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CARDIOVASCULAR AND RESPIRATORY CONTROL MECHANISMS DURING EXERCISE: AN INTEGRATED VIEW

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Summary

Exercise can impose an immense stress upon many physiological systems throughout the body. In order that exercise performance may be optimally maintained, it is essential that a profound and complex series of responses is coordinated and controlled. The primary site for coordination is the central nervous system, whereas control mechanisms (both feedback loops and feedforward activation) involve complex sensory information, often in the form of neural coding but also in the form of blood-borne chemical signals, a number of levels of peripheral and central integration and, finally, the efferent branches of the nervous system coursing *via* sympathetic and parasympathetic nerves to target sites of action.

The neurohumoral control of the cardiorespiratory responses to exercise has received intense attention for over two decades and some particularly important steps forward in its understanding have occurred within the last 10 years. The initial fast increase (phase 1) in cardiovascular and ventilatory flow parameters are brought about by neurally mediated muscle mechanoreceptor *feedback* reflexes and a *feedforward* 'central motor command'. The blood pressure operating point is also raised by a combination of these two neural mechanisms. Fine control of the matching of cardiac output to ventilation may occur by means of a *feedforward* ventilatory control of cardiac origin. During the slower phase of adjustment (phase 2), the neurally mediated mechanisms are augmented by a cohort of humorally mediated *feedback* reflexes involving muscle and vascular chemoreceptors as well as being supported by central neural reverberation. A steady state of cardiorespiratory responses is achieved (phase 3) by an amalgamation of neural and humoral, i.e. 'neurohumoral', control mechanisms, which then must further modulate the cardiorespiratory responses to exercise in the face of increasing competition from other basic physiological requirements, such as thermoregulation and fluid homeostasis.

The myriad of subtle modifications in the basic blueprint found throughout the vertebrates illustrates the flexibility of the principal design and also how it can be applied to an extraordinary number of specific ecophysiological niches.

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Introduction

The cardiorespiratory responses to the onset of mild or moderate exercise (phase 1) are rapid (0–15 s), in fact so rapid that purely neural control mechanisms are probably responsible for the initial actions of the various physiological systems. As exercise proceeds (15 s to 2 or 3 min), slower increases in the cardiorespiratory variables occur (phase 2) until a new steady state is reached (phase 3, 3 min onwards). Neural and humoral control mechanisms now combine to bring about an appropriate response (Fig. 1).

The two most important neural control systems responding during phase 1 are (1) mechanical *feedback* reflexes originating from the active muscle mass and (2) a centrally generated *feedforward* motor pattern. In addition, there may also be a non-neurally mediated 'cardiodynamic' *feedforward* mechanism also operating during phase 1, which could couple an increase in ventilation to an increase in cardiac output.

As the cardiovascular and respiratory systems more slowly begin to attain a steady-state response profile (phase 2), each physiological system comes increasingly under the influence of further neural and humoral *feedback* control mechanisms and central neural reverberation. These *feedback* mechanisms may arise either from neural afferent inputs, originating in the lungs, the heart, the carotid body and muscle chemoreceptors, the arterial baroreceptors and thermoreceptors, or from humoral inputs (blood-borne substances), acting directly on the central nervous system or indirectly *via* peripheral receptor systems. Furthermore the control mechanisms, predominant during phase 1, may still be operative during phase 2. During the steady state (phase 3), further prolonged exercise may be compromised by thermoregulatory and fluid homeostatic control mechanisms as well as changes in substrate utilization and delivery. There may also be modulation brought about by an array of hormones or other chemical substances (Table 1).

This review will describe the way in which each phase of physiological adjustment to exercise is controlled and coordinated. The intention is to produce an up-to-date synthesis of recently obtained evidence of these control mechanisms and then to discuss how they may be integrated into an overview of control mechanisms operating during exercise.

Control mechanisms operating during phase 1

The century-old concept of a neural control mechanism operating during all three phases of exercise, commonly known as the 'exercise reflex', has been attributed to the German physiologist Zuntz (Rowell, 1986). Although numerous addenda and modifications have been made, the major core of the concept remains intact. Simply, the reflex would be initiated within the active muscle mass by a build-up of metabolites, due to a mismatch between perfusion and muscle metabolism. Chemoreceptors of some kind would sense this 'imbalance' and the increased firing rate in the chemosensitive afferent nerves would be detected in the

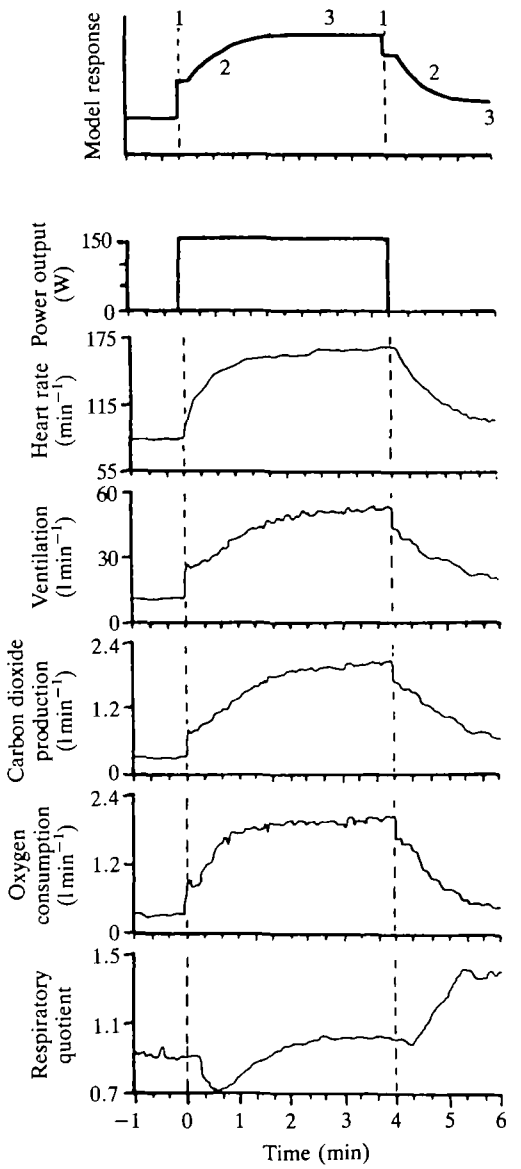

Fig. 1. The cardiorespiratory responses to moderate sub-maximal cycling exercise in humans. Phase 1 lasts about 15 s from the onset of exercise, phase 2 lasts for another 2–3 min, followed by a steady state (phase 3). Recovery from exercise has qualitatively similar periods of adjustment (modified from Wasserman *et al.* 1986).

central nervous system and, as a result, the inadequacy of blood flow within the muscle would be registered. The appropriate increases of, for example, ventilation, central and peripheral components of perfusion and blood pressure, would then be activated by the efferent arm of the reflex arc, namely the autonomic

Table 1. *Possible control mechanisms operating during exercise*

Neurally mediated
1. Muscle receptor reflexes
2. Supramedullary command
3. Cardiopulmonary mechanoreceptor reflexes
4. Baroreceptor reflexes
5. Chemoreceptor reflexes
Non-neurally mediated
1. Cardiodynamic coupling
2. Cardiac Starling mechanism
3. Lung–heart mechanical pumping assistance
4. Heart–lung mechanical pumping assistance
Neurohumorally mediated
1. Decreased O_2 partial pressure
2. Increased CO_2 production
3. Increased H^+ production
4. Increased temperature
5. Increased catecholamine production
6. Increased potassium release
Long-term modulation
1. Hormonal and opioid release
2. Exercise training
3. Other competing stresses

nervous system. This would result in a restoration of the metabolite concentrations to normal levels. The 'muscle chemoreflex' has been implicated in the 'exercise reflex' since the 1930s in the pioneering work of Alam and Smirk (1937) up to the present day (for example in McArdle syndrome patients; Lewis *et al.* 1991), primarily because of the undisputed existence of chemosensitive nerve fibres that originate in the muscle and act upon the medullary cardiorespiratory control centres in the brainstem (Mitchell and Schmidt, 1983). In the context of phase 1 control, the proven existence of mechanosensitive nerve fibres originating from muscles is also particularly relevant.

There is a growing body of direct and circumstantial evidence that, for example, increases in ventilation, heart rate and blood pressure can be elicited to a degree even when the muscle chemoreflex is partially or wholly inoperative (Hobbs, 1982; Eldridge *et al.* 1985; Galbo *et al.* 1987; Eldridge and Waldrop, 1991). This evidence has led to the belief that supramedullary brain centres can confer a strong central command, primarily locomotor in nature, which may also interact with respiratory and cardiovascular control centres in the brainstem (Krogh and Lindhard, 1913, 1917). The result would be a cardiorespiratory response that is more or less matched to the intensity of muscular activity and needed only fine continual adjustment, from the myriad of peripheral neural and neurohumoral receptor mechanisms as exercise proceeded.

A third completely different mechanism has been proposed for the linking

instantaneous increases in cardiac output and ventilation during phase 1. The idea of a 'cardiodynamic coupling' involves the direct activation of ventilation by a signal from the heart itself or from within the blood flowing from it. This may be either chemical or mechanical (Whipp and Ward, 1982; Wasserman *et al.* 1986). These three control mechanisms constitute the main methods by which the initial fast component of cardiovascular and respiratory responses can be activated during exercise. Other (non)neural mechanisms may play minor roles.

Neural mechanisms

Muscle sensory afferent fibres

The most important prerequisite for demonstrating a reflex neural control system that arises within the skeletal muscle mass is the presence of afferent sensory neurones. There are four groups of sensory afferent nerves that arise from muscle, classified by roman numerals I–IV. Groups I–III have nerve fibres with a myelin sheath, whilst group IV afferent nerves have nerve fibres that are non-myelinated. Group I and II nerve fibres are relatively large in diameter, generally between 6 and 20 μm, with conduction velocities of more than 30 m s^{-1}. They originate from within the muscle spindles, where sensory endings are either primary (i.e. annulospiral endings in spindles or innervating Golgi tendon organs, mainly group I) or secondary (i.e. sensory endings on the intrafusal fibres, mainly group II). Group I and II nerve fibres do not have a systematic, important role in chemoreception or cardiorespiratory control (Kaufman *et al.* 1982; Waldrop *et al.* 1984) and so will not be dealt with further in this review. Group III and IV nerve fibres are both thin, between 1 and 6 μm in diameter, with correspondingly slower conduction velocities (<15 m s^{-1}) than group I and II nerve fibres. Most group III and all group IV endings terminate as 'free nerve endings' or, as more recently suggested, 'unencapsulated nerve endings' in the musculature. Group III nerve endings seem to be associated with collagen structures in the skeletal muscle, whilst the endings of group IV afferent nerves are more often associated with blood and lymphatic vessels (von Düring *et al.* 1984). This *anatomical* distinction is indicative of mechanoreceptive (group III) or chemoreceptive (group IV) functions (Mitchell and Schmidt, 1983).

Within group III and IV nerve afferents, there are nerve fibres that have receptors sensitive to non-noxious stimuli, such as muscular contraction or movement, local touch, pressure and tendon or muscle stretch (Kaufman *et al.* 1988; Stebbins *et al.* 1988). These units have a low stimulus threshold, are commonly known as 'ergoreceptors' and make up about 65 % of group III afferents and 45 % of group IV afferents. The remaining units in both groups are particularly sensitive to more noxious stimuli and are thus commonly termed nociceptors. These units have a high stimulus threshold to mechanical distortion, and to chemical and thermal stimuli, some even showing polymodal receptive characteristics (Kaufman *et al.* 1988). Chemical stimulants include potassium, decreased pH, bradykinin and arachidonic acid (Kaufman *et al.* 1988; Stebbins

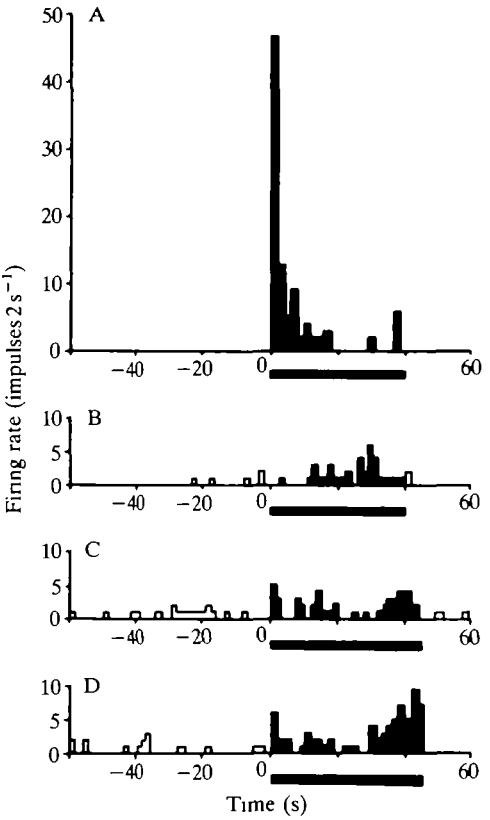

Fig. 2. The firing activity recorded from group III (A) and group IV (B–D) fine muscle afferent fibres in response to an induced muscular contraction lasting 40–45 s (filled bar and columns). B and C represent the activity in two group IV fibres and D represents the activity in a group IV afferent fibre, whilst the muscle was kept ischaemic, before and during an induced contraction. Note the instant, strong response of the group III fibre and also its rapid adaptation compared to the sustained, weaker response of the group IV fibres (redrawn from Mitchell, 1990).

et al. 1990). During exercise, all of these stimuli may be present within the receptive fields of the group III and IV nerve fibre endings and thus elicit a change in afferent nerve firing rate.

The immediate onset and rapid recovery of group III afferent activity during induced muscular contraction is *functionally* consistent with a predominantly mechanoreceptor function, whilst the slower onset and more sustained activity within group IV afferent units is *functionally* consistent with a more chemoreceptive function. Muscle ischaemia, caused by upstream arterial occlusion or increased intramuscular pressure during isometric contraction, seems to stimulate further the firing rate of afferent fibres during exercise (Fig. 2).

There is ample evidence suggesting that the group III and IV muscle afferents are heavily involved in the cardiovascular responses during all phases of exercise

The increase in firing rate elicits an increase in blood pressure, heart rate and contractility, as well as a significant and subtle redistribution of blood flow towards the working muscle, heart (in cats at least) and selected areas of the brain, but away from the kidneys (McCloskey and Mitchell, 1972; Mitchell *et al.* 1977; Crayton *et al.* 1979; Waldrop and Mitchell, 1985), a pattern similar to that seen in conscious, exercising animals and humans (Rowell, 1986; Musch *et al.* 1987; Armstrong, 1988; Butler *et al.* 1988). When most of the increase in afferent information is blocked by dorsal root section, the cardiovascular responses, in particular to muscular contraction, are attenuated or abolished in anaesthetized animals (McCloskey and Mitchell, 1972).

The evidence for the role of muscle afferent input in eliciting the increase in ventilation is not quite so compelling as it is for activation of the cardiovascular system. Certainly, ventilation does increase and total pulmonary resistance is reflexly decreased during electrically induced muscular contraction (McCloskey and Mitchell, 1972; Bennett, 1984; Rybicki and Kaufman, 1985) and partial spinal cord ablation in conscious ponies significantly attenuates the initial hyperpnoea during phase 1 of low-level voluntary exercise. Taken together, this evidence implies at least some role for muscle afferent feedback in the control of ventilation (Pan *et al.* 1990). However, ventilation still increases in proportion to metabolic rate during electrically induced muscular contraction in patients and anaesthetized animals with complete spinal cord lesions, where all sensory muscle afferent input is presumably lost, suggesting that muscle afferent information is not involved in the ventilatory responses to exercise (Cross *et al.* 1982*a*; Adams *et al.* 1984; Brice *et al.* 1988). Muscle mechanoreceptor afferent information may contribute to the linkage between respiratory frequency and locomotory gait, which has been shown to be present in several species during exercise (Bramble and Carrier, 1983).

Group III and IV afferent nerves enter the spinal cord mainly through the dorsal roots and disseminate throughout the dorsal horn of the segment of entry and also neighbouring segments, making synaptic connections with a group of spinal neurones in laminae I–V of the spinal cord, the dorsal column nuclei and directly in the nucleus tractus solitarius (Kalia *et al.* 1981), which together form part of a pathway leading to integrative areas of the brain. Suggested ascending neural spinal pathways, illuminated, for example, by retrograde horseradish peroxidase labelling or lesioning, include the lateral funiculus tract (Kozelka *et al.* 1987) and spino-thalamic and spino-reticular tracts. Putative neurotransmitters or neuromodulators at the first synaptic relay point in the reflex arc include both substance P and somatostatin (Kaufman *et al.* 1988), the release of which may be modulated by opiates (Hill and Kaufman, 1990) acting at opiate receptor sites on the afferent nerves (Pomeroy *et al.* 1986). In the central brain areas, the spinal neurones furnish information to a number of important regions of cardiorespiratory control, including the lateral reticular nucleus (Ciriello and Calaresu, 1977; Iwamoto *et al.* 1984) and possibly the cells of the lateral tegmental field, which are both within the caudal ventrolateral region of the medulla (Bauer *et al.* 1990; Iwamoto *et al.* 1989). Thus, the muscle afferent nerve fibres can be *structurally* and *functionally*

identified from their origin in the collagen matrix and in the blood and lymph vessels of the muscle, through the spinal cord to their target brainstem areas and the nuclei involved in eliciting the appropriate cardiovascular and respiratory responses to muscular contraction.

Central command

The evidence that afferent input can originate from supramedullary centres of the central nervous system, interact with medullary neurone pools and have an influence on physiological responses to exercise in man is mainly circumstantial. Recent advances have been made in functionally dissecting central afferent input from peripheral afferent input (for example from muscle chemoreflexes) using partial neuromuscular blockade. Concurrently, in anaesthetized or decerebrate animals, lesion and/or stimulation of putative nuclei conferring or relaying a central command have also led to a significantly better understanding of the complex central afferent command.

Experiments involving human exercise. The basic experimental protocol for establishing the existence of the central component of the 'exercise response' of the cardiovascular system, in particular heart rate and blood pressure, is as follows. During partial neuromuscular blockade, for example with tubocurarine, muscle isometric strength is reduced, so that to obtain the same *absolute* isometric force production, there must be a greater central motor drive or effort (Leonard *et al.* 1985). Locomotion, respiration and cardiovascular responses can all be elicited in parallel by stimulation of the central motor centres (Eldridge *et al.* 1985). Therefore, after partial neuromuscular blockade, the increases in central motor drive lead to greater increases in the cardiorespiratory variables than in the control muscle contraction (Fig. 3). In this experimental condition, the chemical milieu of the contracting muscle is the same and is not, therefore, correlated to the increases in ventilation, heart rate and blood pressure. When the same subjects produced a contraction that represented the same *relative* proportion of, in the first instance, the control maximal voluntary contraction (MVC) and, in the second instance, the MVC measured during partial neuromuscular blockade, the central command was the same but the absolute force production (and by inference the muscle afferent information) was less in the blocked state. Heart rate and blood pressure increased to the same extent in the non-blocked and blocked state, i.e. were correlated to central command and not to the chemical milieu existing in the contracting muscle and thus not to the neural activity of muscle chemo- and mechanosensors (Mitchell, 1990). The role of central command in eliciting both locomotor and cardiovascular responses by parallel activation during exercise is represented schematically in Fig. 4.

Recently, heart rate and blood pressure have been shown to recover at different rates after a subject has performed a powerful MVC. If blood flow is occluded at the end of the contraction, heart rate returns to resting levels very quickly. In contrast, blood pressure decreases to a level that is still significantly higher than that at rest and remains there until the occlusion is relieved. The interpretation

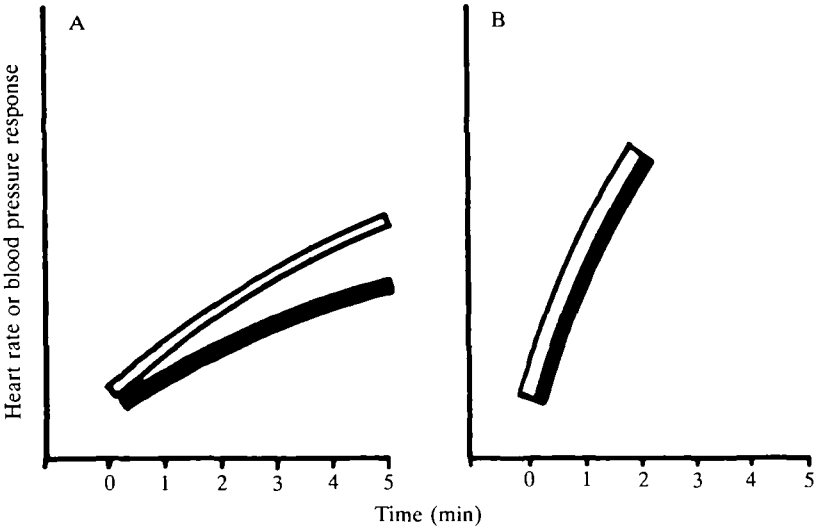

Fig. 3. The effect of partial neuromuscular blockade on heart rate and blood pressure responses to static exercise. In A, the same absolute force is maintained without (filled curve) or with (open curve) neuromuscular blockade, whereas in B the same relative percentage of the measured maximal voluntary contraction force is maintained without (filled curve) or with neuromuscular blockade (open curve). See text for an interpretation of these findings (redrawn from Mitchell, 1990).

this finding is that heart rate is increased mainly by increased central command or muscle mechanoreceptors *via* vagal withdrawal, whereas blood pressure is increased in part by central command and muscle mechanoreceptor feedback but also in part by increased afferent input from muscle chemoreceptors sensing a build-up of metabolites during the MVC (trapped in the muscle by occlusion, Fig. 5). When an *attempted* contraction is performed during neuromuscular blockade, the build-up of metabolites is not enough to stimulate the muscle chemoreceptors and so blood pressure rapidly returns to normal, even during occlusion (Rowell and O'Leary, 1990). The increases in blood pressure and heart rate in response to moderate intensities of static contraction or dynamic contraction, when there is little or no build-up of metabolites, must be elicited primarily by central command or muscle mechanoreceptors (Gandevia and Hobbs, 1990). Heart rate appears to be controlled more by central command, *via* vagal withdrawal and increased sympathetic drive, than by muscle mechanoreceptors during all intensities of static contraction (Victor *et al.* 1989). Hypnotic suggestion has been used to increase the perception of muscular effort during a muscular contraction and can lead to a hyperventilation (Morgan *et al.* 1973). This finding agrees with the evidence concerning the role of central command in determining the cardiovascular responses to exercise. Evidence exists that the heart rate response to exercise can be attenuated by behavioural conditioning (Talan and Engel, 1986; Perski *et al.* 1985). The implication of this is that when the muscle

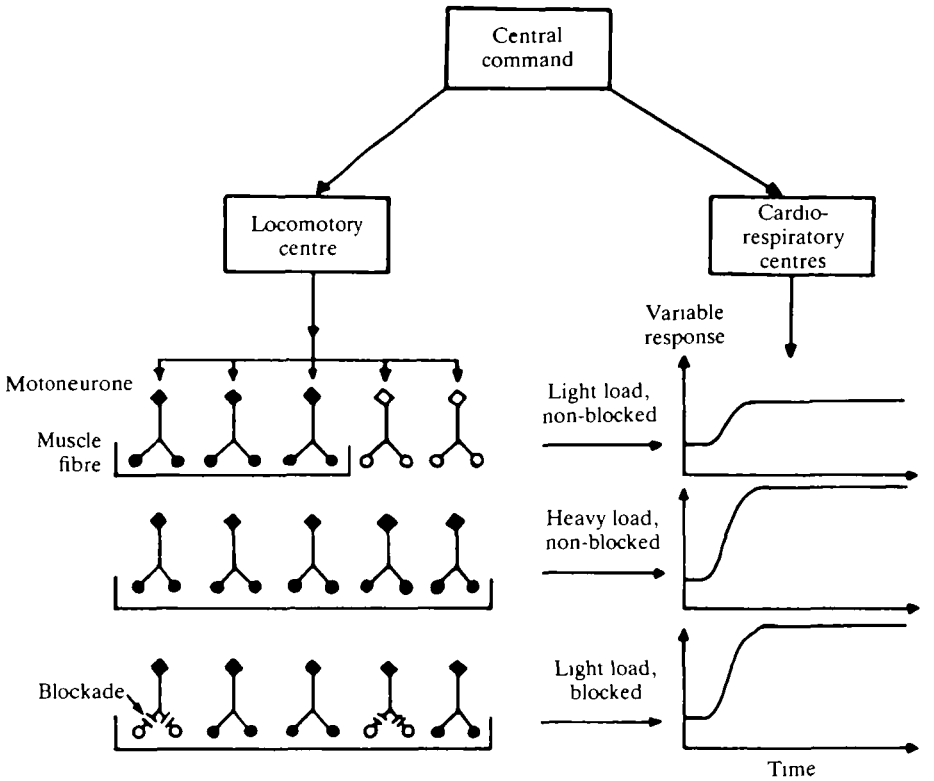

Fig. 4. A hypothesis in which descending central motor command activates, in parallel, a recruitment of muscle fibres and an appropriate cardiorespiratory response, be it blood pressure, heart rate or ventilation. The cardiorespiratory response is graded to the degree of muscular contraction in the non-blocked state. However, during neuromuscular blockade the cardiorespiratory response is apparently stronger than the muscular response. This is due to a larger central motor command being necessary to maintain the force production of the muscle mass (adapted from Hobbs, 1982, and redrawn from Rowell, 1986). Filled symbols represent active motoneurones and muscle fibres; unfilled ones represent inactive ones.

afferent input is constant (same absolute workload), some cerebral influence on the central motor command can still occur.

Experiments involving electrical or chemical lesions and stimulation. Obviously, the limitation of the experimental protocols described previously is that they offer purely circumstantial evidence of a functional central command but they offer no information about its anatomical location. Traditionally, the search for the anatomical loci conferring the functional central afferent command has followed two lines of enquiry. First, areas suspected of being involved in originating a command can be rendered non-functional by coarse or, as techniques become available, fine lesion, be it surgical or chemical. Second, those same areas can be stimulated electrically or chemically and the consequent physiological responses monitored (Spyer, 1990).

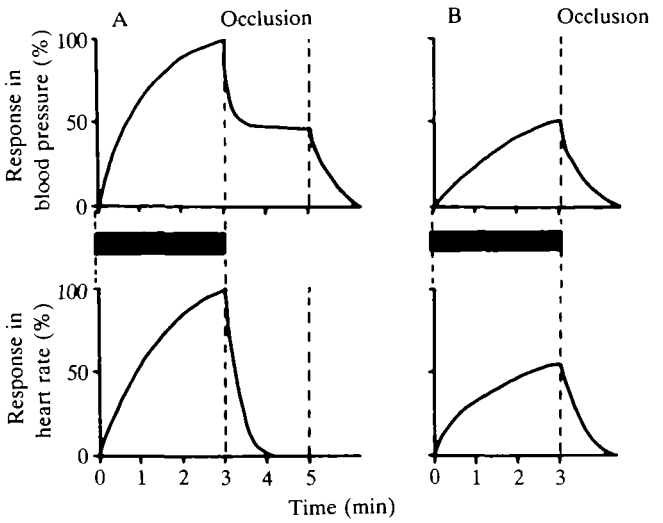

Fig. 5. The partitioning of importance of central motor command, muscle mechanoreceptors and muscle chemoreceptors in bringing about a response in blood pressure (upper panel) and heart rate (lower panel) during a muscular contraction (filled bars), with (B) or without (A) neuromuscular blockade. Arterial occlusion is initiated at the end of the 3-min contraction to trap any released metabolites within the muscle. In the unblocked state, blood pressure does not fall back to resting levels immediately after the contraction, because muscle chemoreceptor activation by metabolites maintains a pressor reflex, even in the absence of central command and muscle mechanoreceptor control. The muscle chemoreceptors do not appear to maintain an elevated heart rate. In the blocked state, an attempted contraction does not produce a large enough build-up of metabolites to stimulate muscle chemoreceptors significantly and, therefore, blood pressure falls rapidly back to resting levels during occlusion (redrawn from Rowell and O'Leary, 1990).

The many nuclei within the central nervous system that have direct or indirect influences on the cardiorespiratory centres in the medulla also have many interconnections among themselves. This makes unravelling individual roles for each nucleus extremely difficult and any lesion or stimulation of one nucleus will inevitably have repercussions for neural activity originating from other nuclei. Nevertheless, a number of experiments has highlighted the importance of a large number of brain areas. The lesion of neurones in the subthalamic area of the brain in primates has been shown to eliminate the increase in blood pressure during exercise. This finding implies that the descending command from the motor cortex, principally responsible for driving an orchestrated set of muscle fibre contractions necessary, for example, during walking, also sends a parallel drive to cardiorespiratory control centres in the medulla (Fig. 4; Hobbs, 1982). When the intact subthalamic locomotor region is electrically or chemically stimulated in unanaesthetized animals, increases in ventilation, blood pressure and heart rate as well as a redistribution of blood flow can be elicited. Similar responses can be elicited in animals that are deeply anaesthetized or paralysed and which obviously

do not walk (DiMarco *et al.* 1983; Eldridge *et al.* 1985; Waldrop *et al.* 1986*a*). In addition to the subthalamic locomotor region, the neighbouring brain area, known as the fields of Florel, can elicit, when directly stimulated, substantial increases in blood pressure and heart rate coupled with increased phrenic nerve activity and a bronchodilator response. Together, these two anatomically distinct regions have been regarded as the main location for the functional central command (Eldridge *et al.* 1985; McCallister *et al.* 1988; Rybicki *et al.* 1989). Interestingly, lesions in the fields of Florel do not alter the cardiorespiratory responses to running in conscious dogs (Ordway *et al.* 1989). Thus, merely abolishing the role of one important site will not necessarily compromise the overall pattern of central neural *feedforward* command or the resultant efferent outflow and pattern of responses. This implies a degree of redundancy or neural plasticity. Superimposed on the drive from these nuclei is the influence of the defence-arousal system. The perifornical region of the hypothalamus, and particularly the amygdala, forms a functional centre, receiving projections from the hippocampus, forebrain and brainstem (summarized in Spyer, 1984). Efferent projections connect the hypothalamic defence area with the medullary cardiorespiratory control areas (Hilton, 1982; Spyer, 1990) and may also relay information *via* the nucleus reticularis gigantocellularis (Richard *et al.* 1989).

Cardiopulmonary mechanoreceptor afferent information

Afferent fibres from the cardiopulmonary region course with the vagus nerve towards the brain or alternatively with the sympathetic nerves, which enter the spinal cord. Vagally mediated mechanoreceptors, which have receptive fields in the four chambers of the heart and also in the pulmonary artery, are responsive to distension brought about by the increase in end-diastolic volume in the atria and ventricles that may occur during exercise (Plotnick *et al.* 1986) or increased atrial or pulmonary artery pressure. Their activation could lead to a reduction in heart rate and so would function as a peripheral *feedback* mechanism during exercise. However, experimentally increased pulmonary artery pressure during maximal exercise in humans did not result in any change in cardiac output, heart rate or ventilation (D. L. Turner, H. Hoppeler, C. Noti, H.-P. Gurtner, H. Gerber and G. Ferretti, in preparation) nor did experimentally raised right ventricular pressure in the anaesthetized dog (Crisp *et al.* 1988). Patients with denervated heart and lungs through transplantation or cardiac denervated goats still demonstrate an appropriate ventilatory response to exercise, but not an adequate cardiovascular response (Banner *et al.* 1988; Brice *et al.* 1991). Blocking of sympathetically mediated information by removal of the left stellate ganglion does not lead to major changes in cardiovascular responses to exercise, apart from possibly changing the distribution of blood flow across the myocardial wall (Stone, 1983). Thus, cardiac receptors probably, at most, only play a minor role during exercise in normal environmental conditions. Incidentally, during exercise with peripheral pooling of blood, for example brought about by lower-body negati

pressure, cardiopulmonary mechanoreceptor afferent information may play a role in maintaining blood pressure (Mack *et al.* 1990).

The effect of chronic or acute hilar nerve section, with a consequent loss of lung-volume afferent *feedback* to the medullary centres, has been studied in dogs and ponies. Minute ventilation is not affected, although the pattern by which it is maintained may be altered (Flynn *et al.* 1985; Clifford *et al.* 1986). This is similar to the role ascribed to lung mechanoreceptors in exercising humans (Lind and Hesser, 1984). Irritant or rapidly adapting receptors and J receptors also convey afferent information *via* the pulmonary vagal nerves, the former potentially facilitating respiration during exercise. The latter, stimulated by pulmonary congestion or oedema, are situated in the alveolar wall and could potentially have an important role during extreme exercise when pulmonary oedema is thought to occur (O'Brodovich and Coates, 1991). Neither appear to have a role in controlling ventilation following vagotomy, but again may be more important in controlling the respiratory pattern. Recently, the ventilatory response to exercise has been shown to persist even after heart or heart–lung transplantation (i.e. cardiac or cardiopulmonary deafferentation) and again indicates a relatively small role for cardiopulmonary receptor control mechanisms during exercise.

Baroreceptor afferent information

Recent evidence suggests that during exercise the baroreflex is reset to a higher operating level during phase 1 as a result of a central command impinging upon the baroreflex neuronal pool in the medulla (Ludbrook, 1983; Mitchell *et al.* 1983; Rowell, 1986). The maintenance of blood pressure at this new higher level is still, however, adequately controlled by the reflex involving carotid sinus and aortic baroreceptors and cardiac output and vascular resistance, even during severe exercise (see later; Rowell and O'Leary, 1990). Cardiac output is unaffected by baroreceptor isolation in exercising dogs (less afferent input), with maintenance of adequate blood pressure due to increased vascular resistance (Walgenbach and Donald, 1983). During severe exercise, this may even occur in the active muscle (Rowell and O'Leary, 1990).

Chemoreceptor afferent information

During phase 1 of exercise, the delay between measurable changes or 'errors' in the levels of blood gases and blood-borne metabolites occurring in the contracting muscles and their reception in peripheral or central arterial chemoreceptors precludes a role of these receptive sites in initiating cardiorespiratory responses. However, in humans, relatively hypoxic and hypercapnic blood has been shown to reach the pulmonary artery at the onset of exercise as a bolus from the inferior vena cava before any return of venous blood from the exercising leg muscle (Casaburi *et al.* 1989). The functional significance of this has yet to be fully determined. The central chemoreceptors have been ruled out as an important

source of afferent input in the control of ventilation or circulation in all phases exercise (Casey *et al.* 1987).

Non-neural mechanisms

An entirely different approach to the possible control of coupled cardiorespiratory responses during exercise has been proposed. The 'cardiodynamic coupling' hypothesis involves a direct linkage between cardiac output and ventilation, consisting of some kind of *feedforward* mechanism by which a pulmonary circulatory stimulus (or stimuli) activates an increase in ventilation. There is a large body of evidence that lends circumstantial support to this hypothesis. Wasserman *et al.* (1974) found that ventilation rose immediately and in proportion to an induced increase in cardiac output. Owing to the time delays between the pulmonary artery and peripheral and central chemoreceptors, the rise in ventilation could not be mediated by a chemoreflex from these receptors. In addition, in humans with resected carotid bodies, cardiodynamic coupling is still present during phase 1 of exercise (Wasserman *et al.* 1975). The activating stimulus for an increase in ventilation secondary to an increase in cardiac output may be a mechanical signal arising from distension of the right atrium and ventricle or even the pulmonary artery. Thus, when stroke volume is increased (for example by increasing right ventricular work as a result of altered peripheral resistance and/or venous return), ventilation increases accordingly and with the appropriate time course (Jones *et al.* 1982). Incidentally, altering heart rate only (for example by increasing the output of an artificial pacemaker) does not affect ventilatory responses to exercise (Jones *et al.* 1981). However, the occurrence of this *feedforward* cardiodynamic mechanism has been seriously questioned in studies of exercising ponies (Pan *et al.* 1983, 1984) and humans (Adams *et al.* 1987; Turner *et al.* 1991) and also in isolated subsystems involving the heart, pulmonary arteries and lungs (Lloyd, 1984).

Stretching of the walls, and therefore muscle fibres, of the heart by an increase in venous return may, at least during mild exercise, lead to an increase in stroke volume (and thus cardiac output) *via* the Frank–Starling mechanism (Plotnick *et al.* 1986). The role of heart–lung and lung–heart mechanical pumping assistance due to physical movement during exercise is potentially of importance, but as yet has not been thoroughly investigated (Agostoni and Butler, 1991). These two mechanisms could occur without neural or neurohumoral involvement.

Control mechanisms operating during phases 2 and 3

The neurohumoral drive

Phase 1 only lasts for a few seconds, after which there is a slower increase in a number of cardiorespiratory variables towards an asymptotic level (Fig. 1). The phase 2 and 3 periods can obviously still be under the control of the mechanisms operating during phase 1. However, their delayed onset coincides roughly with the delay for blood-borne chemical transfer from muscles to heart, pulmonary

teries, lungs, carotid bodies and cerebral circulation. Thus, phases 2 and 3 have long been associated with a number of possible humoral mediators of the cardiorespiratory exercise responses. The original synopsis of the two-stage 'neurohumoral' control mechanism during exercise was popularised by Dejours (1964). Humoral mediators can conceivably work directly upon target organs (for example the heart, smooth muscle of the lungs or medullary centres) or indirectly *via* peripheral chemoreceptors from which neural pathways mediate control (Flandrois, 1988).

Humoral mechanisms

There are many possible candidates for the all-important chemical blood-borne mediator that may arise from the active muscle mass during exercise. Increased partial pressure or content of carbon dioxide, decreased oxygen partial pressure, increased hydrogen ion concentration, increased temperature, increased catecholamine concentrations and increased potassium concentration are all potential signals that exist during exercise.

Mixed venous chemoreceptors

During phase 3 of exercise, there is a large increase in carbon dioxide flow (cardiac output × mixed venous carbon dioxide content) to the heart and lungs. When the flow of carbon dioxide is decreased in non-exercising humans, ventilation also decreases, indicating a potentially strong direct role for carbon dioxide flow in ventilatory control (Dolan *et al.* 1981). When the carbon dioxide flow to the lungs, during exercise, is altered by removing or adding carbon dioxide using a gas exchanger, increased carbon dioxide flow is associated with an increase in ventilation (Wasserman *et al.* 1986).

There is possibly a vagally mediated pulmonary chemosensitivity to an increase in carbon dioxide that may be an indirect humoral activator of ventilation during exercise (Green and Sheldon, 1983), although other studies have shown that lung denervation does not alter the total ventilatory response, only the pattern by which it is achieved (Clifford *et al.* 1986; Favier *et al.* 1982). Unfortunately, there appears to be very little evidence suggesting the existence of mixed venous or pulmonary arterial chemoreceptors and so their role as part of an indirect humorally activated reflex during exercise can be considered negligible (Wasserman *et al.* 1986). Indeed, the increases in venous carbon dioxide concentration and ventilation can be disassociated by occlusion of the thigh during cycling exercise (Stanley *et al.* 1985).

Arterial chemoreceptors

During steady-state exercise (phase 3), arterial oxygen and carbon dioxide partial pressures and pH are all maintained at normal levels and there will be no mean increase in stimulus to the carotid body or central chemoreceptors. Thus, when the carotid body chemoreceptors are surgically resected in some humans, verall ventilatory responses during phase 3 are the same as those in normal

subjects (Wasserman *et al.* 1975) and their importance has been ruled out in phase 3 ventilatory control. Nevertheless, in further studies on humans (Honda *et al.* 1979) and the dog (Bouverot *et al.* 1981), resecting or denervating the carotid body chemoreceptors caused a hypoventilatory response to exercise, implying that in these cases the carotid bodies do subserve some role in the ventilatory exercise response. Respiration is an oscillatory phenomenon and so it is possible that the oscillation in arterial carbon dioxide partial pressure and pH in the blood leaving the lung capillaries can be measured in the carotid body. Since, during phase 2 of exercise, the amplitude, frequency and rates of rise and decline of these oscillations may all increase, they can be potent ventilatory stimuli (Cross *et al.* 1982*b*; Allen and Jones, 1984). Indeed, in carotid-body-resected, exercising humans the phase 2 responses in ventilation are sluggish (Wasserman *et al.* 1975).

Thermal and other chemical humoral factors

During phases 2 and 3 of moderate exercise, muscle and core temperatures only increase slightly and can be discounted as important ventilatory stimuli in normal conditions (excluding prolonged exercise). Ventilation still increases in isothermic, exercising animals (for example, the duck; Kiley *et al.* 1982). Catecholamine release is only significant after prolonged exercise, at high unsustainable levels of exercise (Kjaer *et al.* 1987*b*) or during exercise in hypoxia (Favier *et al.* 1985). The total ventilatory response is not affected by increased catecholamine concentration, but the respiratory pattern may change (Favier *et al.* 1985). Acute or chronic administration of dobutamine (a sympathomimetic drug) uncovers subtle changes in the cardiac responses to exercise (i.e. heart rate) and locomotor muscle blood flow, but no major changes in overall levels of cardiac output (Haidet *et al.* 1989; McKirnan *et al.* 1989). Increased potassium release from exercising muscle into the circulation has been documented (Paterson *et al.* 1990; Yoshida *et al.* 1990). An increase in the level of circulating potassium can stimulate carotid body chemoreceptors, and thus ventilation, in normal subjects and McArdle's syndrome patients (Paterson *et al.* 1990; Yoshida *et al.* 1990). However, two observations suggest that this humoral signal might not be important: (1) during phase 3, some carotid-body-resected patients may have an appropriate ventilatory response (Wasserman *et al.* 1975) and (2) the increases in ventilation and arterial potassium concentration during exercise can be disassociated (Paterson *et al.* 1991).

Coordination of control mechanisms

Recent evidence suggests that the central command and muscle afferent information are both operating during phase 1 of exercise but, as they both act on the same central neural pathways, they are said to be 'redundant' systems. That is, there exists a degree of neural occlusion, such that when one input is present, th

ther is partially blocked. This has been studied in an elegant experiment involving stimulation of both the diencephalic or subthalamic locomotor regions (central command) and group III and IV muscle afferents. Both pathways, when stimulated separately, could elicit a strong pressor or ventilatory response. However, upon simultaneous stimulation of both central and peripheral afferent pathways, the pressor and ventilatory responses were not the algebraic sum of the two separate responses, implying that a degree of integration or neural occlusion had taken place (Waldrop *et al.* 1986*b*; Rybicki *et al.* 1989). Furthermore, recent evidence suggests that muscle afferent input can directly cause an increase in nerve cell activity within the posterior hypothalamus (Waldrop and Stremel, 1989). This implies that integration outside the medulla can take place.

The ventrolateral medulla is generally considered to be the main integration centre for cardiovascular control. Both efferent sympathetic neural drive and an adequate baroreflex are lost when this area is rendered non-functional by electrical or chemical lesion (Ciriello *et al.* 1986). There is substantial evidence that efferent fibres originate from the ventrolateral medulla and synapse with sympathetic preganglionic neurones in the intermediolateral nucleus of the thoracic spinal cord (Barmen and Gebber, 1985). There are also diverse sympathetic reflexes in which the ventrolateral medulla plays a pivotal role, for instance the baroreflex, chemoreflexes and somatosympathetic reflexes (Ciriello *et al.* 1986; Reis *et al.* 1988; Morrison and Reis, 1989). Furthermore, recently performed direct extracellular recordings from the ventrolateral medulla indicate that single units in this region respond to induced muscular contraction by altering their discharge frequency (Bauer *et al.* 1990). Some cell bodies responsible for cardioinhibitory action (Machado and Brody, 1988, 1990), notably in the nucleus ambiguus, show patterns of inhibition. This is thought to represent the mediation of the withdrawal of vagal activity induced by muscular contraction (Iwamoto and Kaufman, 1987). Therefore the combined evidence suggests that the ventrolateral medulla acts as a centre important for the inhibition of the baroreflex, for eliciting the withdrawal of vagal action on the heart and, lastly, in studies using spike-triggered averaging techniques, for producing sympathetic tone (Barmen, 1987; Iwamoto *et al.* 1989).

Both caudal and rostral parts of the ventrolateral medulla have been implicated in cardiovascular control. Using electrical and chemical lesioning, stimulation and active cell labelling with 2-[^{14}C]deoxyglucose, the lateral reticular nucleus in the caudal part of the ventrolateral medulla has been suggested to represent an important relay or integrative area. It may, by its afferent input and *via* its efferent projections to the cerebellum and in particular the fastigal nucleus, form part of a spino-medullary-cerebellar-medullary-spinal reflex arc (Mitchell *et al.* 1983). The rostral portion of the ventrolateral medulla with adrenaline-containing cells must be functional for adequate catecholamine and plasma vasopressin levels to be maintained (Ross *et al.* 1984), but more importantly in this context for adequate pressor responses during exercise in conscious dogs (Dormer and Bedford, 1989). The nucleus reticularis gigantocellularis, which constitutes a large portion of the brainstem reticular formation and resides on the pontomedullary border, can have

an inhibitory effect on heart rate and respiratory responses elicited by hypothalamic stimulation (central command). In this way it may act as a throttle on the strong *feedforward* command arising from higher brain centres (Richard *et al.* 1989). Stimulation of the rostral autonomic region of the fastigal nucleus in the cerebellum causes large increases in heart rate and arterial blood pressure, as well as obviously playing a significant role in coordinating movement (Dormer and Stone, 1982).

Also within the medulla region of the brainstem is situated what has been comprehensively described as the respiratory centre (reviewed by Long and Duffin, 1986; von Euler, 1986; Feldman, 1986). The detailed description of the neuronal networks and their interaction is beyond the scope of this review, but can be summarized as follows. There is a centrally driven respiratory rhythm, which is set by a number of interacting neuronal pools. For its basic operation, it does not depend on any extrinsic feedback loops or on higher central nervous influences. However, the pattern of respiratory responses, for example during exercise, is not only heavily dependent on many afferent inputs, including all those mentioned earlier, but is also dependent upon additional inputs from cardiovascular reflex pathways. The reverse is also true. The efferent neural outflow to cardiovascular organs and also blood pressure are certainly neurogenically modulated by the central respiratory neuronal drive at a number of possible neuraxial levels (Feldman and Ellenberger, 1988).

It has been proposed that the central neural 'respiratory centre' within the medulla may have slow-decay type neural dynamics capable of sustaining an increased ventilation during and even after locomotion (i.e. when central command and muscle mechanoreceptor inputs are zero). Thus, there is a persistently increased hyperventilation following exercise and this phenomenon of increased respiratory drive has been attributed to a 'central neural reverberation' or 'short-term potentiation' present within the brainstem (Eldridge, 1976; Eldridge and Waldrop, 1991). The role of cardiodynamic coupling of cardiac output and ventilation may be to fine tune the centrally generated command. Furthermore, it may act once more as a redundant control mechanism, its potential only being uncovered when central command and muscle afferent mechanisms are compromised.

During phases 2 and 3, the prevailing neural mechanisms and cardiodynamic coupling are augmented by a number of humorally based mechanisms acting *via* the central cardiovascular and respiratory centres in the medulla or independently between the heart and lungs. Thus, the control of the detailed cardiorespiratory responses to exercise becomes increasingly complex. For example, it is probable that muscle chemoreceptors have an increasingly important role to play during phases 2 and 3, as befits their anatomical and functional stimulus and response characteristics (see above). The major neural control pathways for cardiorespiratory responses during exercise are schematically represented in Fig. 6. Humoral stimulants will act upon chemoreceptors, from where neural mechanisms take over.

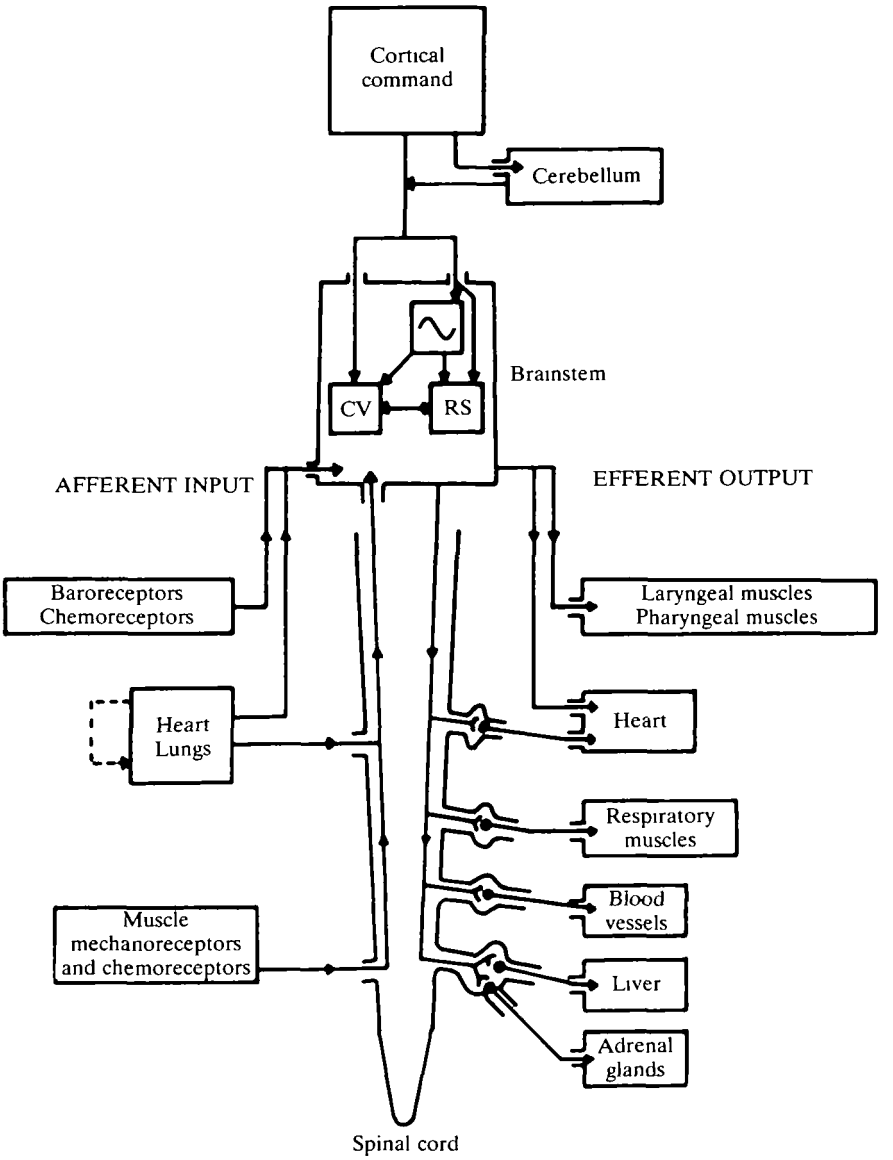

Fig. 6. A summary of the main pathways involved in the control and coordination of cardiorespiratory responses to muscular exercise. Supramedullary input impinges on the brainstem, where the cardiovascular (CV), respiratory timing (~) and drive (RS) centres are located in the medulla. Interaction between these centres and integration of various sources of afferent input result in an efferent neural output. This output, mainly in the form of sympathetic and parasympathetic neural activity, brings about a complex pattern of cardiorespiratory and metabolic responses.

Central neural efferent outflow

Efferent sympathetic outflow from the central integrating brainstem areas courses *via* descending dorsolateral spinal tracts, and essentially all integration and modulation of at least the intersegmental cardiorespiratory outflow is complete below the lower medullary level (Iwamoto *et al.* 1985). Anterograde and retrograde labelling has been used to show that there are major efferent projections from the medullary areas involved in cardiovascular control to the intermediolateral cell column, where the preganglionic cell bodies are located. These cell bodies are either cardioacceleratory or vasoconstrictor neurones and the descending tracts are mainly in the bilateral dorsolateral funiculus (Caverson and Ciriello, 1987). The preganglionic neurones pass out of the spinal cord in the thoracic or lumbar regions. Vagal cardioinhibitory neurones leave the medulla and course in cranial nerves to the sinoatrial node of the heart.

The phrenic nerve arises from the mid-cervical ventral horns of the spinal cord and transmits sympathetic neural output to the diaphragm. The inspiratory and expiratory intercostal muscle groups receive their own motoneurone supply arising from thoracic ventral horns, whilst the abdominal muscles receive their innervation from lower thoracic and upper lumbar motoneurones. Also involved in the mechanics of breathing are the laryngeal and pharyngeal muscles. These receive innervation from cranial motoneurones and play a role in determining airway resistance along with tracheal and bronchial smooth muscles innervated by parasympathetic vagal motoneurones (Feldman, 1986). There is now considerable evidence, from anterograde labelling studies, to suggest that the central respiratory drive command, arising from both dorsal and ventral respiratory neurone groups in the ventrolateral medulla, is projected *via* inspiratory and expiratory bulbospinal neurones to spinal motoneurones (Feldman *et al.* 1985; Berger *et al.* 1989). Furthermore, the bulbospinal premotor and motor neurones may not be involved in the primary generation of the respiratory rhythm, but rather serve to integrate the rhythm with other central and peripheral inputs, in order to produce the final pattern of neuromuscular activity (Feldman, 1986; Feldman *et al.* 1990).

The pattern of cardiorespiratory responses to exercise

The major cardiorespiratory responses to exercise consist of an increase in regional vascular resistance and an upward resetting and stabilization of blood pressure, along with an increase in cardiac output, a redistribution of blood flow and an increase in ventilation.

Cardiorespiratory responses

Whether it is measured directly using microneurographic recordings of postganglionic neurones (Wallin and Fagius, 1988) or by measuring the spillover plasma noradrenaline concentration (Christensen and Galbo, 1983), sympathetic outflow is increased during exercise and is responsible for an increase in resistance in many vascular beds. Noradrenaline released from postganglionic neurones ac

alpha-adrenergic receptors in the smooth muscle of arteriolar and venular blood vessels, leading to reflex vasoconstriction. The increase in sympathetic activity may not evoke the same vasoconstriction in different vascular beds because of (1) differential outflow from the central nervous system, (2) different abundances of receptors in different vascular beds, (3) different affinities of the receptors for noradrenaline in different vascular beds, and (4) prejunctional modulation of noradrenaline release (Taylor *et al.* 1989). The fourth proposal exists in the active muscle mass. The release of local vasodilator metabolites or other factors, for example potassium and hydrogen ions, inorganic phosphate, histamine, adenosine and increased osmolality, can all reduce or prevent noradrenaline release and thus overcome the incoming sympathetically mediated vasoconstrictor signal. Interestingly, the control of the continual progressive adjustment of blood flow to different muscle fibres within the same muscle during exercise is not fully explained solely by local vasodilator factors, sympathetic efferent input, mechanical influences or endogenous opioid action (Armstrong, 1988; Mohrman *et al.* 1989). This suggests that the gross control of tissue resistance by sympathetic nerves must be modulated in a particularly complex manner. The sympathetically mediated increase in resistance in many vascular beds during exercise is essential to maintain blood pressure in the face of the potentially substantial vasodilation in the active muscle mass. It is thought that even in active muscle masses there remains a sympathetically mediated vasoconstriction, acting as a throttle on vasodilation and thus preserving arterial blood pressure during severe exercise (Rowell, 1986; Rowell and O'Leary, 1990). During the onset of exercise (phase 1), the upward resetting of blood pressure, brought about by medullary excitation from central command and/or muscle mechanoreceptor afferent input, is quicker than the response of the baroreceptor reflex arc. Thus, upon the onset of exercise when cardiac output and blood pressure increase substantially, the baroreflex-induced loss of peripheral vasoconstriction is relatively attenuated (Ludbrook and Graham, 1985). The result of this is that, against a background of only a slowly increasing sympathetically mediated vasoconstriction, there is an immediate redistribution of blood. As exercise continues into phase 2, the baroreflex gradually stabilizes blood pressure, albeit at a higher set point (Waldrop and Mitchell, 1985; Hales and Ludbrook, 1988).

Cardiac output increases immediately upon the onset of exercise in order to increase oxygen delivery (Cummin *et al.* 1986; Eriksen *et al.* 1990). Efferent vagal activity is inhibited by the central cardiovascular centre (either by central command or reflexly by muscle afferent mechanoreceptor input, see above) and heart rate increases simultaneously. A further increase in heart rate is the result of increased sympathetic activity on the heart *via* beta-receptor activation. Thus, in denervated hearts of, for example, heart transplant recipients, resting heart rate is higher because there is no vagal inhibition and no sympathetically mediated increase in heart rate occurs upon exercise. Consequently, there is a reduced cardiac output response (Banner *et al.* 1988). During exercise, myocardial contractility is also increased somewhat, which, together with the Frank–Starling

mechanism, leads to an increase in stroke volume and thus cardiac output. A increase in stroke volume is generally limited to mild intensity, upright exercise in humans and an increase in heart rate is solely responsible for the further elevation in cardiac output at higher exercise intensities (Plotnick *et al.* 1986; Cummin *et al.* 1986). The role of the Frank–Starling mechanism and heart–lung mechanical interaction (Agostoni and Butler, 1991) may be to help increase cardiac output before sympathetic activity can have its powerful influence.

Arterial blood pressure is reset upwards during exercise but well stabilized at this new level during phase 3. This implies that any increase in cardiac output is precisely matched by a decrease in total peripheral resistance and that any major mismatch would be catastrophic for maintained blood pressure and therefore, presumably, perfusion of vascular beds. Thus, although the baroreflex seems to be unimportant in the initial activation of the cardiovascular system during exercise, it may well be that during phase 3, in the absence of central command and muscle afferent feedback, blood pressure would be shown to be the primary controlled variable (Rowell, 1986; Rowell and O'Leary, 1990). This implies that during steady-state exercise there are three 'redundant' cardiovascular reflexes occurring and that there is a neural occlusive mechanism operative, which is similar to that shown to occur in stimulation experiments involving only central command and muscle afferent input (Rybicki *et al.* 1989). Thus, when barodenervation is superimposed on muscle afferent stimulation, the pressor response to induced exercise in anaesthetized cats (with no central command) is attenuated but not nullified (Waldrop and Mitchell, 1985).

Ventilation increases abruptly at the initiation of exercise (phase 1). This is due to neural outflow from the central respiratory centres *via* motoneurones to the intercostal, abdominal and diaphragm muscles. Thereafter (phases 2 and 3), the pattern of ventilation is modified by controlling both respiratory frequency and tidal volume, with further coordination involving the respiratory airway calibre (see above).

Long-term modulation of cardiorespiratory responses

Modulation of the control mechanisms of cardiorespiratory responses to exercise could be achieved by at least three influences: hormonal and opioid modulation, exercise training and other competing stresses.

Hormonal and opioid modulation

During prolonged exercise, several hormones are secreted into the systemic circulation. It is beyond the scope of this discussion to review comprehensively the role of all the secreted hormones during exercise (see Galbo, 1983, for a review), but recent evidence and proposals about one group of secreted chemicals are worthy of mention.

Exercise can stimulate endogenous opioid production. Although the mechanisms are poorly understood, it has been hypothesized that activation of group III muscle afferents may play a role (Thoren *et al.* 1990). During muscular contractio

These muscle afferents evoke cardiorespiratory responses *via* the ventrolateral medullary integration centres (see above). As well as this action, it is thought that they may also impinge on other brain regions, including the hypothalamus, thalamus, nucleus raphe magnus and the periaquaductus grey nucleus. These regions are known to be involved in pain reception, blood pressure control and release of opioids. Within the hypothalamus, the nucleus arcuatus is thought to be stimulated by afferent ascending signals and has projections to the thalamus, periaquaductus grey nucleus and brainstem. Synaptic release of opioids from neurones originating in the nucleus arcuatus would inhibit pain sensation, attenuate the baroreflex and reduce heart rate by increasing vagal tone. During exercise, central command is also present to increase heart rate and blood pressure and nullify any centrally directed opioid inhibitory action. However, after exercise, when acute central and muscle mechanoreceptor command signals have stopped, the well-documented, long-lasting opioid-induced attenuation of heart rate and blood pressure with a redistribution of blood flow could then become manifest (Rosen *et al.* 1989; Thoren *et al.* 1990). Further supportive evidence for a central opioid action comes from the finding that analgesic drugs such as morphine, an opiate agonist, can depress ventilation at rest and alter the pattern of ventilation during exercise, presumably by affecting respiratory centres responsible for drive and timing in the medulla (Favier *et al.* 1983).

Exercise training

Endurance training has been proposed to induce a lower resting and submaximal heart rate by inducing an increase in the cardiac parasympathetic dominance over the sympathetic influence (Smith *et al.* 1989). Recent evidence suggests that in middle-aged men, who have undergone a short-term endurance training programme, there is an increase in vagal tone but no change in the baroreflex control of heart rate (Seals and Chase, 1989), although the same may not be true for endurance-trained athletes (Reiling and Seals, 1988). Sympathetic activity at rest and during exercise is not affected by physical training (Seals, 1991). Training does not necessarily increase total blood flow to locomotory muscles in rats, but can change the distribution within the muscle groups (Armstrong and Laughlin, 1984). The mechanism by which this occurs is unknown. The effect of altered vagal tone on ventilation during exercise is not known. Although training does seem to strengthen intercostal muscles (Coast *et al.* 1990), the effect of endurance training on respiratory muscle function is, at present, a matter of considerable debate (Dempsey and Fregosi, 1985). The effect of training on the afferent sensory receptors and integrative neural centres of the medulla is unknown.

Other competing stresses

When breath-hold diving is imposed on a background of exercise in man, there ensue an instant apnoea, a gradual bradycardia and a reduction in cardiac output accompanied by increases in radial, pulmonary and right atrial pressures (Bjertnaes *et al.* 1984). In this situation, the facial and trigeminal receptors are thought

to play an important role, together with chemo- and baroreceptors, in controlling the cardiovascular responses to exercise in the presence of apnoea.

Prolonged exercise or exercise in a hot environment is accompanied by a rise in core temperature. In this situation, the cardiovascular system has two roles, first to preserve muscle blood flow, but also to increase blood flow to sites of heat loss, thus aiding thermoregulation. In panting animals, modulation of breathing may also play an important role in thermoregulation. Clearly, this conflict in function can limit performance by putting a great strain on the cardiovascular and respiratory systems. The compromise is excellently described by Rowell (1986) with respect to control of central and peripheral cardiovascular responses.

Recently, central command has been shown to be important in mediating an appropriate hormonal and, hence, metabolic response to exercise. Activity within the motor centres can elicit, in parallel with cardiorespiratory and locomotor responses, a complex hormonal response *via* a *feedforward* control mechanism (Kjaer *et al.* 1987*a*; Vissing *et al.* 1989*a*). For example, the ventromedial hypothalamus is involved in originating a *feedforward* control of glucose mobilization (Vissing *et al.* 1989*b*). Even muscle afferent activity conferring a *feedback* control seems to be important for the release of some hormones (Kjaer *et al.* 1989).

An integrated view

The hypothesis of a neurohumoral two-phase control system operating during exercise has been found to be very attractive. There is unequivocal evidence for the existence of at least two neurally mediated control systems acting simultaneously during phase 1, namely a central *feedforward* command and a muscle mechanoreceptor *feedback* reflex. These may be accompanied by a non-neural cardiodynamic *feedforward* coupling mechanism linking ventilation to cardiac output. All three control mechanisms can operate with almost instant response profiles and can, on their own, elicit the appropriate pattern of cardiovascular and respiratory responses to exercise. When operating simultaneously, there appears to be neural occlusion within the central pathways involving the two neurally mediated control systems. The result of this is a non-algebraic summation of the individual cardiovascular and respiratory responses, implying that there is some kind of integration. The role of the proposed 'cardiodynamic' coupling of ventilation to cardiac output could be twofold: first, to finely tune the gross phase 1 response pattern of the neurally mediated efferent outflow and, second, to act as a 'redundant' back-up system when central *feedforward* command and muscle *feedback* input are impaired.

The second part of the neurohumoral control system relies upon blood-borne substances conferring a 'chemical error' signal in a classical *feedback* reflex. The substance(s) may act directly on the target organ or have an indirect action *via* a peripheral receptor system. However, it has proved difficult to ascribe a particular importance to any one of the many potential humoral stimuli, because peripheral receptor denervation has been such a powerful tool with which to abolish o

minimize any potential role. This is particularly the case with the cardiorespiratory responses during phase 3. During phase 2, however, the carotid body chemoreceptors have been implicated in being responsible for bringing about a ventilatory response with the correct time course and magnitude. What humoral factor(s) stimulate(s) them is a matter of considerable debate. Central neural 'reverberation' or 'short-term potentiation', which is activated at the onset of exercise, may maintain adequate cardiorespiratory responses further into phases 2 and 3 of exercise. In the absence of an important humoral signal governing cardiorespiratory responses to exercise in phases 2 and/or 3, central neural reverberation may be a crucial controlling mechanism (Eldridge and Waldrop, 1991). Humoral signals, if they exist, may be responsible for the precise matching of cardiorespiratory adjustments to metabolic intensity and gradually developing problems of thermoregulation, fluid homeostasis and substrate delivery.

That there seem to be a multitude of 'redundant' control systems apparently active during exercise and readily demonstrable in specifically designed studies, clearly shows that the overall control of cardiovascular and respiratory systems is an emergent property and not the result of one sole controlling mechanism. Furthermore, because there are a number of 'redundant' control systems influencing any one variable, that particular variable must be envisaged as extremely important to safeguard. It is only with a vast array of control mechanisms that an organism can survive in a chosen ecophysiological niche or adapt to new environments.

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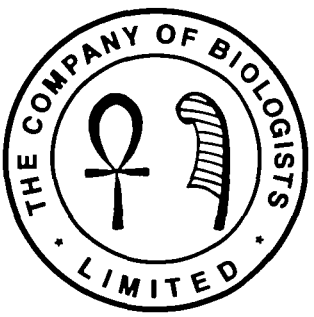
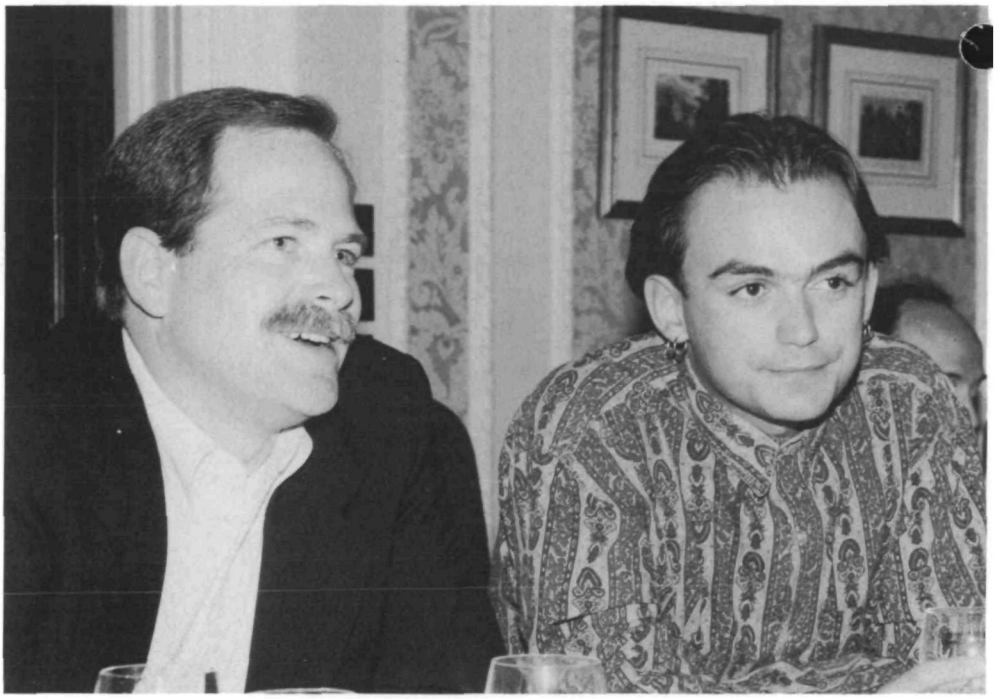
Photographs by William Foster

Back row:	Tony Woakes	Todd Gleeson	Neill Alexander	Ron O'Dor	Russ Baudinette	Charlie Ellington	Ian Johnston	Pat Butler	William Foster	
[redacted]ont row:		Al Bennett	Alfred Heusner	*Not* Dave Randall	Chris Wood	David Goldspink	Hans Hoppeler	Jan Henriksson	*Not* Duncan Turner	

Photographs taken at the Discussion Meeting held in Birmingham in April 1991



Back row:	Russ Baudinette	Duncan Turner	Jan Henriksson	Ian Johnston	Charlie Ellington		Neill Alexander
Front row:	Ron O'Dor	Alfred Heusner	Al Bennett	Todd Gleeson	Pat Butler	Chris Wood	Dave Randall
Reclining:				Tony Woakes			

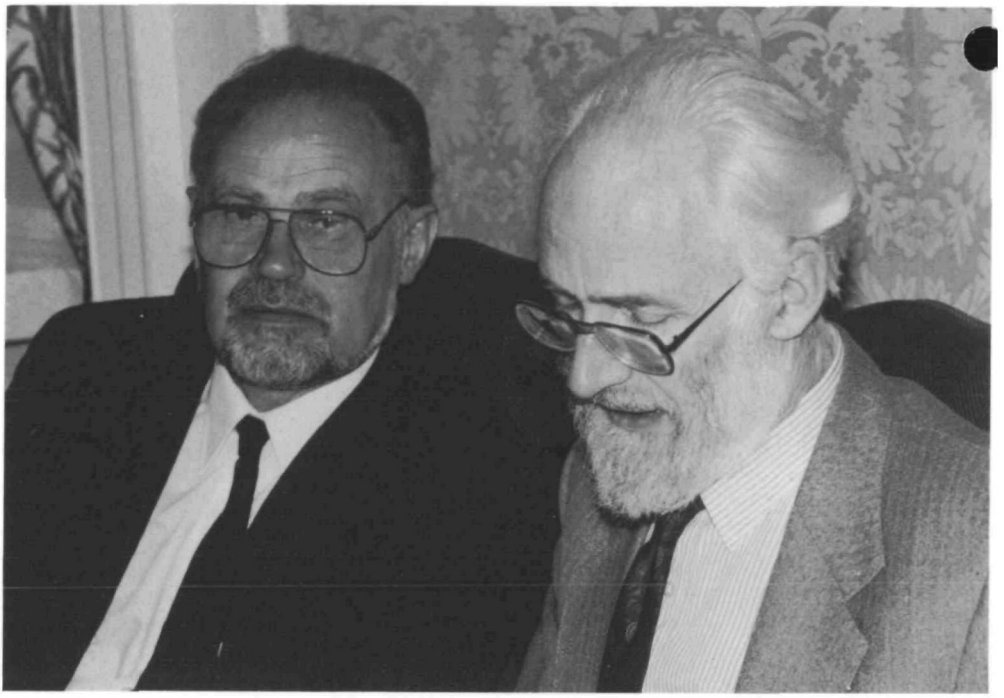


Todd Gleeson Duncan Turner

Ian Johnston David Goldspink

Tony Woakes Pat Butler Ron O'Dor

Charlie Ellington Ron O'Dor



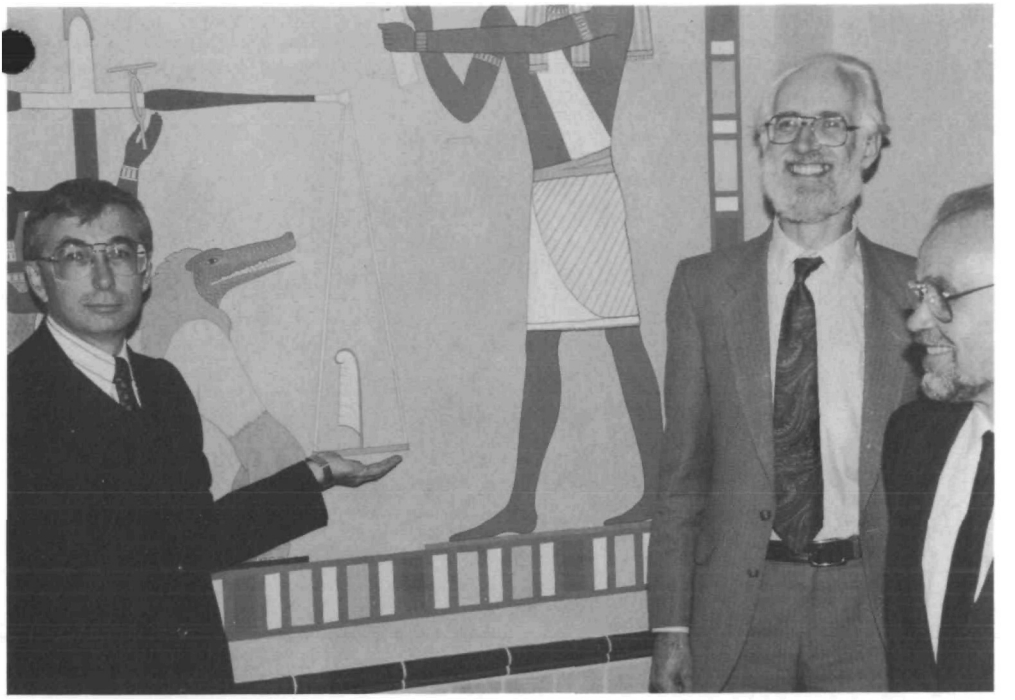
Alfred Heusner

Neill Alexander

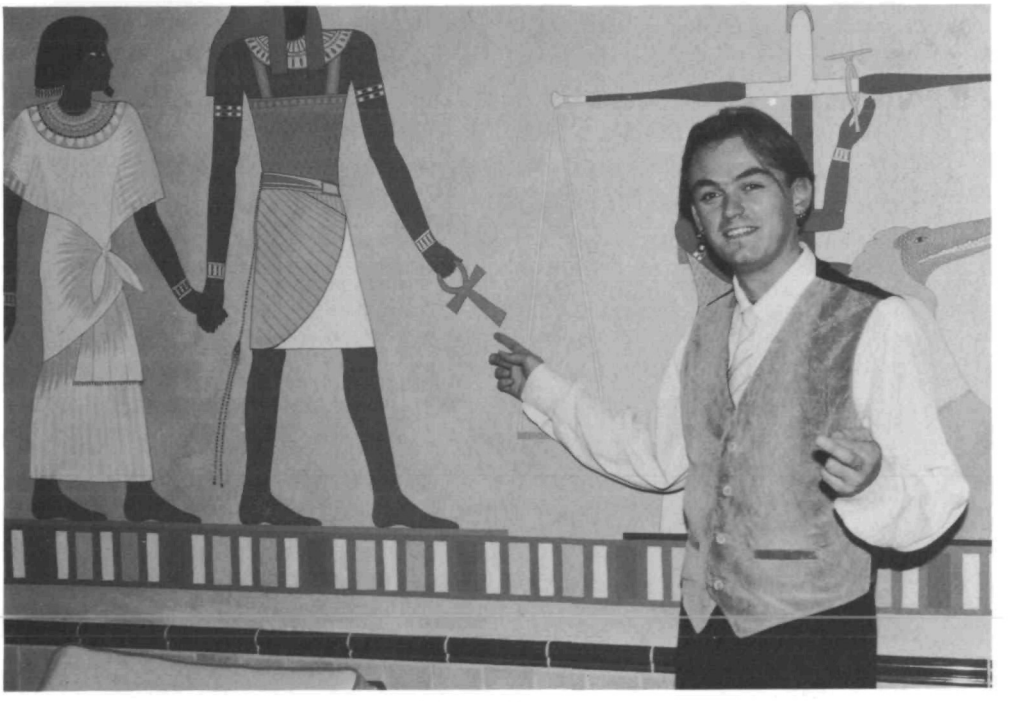
Todd Gleeson

Ron O'Dor

Jan Henriksson



Al Bennett The maat Neill Alexander Alfred Heusner

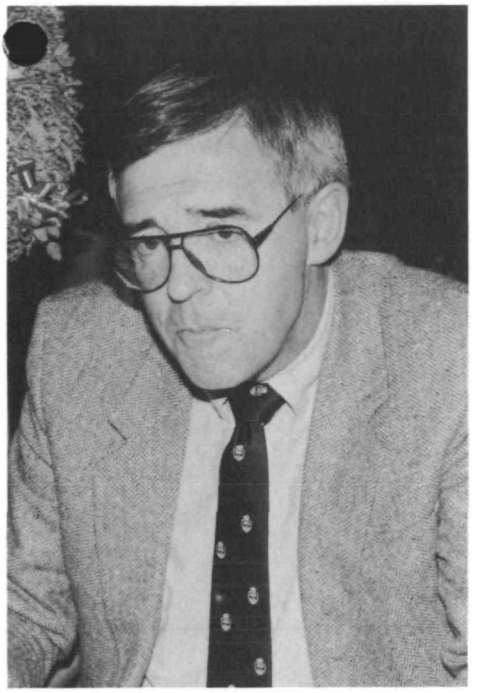


The ankh Ducan Turner

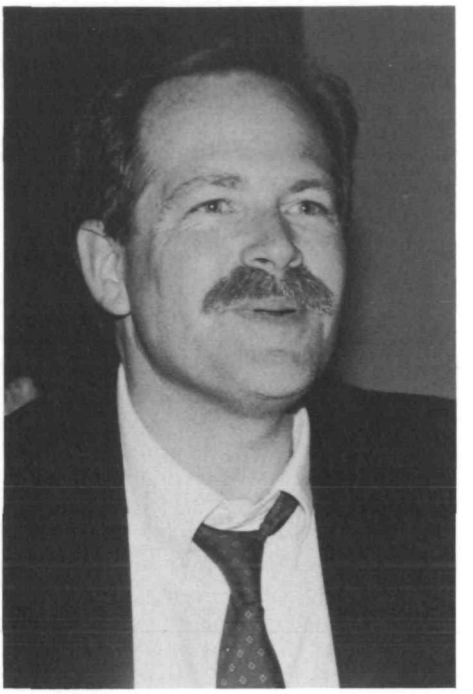
The two hieroglyphics (the maat 'truth' and the ankh 'life') are incorporated in the seal of The Company of Biologists that was adopted on 25 October 1925

Dave Randall Russ Baudinette

Margaret Clements Chris Wood

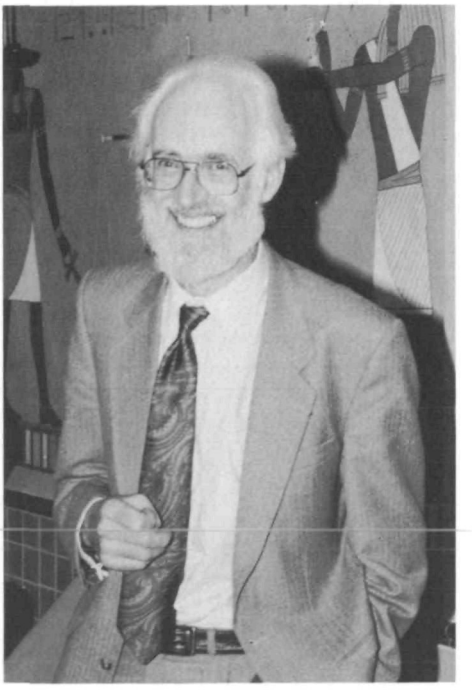


Russ Baudinette



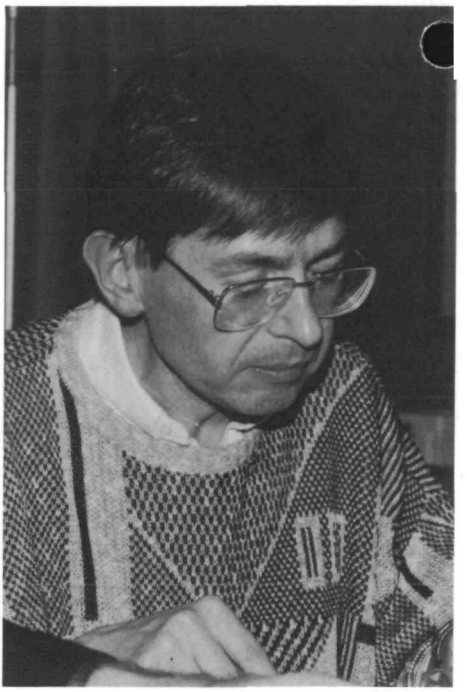
Todd Gleeson

Hans Hoppeler



Neill Alexander

Al Bennett



Chris Wood

Alfred Heusner

Ian Johnston