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growth and development

Symposium: Exercise Modulation of Human Growth

Dan M. Cooper

Evidence for and mechanisms of exercise modulation of growth—an overview

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ABSTRACT

COOPER, D. L. Evidence for and mechanisms of exercise modulation of growth—an overview. *Med. Sci. Sports Exerc.*, Vol. 26, No. 6, pp. 733–740, 1994. This symposium was organized to highlight new information regarding the mechanisms through which physical activity and exercise may affect the process of growth. Exercise associated anabolic effects (i.e., constructive or biosynthetic metabolic processes involved in tissue adaptation to physical activity) are varied and modulated by maturational and nutritional factors. Nonetheless, identifying common processes responsible for the many anabolic effects of physical activity may improve the ways exercise can be used in rehabilitation programs and to promote health. Thus, the overall aim of this symposium is to explore the diverse mechanisms that link physical activity with growth at both the cellular and somatic level. A conceptual model is presented that includes the interaction of *central* and *local* components of exercise modulation of growth. Central components encompass the mechanisms through which exercise of skeletal muscle groups can seemingly affect cellular growth and function throughout the body. Local components encompass those mechanisms that stimulate growth, hypertrophy, and the appearance of new mitochondria and capillaries in the muscle, bone, vascular and connective tissues involved in the specific exercise. The physiology of these putative mechanisms and their clinical applications are developed from six different perspectives.

EXERCISE, GROWTH, GROWTH HORMONE, IGF-1, FGF, CHILDREN, ANABOLISM

Naturally occurring physical activity in humans plays a profound role in tissue anabolism, growth, and development. Yet, little is understood about the mechanisms that link patterns of exercise with muscle hypertrophy (53), increased capillarization and mitochondrial capacity (14), stronger bones (38), changes in body composition (5,8), and modulation of puberty and menarche (50). For the purposes of the symposium, we define "anabolic effects" as constructive or biosynthetic metabolic processes involved in tissue adaptation to physical activity. Clearly, these effects are modulated by a host of factors such as the type and duration of physical activity as well as the nutritional, maturational, and health status of the individual. Nonetheless, identifying common processes responsible for the many anabolic effects of physical activity may improve clinical applications of exercise in preventing coronary artery disease (60) and obesity (30,41), and as a rehabilitation tool for children and adults suffering from chronic diseases.

Anabolic effects of exercise are not limited to individuals engaged in competitive sports and athletics who are particularly focused on improvements in strength or cardiorespiratory function. For example, limb immobilization, neural injury, or prolonged bed rest cause reductions of muscle mass and bone density even in individuals who live a "sedentary" lifestyle (15). This observation implies that a sizeable anabolic stimulus arises from the relatively modest physical activity of daily living. Conversely, excessive training may have adverse effects. For example, Theintz and coworkers (61) recently reported a *reduction* in the growth potential of adolescent female gymnasts engaging in intense training.

The magnitude and tissue specificity of anabolic effects of exercise likely change with maturation and aging. It is striking that *naturally occurring* levels of physical activity, energy expenditure, and muscle strength exhibit some of their most rapid increases during child-

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hood and puberty. This particular combination of rapid growth and development, high levels of naturally occurring physical activity, and spontaneous, puberty-related increases in anabolic hormones [growth hormone (GH), testosterone, and estradiol] suggest the possibility of integrated mechanisms linking exercise with a variety of anabolic responses. The role played by *neuroendocrine* factors in growth effects of exercise is outlined by Dr. Katarina Borer, and recent insight into anabolic hormonal changes occurring during puberty are reviewed by Dr. Alan Rogol.

PHYSICAL ACTIVITY, GROWTH, AND DEVELOPMENT

Little is known about the specific biologic role of exercise during childhood, but observations of children under natural conditions suggest several possibilities. Most children, even those not involved in sports or training programs, likely pass through phases where the physical activity of daily life far exceeds that of adults, and that some biologically essential, minimal threshold of activity is reached by the vast majority of healthy children. Thus, the effects of exercise on somatic growth (height, weight) *per se* become important only if the child's level of activity fall below this biological threshold. This may occur as a result of social or psychological factors or from chronic disease when cardiorespiratory or metabolic impairment prevents normal vigorous activity.

Thus, exercise modulation of growth need not imply that increasing levels of physical activity will increase *somatic* growth in healthy children (i.e., body height and weight). Increases in heart mass or skeletal muscle mitochondrial density may have little impact on overall body size. Conflicting results have been obtained from studies done to test the effect of training on growth rates in children. Although some investigators have concluded that training increases growth velocity by a small but significant degree (4,46), their studies were not carefully controlled for onset of maturity (6). Other workers could find no such activity-related growth effect despite a significant effect of training on maximal oxygen uptake ($\dot{V}O_{2max}$) and lung function (48,59). Unfortunately, detailed analyses of energy expenditure were provided in none of these studies. This topic is reviewed in the accompanying article by Dr. Malina.

It may be more useful to focus on exercise anabolic effects in terms of *cardiorespiratory adaptation* rather than *somatic* growth *per se*. There is evidence that *integrated* cardiorespiratory and muscular response to exercise may be modulated by childhood patterns of physical activity. An intriguing example of this was demonstrated by Maloiy and coworkers (43), who investigated the ability of women of the Luo and Kikuyu tribes in East Africa to carry up to 80% of their body weight. The job of carrying large loads throughout the village is assumed by girls at a relatively young age. $\dot{V}O_2$ during treadmill walking was measured in village women, and the investigators were surprised to find that their subjects could carry loads of up to 20% of their body weight before an increase in $\dot{V}O_2$ was detected (Fig. 1). This was in marked contrast to control subjects whose $\dot{V}O_2$ increased in proportion with the increasing load. One can hypothesize that the habitual load-bearing had influenced the development of elastic properties of tendons and muscles in the tribal women, and they had become physiologically more efficient in the complex energy metabolism of walking.

Data from our laboratory also suggest that functional aspects of the cardiorespiratory response to exercise may change markedly during childhood and maturation, and these may reflect anabolic effects of physical activity and exercise. A useful way of quantifying cardiorespiratory responses to exercise is to measure the time required to achieve a steady-state of $\dot{V}O_2$ or CO_2 production ($\dot{V}CO_2$) in the transition from rest to constant work rate exercise. We found, for example, that the time required to increase $\dot{V}CO_2$ at the onset of exercise (and to return to baseline during recovery) is markedly faster in children than in adults (3,22). These responses are also faster in lean compared with obese children (23), suggesting perhaps that CO_2 transport from cells to the lung is delayed by the high solubility of CO_2 in adipose tissue. This may explain the differences in CO_2 transport dynamics between adults and children since adiposity increases with age in adults.

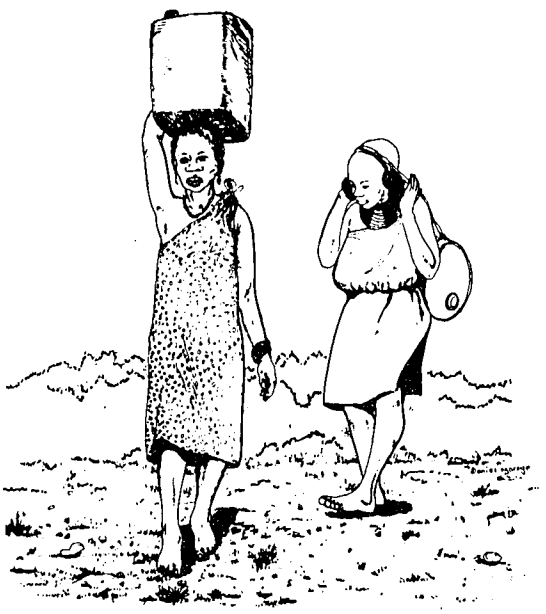

Figure 1—Women of the Luo and Kikuyu tribes carrying loads that sometimes equal 80% of their body weight (43). When walking on a treadmill, $\dot{V}O_2$ in these subjects did not increase until the carried load was equal to 20% of their body weight, while $\dot{V}O_2$ in control women increased as weight was added. Women of these tribes begin carrying heavy weights in childhood. Perhaps, the adaptation to this physical activity began at a young age and resulted in a more efficient elastic response of muscles and tendons to carrying heavy loads. Figure reprinted with permission.

Thus, there exists the potential for exercise associated alterations in the ratio of lean-to-fat tissue and the distribution of adipose tissue throughout the body to affect cardiorespiratory responses to exercise. Zanconato et al. (70) also found remarkable differences in the oxygen cost of 1-min bouts of exercise between children and adults (Fig. 2). Children required more oxygen than did adults to perform work (n.b., the oxygen cost was normalized to the external work performed on the cycle ergometer). While the mechanism responsible for these differences is not readily apparent, it is likely that some maturation of fiber types or, alternatively, of the efficiency of oxidative phosphorylation may play a role. How habitual physical activity in children affects this aspect of functional maturation is simply not known.

Patterns of physical activity during childhood may affect the incidence and morbidity of disease later in life. For example, Freeman and coworkers (30) recently studied potential risk factors among children who lived in neighborhoods in England where adults had a high incidence of coronary artery disease. Lack of physical activity was more predominate in children living in the high-risk neighborhoods. These observations may prove to be clinically important, but the mechanism of these effects remains unknown.

A MODEL OF EXERCISE MODULATION OF GROWTH

A conceptual model is presented that includes the hypothesis of "central" and "local" components of exercise modulation of growth (Fig. 3). Central components encompass the mechanisms through which exercise of skeletal muscle groups can seemingly affect cellular growth

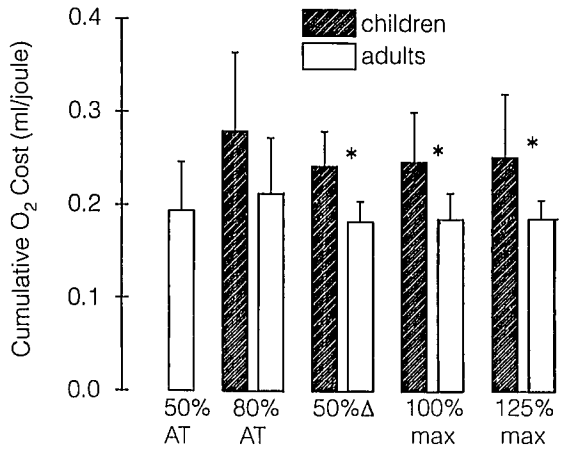

Figure 2—Cumulative O_2 cost per joule at different work intensities in adults and children. Values are means ± SD. Cumulative O_2 cost was not affected by increasing work intensity in children and adults. However, cost was significantly higher in children than in adults at work rates above the subject's anaerobic or lactate threshold (LT). 50%Δ refers to the work rate comparable to the AT work rate plus 50% of the difference between it and maximal work rate (*$P < 0.001$, **$P < 0.01$). Data from Zanconato et al. (70). Reprinted with permission.

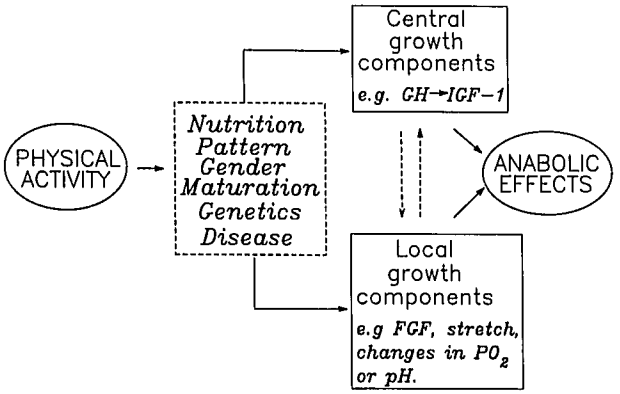

Figure 3—A conceptual model of exercise modulation of growth showing possible central and local components. Emphasis is placed on GH and IGF-1 and IGF BP3. Other factors such as FGF and GH binding protein are likely to play a role as well.

and function throughout the body [for example, cardiovascular effects or the increase in lean-to-fat ratio that accompanies virtually all types of training programs (56)]. Growth hormone, as outlined below, is clearly involved in the central pathways as well as IGF-1, which is a potent growth factor and is stimulated by GH in many tissues. Local components encompass those mechanisms which stimulate growth, hypertrophy, and the appearance of new mitochondria and capillaries in the muscle, bone, vascular and connective tissues involved in the specific exercise. For example, insulin-like growth factor-1 (IGF-1) may be stimulated in tissues independently of GH and act in both an *autocrine* and *paracrine* manner (40). Moreover, there is new evidence that fibroblast growth factors (FGF) play a role in local mechanisms of exercise modulated growth.

PERIPHERAL MECHANISMS

These include processes in which energy generated by exercise is transformed into signals that stimulate cellular anabolism at the site of the exercise. For example, current understanding of *vascular growth*, an important component of exercise anabolism, includes the activation of both intrinsic and extrinsic growth factors (by stimuli like local hypoxia) as well as cell-cell interaction (25). Moreover, physical stretch itself profoundly influences endothelial cell orientation and actin cytoskeleton organization in cell cultures grown on silicon membranes (58). Vandenburgh and coworkers (62,63) also demonstrated this phenomenon using avian skeletal myoblasts grown on collagen coated medium. Mechanical stretch led to an increase in protein production. It is noteworthy that muscle cell growth was significantly reduced in basal medium without growth factors prompting the authors to comment that mechanically stimulated cell growth was dependent on these growth factors.

In addition to IGF, there is evidence that FGF acts locally and, most likely, without direct GH control in

exercise-induced anabolism. Morrow and coworkers (49) demonstrated increased amounts of basic and acidic FGFs in the skeletal muscle of rabbits treated with continuous electrical stimulation—a regimen that might mimic exercise and one known to convert fast-twitch muscle fibers to slow-twitch fibers. Yamada and coworkers (69) showed that FGFs were stored in fiber extracellular matrix and appeared to be involved in the process of muscle hypertrophy in the rat. Muscle satellite cells [currently identified as the precursor cell for muscle growth and hypertrophy in the postnatal organism (1)] are now known to express the mRNAs for both acidic and basic FGF (2). Cell culture studies indicate that satellite cell proliferation and differentiation are regulated by IGF-1, FGF, and transforming growth factor-β (TGF-β) (1,66). TGF-β tends to inhibit both differentiation and proliferation while FGF stimulates proliferation and IGF-1 stimulates both proliferation and differentiation. Finally, the FGFs play a particularly important role in vascular growth (25), observations which provide a possible mechanism for the increased capillarization that accompanies physical training.

In exercising muscle, PO_2 and pH are low and lactate concentrations are high. Similar conditions can be found in the interior milieu of wounds. The healing wound is characterized by new capillary and collagen formation, and a number of investigators have focused on possible growth promoting effects of the changes in pH and respiratory gas concentrations. Might there be common mechanisms at the tissue level linking wound healing with exercise-induced anabolism? This question is addressed by Dr. T. K. Hunt in an accompanying article.

CENTRAL MECHANISMS

At least two independent studies of healthy human beings have demonstrated significant correlations between physical fitness (determined by the subject's maximal $\dot{V}O_2$) and blood levels of insulin-like growth factor 1 (IGF-1) (38,55). Presumably, the increased levels of IGF-1 [which is now known to stimulate growth in almost all tissues (65)] reflect the increased anabolism associated with physical fitness. But the mechanisms linking exercise and increased IGF-1 are unknown. Since the observations of Hunter and coworkers in *Science* in 1965 (35), it is well recognized that physical activity is a naturally occurring stimulator of GH release into the circulation (29). Moreover, GH induces tissue production of IGF-1 and elevations in serum IGF-1 (42). Thus, the intriguing hypothesis exists that exercise induced GH release is in part responsible—directly or indirectly—for anabolic effects of exercise.

Studies in both humans and other mammals suggest the importance of GH in exercise-induced anabolism. Cuneo and coworkers (24) showed that exogenous GH improved exercise performance and muscle mass in a group of GH deficient adults. Grindeland and coworkers (32) showed in detrained, hypophysectomized rats that GH was required in combination with exercise to bring about a retraining of atrophied muscles (32). These same investigators also recently demonstrated that physical inactivity in the rat (i.e., rat hindlimb suspension) results in impaired *pituitary cell* GH secretory capacity (36,57), a finding similar to their observations on the effects of zero-gravity during spaceflight. Using the hamster model, Dr. Katarina Borer has pioneered research into the role of GH and other neuroendocrine factors in exercise modulated growth and reviews her work in an accompanying article.

While the role of GH as a powerful tissue growth factor has been recognized for many years, current understanding of growth regulation holds that the GH effect on tissue growth is mediated, in part, by a variety of polypeptides, such as IGF-I and IGF-II (7) [n.b., it has been theorized that GH acts to promote cell differentiation rendering cells sensitive to IGF-1 actions (31)]. *In vitro* IGF-I stimulates DNA synthesis and induces cellular growth phase progression from the G_1 to S phase. IGF-I promotes anabolism in almost all tissues studied, ranging from hematopoietic to bone and cartilage. Originally the liver was considered the only source of IGF-I, but, as noted above, it is now known that most, if not all, tissues of the body produce IGF-I and IGF-II.

The effect of exercise on circulating IGF-1 has been examined by several investigators with differing results (9,33,68). For example, Wilson and Horowitz (68) reported no increase in serum IGF-1 in children after 15 min of an unspecified cycle ergometer exercise protocol; nor did Hagberg and coworkers (33) find an increase in IGF-1 after 60 min of treadmill exercise comparable to 70% of the subject's $\dot{V}O_{2max}$ in young and old adults. More recently, Bang and coworkers (9) reported a 26% increase in IGF-1 at the 10-min point of a 30-min exercise protocol in six healthy subjects (three women).

There are a number of possible explanations for these apparent discrepancies. First, the exercise intensity is frequently determined as a percentage of the $\dot{V}O_{2max}$, but the subjects' $\dot{V}O_{2max}$ is often extrapolated from constant work rate tests rather than an actually measured value. As noted previously (21), this can lead to a sample population in which some subjects exercise below, while others exercise above, their LT. This is an important distinction since hormonal and metabolic responses to exercise are not related to work intensity in a simple, linear manner. For example, the rate of glucose turnover and serum levels of lactic acid and catecholamines are much higher for above- vs below-LT exercise (20,21).

The data of Bang et al. (9) suggest that the time course of the IGF-1 response is rapid, peaking at about 10 min after the onset of exercise. But it is possible that circulating IGF-1 might increase *hours* after an exercise-induced increase in GH, reflecting *de novo* IGF-1 synthesis in the liver and transport into the circulation. Indeed, in

animal experiments and in studies following GH administration to GH-deficient children and adults, IGF-1 does not begin to increase in the blood until several hours after GH administration (13,42,44,45). Finally, care must be taken to fully extract the IGF-1 polypeptide from its binding proteins, otherwise, falsely low levels of IGF-1 may be measured in the serum (26). The question of whether or not IGF-1 acutely increases in response to exercise has yet to be resolved.

The IGF-I membrane receptor protein and its mRNA have been isolated (65). Similar to the insulin receptor, the IGF-I receptor is a member of the tyrosine-kinase group of membrane receptors. Regulation of the physiological function of IGF-I is tied to receptor dynamics. Circulating IGF-I is bound to a variety of binding proteins, the most abundant of which (IGF BP-3) is made in the liver and is regulated, in part, by GH (19). There is a growing body of evidence suggesting that binding proteins may actually serve as regulators of IGF-I action by controlling the availability of circulating IGF-I to target organs (19).

GH clearly plays an important role in anabolic effects of exercise, but the mechanism of this regulation is not known. At the simplest level, GH pulses caused by frequent, individual exercise bouts may have an additive effect, increase tissue IGF production, and synergistically promote tissue anabolism. In this context, the role of the *pattern* of physical activity in the adult or developing child may prove to be particularly important. Maiter et al. (42), for example, used the hypophysectomized rat to demonstrate that when exogenous GH was administered in pulses, the resulting serum IGF-1 and growth rates were significantly greater than when equivalent doses of GH were given continuously (Fig. 4). It is intriguing that activity patterns in children are characterized by short

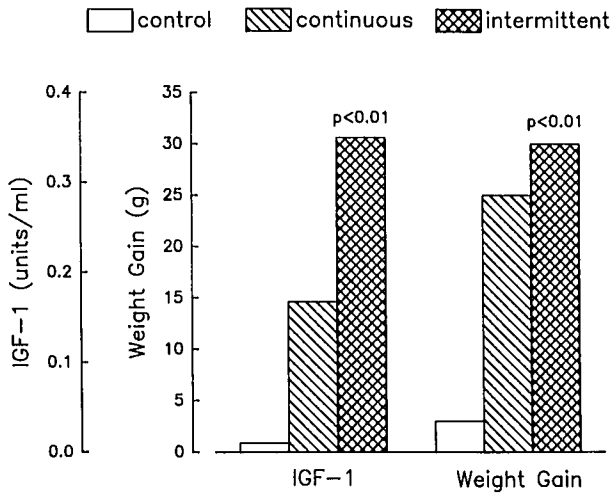

Figure 4—Effect of continuous vs intermittent GH administration in hypophysectomized rats. Levels of IGF-1 and weight gain were both significantly increased even though the total dose of GH in the intermittent and continuous groups was the same. Figure drawn from data of Maiter et al. (42).

bursts of exercise; perhaps, this pattern optimizes the anabolic effects of exercise in the growing child.

Alternatively, it is possible that the correlation between physical fitness and IGF-1 noted above (38,55) may result from an exercise effect on the overall pattern of GH secretion, rather than from the GH-effects of single exercise bouts. Recently, for example, Weltman et al. (64) noted a significant increase in the amplitude of spontaneously occurring GH-pulses in women following 1 yr of training at above-LT work intensities. The mechanism of this effect is not known. Finally, it is noteworthy that exercise associated increases in IGF-1 mRNA can occur in the absence of GH. For example, DeVol and coworkers (28) hypothesized that non GH-dependent, local regulation of IGF-1 production also existed, and Dr. DeVol reviews his studies on IGF-1 mRNA expression in compensatory muscle hypertrophy in an accompanying paper. Thus, both GH-dependent and GH-independent pathways likely exist that link exercise with tissue anabolism.

NUTRITIONAL FACTORS

Nutrition and activity patterns may affect exercise-induced anabolism through common mechanisms [for example, the similarity between IGF and insulin receptors (40)]. The interactions between diet and exercise are not only biologically intriguing, but also relevant clinically because both are factors that *can be modified* in ways to substantially benefit the health of human beings. Much attention has been paid to the role of substrate availability on energy metabolism during exercise. Far less is known about the hormonal mechanisms through which diet might influence anabolic effects of physical activity. One possible mechanism is that exercise-stimulated GH release could be diminished by diet. This could occur in at least two ways: first, glucose ingestion leads to hyperglycemia that inhibits GH release (27); second, meals high in fat could inhibit pituitary GH release either by a direct effect of free fatty acids (FFA) on the pituitary (18), or might cause release of gastric and pancreatic somatostatin (n.b., increased circulating somatostatin following fatty meals is observed even without increases in blood glucose (54)).

To test this, 11 healthy young adults performed 10 min of high-intensity (above-LT), standardized cycle ergometry in our laboratory on the morning following an overnight fast (16). On separate days they ingested a noncaloric placebo liquid meal or an isovolemic, isocaloric liquid meal high in either fat or glucose. Previous studies by Penman et al. (54) demonstrated that the high-fat meal would result in prolonged elevations of serum somatostatin. Venous blood samples were obtained prior to and for 90 min after exercise began, while gas exchange data were measured breath-by-breath. Although there was no difference in preexercise GH levels, mean peak, postexercise GH was 54% lower following the high-fat meal

compared with placebo ($P < 0.01$) (Fig. 5). There was no significant effect on the GH response after the high-glucose meal. Mean somatostatin for the high-fat protocol (27.0 ± 2.1 pg·ml^{-1}) was significantly greater than after both high-glucose (14.8 ± 1.1) and placebo (13.9 ± 0.7). This study demonstrates that exercise-induced GH release can be significantly attenuated by the contents of a single preexercise meal. The high-fat meal increased circulating somatostatin and was associated with an inhibition of the GH secretion. The data provide a possible specific mechanism to explain how diet can acutely modulate the anabolic effects of exercise.

STRUCTURE-FUNCTION INTERACTIONS

The changes in cellular structure that occur in response to exercise are often well-reflected in functional capabilities of the whole organism. For example, Milliken and coworkers (47) used magnetic resonance imaging to estimate the mass of the left ventricle in athletes and in relatively sedentary controls. The heart was more massive in athletes (cross-country skiers, cyclists, and endurance runners) both in absolute terms and when normalized to body weight. In addition, sedentary subjects who undergo programs of exercise training show marked improvement in cardiorespiratory fitness as evidenced by increases in the anaerobic (or lactate) threshold and the $\dot{V}O_{2max}$—Figure 6 (17). By combining methodological approaches (e.g., MRI, magnetic resonance spectroscopy, and breath-by-breath measurements of gas exchange), it is now possible to determine how growth or other changes in the structure of specific tissues correlate with functional responses to training and physical activity.

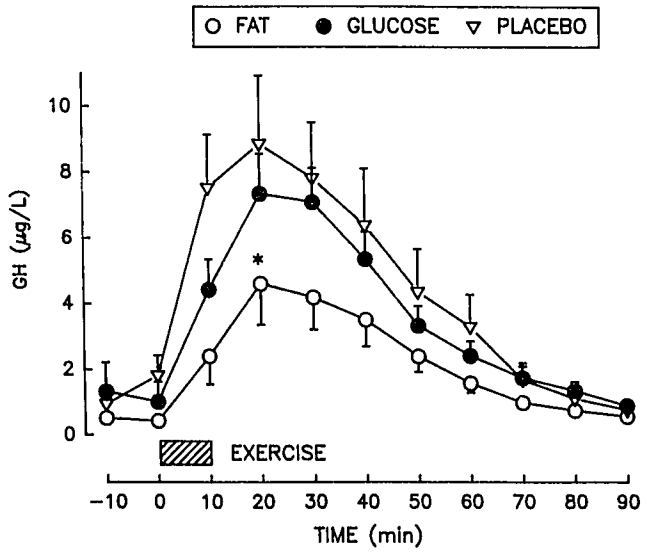

Figure 5—Growth hormone response to high-intensity exercise following meals high in fat or glucose, or placebo. Values are presented as mean and SE. Hatched area indicates the 10-min period of high-intensity exercise. GH peak was significantly reduced following the high-fat meal ($P < 0.05$). Figure from Cappon et al. (16). Reprinted with permission.

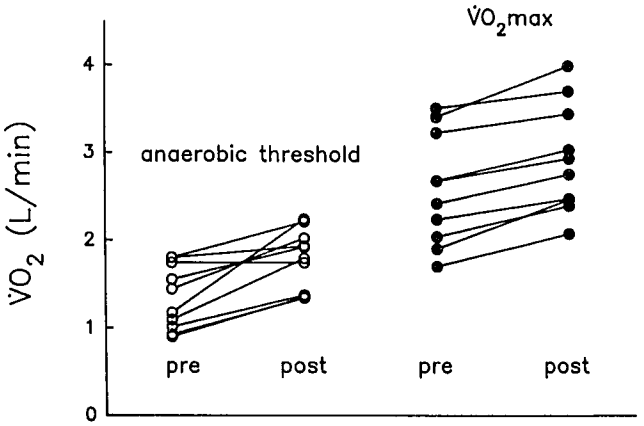

Figure 6—Effect of training on anaerobic threshold and $\dot{V}O_{2max}$. The functional consequences of anabolic effects of exercise are seen as increases in cardiorespiratory gas exchange during exercise. Figure based on data from Casaburi et al. (17).

CLINICAL APPLICATIONS

There has been a recent surge of interest in health benefits of exercise. In the document *Healthy People 2000* (34), prepared under the auspices of the Department of Health and Human Services, the health promoting role of exercise is repeatedly noted, and a major goal is to promote physical fitness for all Americans regardless of age, gender, or ethnic origin. Patterns of physical activity, particularly in combination with specific diets, can either benefit or harm human health. For example, the combination of a diet high in fat with a sedentary life style contributes to the development of obesity, hypercholesterolemia, hypertension, and coronary artery disease (11,39,52). Conversely, appropriate manipulations of diet and exercise may prevent these diseases as well as promote cardiorespiratory rehabilitation (10,51). Understanding mechanisms of exercise anabolism may lead to answers of a number of clinically important questions including:

1. What is the role of exercise (with or without growth promoting agents) in mitigating the frailty that often accompanies aging?
2. Is it possible to engender patterns of physical activity in children which act to prevent disease later in life?
3. Can exercise be "optimized" following chronic diseases in adults or children to exploit the anabolic effects of physical activity on particular target organs?

This latter question is particularly difficult. One could argue, for example, that there is no need in healthy children to attempt to impose patterns of physical activity since the natural inclination of children is to be active, and thereby, maximize anabolic effects of exercise. But

in the case of the child with chronic lung or heart disease [who often grow and develop abnormally (12,37)], it is our clinical experience that the child's desire to participate often exceeds his or her ability. Approaches to balance the physiological constraints of a particular disease with the positive physical and social impact of exercise have yet to be developed.

New knowledge of growth regulation at the molecular level has raised the hope that growth factors can be used therapeutically for catabolic illnesses in adults and children (67) or to mitigate the frailty that accompanies aging. While the prospect of augmenting the healing response in a child following a severe burn injury or in child recovering from severe lung injury is appealing, the use of growth promoting agents may have different long-term physiological consequences in children compared with adults. This must be investigated to ensure the safe clinical use of growth factors in children. At the same time, there appears to be an increasing abuse of drugs touted to boost body height, strength, and athletic prowess in normal children and young adults. Our challenge is to vigorously oppose the use of alleged growth promoting drugs in healthy children, while continuing to explore therapeutic interventions that truly benefit growth, development, and the quality of life in children with chronic disease.

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