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Dietary supplements

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For the athlete training hard, nutritional supplements are often seen as promoting adaptations to training, allowing more consistent and intensive training by promoting recovery between training sessions, reducing interruptions to training because of illness or injury, and enhancing competitive performance. Surveys show that the prevalence of supplement use is widespread among sportsmen and women, but the use of few of these products is supported by a sound research base and some may even be harmful to the athlete. Special sports foods, including energy bars and sports drinks, have a real role to play, and some protein supplements and meal replacements may also be useful in some circumstances. Where there is a demonstrated deficiency of an essential nutrient, an increased intake from food or from supplementation may help, but many athletes ignore the need for caution in supplement use and take supplements in doses that are not necessary or may even be harmful. Some supplements do offer the prospect of improved performance; these include creatine, caffeine, bicarbonate and, perhaps, a very few others. There is no evidence that prohormones such as androstenedione are effective in enhancing muscle mass or strength, and these prohormones may result in negative health consequences, as well as positive drug tests. Contamination of supplements that may cause an athlete to fail a doping test is widespread.

Keywords: bicarbonate, caffeine, carnitine, creatine, dietary supplements, drugs, nutrition.

Introduction

Talent is undoubtedly the most important attribute of the elite performer, but it is difficult to define. Other factors that characterize the elite athlete include a sustained effective training programme, a range of psychological and cognitive characteristics, resistance to injury and effective nutrition support. At a time when the world standard in sport is moving to ever-higher levels, the athlete who wants to make it to the top and to stay there must explore all possible means of securing an advantage.

As training programmes become ever more demanding, every possible advantage must be seized, and nutrition is an obvious area that can make a difference. The foods that an athlete chooses can make the difference between success and failure. Although wise food choices will not make a champion out of the athlete who does not have the talent or motivation to succeed, an inadequate diet can prevent the talented athlete from making it to the top. A varied diet eaten in an amount sufficient to meet the energy needs of the athlete in training should provide all the essential nutrients in adequate amounts, but not all athletes eat a varied diet and the total food intake may at times be restricted. Because nutritional deficiencies may be difficult to detect in their early stages, athletes are often tempted to take individual nutrients in a concentrated form to guard against the possibility of a deficiency developing. To cater for the demand for specialist nutritional supplements for athletes, an enormous multinational industry has grown up, encouraged by a popular culture of supplement use among the general population in the belief that this can in some way compensate for poor food choices and the increased stresses of modern life. This supplement culture has extended to include an enormous diversity of compounds that extends beyond nutritional components to embrace more exotic edible compounds.

The following sections will review the various categories of nutritional supplements that are used by athletes and will present evidence for or against the use of selected supplements. Some recent comprehensive publications have reviewed a wide range of individual supplements (Antonio and Stout, 2001; Talbott, 2003).

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In this review article, we do not attempt to review all of the available information on even a few of the hundreds (perhaps thousands) of different supplements in widespread use, but instead focus on some of the general issues associated with supplement use, using examples to highlight specific issues. Further information on some of these supplements will be found in some of the other reviews contained in this issue.

The use of any nutritional supplement that is effective in improving performance inevitably raises ethical issues. Ergogenic aids are banned by the governing bodies of sport for one of two reasons: on the grounds that they pose threat to the health of the individual, or because they confer what is seen to be an 'unfair' advantage. These issues must always be borne in mind when considering the use of any supplement.

The scope of supplement use

Limited information is available on the extent of dietary supplement use among athletes. The global market for supplements in 2001 was estimated at US$46 billion, with the US supplement market in 2000 being estimated at US$16.7 billion (*Financial Times*, 19 April 2002). Athletes account for a significant fraction of the total market and a wide range of products are aimed at both the active population and at those engaged in competitive sport.

Many surveys of supplement use in athletes have been published, with a meta-analysis of 51 published surveys involving 10,274 male and female athletes showing an overall prevalence of use of 46% (Sobal and Marquart, 1994). Prevalence of use, however, varies widely among sports and among athletes of different ages, standards of performance and cultural background. In some sports, especially strength and power sports, supplement use is the norm. A report of supplement use among 100 Norwegian national-level competitors from various sports revealed that 84% surveyed used some form of micronutrient supplement (Ronsen *et al.*, 1999). Most athletes in this survey took multiple supplements, although many had nutritional habits that were described as 'unsatisfactory', implying that these athletes might have benefited more from attention to the foods they ate.

Only a few surveys have attempted to quantify the frequency or amount of supplement use, but it appears to be common for athletes to exceed the recommended doses of supplements. This may be because of a feeling that 'more is better' or because team-mates or opponents are known to use higher doses. In some cases, for example creatine, the dose recommended by some suppliers may be far higher than the maximum effective dose. On the other hand, the amount of supplement in some preparations may be far less than the amount used in laboratory studies of efficacy, especially where expensive ingredients are concerned. Estimates of use by individual athletes suggest that some may ingest very large numbers of different supplements on a regular basis and that the amounts used may be far in excess of those shown to be safe. Most people believe that 'natural' supplements are harmless, but high intakes of many of these supplements on a long-term basis may be harmful. Iron, zinc and other metallic elements are frequently consumed in amounts that are known to be harmful. It would appear that athletes – and often also those who advise them – are usually unaware of the risks.

Most surveys have failed to examine the reasons for supplement use by athletes, information that is fundamental to any effort to change the behaviour of athletes. In one study, attitudes to dietary supplement use were assessed in 1737 young (14–19 years) male and female (58% male, 42% female) high school athletes (Perko, 2000). Coaches, parents, physicians, athletic trainers and peers all influenced the decision to take supplements. There was a good relationship between behaviour and perceived normal behaviour, but knowledge about the effects of supplements was poor. Other surveys have found no association between the prevalence of supplement use and gender, race, marital status, educational background, dietary habits or training status. Commonly cited reasons for supplement use include:

- to compensate for an inadequate diet;
- to meet abnormal demands of hard training or frequent competition;
- to benefit performance;
- to keep up with team-mates or opponents;
- recommended by coach, parent or other influential individual.

However, even when athletes are informed on the basis of biochemical measurement of nutrient status that their diet is adequate or that the status of their body stores is normal (e.g. iron), the use of supplements persists, suggesting that the decision to use supplements is not a rational one.

Improving strength and power: promoting tissue growth and repair

The use of dietary supplements seems to be particularly prevalent among athletes in strength and power sports, with some surveys showing that all athletes from these events were using one or more supplements. A wide range of supplements are sold as 'anabolic' or 'anti-

catabolic' agents, with either direct or indirect effects on protein synthetic pathways in muscle. Proposed mechanisms of action include a mass action effect on synthetic pathways by increasing amino acid availability, stimulation of hormone release or potentiation of hormone action, an increase in cell volume, or by acting as an adaptogen (i.e. promoting adaptation to training). Supplements on sale in this broad category include amino acids, boron, chromium, chrysin, colostrum, creatine, hydroxymethylbutyrate (HMB), ornithine alphaketoglutarate, protein, tribulus terrestris, vanadium and zinc.

Although protein products are by far the largest selling products in this group, sales of creatine (a product that is not used except in sports nutrition) and of some other products are also substantial. For most of these supplements, there are few supporting data – indeed, few experimental data at all. In many cases, there are suggestions from *in vitro* studies of effects that may be relevant, but there is no experimental evidence from studies on healthy humans.

Proteins and amino acids

The use of high-protein diets has a long history in sports nutrition and such diets were reportedly popular with athletes in the Olympics of ancient Greece. There is good evidence that protein requirements are increased by hard training and it is often recommended that the protein intake of strength athletes should be 50–100% greater than that of their sedentary counterparts (Tarnopolsky, 2001). Athletes often insist that much higher amounts of protein are necessary to increase muscle mass, but the literature does not support this supposition. This apparent inconsistency may be explained by Millward's adaptive metabolic demand model, which proposes that the body adapts to either high or low intakes, and that this adjustment to changes in intake occurs only very slowly (Millward, 2001). With high protein intakes, there is an up-regulation of protein degradation and amino acid oxidation. The athlete consuming a high protein diet who acutely reduces protein intake will experience a loss of lean tissue until a new equilibrium has been achieved.

Whether protein supplements are necessary is a separate issue, and this is discussed by Tipton and Wolfe (2004). It is clearly possible to achieve very high protein intakes by choosing appropriate foods, but it is also true that many high protein foods have a high fat content. Knowledge about the composition of foods among athletes is not generally good, which means that a restricted choice of foods is almost inevitable. Protein supplements offer athletes the possibility of achieving their desired protein intake without an unacceptable increase in fat intake and without major changes to their eating habits.

In the case of some amino acids, there are data from clinical studies involving severely stressed individuals (by trauma, burn injury or surgery) showing that supplementation may reduce the extent of muscle wasting that occurs, but this catabolic state is hardly relevant to the healthy athlete trying to increase muscle mass. Individual amino acids claimed to promote muscle growth include glutamine, branched-chain amino acids, leucine, lysine, arginine and ornithine. There is little evidence to support the benefit of supplementation of any of these amino acids for athletes eating a normal diet. Although high doses of arginine, ornithine and lysine may result in increased circulating growth hormone and insulin concentrations, these have not been shown to result in changes in lean body mass or in muscle function (Merimee *et al.*, 1969). The changes in growth hormone that result are transient and small relative to the normal fluctuations that occur and are also small relative to the increases that result from even a short period of very high-intensity effort.

β-Hydroxy-β-methylbutyrate

A relatively recent addition to the plethora of nutritional supplements is β-hydroxy-β-methylbutyrate (HMB), a metabolite of leucine. Although the mechanism of action of HMB is unknown, it has been hypothesized that it either acts by decreasing muscle proteolysis or by improving cell integrity by providing substrate for cholesterol synthesis (Nissen and Sharp, 2003). In previously untrained individuals, HMB may increase lean body mass and strength more than resistance training alone (Nissen *et al.*, 1996; Gallagher *et al.*, 2000a; Panton *et al.*, 2000). Direct measures of muscle membrane integrity have not been made, but intake of HMB has been reported to reduce blood concentrations of creatine kinase during resistance training in previously untrained individuals (Nissen *et al.*, 1996; Gallagher *et al.*, 2000a; Panton *et al.*, 2000). In addition, Nissen *et al.* (1996) reported that HMB intake reduced urinary excretion of 3-methylhistidine, a finding that is consistent with a decrease in muscle proteolyis. In trained individuals and elite power athletes, however, HMB intake does not appear to enhance lean body mass or strength (Kreider *et al.*, 1999; Slater *et al.*, 2001; Ransone *et al.*, 2003) or anaerobic exercise capacity (O'Connor and Crowe, 2003). β-Hydroxy-β-methylbutyrate also does not appear to affect markers of catabolic status or muscle membrane integrity in well-trained individuals (Kreider *et al.*, 1999; Paddon-Jones *et al.*, 2001; Slater *et al.*, 2001).

A recent meta-analysis on studies of both trained and untrained individuals (Nissen and Sharp, 2003) reported that HMB intake increases lean body mass by 0.28% per week and strength by 1.40% per week compared with resistance training alone. Effect sizes for these improvements were small (0.15 and 0.19 for lean mass and strength, respectively). Taken together, these findings suggest that HMB may have some value for athletes beginning a resistance training programme. β-Hydroxy-β-methylbutyrate has been reported to reduce the accumulation of creatine kinase in the blood of runners after a 20-km time-trial (Knitter *et al.*, 2000), and may reduce blood lactate accumulation during endurance exercise (Vukovich and Dreifort, 2001). Although HMB appears to be a safe supplement (Gallagher *et al.*, 2000b; Nissen *et al.*, 2000), its relative expense (US$1.8–2.4 per day) and the limited likelihood of a beneficial effect suggest that it may not have much to offer the athlete.

Trace elements

Several single elements are also promoted as anabolic agents. Chromium plays a role in insulin sensitivity and insulin is a potent anabolic hormone. Exercise may increase urinary chromium excretion, raising concerns among athletes that deficiency may occur. There are limited data on the effects of chromium supplements in athletes, with published studies of chromium supplementation showing an increase, decrease or no change in body mass. The best-controlled studies, however, show no effect on muscle mass or strength (Clarkson and Rawson, 1999; Nissen and Sharp, 2003). In addition, concern has recently been expressed that chromium, if taken as the picolinate salt, may not be entirely safe, with several adverse effects having been reported (Vukovich, 2001).

Vanadium is also advertised as a promoter of the action of insulin, and there are limited animal data to support this. Human data, however, show no effect of supplementation on body composition or strength in resistance-trained athletes (Fawcett *et al.*, 1996). There is some debate as to whether boron is an essential element in human nutrition, but boron supplementation is claimed to increase circulating testosterone, with the prospect for an anabolic action. This result, however, was obtained in post-menopausal women who had been fed a low-boron diet (Nielson *et al.*, 1987), and there are no studies showing that boron feeding results in muscle hypertrophy in normally nourished individuals with normal endocrine function. Administration of boron supplements to a group of male bodybuilders had no effect on circulating free or total testosterone or on muscle size or strength (Ferrando and Green, 1993).

Prohormones and related compounds

A variety of precursors of testosterone and nandrolone (19-nortestosterone) – together referred to as prohormones – are sold as dietary supplements: these include in particular androstenedione ('andro') and 19-norandrostenedione. These are not legal in those countries where they are classified as prescription-only drugs, and are banned in Olympic sports. Nonetheless, their use is permitted in some sports, including baseball, where they have been promoted by successful players, and they are readily available via the internet or from countries where their sale is not restricted. Recent research in this area has focused on dehydroepiandrosterone (DHEA), androstenedione, androstenediol and 19-norandrostenedione. The rationale for taking these supplements is that these androgens are only one or two chemical reactions away from testosterone.

Dehydroepiandrosterone is formed primarily in the adrenal glands, and is found in high concentrations in the blood, but its physiologic roles(s) are unclear; it can also be converted to androstenedione (Geller, 1985) or androstenediol (Schindler and Aymar, 1975). The intake of DHEA does not increase blood testosterone in men or augment gains in muscle size and strength due to resistance training (Brown *et al.*, 1999; Wallace *et al.*, 1999). While replacement doses of DHEA in ageing women increase both serum testosterone and dihydrotestosterone (DHT) concentrations (Morales *et al.*, 1994), the effect of DHEA intake on serum sex hormones, muscle size and muscle strength in young healthy women is not known.

In men, the intake of 100–200 mg of androstenedione or androstenediol does not affect blood testosterone concentrations (King *et al.*, 1999; Wallace *et al.*, 1999; Ballantyne *et al.*, 2000; Earnest *et al.*, 2000). The effect of higher doses of androstenedione on blood testosterone is not clear (Leder *et al.*, 2000). Chronic intake of 200–300 mg androstenedione or 200 mg androstenediol per day does not result in greater gains in muscle size and strength during resistance training than training alone (King *et al.*, 1999; Broeder *et al.*, 2000). Norandrostenedione and norandrostenediol have also been shown not to raise blood concentrations of nandrolone (19-nortestosterone) or to affect body composition or strength in young healthy men (Dehennin *et al.*, 2002; van Gammeren *et al.*, 2002). In middle-aged (30–60 years) men, 300 mg of either androstenedione or androstenediol per day raises blood free testosterone by approximately 35%. In healthy young women, the effect of androstenedione intake is not clear. One study reported that the intake of 100 mg androstenedione increases blood total testosterone to concentrations typically observed in young healthy men (Kicman *et al.*, 2003). In another study, however, blood

testosterone was elevated after the intake of 300 mg of androstenedione, but remained at levels less than one-half of normal values for young men (Brown *et al.*, in press). Although the effect of androstenedione on muscle size and strength in women has not been studied, the likely virilization and other possible side-effects of androstenedione use in women suggest that women should not take this supplement.

Since androstenedione is similar in structure to testosterone, it is reasonable to hypothesize that androstenedione might be an anabolic agent, independent of any effect on testosterone concentrations. However, androstenedione does not increase muscle protein synthesis *in vivo* (Rasmussen *et al.*, 2000) and does not increase satellite cell proliferation or differentiation *in vitro* (Vierck *et al.*, 2003).

The intake of androstenedione and androstenediol decreases blood concentrations of high-density lipoprotein cholesterol in males (Brown *et al.*, 2000a,b, 2001a,b), corresponding to a 10–15% increase in the risk for cardiovascular disease. In all participants, ingested androstenedione and androstenediol appeared to be preferentially converted to oestrogens and DHT, rather than to testosterone. Dihydrotestosterone is associated with male pattern baldness and benign prostate hypertrophy. Elevated concentrations of oestrogens have been linked to pancreatic cancer and gynecomastia (breast growth). Increased blood concentrations of androstenedione may increase the risk of pancreatic and prostate cancer, and may promote behavioural changes.

Because the liver removes a significant amount of androgen that is taken orally, it is possible that an androgen that is taken by allowing a pill to dissolve under the tongue may be more readily converted to testosterone. Androstenediol taken in this form increases blood total testosterone by 125% (Brown *et al.*, 2002). Whether this product enhances muscle size or strength remains to be determined. Finally, androstenedione and other prohormones undergo extensive metabolism to other steroids. Recent reports suggest that athletes taking these steroids are at risk for positive drug tests (Catlin *et al.*, 2000; Uralets and Gillette, 1999).

In summary, 'testosterone prohormones' taken orally do not significantly raise blood testosterone in young men and do not increase muscle size or strength. These supplements may pose significant health risks and may result in positive drug tests.

Herbal supplements

Many herbal supplements are claimed to increase testosterone concentrations and hence have an anabolic action. These include tribulis terrestris, chrysin, indole-3-carbinol, saw palmetto, gamma-oryzanol, yohimbine, smilax and mummio. All of these claims are based on *in vitro* data. Attempts have been made to formulate combinations of some of these herbal extracts with androstenedione and androstenediol to minimize aromatization to oestrogens and reduction to DHT. Recently, it has been shown that a formulation containing tribulus terrestris, chrysin, indole-3-carbinol and saw palmetto, together with androstenedione or androstenediol and DHEA, does not increase serum testosterone or augment the increases in muscle size and strength achieved through strength training alone (Brown *et al.*, 2000a,b, 2001a,b). These human data suggest that these herbal extracts are of no value.

Weight loss and fat loss

Supplements in this category are used by athletes who need to limit body mass, and especially body fat, in weight category, weight-sensitive or aesthetic sports.

Carnitine

The supply of plasma free fatty acids to the exercising muscle is important for determining the relative contributions of fat and carbohydrate to oxidative metabolism, but a number of other steps are recognized as being involved in fat oxidation. Fatty acid uptake into the cell and translocation across the mitochondrial membrane are also key steps. Carnitine combines with fatty acyl-coenzyme A (acyl-CoA) in the cytoplasm and allows that fatty acid to enter the mitochondrion. The first step is catalysed by carnitine palmitoyl transferase 1 (CPT1) and the trans-membrane transport is facilitated by acylcarnitine transferase. Within the mitochondrion, the action of carnitine palmitoyl transferase 2 (CPT2) regenerates free carnitine and the fatty acyl-CoA is released for entry into the β-oxidation pathway.

Within the mitochondrion, carnitine also functions to regulate the acetyl-CoA concentration and the concentration of free CoA. Free CoA is involved in the pyruvate dehydrogenase reaction as well as in the process of β-oxidation and thus plays a key role in the integration of fat and carbohydrate oxidation. It has been proposed that an increased availability of carnitine within the mitochondrion might allow the cell to maintain a higher free CoA concentration, with a stimulatory effect on oxidative metabolism.

Because of the key role of carnitine in the oxidation of both fat and carbohydrate, it has been proposed that carnitine supplementation may improve exercise performance. On the basis of this logic, carnitine is widely sold in sports shops as a supplement for endurance athletes. It is also sold as a weight loss product with

claims of increased fat oxidation. There is, however, no good evidence that carnitine deficiency occurs in the general population or in athletes. Carnitine is present in the diet in red meat and dairy products, so it might be thought that individuals who follow a vegan lifestyle might be at increased risk of deficiency, but carnitine can also be synthesized from lysine and methionine in the liver and kidney. Measurement of the effects of exercise and diet on muscle carnitine concentrations in humans (muscle accounts for about 98% of the total body carnitine content) has only been carried out relatively recently, and there have been few attempts to measure the effects of supplementation on muscle carnitine. Barnett *et al*. (1994) and Vukovich *et al*. (1994) reported that short-term supplementation with carnitine (4–6 $g \cdot day^{-1}$ for 7–14 days) had no effect on muscle carnitine concentrations or on the metabolic response to exercise. Even when fatty acid mobilization was stimulated by high fat meals or heparin, there was no effect of carnitine supplementation on fat oxidation (Vukovich *et al*., 1994).

In contrast to these negative findings, there are published reports suggesting that carnitine supplementation can increase the contribution of fatty acids to oxidative metabolism and thus promote the use of body fat stores. In a comprehensive review of the literature, Spriet (1997) identified eight studies that examined the effects of supplementation on the metabolic response to endurance exercise, and found that three of those studies reported an increased rate of fat oxidation. There is more recent evidence to support this, with one study showing an increased oxidation of 13C-labelled palmitate after 10 days of carnitine supplementation (Muller *et al*., 2002). This finding alone is not, however, evidence that weight loss and a reduction in body fat content will result.

Most of the products that have been shown to be effective in promoting weight loss contain ingredients prohibited by doping regulations and also raise questions about safety. Combinations of caffeine (sometimes in the form of guarana), ephedrine (sometimes as herbal ephedra) and aspirin (sometimes as naturally occurring salicylates) have been shown to be more effective that any of these ingredients in isolation, but both caffeine and ephedrine can cause positive doping results and ephedrine has been associated with a significant number of positive doping results. There also appear to be significant health risks associated with the use of ephedrine (Bent *et al*., 2003) and the use of these products is strongly discouraged.

Promoting energy supply

One view of exercise-induced fatigue is that it occurs when the rate of ATP hydrolysis in the active muscles exceeds the rate at which ATP can be regenerated. It follows that the onset of fatigue can be delayed and exercise performance improved if a higher rate of ATP resynthesis can be maintained. Supplements that are claimed to improve performance by increasing energy supply and delaying fatigue include bicarbonate, caffeine, carnitine, creatine, guarana, hornet juice, iron, magnesium, pyruvate and ribose. It must be emphasized at the outset that not all of these claims are supported by experimental evidence. There is reason to believe that some athletes may benefit in some circumstances from the use of bicarbonate, caffeine, creatine and iron. Caffeine will be discussed later in this review and is also discussed by Spriet and Gibala (2004).

Bicarbonate

For exercise that results in fatigue within a few minutes, anaerobic glycolysis makes a major contribution to energy metabolism. Although glycolysis allows higher rates of ATP resynthesis than can be achieved by aerobic metabolism, the capacity of the system is limited, and fatigue is inevitable when high rates of anaerobic glycolysis occur. The metabolic acidosis that accompanies glycolysis has been implicated in the fatigue process, either by inhibition of key glycolytic enzymes, by interfering with calcium transport and binding, or by a direct effect on the actin–myosin interaction. Therefore, it is intuitively attractive to believe that induction of alkalosis before exercise, an increase in the muscle buffering capacity, and an increased rate of efflux of hydrogen ions from the active muscles all have the potential to delay fatigue and improve exercise performance. Many studies have looked at the effects of metabolic alkalosis (usually induced by ingestion of sodium bicarbonate or sodium citrate) on the performance of high-intensity exercise, but the results are by no means consistent or conclusive (Maughan, 1999; McNaughton, 2000).

In one study designed to simulate athletic competition, trained non-elite (best 800-m time about 2 min 5 s) middle-distance runners performed a simulated 800-m race. In the alkalotic condition, they ran almost 3 s faster than in the placebo or control trials (Wilkes *et al*., 1983). A more recent report indicated similar improvements (3–4 s) over a distance of 1500 m in runners who completed simulated races in about 4 min 15 s (Bird *et al*., 1995). Although these effects on performance might appear small, they are of considerable significance to the athlete, for whom an improvement of even a fraction of a second in these events is considered to be a major achievement.

The reasons for the conflicting effects reported in the published literature are not altogether clear, but are at

least in part due to variations in the intensity and duration of the exercise tests used, the nature of the exercise task, the dosage of sodium bicarbonate administered and the time delay between bicarbonate administration and the beginning of the exercise test (i.e. the amount of metabolic alkalosis induced). Performance has been monitored over exercise durations ranging from a few seconds to more than 1 h, and during continuous, incremental and intermittent dynamic exercise as well as during sustained isometric contractions.

There is no clear pattern of exercise duration between those studies where a positive effect was observed and those where no effect was seen. In most studies, a dose of 0.3 g of sodium bicarbonate or citrate per kilogram of body weight has been used to induce alkalosis, and this has usually been administered orally in solution or in capsule form. Such a dose has usually resulted in an increase of 4–5 $mmol \cdot l^{-1}$ in the plasma buffer base 2–3 h after administration, although the time-course of changes in acid–base status was not carefully followed in most of these studies. Horswill *et al*. (1988) examined the effects of ingesting 0.1–0.2 g bicarbonate $\cdot kg^{-1}$ BW (where BW = body weight) on cycle ergometer sprint performance over 2 min. They found no improvement in performance even though the blood bicarbonate concentration was elevated; on the basis of these results, they suggested that a dose of less than 0.3 $g \cdot kg^{-1}$ BW might be ineffective in improving exercise performance. McKenzie *et al*. (1986), however, reported that a dose of 0.3 $g \cdot kg^{-1}$ BW was no more effective than one half this dose.

There are potential problems associated with the use of high doses of bicarbonate. Vomiting and diarrhoea are frequently reported as a result of ingestion of even relatively small doses of bicarbonate, thus limiting any improvement in performance among those individuals susceptible to gastrointestinal problems. There are anecdotal reports of athletes using this intervention, which is not prohibited by the rules of sport, being unable to compete because of the severity of these symptoms. Although unpleasant and to some extent debilitating, these effects are not serious and there seem to be no long-term adverse consequences of occasional use. Sodium citrate administration, which also results in an alkaline shift in the extracellular fluid, has also been reported to improve peak power and total work output in a 60-s exercise test, but without any adverse gastrointestinal symptoms (McNaughton, 2000).

When an increase in performance after bicarbonate ingestion has been observed, it has been ascribed to an increased rate of hydrogen ion efflux from the exercising muscles, which reduces both the rate of fall of intracellular pH and the pH-mediated inhibition of phosphofructokinase (Sutton *et al*., 1981). The higher blood lactate concentrations after exercise associated with metabolic alkalosis, even when the exercise duration is the same, may therefore be indicative not only of a higher rate of lactate efflux, but also of an increased contribution of anaerobic glycolysis to energy production. Associated with the development of fatigue during high-intensity exercise is a decline in the muscle adenine nucleotide content. The extent of the fall in muscle ATP concentration that occurs during maximal exercise in humans has been shown to approach 40% of pre-exercise values: even greater losses of ATP (60%) have been reported upon exhaustion in the horse (Snow *et al*., 1985). There is evidence to suggest that an increase in hydrogen ion efflux during near maximal intensity exercise after bicarbonate administration may decrease the extent of muscle adenine nucleotide loss during exercise (Greenhaff *et al*., 1990), but whether this is due to a pH-mediated decrease in the activation of AMP deaminase or an increased rate of ADP rephosphorylation via glycolysis is not clear. Whatever the mechanism, it seems reasonable to suggest that bicarbonate administration before high-intensity exercise will only enhance performance when the intensity and duration of the exercise are sufficient to result in significant muscle acidosis and adenine nucleotide loss.

Creatine

Creatine has been used by many successful athletes, particularly in track and field athletics, but in many other sports as well. Some indication of the extent of its use comes from the fact that the estimated sales of creatine to athletes in the USA alone in 1997 amounted to over 300,000 kg. This represents a remarkable growth, as its use first became popular in sport after the 1992 Olympic Games in Barcelona. What distinguishes creatine from most other purported ergogenic aids is that it seems to be effective in improving performance. More significantly, perhaps, its use is not prohibited by the governing bodies of sport and, although long-term safety studies have not been undertaken, there appear to be no harmful side-effects even when very large doses are taken, at least in the quantities that are necessary to produce an ergogenic effect. There are many excellent reviews of the effects of creatine supplementation, but the picture changes rapidly as new information emerges in this topical area. Greenhaff (2000) and Williams *et al*. (1999) have provided recent overviews.

The highest tissue concentrations of creatine are found in skeletal muscle, and approximately two-thirds of the total is in the form of creatine phosphate. Creatine phosphate is capable of rapid regeneration of ATP within the cell cytoplasm, but a limited amount is available. Increasing muscle creatine phosphate should

increase the available energy supply. Creatine occurs naturally in the diet, being present in meat: 1 kg of fresh steak contains about 5 g of creatine. The normal daily intake is less than 1 g, but the estimated daily requirement for the average individual is about 2 g. The body has a limited capacity to synthesize creatine in the liver, kidney and pancreas and in other tissues, but the primary site of synthesis in humans is the kidney. This supplies the amount required in excess of the dietary intake, and is also the only way in which vegetarians can meet their requirement. Synthesis occurs from amino acid precursors (arginine and glycine), but the synthetic pathway is suppressed when dietary creatine intake is high.

The first study to systematically investigate the effects of supplementation of large amounts of creatine was that of Harris *et al.* (1992). In a comprehensive study, they showed that ingestion of small amounts of creatine (1 g or less) had a negligible effect on the circulating creatine concentration, whereas feeding higher doses (5 g) resulted in an approximately 15-fold increase. Repeated feeding of 5-g doses every 2 h maintained the plasma concentration at about 1 $mmol \cdot l^{-1}$ over an 8-h period. Repeated feeding of creatine (5 g four times a day) over 4–5 days resulted in a marked increase in the total creatine content of the quadriceps femoris muscle. An increase in muscle creatine content was apparent within 2 days of starting this regimen, and the increase was greatest in those with a low initial concentration; in some cases, an increase of 50% was observed. Approximately 20% of the increase in total muscle creatine content is accounted for by creatine phosphate. Co-ingestion of creatine and carbohydrate, which results in high circulating insulin, may increase the storage of creatine in muscle (Green *et al.*, 1996a,b).

Most authors who have reviewed the published literature have concluded that the available evidence supports a beneficial effect of creatine on performance in short-term high-intensity exercise (Greenhaff, 2000). Of three recently published meta-analyses, two have concluded that creatine supplementation has positive effects on strength, power and lean body mass (Branch, 2003; Nissen and Sharp, 2003), while the other (Misic and Kelley, 2002) concluded that there was no effect. The reasons for this discrepancy are not entirely clear. Effects are seen in particular in the later stages of multiple short efforts with limited recovery, but improvements are sometimes seen in single sprints lasting less than 30 s. There is little information on the effects of creatine supplementation on the performance of more prolonged exercise, but there is little reason to suspect a positive effect.

The mechanism by which creatine supplementation might improve performance is not entirely clear, although it is clear that this effect is related to increased muscle creatine phosphate. The rate of creatine phosphate resynthesis after intense exercise is enhanced after high-dose creatine supplementation (Greenhaff *et al.*, 1994). This allows faster recovery after sprints as well as allowing more work to be done during each subsequent high-intensity effort. These effects will allow a greater amount of work to be done in training and should therefore result in a greater training response, although it is possible that by maintaining the energy charge better during training, the response will be less. This is especially important in that the muscle creatine content remains high for weeks or even months after only a few days of high-dose dietary creatine supplementation (Hultman *et al.*, 1996).

Many studies and much anecdotal evidence support the suggestion that acute supplementation with creatine is associated with a prompt gain in body mass. This typically amounts to about 1–2 kg over a supplementation period of 4–5 days, but may be more than this. In reviewing those studies where changes in body mass were reported, Branch (2003) reported 43 studies in which body mass increased and 24 where no change was seen; there was a statistically significant effect size for both body mass and lean body mass. Another recent meta-analysis puts the increases in muscle size and strength in perspective. Nissen and Sharp (2003) reported that creatine supplementation increases lean mass and strength by 0.35% and 1.09% per week in excess of the changes observed with resistance training alone, but again effect sizes for the increased lean mass and strength were small (0.26 and 0.36, respectively).

The rapid increases in body mass may be accounted for by water retention. Increasing the creatine content of muscle by 80–100 $mmol \cdot kg^{-1}$ will increase intracellular osmolality, leading to water retention. Hultman *et al.* (1996) found a reduction in urinary output during supplementation, which tends to confirm this. The increased intramuscular osmolality due to creatine itself, however, is not likely to be sufficient to account for all of this water retention. It has been suggested that co-ingestion of creatine and carbohydrate, which results in high circulating insulin (Green *et al.*, 1996a,b), may stimulate glycogen synthesis, which will further increase the water content of muscle. There is some preliminary evidence for a stimulation of protein synthesis in response to creatine supplementation (Ziegenfuss *et al.*, 1997), but further experimentation is required. It is unlikely that major effects on muscle protein content can be achieved within 4–5 days, so the reported gains in muscle strength within the same time-scale are difficult to explain.

The effects of the long-term use of large doses of creatine are unknown and its use may pose a health risk. There is concern about possible adverse effects on renal

function, in particular in individuals with impaired renal capacity. Studies on the response to long-term creatine use are in progress but results are not yet available. There have, however, been no reports of adverse effects in any of the studies published in the literature. One study that specifically examined renal function in individuals supplementing with creatine found no reason to believe that renal complications were likely (Poortmans *et al.*, 1997). Anecdotal reports of an increased prevalence of muscle cramps in athletes taking creatine supplements have been circulating for some time, but there is no substance to these stories. It is likely that any injury suffered by an athlete will be ascribed to an easily identifiable change in habit, such as the introduction of a new supplement.

Uninformed comment ascribed the deaths of three American collegiate wrestlers in December 1999 to creatine use, but this was not substantiated at the formal inquiries conducted. Given the increase in body mass that often accompanies supplementation, it is possible that athletes who must reduce body mass acutely to qualify for a particular weight category might face particular problems. It is not unusual in some sports for body mass to be reduced by as much as 10% in the few days before competition: if the mass loss necessary to make the qualifying weight is 1–2 kg more than anticipated, the measures required to achieve the target mass will be unusually severe and may provoke serious and potentially fatal complications related to dehydration and hyperthermia.

It is usually recommended that athletes take 20 g creatine $\cdot$ day^{-1} for 4–5 days (a loading dose) followed by 1–2 g $\cdot$ day^{-1} (maintenance dose). The muscle may be saturated with creatine when a dose as small as 10 g $\cdot$ day^{-1} is consumed for 3–4 days if this is taken together with sufficient carbohydrate to stimulate a marked elevation in circulating insulin. Many athletes, however, work on the principle that more is better and may greatly exceed these amounts. Even with very large doses, however, the possibility of adverse effects is remote. Creatine is a small water-soluble molecule easily cleared by the kidney, and the additional nitrogen load resulting from supplementation is small. The same concerns about renal damage have been raised in the context of protein supplementation among strength athletes and bodybuilders: these athletes may consume up to 3–4 g protein $\cdot$ kg^{-1} BM $\cdot$ day^{-1} over very long periods (Burke and Inge, 1994), but there is no evidence that the theoretical problems of clearance of the extra solute load are real.

Although there is no reason to suppose that there are any risks to health associated with the long-term use of high doses of creatine, the studies quoted above that have used high doses (in the order of 20–30 g $\cdot$ day^{-1}) have been of relatively short duration (5–14 days), and long-term safety studies have not been performed. Studies are currently under way to determine some of the effects of long-term creatine supplementation; their results will become available in due course. This leaves the ethical question of whether the use of creatine should be disallowed on the grounds of its ergogenic effect, as is the case with other normal dietary components such as caffeine. As more information emerges, this issue will be resolved and the governing bodies of sport will make a decision.

Carnitine

Depletion of intramuscular glycogen stores is one of the main factors involved in the fatigue that accompanies prolonged exercise. A recent review of published work in this area is provided by Coyle (1997). The importance of carbohydrate as a fuel for the working muscles is confirmed by the close relationship between the pre-exercise glycogen concentration and the length of time exercise can be sustained. Further evidence comes from studies which showed that increasing the combustion of fat during prolonged exercise, and thus sparing the limited carbohydrate stores, can improve endurance capacity. Increasing fatty acid mobilization by heparin administration after ingestion of a high fat meal or by caffeine ingestion has been shown to be effective in improving performance. The former method, however, is not acceptable in sport.

The possible effects of carnitine supplementation on fatty acid metabolism are described above. In a review of studies that examined the effects of carnitine supplementation on exercise performance, Spriet (1997) concluded that their findings did not generally support an ergogenic effect of carnitine. It must be concluded that, although there is a theoretical basis for an ergogenic effect of carnitine on performance of both high-intensity and prolonged exercise, this is not supported by the experimental evidence. Supplementation of the diet with carnitine is unlikely to be beneficial for athletes. Spriet also cautioned against the use of racemic mixtures of L- and D-carnitine, as these may result in depletion of L-carnitine.

Promoting immune function and resistance to illness and infection

Exercise, nutrition and immune function are covered in detail elsewhere in this issue (Gleeson *et al.*, 2004) and will be discussed only briefly here in relation to supplement use. Modest amounts of regular exercise

are generally associated with an increased sensation of physical well-being and a decreased risk of upper respiratory tract infections (URTI) (Nieman *et al.*, 1993, 1998). The consequences of minor URTI symptoms are usually minimal, but any injury or illness that interrupts training or prevents participation in competition can have a devastating effect on an athlete. Several recent epidemiological surveys have suggested that athletes in intensive training or competing in extreme endurance events are more susceptible to minor opportunistic infections than sedentary individuals (Nieman, 1997; Peters-Futre, 1997; Shephard and Shek, 1997). It has been suggested that severe exercise results in a temporary reduction in the body's ability to respond to a challenge to its immune system and that an inflammatory response similar to that which occurs with sepsis and trauma is invoked (Nieman, 1997). On this basis, a wide range of nutritional supplements is promoted for use by athletes (Table 1). For most of these supplements, there is little evidence of efficacy from properly controlled trials in humans. For many, there is some evidence of some anti-bacterial or immune stimulating effect *in vitro*, but this is far removed from evidence to support their use in athletes.

In view of the role of glutamine as a fuel for the cells of the immune system, the fall in circulating glutamine that occurs in response to prolonged exercise has been proposed as a mechanism that compromises the ability to respond to infection (Newsholme, 1994). Other studies have shown that athletes suffering from chronic fatigue symptoms attributed to overtraining also have low circulating glutamine concentrations (Rowbottom *et al.*, 1995). At present, the limited information on glutamine supplementation provides no clear pattern of results. Studies by Newsholme and colleagues suggest a beneficial effect of glutamine supplementation on resistance to infection after endurance exercise (Castell *et al.*, 1996; Castell and Newsholme, 1997), although a positive effect was not always seen (Castell *et al.*, 1997). In the rat, prolonged treadmill running has been shown to reduce the plasma glutamine concentration after exercise and to reduce the proliferative response of leucocytes to a mitogen challenge (Moriguchi *et al.*, 1995); in contrast, animals fed a glutamine-supplemented diet for 3 weeks before exercise maintained their plasma glutamine concentration and showed a higher response to mitogens than the control group. A similar study carried out with humans found no beneficial effect of acute glutamine supplementation on these same parameters (Rohde *et al.*, 1998). Although this hypothesis is undoubtedly attractive, a clear link between hard exercise, compromised immune function and susceptibility to infection has not been established. Nonetheless, glutamine supplementation for athletes is being promoted and supplements are widely available in sports nutrition outlets.

Zinc is commonly believed to be effective in protecting against the common cold and other infectious illnesses. Since 1984, 11 studies of zinc for treatment of the common cold have been published in reputable medical journals. Of these, five found that zinc had beneficial effects and six did not, so the picture is unclear. The study that has drawn the most attention was a 1996 report from the Cleveland Clinic (Mossad *et al.*, 1996). Participants who started taking zinc lozenges within 24 h of the onset of symptoms were free of cold symptoms on average by about $4\frac{1}{2}$ days. Those who took a placebo had symptoms for $7\frac{1}{2}$ days. Twenty percent of zinc-takers reported nausea, as opposed to only 4% of those taking the placebo. A subsequent study involving children did not confirm these results (Macknin *et al.*, 1998) and a later review by the same authors concluded that further research is necessary before the use of zinc supplements can be recommended (Macknin, 1999). There is no evidence that taking zinc prevents anyone from catching a cold, although there may be benefits by reducing the severity and duration of symptoms. However, it would appear that supplementary zinc must be taken within 24 h of the onset of symptoms to have any benefit. This effectively means continuous supplementation, and side-effects include nausea and bad taste reactions. Long-term high doses of zinc are probably not a good idea, as they lower high-density lipoprotein cholesterol, suppress immune system function and interfere with the absorption of copper, resulting in microcytic anaemia. It has been suggested

Table 1. Supplements sold as immune system stimulants

Antioxidants	*Echinacea*	Pycnogenol
Astragalus	Ginseng	Selenium
Bee pollen	Glutamine	*Spirulina*
Chlorella	Hydroxymethylbutyrate	Vitamin C
Co-enzyme Q10	Inosine	Zinc
Cordyceps	Multivitamins	

that when zinc is taken in lozenge form, it may act locally on the upper respiratory tract.

Preparations made from various plants and plant parts of the genus *Echinacea* constituted the top-selling herbal medicine in health food stores in the USA over the last 5 years and it is also popular in Europe. *Echinacea* is promoted for preventing and treating the common cold, flu and upper respiratory tract infections. It is also claimed to increase general immune system function and is used to treat vaginal candidiasis. The clinical literature tends to provide some support for its use in the treatment for symptoms of colds, flu and URTI. Recent studies do not support its use to prevent URTI. Melchart *et al*. (2000) reviewed the available literature and identified 16 trials with a total of 3396 participants that investigated the effects of preparations containing *Echinacea* extracts. The methodological quality of the trials was assessed and deemed insufficient to perform a quantitative meta-analysis. However, the authors concluded that existing controlled clinical trials indicated that preparations containing the juice or extracts of *Echinacea* can have a positive effect. In the most recent literature review of clinical trials conducted on various *Echinacea* preparations for prevention or treatment of URTI, Barrett (2003) concluded that 'while there is a great deal of moderately good-quality scientific data regarding *E. purpurea*, effectiveness in treating illness or in enhancing human health has not yet been proven beyond a reasonable doubt'. In both of these reviews, the authors emphasized that the highest quality trials suggest that early dosing of sufficient doses is important. As with all herbal supplements, there must be concerns about possible adverse effects in some individuals and the use of *Echinacea* is not free from risk.

Antioxidant nutrients

It has long been common practice for athletes to take vitamin supplements, usually without any thought as to the vitamin status of the individual concerned. There has been much interest recently among athletes in vitamins C and E, which have been shown to have antioxidant properties, and which may be involved in protecting cells, especially muscle cells, from the harmful effects of the highly reactive free radicals that are produced when the rate of oxygen consumption is increased during exercise (Kanter, 1995). Many studies have shown that unaccustomed exercise, particularly if it involves eccentric exercise in which the muscle is forcibly lengthened as it is activated, results in damage to the muscle structure and post-exercise soreness. Because it normally peaks 1–3 days after exercise, this is often referred to as delayed-onset muscle soreness. It is believed that free radicals, highly reactive chemical species, may be involved in the damage that occurs to muscle membranes. Alleviating or avoiding these symptoms would allow a greater training load to be sustained. An increased generation of free radicals is also associated with damage to cellular DNA and to a variety of lipids and proteins. If the post-exercise damage can be reduced by an increased intake of antioxidants, then recovery after training and competition may be more rapid and more complete. The evidence for this at present suggests a possible role but is not conclusive. Even the suggestion, however, is enough to convince many athletes to take supplements of these vitamins 'just in case'.

The source of the free radicals generated during exercise seems to be primarily related to the increased oxygen use within the mitochondria (McCord, 1979). This suggests that the extent of free radical generation will be directly proportional to the intensity and duration of exercise. Infiltration of damaged muscle by leucocytes may also account for some of the elevation in free radicals that is observed after exercise as these cells generate free radicals as part of their cytotoxic defence mechanisms (Smith *et al*., 1989). A variety of other mechanisms that may promote free radical generation has been described (Kanter, 1995).

Free radicals have been implicated in several disease processes, including cardiovascular disease, diabetes and some forms of cancer, as well as in the ageing process. The body has a number of endogenous defence mechanisms that effectively neutralize free radicals before they cause tissue damage: important enzymes are superoxide dismutase, glutathione peroxidase and catalase. Several nutritional antioxidants also play important roles. Nutritional antioxidants include vitamins A, C and E. Other dietary components, including selenium, which has a structural role in glutathione peroxidase, and ubiquinone (or co-enzyme Q10) may also play important roles but are less well researched. Copper, zinc and manganese are structural components of superoxide dismutase and iron is a co-factor for catalase.

Several studies have examined the effects of antioxidant supplementation on indices of free radical-induced muscle damage in exercise, and there is some evidence of a protective effect of supplementation; for reviews of these studies, see Kanter (1995) and Dekkers *et al*. (1996). The evidence appears to suggest that there may be a reduction in the signs of muscle damage after supplementation, but there is no evidence for any beneficial effect on performance. There are concerns about possible adverse effects of supplementation, as several of these nutrients can also function as pro-oxidants. Toxic effects of megadose supplementation are unlikely, but there are concerns about the possible consequences of the long-term use of megadoses of

single antioxidants. One study has reported increased exercise muscle damage after supplementation with ubiquinone (Malm *et al.*, 1996), and it is well recognized that many antioxidant nutrients can function as pro-oxidants at high doses.

Regular training increases the effectiveness of the endogenous antioxidant mechanisms so that even extreme exercise (e.g. long-distance triathlon) may not cause any indications of oxidative damage in well-trained athletes (Margaritis *et al.*, 1997). In contrast, short periods of modest exercise (8 weeks of training, 3 sessions of 35 min per week) do not result in any signs of increased capacity to neutralize free radicals (Tiidus *et al.*, 1996). It is not clear from this whether individuals engaged in regular exercise have an increased requirement for exogenous antioxidants.

In conclusion, there is little evidence to support the suggestion that supplementation with antioxidant nutrients can improve exercise performance, but there is a growing body of evidence to suggest that supplementation may reduce the extent of exercise-induced oxidative damage to tissues. If this is indeed the case, it may be that the athlete undertaking a strenuous training programme may benefit in the long term by being able to sustain a higher training load. There is also evidence, however, that prolonged exposure to training increases the effectiveness of the endogenous antioxidant mechanisms, and it may be that supplementation is unnecessary (Margaritis *et al.*, 1997).

Promoting joint health

Many products are sold with the aim of promoting joint health and reducing the wear and tear caused by overuse, ageing and inflammatory conditions, including arthritis. Some of the products sold are listed in Table 2. An extensive range of herbs, botanicals, and so on are also sold, including turmeric, *Boswellia serrata*, cayenne pepper, ashwagandha, autumn crocus, meadowsweet, stinging nettle, willow bark (*Salix*) and devil's claw. Animal extracts, including green-lipped mussel and sea cucumber, are also promoted.

The cartilage in joints is made up of proteoglycans (protein molecules to which are bound various complex sugars) and the protein collagen. Chondroitin, one of the main glycosaminoglycans, is a long-chain molecule consisting of many molecules of two components: galactosamine and glucuronic acid. Commercial preparations are extracted from the cartilaginous tissues of animals. Glucosamine is a carbohydrate–amino compound that is produced from the chitin that forms the main structural element of sea shells. Both compounds are reported to stimulate the formation of components of cartilage when given orally to humans.

Table 2. Supplements promoted for joint health and protection against ageing and overuse

Antioxidants
Essential fatty acids
Vitamins: niacin (B3), pantothenate (B5), D
Minerals: boron, calcium
Proteolytic enzymes
Glucosamine
Chondroitin
Methylsulphonylmethane (MSM)
S-Adenosyl methionine (SaME)
Type 2 collagen
Hyaluronic acid
Soy isoflavones

There is now a considerable amount of information from clinical trials involving patients with osteoarthritis to show that regular (once or twice per day) long-term (about 2–6 months) treatment with glucosamine and chondroitin sulphate can reduce the severity of subjective symptoms and prevent progression of the disease (Fillmore *et al.*, 1999). A meta-analysis of published studies concluded that 'some degree of efficacy appears probable for these preparations' but did express cautions about the quality of the available data (McAlindon *et al.*, 2000). A recent report (Braham *et al.*, 2003) of the effects of 12 weeks of supplementation in individuals with knee pain showed similar improvements in clinical and functional tests in the treatment and placebo groups, but 88% of the treatment group reported some improvement in knee pain compared with only 17% in the placebo group. At present, there is no evidence of a benefit for athletes with joint pain, but there seem to have been no properly controlled trials in athletes. One study of US military special operations personnel with knee and back pain showed subjective improvements after treatment but no effect on tests of running performance (Leffler *et al.*, 1999). Nonetheless, subjective relief alone has some value and this possible benefit cannot be ignored. There seems to have been little discussion of possible adverse effects of supplementation, but the widespread use of these products means that any problems should have become apparent.

Central nervous system effects

The list of compounds prohibited for use by athletes includes stimulants, and there is a long history of

stimulant use in sport. In some cases, fatalities have resulted from the use of amphetamines, sympathomimetics and other stimulant compounds. Some of these agents (including, for example, cocaine) are more commonly used as social drugs rather than for performance enhancement, while others are commonly found in low doses in cough medicines and herbal tonics.

Caffeine

Caffeine occupies a unique place in that it is consumed in a wide range of foods and beverages and is prohibited in competition above a urinary threshold value but its use is not monitored in out-of-competition testing. Caffeine has effects on the central nervous system and on adipose tissue and skeletal muscle that give reason to believe that it may influence exercise performance. Early studies on the effects of caffeine on endurance performance focused on its role in the mobilization of free fatty acids from adipose tissue to increase fat supply to the muscle, which, in turn, can increase fat oxidation, spare glycogen and thus extend exercise time. Caffeine ingestion before exercise to exhaustion at 80% $\dot{V}O_{2max}$ increased exercise time from 75 min on the placebo trial to 96 min on the caffeine trial (Costill *et al.*, 1978). A positive effect was also observed on the total amount of work achieved in a fixed 2-h exercise test. In this and other studies, caffeine was shown to increase circulating free fatty acids, increase fat oxidation and spare muscle glycogen during prolonged exercise (see Spriet, 1995, for a review of these studies). The consistency and clarity of these findings led to the widespread popularity of caffeine consumption (usually in the form of coffee) before marathon running, although caffeine in much higher doses had long been used, especially in professional cycling. It is also important to note that coffee may not produce an ergogenic effect in circumstances where caffeine is effective, even though the same plasma caffeine concentration results (Graham *et al.*, 1998).

Growing evidence of a positive effect of caffeine on performance in the absence of any glycogen sparing effect, and of effects on high-intensity exercise where glycogen availability is not a limiting factor, has stimulated the search for alternative mechanisms of action. There is evidence for a number of effects of caffeine directly on skeletal muscle. It may affect the activity of Na/K ATPase and the intracellular localization and binding of calcium, it can cause an elevation in intracellular cyclic AMP as a result of inhibition of the action of phosphodiesterase, and it may have direct effects on a number of enzymes, including glycogen phosphorylase (Spriet, 1997; Graham, 2001). Whether all these effects can occur at the tissue concentrations of caffeine that occur after ingestion of moderate doses of caffeine remains unclear. Effects on the central nervous system, either in modifying the perception of effort or affecting the higher motor centres, have been proposed, but in the absence of evidence this remains speculation.

There have been several recent and comprehensive reviews of the effects of caffeine on exercise performance, and a detailed review of the literature will not be attempted here (Spriet, 1997; Graham, 2001). Several studies have reported beneficial effects of caffeine ingestion on a variety of laboratory tests of endurance performance. An increased time to exhaustion has been observed in a number of tests, but performance in simulated race conditions, where a fixed amount of work has to be done in the shortest possible time, is also improved. There appears to be no effect on maximal oxygen uptake. More recent studies have focused on exercise of shorter duration, and a number of studies have shown beneficial effects on performances lasting only a few (about 1–6) minutes; there is less information on performance in sprint tasks or on resistance exercise, but the available evidence does support performance-enhancing effects, although there is no effect on muscle strength (Graham, 2001).

It is clear from the published studies that positive effects of caffeine can be obtained in a variety of exercise conditions with caffeine doses of 3 $mg \cdot kg^{-1}$ or less. The reasons for this variability are not altogether clear, but, perhaps surprisingly, they do not appear to be related to the habitual amount of caffeine consumption.

Caffeine has a number of unwanted side-effects that may limit its use in some sports or by sensitive individuals: these effects include insomnia, headache, gastrointestinal irritation and bleeding, and a stimulation of diuresis. There are also some suggestions that high caffeine intakes may be a risk factor for bladder cancer. This is unlikely to be modified by occasional use of modest doses before competition, but the athlete who may contemplate using high doses of caffeine before training on a daily basis should consider this. With the very high doses sometimes used by athletes, noticeable muscle tremor and impairment of coordination have been noted (Spriet, 1995).

The diuretic action of caffeine is often stressed, especially when dehydration is a major issue. This affects in particular competitions held in hot, humid climates where the risk of dehydration is high, and is more important for endurance athletes for whom dehydration has a greater negative effect on performance. Athletes competing in these conditions are advised to increase their intake of fluid, but are usually also advised to avoid tea and coffee because of their diuretic effect. It would appear, however, that this effect is small for those habituated to caffeine use (Wemple *et al.*, 1997) and the negative effects caused by the

symptoms of caffeine withdrawal may be more damaging.

Until January 2004, an athlete found to have a urine caffeine concentration of more than 12 $mg \cdot l^{-1}$ was deemed to be guilty of a doping offence and was liable to suspension from competition. It is clear from this that caffeine is considered by the International Olympic Committee to be a drug, but an outright ban on its use is impractical and manifestly unfair to those who normally drink tea and coffee. It is equally clear, however, that the amount of coffee that must be drunk to exceed the permitted limit (about six cups of strong coffee within about 1 h) is such that it is unlikely that this would normally be achieved. In addition, in endurance events, a urine sample taken after the event would probably not register a positive test, even if large amounts had been consumed before the start.

It is also clear that beneficial effects on performance can be achieved with caffeine doses that are less than those that would result in the old IOC urine threshold concentration of 12 $mg \cdot l^{-1}$ being exceeded, so athletes may feel justified in their view that using these amounts is acceptable. It is difficult, but not impossible, to achieve an effective intake from drinks such as tea or coffee, but there are various products on the market that contain significant amounts of caffeine (Table 3). Caffeine tablets, commonly used by overworked students studying for examinations, are also commonly used, and these can easily lead to an intake that exceeds the permissible limit. These concerns resulted in the decision by the World Anti-Doping Agency to remove caffeine from the list of prohibited substances with effect from January 2004.

Contamination of dietary supplements

The Dietary Supplements Health and Education Act 1994 (DSHEA) passed by US Congress has meant that nutritional supplements that do not claim to diagnose, treat, prevent or cure disease are not subject to regulation by the Food and Drug Administration (FDA). From this it follows that there is no requirement to prove claimed benefits, no requirement to show safety with acute or chronic administration, no quality assurance and liberal labelling requirements. Product recalls by the FDA because of inadequate content include a folic acid product with 34% of the stated dose (FDA, 2003). They have also recently recalled products containing excessive doses of vitamins A, D, B6 and selenium because of potentially toxic effects (FDA, 2003). Some products have been shown to contain impurities (lead, broken glass, animal faeces, etc.) because of poor manufacturing practice (FDA, 2003). Some products do not contain the expensive ingredients listed on the label but only inexpensive materials. There is no way for athletes to know what is in any of these products.

Table 3. Caffeine content of some commonly used beverages when prepared and consumed in standard amounts

Beverage	Caffeine content (mg)
Tea	15–50
Instant coffee	50–70
Filter coffee	60–120
Hot chocolate	8–15
Cola	20–50

Note: Doses of as little as 2–3 $mg \cdot kg^{-1}$ BM can result in performance enhancement.

A paper from the IOC laboratory in Cologne reported the results of an analysis carried out on legitimate dietary supplements, none of which declared on the label that they contained steroids, none of which would reasonably be expected to contain prohibited compounds, and none of which gave any warning to athletes that problems might result from their use. Nandrolone, testosterone and other steroids were identified in these supplements: when they were fed to healthy volunteers, they resulted in urinary norandrosterone concentrations of up to 360 $ng \cdot ml^{-1}$ (the threshold for a positive test is 2 $ng \cdot ml^{-1}$ for men and 5 $ng \cdot ml^{-1}$ for women). The supplements tested were chrysin, tribulus terrestris and guarana.

The Cologne laboratory followed this up with a much bigger survey. In total, 634 different product samples were purchased from 13 countries and were analysed for the presence of steroid hormones and their precursors. Altogether, 94 supplements (14.8% of the total) were shown definitely to contain prohibited substances, and for another 10% the analysis was not conclusive but steroids may have been present. That is close to a 1 in 4 risk! Substantial numbers of positive tests were obtained from products bought in The Netherlands (26%), the USA (19%), UK (19%) and elsewhere. The names of the prohibited supplements have not been published, but they included vitamins and minerals, protein and amino acid supplements, creatine and many others. Further details of this study can be found on the website of the Cologne laboratory (www.dopinginfo.de).

The IOC-accredited laboratory in Vienna has repeated the Cologne study, although with a smaller number ($n = 57$) of supplements. They found that 12 of these (22%) contained prohibited steroids. Unlike the German results, the identities of the companies and the products have been published on the Internet, and can

also be found on the Cologne website at the address above.

The presence of these various anabolic androgenic steroids is commonly assumed to be the result of inadvertent contamination in the manufacturing or distribution process, as the contamination is generally minimal and highly variable between and within batches. Events took a more sinister turn in 2002, however, when the Vienna laboratory found one of the 'hard' anabolic steroids (methanedieneone, commonly known as Dianabol) in three supplements that were bought in England (Gmeiner, 2002). This drug was present in high amounts, enough to have an anabolic effect, but also enough to produce serious side-effects. These results were confirmed by the Cologne laboratory (Geyer *et al.*, 2002) and the presence of this steroid has been described as a 'deliberate and criminal act'.

More recent results come from the analysis of 110 supplements advertised as having tonic or stimulant properties and bought from different international markets: analysis of these samples showed that a significant proportion of products contained either caffeine (14 samples) or ephedrine (2 samples), even though these were not listed on the label (Parr *et al.*, in press). It is not immediately obvious that this contamination can be accidental. Athletes using these products may be liable to sanctions if a positive doping test results.

The picture has not changed greatly as a result of the availability of this information, although proposed changes in legislation might make the supplement industry more accountable than they are at present. The principle of strict liability still applies, so athletes have to be extremely careful.

Costs and benefits of supplement use

Supplements for use in sport with the aim of improving performance should meet certain criteria, although the considerations will not be the same for all athletes. Supplements used by athletes should have demonstrated effectiveness in laboratory and field conditions. They should have a well-identified and plausible mechanism of action based on what is known of metabolism and of the factors that limit performance. They should be free of harmful side-effects and not pose any health risk, and they should be free of any risk of an adverse drug test.

A full analysis of the costs and benefits cannot be completed for most supplements as several parts of the equation are unknown. The risks of falling foul of the drug testing rules cannot be quantified but they are nonetheless very real. The sensible athlete will want to see positive reasons for using any supplement.

Conclusions

Supplement use is widespread in sport, even though most supplements used are probably ineffective. Athletes who take supplements should only do so after carrying out a careful cost–benefit analysis. Although these supplements are mostly benign, this is not always the case. Routine iron supplementation, for example, can do more harm than good, and the risk of iron toxicity is very real. Athletes are therefore cautioned against the indiscriminate use of dietary supplements. Supplement use can have a role when food intake or food choice is restricted, or as a short-term remedy where a deficiency syndrome has been shown to exist. Supplement use does not compensate for poor food choices. For a few supplements, the balance of evidence supports a beneficial effect on some types of performance; these supplements include creatine, caffeine and bicarbonate. There is no evidence that androstenedione and similar prohormones are anabolic agents, and these supplements may pose serious health risks. The risk of a positive drugs test resulting from the use of sports supplements contaminated with prohibited compounds is also very real. The evidence for a performance benefit must be very strong to outweigh the well-established risks.

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