1000 per minute, that is at about 20 Hz! To supply the energy for this enormous work output the myocardial cells incorporate a large amount of mitochondria which occupy 45 % of the cell volume. It is interesting to note that this volume density of mitochondria is the highest ever found in muscle cells; the fastest contracting muscles in insects also have volume

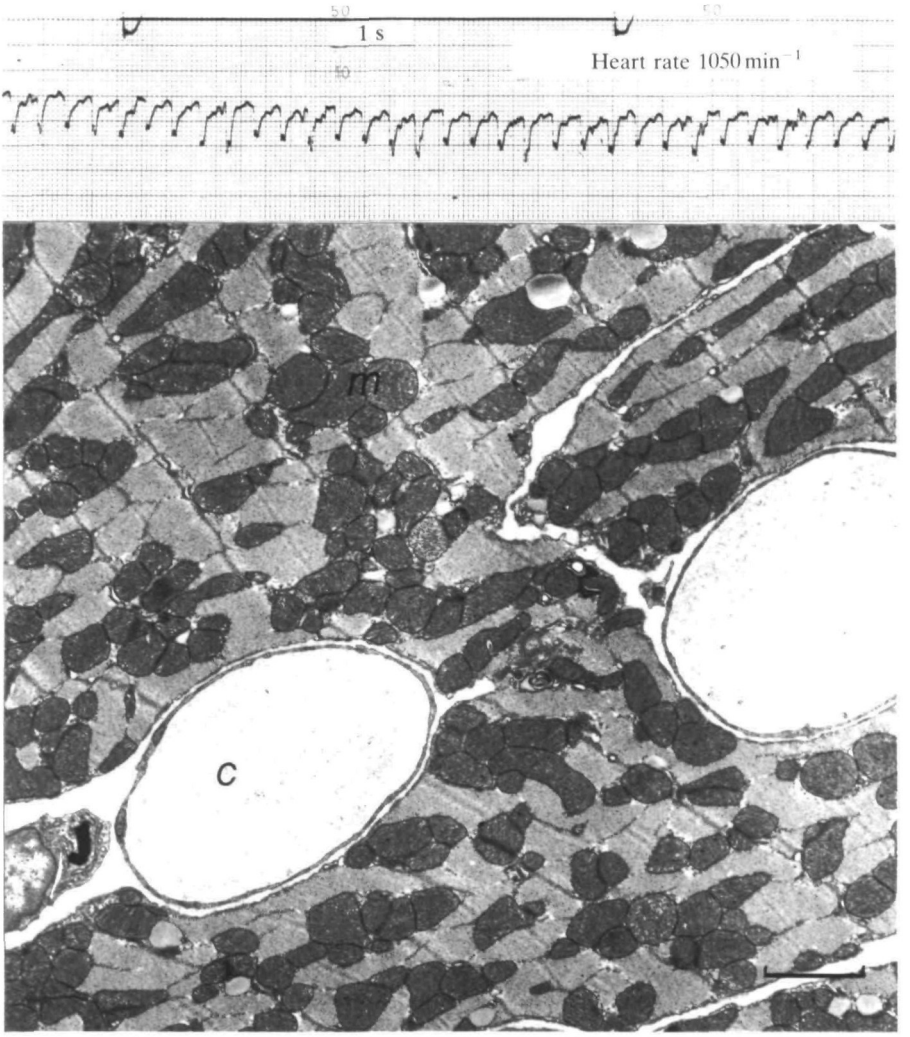
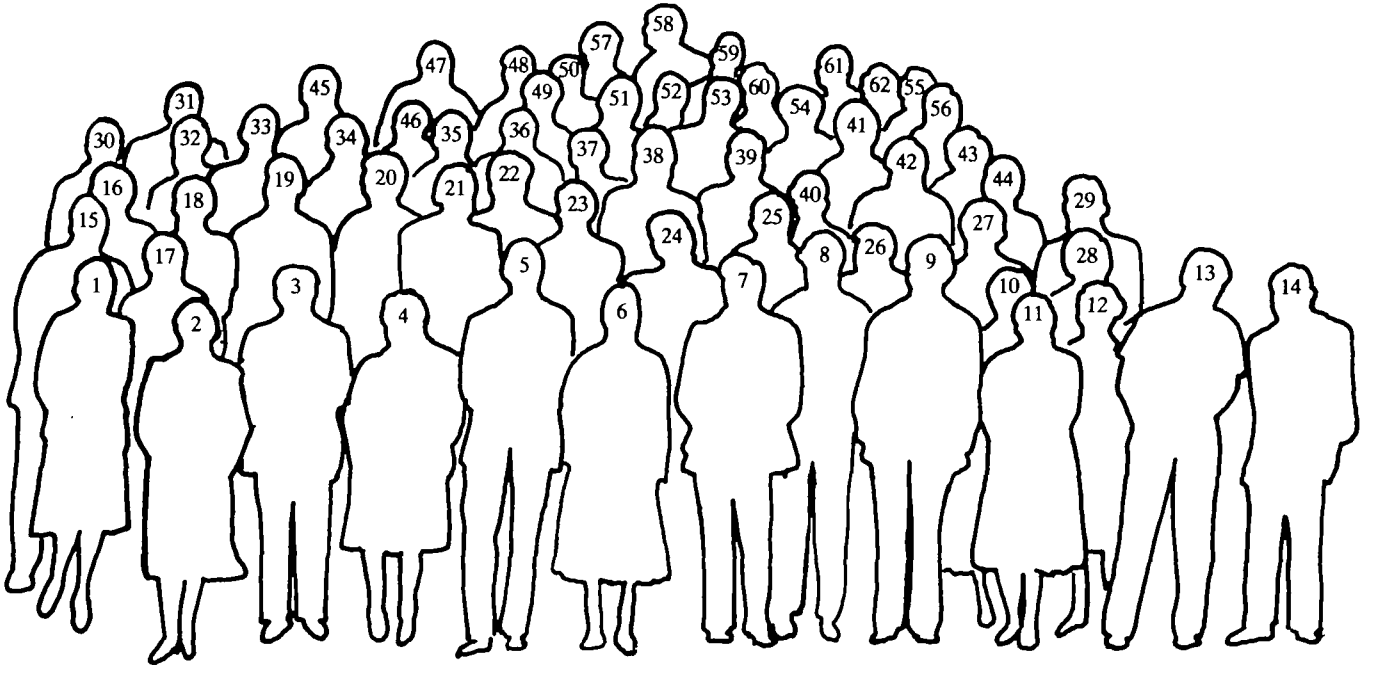


Fig. 5. Electrocardiogram and electron micrograph of heart muscle from Etruscan shrew (*Suncus etruscus*) showing mitochondria (*m*) and capillaries (*c*). Scale marker, 2 μm.

densities of that order of magnitude. In a way, this appears to make sense because it does not seem reasonable to build a muscle fibre where much less than half of the fibre cross-section is available for housing the force generator, that is the myofibrils. If a mammal were made lighter than 2 g, then the heart frequency would have to rise further and accordingly the increased demand for ATP would require an even greater density of mitochondria. Thus, maybe a limit of engineering feasibility has been reached. The coincidence of this construction limit in mammals and in insect muscles is remarkable, and it would be of great interest to explore the animal kingdom in order to see whether this limit is exceeded in some special cases and for what reasons.

It appears worthwhile to look around for limiting cases of this kind because they can help us dissect some of the basic principles underlying the design and performance of muscular systems.

Photographs taken at the Seventh International Conference on Comparative Physiology held at Crans-sur-Sierre in June 1984



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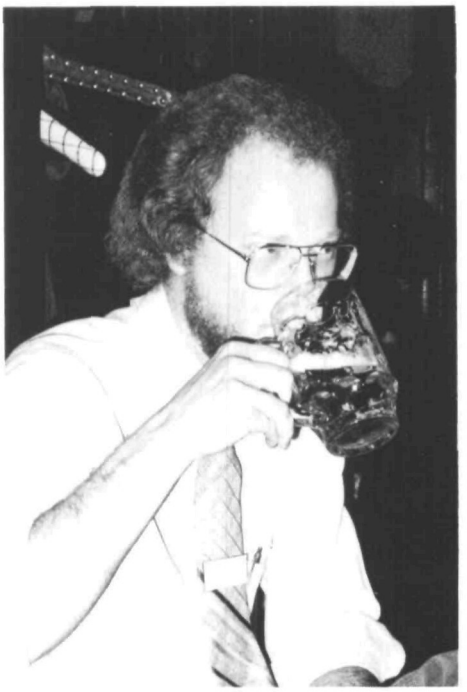

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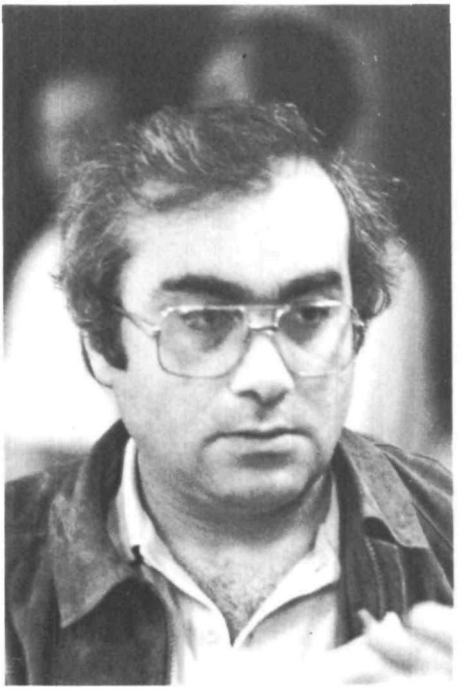

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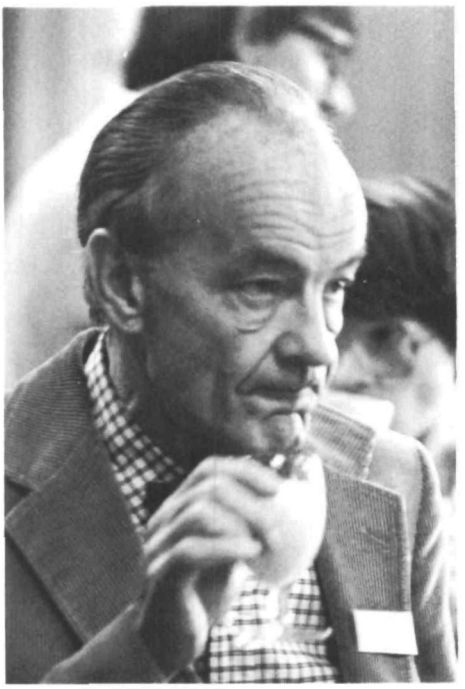

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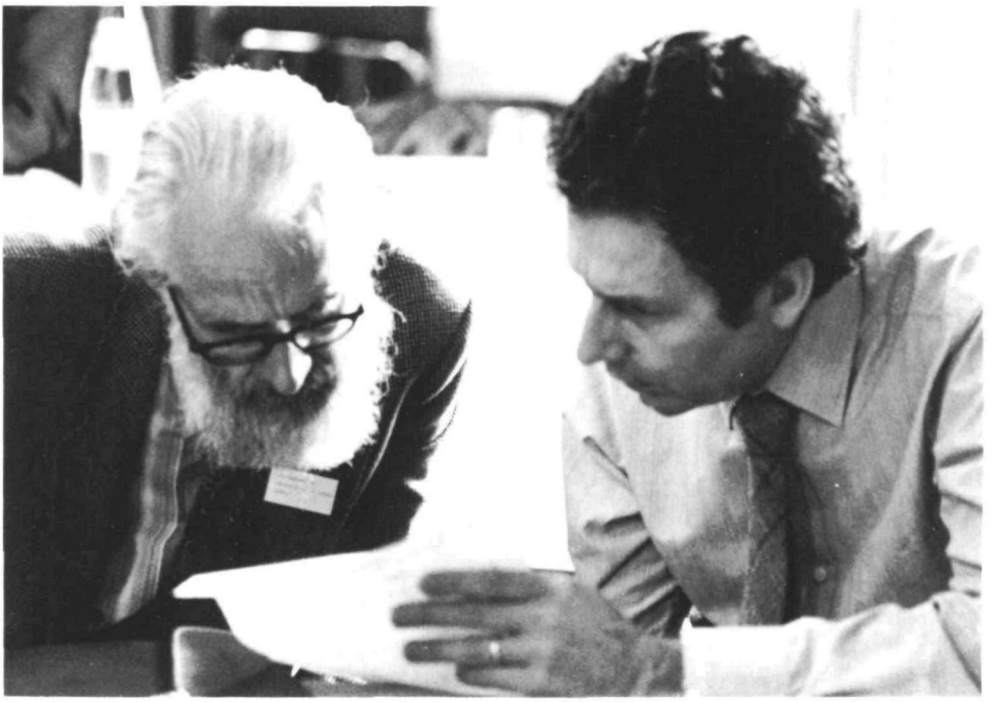

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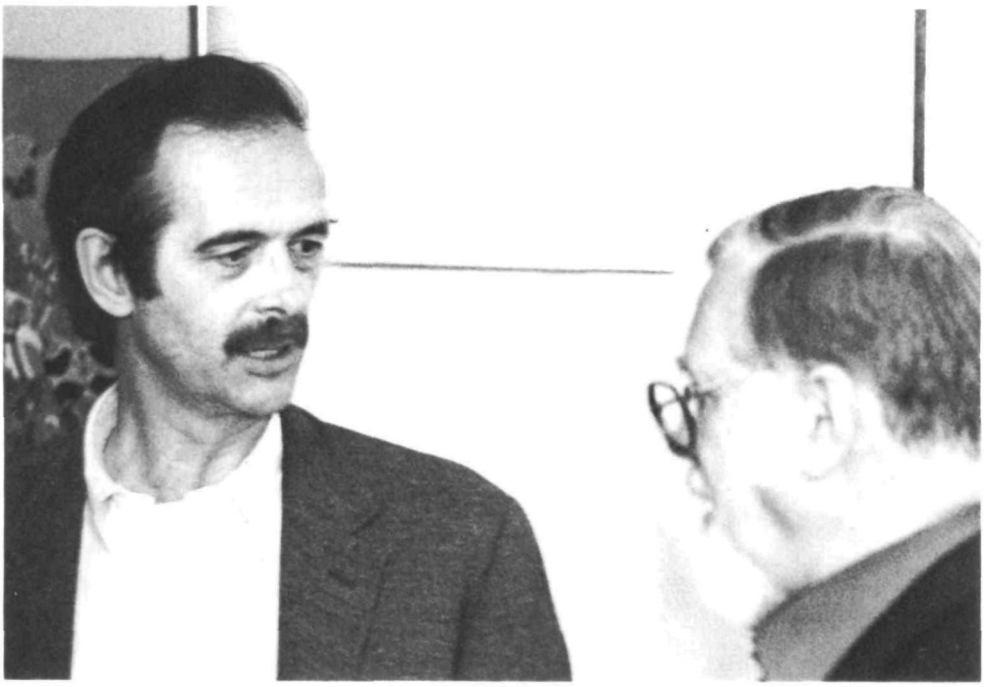

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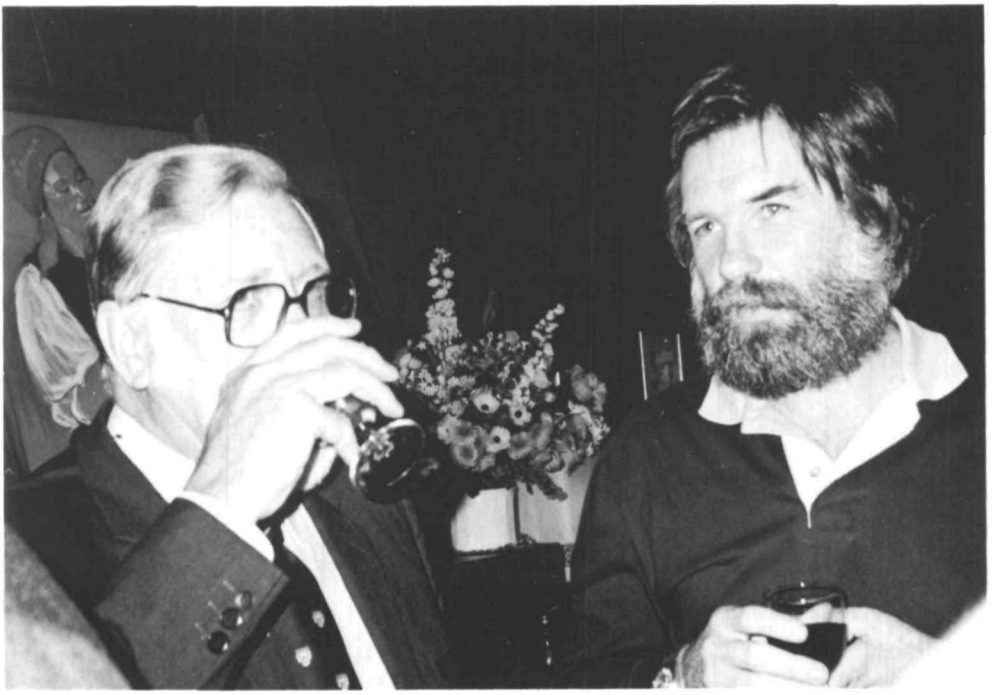

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