FINAL REPORT

Conference on the Science and Policy of Performance-Enhancing Products
Natcher Conference Center, National Institutes of Health
Bethesda, Maryland • January 8-9, 2002

Introduction

The Conference on the Science and Policy of Performance-Enhancing Products was organized by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) and the Council for Responsible Nutrition (CRN). Additional support was provided by the National Institute of Child Health and Human Development, the NIH Office of Research on Women's Health and Office of Behavioral and Social Sciences Research, Phoenix Laboratories, EAS, and Rexall Sundown. The purpose of the Conference was to examine the available scientific evidence that addresses the safety and efficacy of performance-enhancing products and to assess policy concerns related to their use, particularly in potentially vulnerable populations such as teenagers.

Convocation and Welcome

John Cordaro: President and Chief Executive Officer, Council for Responsible Nutrition, Washington, D.C.

Mr. Cordaro thanked the conference speakers and participants and extended his appreciation to Donna de Varona, the keynote speaker, and the staffs of ODS and CRN. Mr. Cordaro noted that the conference was an initial step in broadening a partnership to address cooperatively major societal challenges in the responsible use of sports nutrition dietary supplements. He emphasized that a responsible dietary supplement industry must be science based, with a collaborative research agenda, and must participate in an open fact-based dialog with regulators, NIH and the broader research community.

This fact-based dialog can provide a link between research and public policy, with a win-win-win effect. A win for consumers who would have access to substantiated science-based information and safe products made to quality standards. A win for regulators who would have the resources to make quick and effective enforcement decisions. And a win for industry that chooses to be responsible in providing quality products that consumers want and need. The aim of this conference is to provide the stimulus for a fact-based dialog on sports supplements.

Paul Coates, Ph.D.: Director, Office of Dietary Supplements, NIH, Bethesda, Md.

Dr. Coates reviewed excerpts from the findings section of the 1994 Dietary Supplement Health and Education Act (DSHEA), and noted the following:

- Improving the health status of U.S. citizens' ranks at the top of the national priorities of the federal government.
- The importance of nutrition and the benefits of dietary supplements in health promotion and disease prevention have been documented in scientific studies.

- Preventive health measures, including education, good nutrition, and appropriate use of safe nutritional supplements will limit the incidence of chronic diseases and reduce long-term healthcare expenditures.
- Consumers should be empowered to make choices about preventive healthcare programs based on data from scientific studies of health benefits related to particular dietary supplements.
- Almost 50 percent (of 260,000,000) Americans regularly consume dietary supplements of vitamins, minerals, or herbs as a means of improving their nutrition.

DSHEA called for the creation of an Office of Dietary Supplements in the Office of the Director at the National Institutes of Health. ODS was formally established in 1995. Among its mandated tasks, ODS is to (1) explore the role of dietary supplements to improve health care, (2) promote scientific study of dietary supplements in maintaining health and preventing chronic disease, (3) conduct and coordinate research at NIH, (4) collect and compile databases of scientific literature (i.e., IBIDS) and track federally funded research on dietary supplements (i.e., CARDS), and (5) provide advice to other Health and Human Services (HHS) agencies related to dietary supplements. (http://www.cfsan.fda.gov/~dms/dietsupp.html)

ODS' mandated tasks have been implemented through four dietary supplement research centers, evidence-based reviews, and the Research Enhancement Awards Program (REAP). In addition, ODS supports training and career development, consumer and practitioner education, and sponsors workshops and conferences.

Congressional language for fiscal year (FY) 2001 ODS appropriations specifically encouraged ODS—in consultation with the National Center for Complementary and Alternative Medicine (NCCAM), the Agency for Healthcare Research and Quality (AHRQ) and the Food and Drug Administration (FDA)—"to review the current scientific evidence on the safety and efficacy of dietary supplements now on the market, which could then form a basis for further research, education of practitioners and consumers, and whether further regulatory requirements are necessary." As the first project to address this request ODS and NCCAM have commissioned, through AHRQ, a systematic review of the literature on ephedra efficacy and safety in three general settings—weight management, athletic performance enhancement, and energy enhancement. The review is currently under way, and the report is expected this summer (2002). The review will include relevant reports in all languages, both published and unpublished. The review will assist NIH in the development of an appropriate research agenda that will address ephedra efficacy and safety.

Keynote Address: Donna de Varona, Olympian and Sports Commentator

Sport supplements are widely used by all types of athletes—male and female, young and old. Hydration drinks, energy bars, protein powders, and multivitamins are used safely by millions of young people. Other sports supplements, however, contain ingredients such as steroid hormone precursors and stimulants, which raise concerns. Perhaps the code of silence surrounding the use of these supplements will be broken and athletes can be educated to protect their health. The playing field must be leveled so the sporting environment is not a dangerous place for youngsters.

It is important to embrace science and educate young people to use dietary supplement products in a healthy way and avoid those that may cause disqualification or health consequences. In most schools, however, there is no education on the use of supplements. The Physical Education Training (PET) bill just passed, which will put physical education back in schools. One component of this education should be the use of performance-enhancing products. Also, those who helped to establish the World Anti-Doping Agency (WADA) and the U.S. Anti-Doping Agency (USADA) realize that these organizations need resources. Senator Ted Stevens (R-Alaska) championed funding for USADA, which passed during the last session of Congress.

A first-ever conference like this is a confidence booster for everyone who has been in the trenches of this battle. The industry's participation is welcomed. Industry's effort to deal with its own constituents and reach out to parents, trainers, coaches and athletes who put their trust in sport supplement products is appreciated. There is much confusion about which products are safe, legal, ethical and effective. Until industry—in collaboration with credible partners—finds a way to deal with these issues, controversy will cloud its intent. At risk will be good nutritional products and products with proven health benefits. Ultimately, the good products could be marginalized by the proliferation of bad products.

The Olympic world has struggled for a long time with the issue of regulating the use of dangerous and illegal performance-enhancing drugs. History documents the story of an international community unable to self-regulate. Since the 1960s, those of us who competed in the Olympics have known that steroids have been used, and coaches and managers have readily given athletes an edge to win Olympic medals. After the bribery scandals in Salt Lake City and the discovery of erythropoietin (EPO) use during the 1998 Tour de France, the International Olympic Committee (IOC) finally supported the establishment of an independent anti-doping agency.

WADA consists of government and sport leaders, and its responsibility is to define what constitutes an illegal performance-enhancing substance, as well as recommend and enforce testing procedures and policies. WADA conducts out-of-competition testing and research worldwide. In an effort to support this global initiative, Congress funded its own independent anti-doping agency—USADA, which has been in operation for more than a year.

In February, this century's first Olympics will be held in Salt Lake City. Prepared to conduct the most extensive drug-testing program in the Games history, the IOC has expressed concern about America's willingness to successfully address the use and misuse of performance-enhancing substances. Often, when foreign athletes test positive for the use of illegal performance-enhancing drugs, they use the excuse of buying a product from the United States on the internet, and the product did not list all the ingredients on its label. The U.S. sporting community has the reputation of being more unsavory than the East German sports machine of the 1970s.

Barry McCaffrey—the drug czar during the Clinton Administration—pushed for the establishment of an independent anti-doping agency after the Salt Lake City scandals. While he was pointing a finger at the world, they were pointing back. After the baseball player Mark McGwire admitted using androstenedione, the IOC community said the United States needed to clean up its own house first. Due to General McCaffrey's leadership and persistence, the sports federations' criticism relented, and they embraced WADA.

NIH's leadership is encouraging, and hopefully today's conference participants will discuss guidelines to educate young people regarding safe use of supplements. Everyone in this movement needs to be on the same page. The professional sports leagues, however, are dragging their athletic feet. They have not embraced educational reform, nor do they support research. It is important to talk with one another, and this conference is a very healthy start.

The cancer that threatens to destroy all that is good in sport has been discovered and exposed. In the Olympic arena, controversy has stimulated an incredible amount of change. For example, Johann Koss—a Norwegian Olympic gold medal speed skater and IOC member—has created an Olympic passport. This passport is a document that athletes can use to show they are "clean."

It is critically important to clean up the sports environment. A safe sports environment gives young boys and girls the opportunity to be the best they can be, learn the right way to be healthy and live life to its fullest.

<u>Discussion:</u>

Jean Fourcroy, M.D., Ph.D. (USADA): Who is paid to monitor products with contaminants or inaccurate labels?

Dr. Coates: The vast majority of dietary supplement manufacturers have extensive good manufacturing practices (GMPs) and quality standards. For example, CRN pioneered GMPs by establishing practices for the dietary supplement industry in the mid-1980s. There are rogue manufacturers in this business that do not have a high level of quality control or internal

audit. In those cases, the regulatory system is important—such as FDA and the Federal Trade Commission (FTC). It is this small number of rogue companies that are tarnishing the image of the vast majority of responsible companies. Suggestions on how to rid the marketplace of rogue manufacturers are welcome.

Steve Yannicelli, Ph.D. (Pharmavite): Is there a uniform standard for compounds that are acceptable to all sports governing bodies?

Ms. de Varona: No, this discussion is just beginning and amazingly it has taken 40 years to get there. USADA could be a leader in this endeavor and mediate disagreements between NCAA, IOC and sports federations.

Dr. Yannicelli: In your opinion, will there ever be agreement between professional sports and nonprofessional athletic groups such as NCAA and IOC? The message that comes across is that performance-enhancing products are not okay for amateur athletes, but acceptable for professional athletes and the multi-billion dollar sports industry.

Ms. de Varona: Unfortunately, it's going to take many more Korey Stringers [the Minnesota Viking who died during preseason training] before we get there. The National Hockey League decided to subject their players to the same standards as Olympic athletes regarding out-of-competition testing. Peer pressure is working, too, as with the Olympic passport.

Don Vereen (Nat. Inst. on Drug Abuse): What is your vision of the educational needs for young American athletes?

Ms. de Varona: Research is needed. A list of substances that athletes should avoid is needed. The Amateur Sports Act of 1978 added an amendment that IOC has a responsibility to disseminate information. IOC could work with NIH, the supplement industry and WADA to establish guidelines. Part of physical education should be on the use of supplements and performance-enhancing products.

Mr. Cordaro: To underscore Ms. de Varona's answer, research, education and information should be treated as a package. Exciting, innovative ways are needed to convey information to gatekeepers and athletes, at the professional level and amateur level.

Policy Session: Moderator, John Cordaro

Panel 1: Athletic Organizations

Gary Green, M.D.: Chair, Subcommittee on Drug Testing/Drug Education, National Collegiate Athletic Association (NCAA)

The NCAA began as a health and safety organization in response to football-related deaths in the early 1900s. The NCAA now consists of three divisions and 89 conferences, and represents more than 350,000 athletes in about 20 sports.

NCAA bylaw 16.5.2.2 (effective Aug. 1, 2000 posted at http://www.ncaa.org/sports_sciences/) addresses the use of nutritional supplements. It states "An institution may provide only nonmuscle-building nutritional supplements to a student-athlete at any time for the purpose of providing additional calories and electrolytes, provided the supplements do not contain any NCAA banned substances. Permissible nonmuscle-building nutritional supplements are identified according to the following classes: carbohydrate/electrolyte drinks, energy bars, carbohydrate boosters, and vitamins and minerals." Protein bars are not allowed under this by-law. Nutritional supplements banned by the NCCA are androstenedione and androstenediol, dehydroepiandrosterone (DHEA), norandrostenedione and norandrostenediol, caffeine (>12-15 milligrams/milliliter) and ephedrine.

The NCAA spends about $3 million a year conducting an estimated 10,000 anti-doping tests. Testing is conducted for all championship games, and for year-round testing in some sports. NCAA testing has shifted from primarily in-competition testing to year-round testing, which captures out-of-competition periods. In the 1999-2000 academic year, 1,488 tests were conducted for the in-competition program and 9,206 tests for the year-round program. The NCAA penalty for the first positive drug test is a one-year suspension from competition (regardless of the drug); a second positive test yields permanent ineligibility. There is an appeal process, and the appeal committee is blinded to the student and school.

Appeals for positive tests from supplement use usually include (1) the ingredient was not listed on the label, (2) failure to read the label, (3) the athlete assumed the substance was allowed, and (4) the supplement was contaminated with a banned ingredient. In 1999-2000, most of the positive results from year-round testing were from steroids. The majority of the appeals claimed the steroid was in a supplement. The majority of the positive tests from stimulants were from ephedrine compounds.

NCAA has an extensive education program. One component is the Resource Exchange Center, set up by the Center for Drug-Free Sport. Athletes can call or e-mail the Exchange Center with questions about supplements. The NCAA is concerned about supplement use for several reasons. There are safety issues; several supplement ingredients are included in drug testing, which can affect eligibility; there are legal

liabilities, and negative publicity for the school when athletes test positive. The NCAA approach is to use educational materials, send a clear message, drug test, and support research.

Jon Almquist, ATC: Chair, Secondary School Committee, National Athletic Trainers Association, Fairfax, Va.

Certified athletic trainers (ATC) have anecdotal "on the field" experience regarding supplement use (e.g., football season involves about 6,000,000 high school athletes); understand the differences between high school, college and professional athletes; and publish research in the *Journal of Athletic Training*. Secondary school athletic trainers face some unique challenges. Many high school athletes do not follow recommended doses for supplements because they believe if "some is good, more is better." They view sports supplements as a quick and easy way to improve performance, as unlike professional athletes, they cannot dedicate extended periods of time to training. Additionally, athletic trainers working at the secondary level often do not have an adequate medical history of their athletes, unlike trainers for college and professional athletes.

Parents are often unwilling to take a stand with their children and rely on coaches and trainers to provide direction and guidance. Many elements contribute to the information and policies used by the secondary school athletic staff. The National Federation of State High School Associations (NFHS) is the governing body for the majority of high school athletes and athletic programs, mainly in public schools. The state athletic associations (e.g., Virginia High School League) use policies and recommendations from the NFHS and state legislation. Local school systems (e.g., Fairfax County), individual school athletic programs and individual athletic administrators also play a role.

NFHS has educational material on its website (www.nfhs.org) regarding androstenedione, creatine, and gamma-hydroxybutyric acid (GHB)/gamma-butyrolactone (GBL). The information includes short- and long-term risks, laws and policies for these substances, and what coaches should tell athletes. NFHS has the following policy regarding supplements: "In order to minimize health and social risks to student-athletes, maintain ethical standards, and reduce liability risks, school personnel and coaches should never supply, recommend, or permit use of any drug, medication, or food supplement solely for performance-enhancing purposes."

Larry Bowers: Senior Managing Director, U.S. Anti-Doping Agency (USADA), Colorado Springs, Colo.

The IOC prohibits several classes of substances—stimulants, narcotics, anabolic steroids, diuretics, and peptides, and some substances under certain circumstances (e.g., alcohol, beta-blockers, glucocorticosteroids). USADA's position on supplement use is based on four elements—(1) the athlete is responsible for whatever enters his/her body (strict liability); (2) contamination as a result of lacking GMPs is cause for concern; (3) in the

absence of credible scientific data on safety and efficacy, it is better to err on the side of safety; and (4) potentially misleading information is available on various websites and in promotional statements. For example, the creatine studies examining renal effects were poorly designed. The studies were too short, doses too low (compared to what athletes consume) and inappropriate endpoints were used (e.g., creatine clearance). Credible safety data on creatine are lacking.

USADA uses the following guiding principles: (1) The pharmacological action of a compound is important, not its source. (2) Natural is not the same as safe (e.g., strychnine, cocaine and hemlock are all natural substances). (3) The amount taken is often as important as what is taken (e.g., strychnine in small amounts is a stimulant; in larger amounts it's a poison). (4) The effect of a drug on a mature adult may not be the same as the effect on an adolescent.

John Cardellina, Ph.D.: Vice President, Botanical Science and Regulatory Affairs, Council for Responsible Nutrition, Washington, D.C.

All the participants here would agree that a healthy, balanced diet is important for all people, especially athletes. However, a balanced diet with normal caloric intake might not be sufficient to meet the demands of an athletic during competition or training. Dietary supplements can be used to supplement, not replace, a balanced diet.

A wide variety of supplements are available, and most are safe—providing benefit to athletes of all ages and levels of performance. A few supplements are inappropriate for young athletes, however, and they need informed advice. CRN recently drafted guidelines for the responsible use of sports supplements by young athletes.

The CRN guidelines are based a traffic light analogy—green light for proceed, yellow light for caution and red light for stop. "Green light" supplements include those for normal nutritional support such as vitamins, minerals, beverages to replenish fluids and electrolytes, energy bars, and protein powders. The "yellow light" supplements require caution as long-term effects are often insufficiently studied in youth, and some sports governing bodies set limits on use of some of these ingredients. Supplements that fall into this category include creatine, pyruvate, and stimulants such as caffeine. The "red light" supplements are products inappropriate or contraindicated for persons under 18 years of age, such as those containing steroid hormone precursors (e.g., androstenedione) and ephedrine alkaloids. In addition, these substances are banned by sports governing bodies.

The guidelines also outline responsibilities for various stakeholders. Industry must recognize that some ingredients should not be recommended for young athletes, and it must commit to appropriate product labeling (e.g., not for use by persons younger than 18). Industry should also support educational activities to help young athletes use supplements responsibly. Healthcare professionals must recognize the safe and beneficial role of supplements in nutritional support and provide accurate, balanced

information. Parents, coaches and trainers have important roles, as they are the most frequent contact and source of information for young athletes. They, too, must provide accurate, balanced information and guidance on the use of sport supplements and reinforce that guidance with meaningful sanctions and enforcement of appropriate rules of conduct.

Panel 2: Healthcare Professionals

Gary Wadler, M.D.: Associate Professor of Clinical Medicine, New York University School of Medicine, New York City. Dr. Wadler also serves as medical advisor on doping to the White House Office of National Drug Control Policy, as a member of the Health, Medicine and Research Committee of the World Anti-Doping Agency and as a Fellow and former Trustee of the American College of Sports Medicine (http://www.acsm.org).

DSHEA was not created in a vacuum; it followed on the heels of almost a century of federal regulation of drug policy. In 1906, The Pure Food and Drug Act was passed to address purity and prohibit misbranding. In 1938, the Food, Drug and Cosmetic Act demanded that safety be demonstrated before marketing and the 1962 Kefauver Amendments mandated that efficacy be proven prior to marketing. The abuse of amphetamines gave rise to the Controlled Substances Act (1970), and the abuse of anabolic steroids led to its 1990 amendments. DSHEA was passed in 1994.

Which law governs what substance? When is a tablet a supplement, an OTC drug, a prescriptive drug or a controlled substance?

Under DSHEA, androstenedione—a steroid hormone precursor—is a supplement, but it is metabolized to testosterone, a controlled substance, and estrogens, which are prescribed drugs. In 2000, the National Institute of Environmental Health Sciences (NIEHS) recommended listing estrogen as a known carcinogen. Hormone replacement therapy is prescribed through an informed decision-making process with a physician. Androstenedione, however, is readily available off the shelf with no consultative process with a health professional and no medical monitoring. Androstenedione's first cousin is 19-norandrostenedione, which is converted to the potent anabolic steroid nandrolone. Nandrolone is a banned substance in most international sports and accounted for more than 600 positive urine drug tests in the past two years. Virtually every athlete who tested positive attributed the result to inadvertent ingestion of a supplement tainted with 19-norandrostenedione. The explosion of nandrolone-positive tests directly correlates with the passage of DSHEA.

Ephedrine is an over-the-counter (OTC) drug, but ephedra—a botanical source of ephedrine alkaloids—is a dietary supplement. Because of the potential adverse health effects, FDA proposed restrictions in 1997 that would lower the dosage of ephedrine alkaloids in dietary supplements. In April 2000, however, FDA withdrew its 1997 proposal following an unfavorable report by the General Accounting Office

("Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids, July 1999), which stated that additional evidence was needed to support the restrictions.

Science and politics are on a collision course regarding androstenedione and ephedra, and politics have prevailed. Efforts are currently underway by the Drug Enforcement Administration (DEA) to demonstrate muscle growth in guinea pigs administered androstenedione, so it might be classified as a schedule III controlled substance. It might make more sense to find a middle ground and characterize androstenedione and its congeners as a prescriptive drug, as are estrogens. The 1997 FDA proposed limits on ephedra should be revisited, particularly in light of data indicating increased usage at younger and younger ages.

At the state level, legislation and regulations must mandate explicit and standardized product labeling for contents as well as contraindications for use and dosage limitations. Parental consent should be required for all minors, particularly for those supplements that present a threat to public health. At the federal level, it is time to revisit DSHEA—not to discard it, but to improve it. With respect to DSHEA, to paraphrase the late Justice Cardoza, "Sunshine is the best disinfectant."

Reginald Washington, M.D.: Rocky Mountain Pediatric Cardiology, Denver and American Academy of Pediatrics (AAP) Representative. (http://www.aap.org)
The AAP statements discussed today have not gone through the final approval process.

AAP must address its primary audience—pediatricians. Most pediatricians do not treat elite athletes as patients, but they do treat student athletes and nonathletes who take performance-enhancing substances. The proposed AAP policy must encompass athletes and nonathletes.

Current definitions of performance-enhancing substances are largely based on lists of substances that are banned by collegiate and Olympic organizations. Accordingly, if a substance isn't tested for, there is an implied acceptance of its use. From AAP's perspective, the definition of performance-enhancing substance must include not only substances that are banned but also substances that cannot be detected, are not subject to drug testing, and are not used in athletic settings. For this reason, AAP does not have a list of banned substances, but lists categories of agents. Additionally, the use of supplements or pharmacological agents to help reduce legitimate deficits or meet additional demands is considered good medial practice. The point at which maintenance or replacement requirements are met versus enhancement, however, is not always clear.

AAP defines performance-enhancing substances as any substance taken in nonphysiologic doses specifically for the purpose of improving performance, including improving performance by changing behavior, arousal level, or the perception of pain. For example, pharmacological agents that exceed the recommended therapeutic dose or are used to treat a disease that is not present should be banned. Examples would be decongestants used for stimulant effects, bronchodilators used when asthma is not

present, substances that enhance oxygen carrying capacity, or substances that mask the side effects or detectability of other banned substances.

Pediatricians should discuss performance-enhancing substances at well-child visits, similar to discussions that should occur with smoking and alcohol abuse. If abuse is found, it should be discussed in a fashion similar to alcohol abuse or smoking. Otherwise, the patient should be encouraged not to use performance-enhancing substances. AAP encourages events such as this conference, which further the knowledge in recognizing and treating abuse when it occurs.

Barry Dickinson, Ph.D.: Director, Science Policy and Secretary, Council on Scientific Affairs, American Medical Association (AMA), Chicago

AMA policy is based on reports and resolutions that are adopted by its House of Delegates (HOD). HOD meets twice a year, in June and December. It is comprised of representatives from more than 90 specialty societies and representatives from the 50 state medical societies. The AMA policy compendium is available on the following website: www.ama-assn.org/apps/pf_online/pf_online. In addition to policy, HOD also issues directives, which recommend certain activities of the organization within a limited timeframe.

The HOD policy on dietary supplements and herbal remedies (H-150.954) addresses adverse event reporting, DSHEA, product labeling and advertising, and education. Regarding DSHEA, the policy urges Congress to modify the Act to require that dietary supplements (1) undergo FDA approval for safety and efficacy; (2) meet standards established by the U.S. Pharmacopoeia (USP) for identity, strength, quality, purity, packaging and labeling; and (3) meet FDA postmarketing requirements to report adverse events, including drug interactions. The AMA also will pursue development and enactment of legislation that declares metabolites and precursors of anabolic steroids as drug substances that may not be used in a dietary supplement.

Additionally, AMA proposes an extension to the required product label disclaimer "This product has not been evaluated by the Food and Drug Administration and is not intended to diagnose, mitigate, treat, cure or prevent disease." AMA proposes adding "This product may have significant adverse side effects and/or interactions with medications and other dietary supplements; therefore it is important that you inform your doctor that your are using this product." The HOD policy also advocates requiring manufacturers to investigate and obtain data under conditions of normal use on adverse events, contraindications, and possible drug interactions, and that such information is included on the label. Regarding advertising, the policy supports working with FTC to support enforcement efforts based on the FTC Act and current FTC policy on expert endorsements.

The HOD policy on dietary supplements also outlines the following educational activities: (1) work with FDA to educate physicians and the public about FDA's

MedWatch program, (2) encourage physicians and the public to report potential adverse events associated with dietary supplements and herbal remedies, (3) support FDA's efforts to create a database of adverse event information on these forms of alternative and complementary therapy, and (4) continue efforts to educate parents and physicians about the possible ramifications associated with the use of dietary supplements and herbal remedies.

Other related statements on dietary supplements include Resolution 501(A-01) and public comment. Resolution 501(A-01) states that, "AMA call for a coordinated effort by government, academics, and organized medicine to address the problem of the use of anabolic/androgenic steroids by students…" In response to the April 3, 2000, *Federal Register* notice on ephedra, the AMA submitted comments September 2000, which encouraged FDA to initiate proceedings to remove dietary supplements containing ephedra alkaloids from the U.S. market.

Iris Shaffer: Executive Director, Blue Cross and Blue Shield Healthy Competition Foundation, Chicago

The Blue Cross and Blue Shield Association (BCBSA) represents 44 independent Blue Cross and Blue Shield companies, which collectively provide health insurance coverage to 82 million Americans. The BCBSA Healthy Competition Foundation (HCF) was launched in September 1999 as an outgrowth of Olympic sponsorship.

HCF is a nonprofit foundation that seeks to eliminate the use of performance-enhancing drugs (PEDs) and certain supplements in sports. It educates young athletes and their families about the dangers of PEDs and encourages athletes at all levels of competition to resist the pressures to take PEDs. HCF supports athletes and organizations that take a vocal stance against these drugs. HCF also urges athletes to take the "Healthy Competition is Drug-Free" pledge and to wear the symbol of drug-free athletics. About 5,000 athletes have taken this pledge.

The BCBSA/HCF policy (1) states that the use of PEDs/supplements is a growing public health crisis, (2) supports drug-free competition without the use of performance-enhancing products, and (3) recommends that people of all ages consult with their physician before taking supplements containing androstenedione, ephedra, creatine or related substances.

In summer 2001 BCBSA/HCF conducted a nationally representative survey. The survey, projected to the U.S. population, revealed the following:

- Approximately 1 million young people between the ages of 12-17 have taken potentially dangerous performance-enhancing supplements and drugs.
- Approximately 390,000 10-14 year olds said they have taken performance-enhancing substances.
- 70% of young people and half of the parents surveyed could not identify any specific negative side effects from using these substances.

- 37% of parents rated the use of performance-enhancing products as their greatest concern in youth sports.
- 80% of young people surveyed said they had not had a conversation with their parents about sports supplements.
- Sports supplements are more commonly used than PEDs (61% vs. 15%); 12% of respondents used both.
- Creatine was the most widely used substance (52% of youth who used PEDs/supplements), even though more consumers were aware of steroids. One-fifth of teens personally know someone who has used creatine.
- Among adults, use of ephedra is equal to creatine (18%).
- Performing better in sports, followed by building muscle, are the most common reasons for using sports supplements and PEDs.
- One in five young people believe these substances are used to help people look better.
- 3% of teens (12-17 years old) felt pressured into using these substances.
- Half of 10-17 year olds believe that young people risk serious damage by taking sports supplements.

The HCF educational program for 2002 consists of an Olympic poster contest, an Olympic trading pin with the "Healthy Competition" message (drug-free, integrity, dedication and fair play), a curriculum guide that will be released February 2002, and a Major League Baseball-HCF Youth Baseball Day in April. The curriculum guide is available through the Healthy Competition website (www.healthycompetition.org). It is a one-week curriculum to educate students on the health risks of PEDs and sports supplements, as well as integrity and fair play.

Panel 3: Government Agencies

Kate Malliarakis: Office of National Drug Control Policy (ONDCP), Rockville, Md.

The primary mission of ONDCP is to lead national efforts to reduce illicit drug use and its consequences. ONDCP was created by the Anti-Drug Abuse Act of 1988, as amended, and develops, coordinates and oversees implementation of National Drug Control Strategy. The Office recommends improvements in management and organization of drug control efforts and conducts evaluations and performance measurements to improve program effectiveness. Mr. John Walters directs ONDCP.

The Monitoring the Future Survey on the current use of steroids and performance-enhancing substances revealed the following:

- Rates of steroid use in 2000-2001 are generally stable; 2.8% of eighth graders, 3.5% of 10th graders, and 3.7% of 12th graders reported using steroids at least once in their lives.
- 44.4% of 12th, 33% of 10th, and 23% of eighth grade students reported that steroids are "fairly easy" or "very easy" to obtain.

- Of 19-22 year olds surveyed in 2000, 18.9% reported having a friend who was a current user of steroids.
- In 2001, perceived risk of steroids has increased among those surveyed.

Policy considerations for steroids and performance-enhancing substances should consider public health and safety. Public health considerations include that steroids pose health and behavioral risks for youth. Public safety considerations include that steroids are controlled substances, and procurement and sale of steroids entail contact with a criminal element.

ONDCP led the interagency process to develop a comprehensive federal policy to address the problem of drugs in sport. The policy was released in October 1999. ONDCP's role as the founding member and Chair of the Education and Ethics Committee demonstrates its commitment to anti-doping efforts of WADA. The Office is a strong supporter of USADA and implementation of reliable testing, adjudication and educational efforts. ONDCP's counterdrug technology provides technical support to and participates in developing USADA's and WADA's research agenda.

The ONDCP Interagency Demand Reduction Working Group was created to facilitate communication among relevant federal agencies. The ONDCP working group subcommittee on performance-enhancing substances is an interagency effort involving FDA, FTC, NIH (ODS and the National Institute on Drug Abuse), Department of Justice, DEA and the Substance Abuse and Mental Health Services Administration.

The ONDCP website is: http://www.whitehousedrugpolicy.gov/.

Christine Lewis Taylor, Ph.D.: Director, Office of Nutritional Products, Labeling and Dietary Supplements; Center for Food Safety and Applied Nutrition (CFSAN); FDA; College Park, Md.

The FDA is authorized to regulate dietary supplements through the Food, Drug and Cosmetic Act and the 1994 amendments in DSHEA. A dietary supplement is defined by DSHEA as a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: vitamin, mineral, herb or other botanical, amino acid, dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract or combination of these ingredients.

Dietary substances and metabolites are not clearly defined by the Act, and DSHEA does not address the category of hormones. FDA has not yet taken a position on the hormone category. Regulatory status depends on their intended use. For example, hormones for anabolic use, such as testosterone, are schedule III controlled substances. Androstenedione, however, generally has structure/function claims for bodybuilding. By intended use, androstenedione is considered a dietary supplement, but is androstenedione an ingredient intended to supplement the diet? Hormone precursors, such as

androstenedione, fall into a gray area, and FDA's enforcement actions can determine how they are regulated. To date, FDA has not been very active in the area of hormones.

The primary safety concerns regarding performance-enhancing dietary supplements are the paucity of data, especially for chronic use; marketing to and use by children and adolescents; and combinations of ingredients that may have adverse consequences. Additionally, exercise may change the body's physiological state and response to performance-enhancing products. Furthermore, some analyses have shown that some products contain banned substances.

Safety is the first priority for FDA's limited resources. FDA collaborates with FTC regarding fraudulent claims, with NIH to examine effectiveness, and with DEA for illicit substances. FDA needs clarification of definitions (e.g., dietary substance), additional research (e.g., chronic use effects), and improved reporting of adverse events.

Laura Sullivan, J.D.: Division of Advertising Practices, Bureau of Consumer Protection, FTC, Washington, D.C.

Section 5 of the FTC Act prohibits deceptive and unfair acts and practices in commerce. Claims made in advertising—express or implied—must be truthful, not misleading, and substantiated. Substantiation means competent and reliable scientific evidence. The starting point is always well-controlled human clinical studies. FTC also looks to what appropriate experts consider adequate. The studies must relate to the product, and claims must reflect the strength of the science. Consumer anecdotes are never a substitute for science. Advertising must also include any material information that qualifies a claim, such as significant side effects or safety risks, conditions of use, or limits on efficacy. Disclosures must be clear and prominent (i.e., no fine print, and placed near the claim being qualified), using direct and unambiguous language.

FTC's focus regarding performance-enhancing products has been on unproven safety claims in advertising. Efficacy claims are also required by law to be truthful and substantiated. FTC's priority with sports products has been explicit safety claims for supplements that present serious health risks. Recent actions have involved safety claims for androgen products. Some of the products also contained ephedra and caffeine. FTC challenged the claims of no side effects. FTC required strong warning statements about risks of steroid hormones and ephedra in labeling and advertising.

Rebecca Costello, Ph.D.: Deputy Director, Office of Dietary Supplements, NIH, Bethesda, Md.

Funding for ODS has increased from $1 million in FY 1996 to $10 million in FY 2001. The budget for FY 2001 was divided among the following activities: 45% for botanical center programs, 18% for grants, 10% for databases, 8% for administration, 8% for evidence-based reviews, 5% to support the National Health and Nutrition Examination

Survey (NHANES), 3% for analytical methods, 2% for conferences and workshops, and 1% for training.

Extramural activities that ODS supports include REAP (Research Enhancement Awards Program) awards (e.g., bone density loss in athletes), program announcements (e.g., chromium as adjuvant therapy for type 2 diabetes and impaired glucose tolerance), and requests for applications (RFAs) such as the botanical research centers. ODS also supports initiatives with other federal partners, such as the National Center for Health Statistics/CDC for the NHANES survey activities, a dietary supplement ingredients database as a tool for researchers, and the Institute of Medicine Food and Nutrition Board dietary reference intake (DRI) reports.

In a sense, today's conference is a follow up to the June 1996 workshop on the "Role of Dietary Supplements for Physically Active People." The proceedings of that workshop were published in the *American Journal of Clinical Nutrition* (http://www.ajcn.org/content/vol72/issue2/#SUPPLEMENTS).

James Tolliver: Office of Diversion Control, DEA, Arlington, Va.

Anabolic steroids are schedule III drugs and regulated by the Controlled Substances Act. There are 22 substances defined as anabolic steroids. As there are many more anticipated anabolic substances, DEA has a definition that is used as new substances evolve. If a substance meets the following elements of the definition, it is automatically classified as an anabolic steroid:

- chemical structure similar to testosterone,
- pharmacologically related to testosterone,
- not estrogen, progesterone or a corticosteroid, and
- promotes muscle growth.

The only element lacking for androstenedione to meet the definition is its ability to promote muscle growth. DEA is funding studies to determine whether androstenedione promotes muscle growth. The first step was to find an appropriate animal model. This study was started last year with rats, and should be completed soon. The second study just began with a guinea pig model, and it will examine 10 different steroids available in the dietary supplement market. Each product will be tested for four to six months. Completion of the study is expected in 2003.

Alan Trachtenberg, M.D.: Office of Pharmacologic and Alternative Therapies, Substance Abuse and Mental Health Services Administration (SAMHSA), Rockville, Md.

SAMHSA is divided into three centers—mental health, substance abuse treatment, and substance abuse prevention. SAMHSA is interested in any potential problems with performance-enhancing products related to addiction, particularly ephedra and the ephedrine alkaloids.

There is some concern that performance enhancement might serve as a rationalization for some people to continue their use of substances in an addictive pattern. As part of their denial, they may state that they use the product to enhance performance, not to get high. For example, some addicts who abuse amphetamines may use a series of legal products while in recovery to approximate a "high." They could say they are using sports supplements to enhance performance, but really use them for an adrenalin rush or amphetamine-like effect. Coaches and others who advice youth need to be familiar with the issues of addiction.

Discussion

Skip Pope, M.D. (Harvard Medical School): Advertisements in body-building magazines promote products that sound like anabolic steroids. Can anything be done about this?

Ms. Sullivan: FTC does require that sport product claims must be substantiated, truthful and nondeceptive. Due to limited resources, however, FTC focuses on

explicit safety claims. If there are particular ads that are of concern, they can be forwarded to me (lsullivan@ftc.gov).

Alexandra Knudson (NIH): There seems to be widespread ignorance among physicians and students. Can there be a widespread campaign on radio, television and print that would encourage people to think about what they put in their mouth?

Mr. Cordaro: A public-private partnership with the groups here today for major information and education campaigns could go a long way in helping consumers, industry and regulators.

Ms. Malliarakis: ONDCP has a youth anti-drug media campaign that does not specifically address a particular drug, but covers drug use and drug-taking behavior. Healthy Competition has a spectacular initiative. Congress should give the federal government more money for activities like those in the private sector, but resources are limited.

Ms. Martinelli: Is EPO given intramuscularly (IM), and if so, is there a danger of sharing needles?

Dr. Washington: Yes, IM, and absolutely a danger in sharing needles.

Dr. Green: EPO is given subcutaneously.

Andrew Pipe, M.D. (Center for Ethics in Sport): Dr. Cardellina, can you provide a rationalization for the age 18 cutoff in your guidelines? Why does the use of these "red light" compounds become appropriate for individuals over the age of 18?

Dr. Cardellina: The reason that anabolic steroid or hormone precursors are contraindicated for people under 18 is that they are still in the process of sexual maturation. Altering levels of naturally occurring hormone levels may be detrimental to the maturation process. For ephedra, many of these products are already labeled as not for use by people under the age of 18.

Bob Stevenson (SAMHSA): Increasingly, young people use search engines and the Internet to find information. For the FTC, does a product have to be legal to be advertised? Can the ad be truthful but the product illegal?

Ms. Sullivan: No, illegal substances cannot be marketed for sale.

Dr. Green: NCAA supports a web-based Resource Exchange Center, and it gets hundreds of hits a month. It is very effective in answering students' questions.

Mary Hardy, M.D. (Cedars-Sinai Medical Center): What practical strategies can we institute to improve the quality of adverse event reporting?

Dr. Taylor: Because it is a voluntary system, it has to be well publicized. Health professionals need to be aware that they have some responsibility to use the system.

Regulatory Overview: Eugene Lambert, Esq., Covington & Burling, Washington, D.C.

Regulation of performance-enhancing products encompasses several elements including the type of product, its function, who uses it and when.

Ingredients and product form help define the type of product. There is a wide range of key ingredients, which include protein, vitamins, minerals, electrolytes, prohormones, and stimulants (e.g., ephedra). The ingredient, by itself, does not predict a regulatory category. There is also a broad range of product forms, such as drinks, powders, bars, tablets, and capsules. Product form can be a determinant of regulatory status by excluding the product from some categories. For example, dietary supplements are products that are intended for ingestion. Substances that are injected or used as topical creams cannot be classified as dietary supplements.

The function of the product and when it is used begin to address the heart of regulation. It is the claim that drives the issue of regulatory status. For example, is the claim or function of the product to provide energy—immediate or sustained, build muscle, or enhance alertness? Is the benefit realized before, during or after performance? Is the product used to sustain performance? Is use episodic by type of activity or performance goal? In determining intent, FDA is not limited to claims on the label. FDA can look at any information to discern the explicit or implied intent of the marketer.

Who uses the product generally does not drive how the product is regulated but can affect the labeling, such as directions of use and cautionary statements. If women use the product, there may be language to caution against use while pregnant or lactating. If the product is not intended for children, there may be statement warning against such use.

Integrating the answers to the kind of product used for what purpose, by whom and when helps to classify the product as a conventional food, special dietary food, dietary supplement or drug.

Conventional foods address safety through two mechanisms—adulteration and food additives. Adulteration is the presence of poisonous or deleterious substances in food due to the lack of caution. Food additive is a term of art, and the flip side of GRAS—generally recognized as safe. If an ingredient isn't GRAS, it's a food additive. GRAS status is for intended condition of use; safety of a GRAS food ingredient inherently involves conditions of use, level of use, intended user, and duration of use. An

ingredient that is not GRAS is a food additive, requiring premarket approval, and safety must be demonstrated to FDA in the approval process.

The Food, Drug and Cosmetic Act defines food as articles that are intended to be used as food or drink, which doesn't push the analysis very far. The key point is that food is understood to affect structure or function. Performance is a subset of function—how well muscles work, how quickly they work, reaction time. Food warnings are based on a failure to disclose material facts that are relevant under the intended conditions of use.

Special dietary foods are regulated like conventional foods. FDA specifically defines weight gain and loss as a special dietary use. So, there is another food category that is sometimes used for weight gain/loss products.

Dietary supplements were specifically defined in DSHEA, and to some degree they have separate regulatory scheme. Consumer safety is protected through regulations for adulteration, grandfathering and notifications. Adulteration is based upon the recommended conditions of use, not upon expected conditions of abuse. That is an important distinction. Grandfathered ingredients were those on the market before October 1994; they are presumed safe. Postmarketing surveillance tracks their safety. For new ingredients—those introduced to the market after October 1994—the manufacturer must file notification with FDA. The manufacturer must submit data supporting the safety of the new ingredient.

By law, dietary supplement labels can provide structure/function claims—statements of how the product benefits the body's structure or function. Also by law, the claim must be accompanied by the following disclaimer: "This statement has not been evaluated by the FDA. The product is not intended to diagnose, treat, cure or prevent any disease." The manufacturer is supposed to submit each of these claims to FDA. FDA can issue a "courtesy letter," which informs the manufacturer that FDA believes the claim is a disease claim. Disease claims must be approved by FDA and require significant scientific agreement. The basis for label warnings is the same as for conventional foods—failure to disclose material facts that are relevant under the intended conditions of use. The statute specifically provides that a warning on a dietary supplement label cannot be a reason to declare the product a drug.

Drugs are regulated under a very different scheme. A benefit-risk standard is used in safety assessment rather than simply a risk standard that applies to foods. In part, the drug standard is specifically driven by statutory requirements for current GMPs. Claims have a substantial evidence standard, which requires adequate and well controlled clinical studies, typically two or more. Drug warnings are mandated by statute.

Some examples will serve to highlight the different regulatory categories. Caffeine is considered a food ingredient in coffee, tea and soft drinks. It is a dietary supplement ingredient if there is a claim for alertness and a drug in OTC migraine products. Ascorbic acid as a nutrient or preservative is considered a food; it can also be a dietary

supplement ingredient. Ascorbic acid, if used to treat scurvy, is not considered a drug, as dietary deficiency diseases are excluded from the drug disease category.

In summary, the regulatory framework consists of determining product form, product claims, and product uses, which leads to the product category. The product category will dictate the form of regulation.

Patterns of Use
Moderator: Rebecca Costello, PhD

Performance-Enhancing Dietary Supplement Use among Men and Women in American Gymnasiums. Harrison Pope, Jr., M.D., Chief, Biological Psychiatry Laboratory, McLean Hospital, Belmont, Mass.

In an initial study of performance-enhancing supplement use (*Psychotherapy and Psychosomatics*, 2001, 70: 137-140), 511 single-page questionnaires were distributed to clients at they entered five gyms in the Boston area. The questionnaire asked about the use of protein products, creatine, androstenedione and related substances (e.g., DHEA, 19-norandrostenedione), ephedrine products, and anabolic steroids in the last three years. The survey asked how long each supplement was used and provided the following choice of answers: never, a little (0-1 month), moderate (1-6 months), and a lot (6 or more months). The questionnaire provided brand names of common supplements to assist respondents. A total of 334 men and 177 women completed the questionnaire.

Among the men, more than half (61%) had used some type of protein product, and 27% used these products for more than six months. For creatine, 47% of men reported any use, and 11% used creatine for more than six months. Androstenedione consumption longer than six months was reported by 4% of men, and 2% reported anabolic steroid use for this time interval. Among women, none reported use of anabolic steroids. Protein and ephedrine products were the most frequently consumed among women, 34% and 13%, respectively. Use longer than six months fell to 4% of women for ephedrine and 11% for protein supplements. Creatine was used by 7% of women, and only 1% used creatine for more than six months. Androstenedione supplementation was reported by 3% of women, but none used it longer than six months.

To estimate the rates of supplement and anabolic steroid use among gymnasium clients nationally, data from a national organization of gyms (International Health, Racquet and Sportsclub Association) was used to estimate the number of male and female gymnasium clients. This rough estimate indicates that on a national level 4.3 million men and 2.7 women use protein products, 3.3 million men and about half a million women use creatine, 1.8 million men and 1.0 million women use ephedrine supplements, 1.3 million men and 240,000 women use products from the androstenedione family, and 400,000 men use anabolic steroids. A national household survey in 1994, which included questions on the consumption of anabolic steroids, found that 380,000 men reported use.

An earlier study (*Psychotherapy and Psychosomatics*, 2000, 69: 19-26) examined effects of anabolic-androgenic steroid use in women. Women were recruited for the study by placing advertisements in gymnasiums that asked the following questions: Have you competed in a bodybuilding or fitness contest? Have you lifted weights in the gym at least five days a week for at least two years? Data was collected on 75 advanced women weightlifters—25 anabolic steroid users and 50 nonusers. The women were asked about their use of other performance-enhancing products. Among anabolic steroid users, nine women (36%) reported use of androstenedione, and 20 (80%) used ephedrine products. Among nonusers of anabolic steroids, nine women (18%) used androstenedione and 21 (42%) used ephedrine. Women who use anabolic steroids are about twice as likely to use other performance-enhancing supplements as nonusers of anabolic steroids.

Substance use among advanced male weightlifters is currently under investigation. Male weightlifters were recruited by advertisements in gymnasiums and nutrition stores that asked, Can you bench press 275 pounds for at least one repetition? A total of 87 men completed the questionnaire and evaluation. Creatine use was reported by 88% of the weightlifters; 40% reported use for at least 12 months, and 11% used creatine for at least 36 months. Some men reported using creatine for six to seven years without interruption. More than half the men (56%) reported use of androstenedione and related substances; 28% used it at least six months, and 13% consumed these products for at least a year. Similar results were observed for anabolic steroid use—49% of men reported any use, 23% for at least six months, and 9% for at least 24 months. Ephedrine products were also popular—71% of male weightlifters reported any use, 43% used these products for at least 12 months and 17% for at least 36 months. Some men reported continuous use of ephedrine products for six to seven years. The data were also stratified by anabolic steroid use or nonuse. Among steroid users, 91% of men used creatine, 70% used androstenedione, and 77% used ephedrine products. Among nonusers of anabolic steroids, the respective values were 84%, 41% and 66%.

Use of Dietary Supplements in Elite U.S. Army Populations: Harris Lieberman, Ph.D., Military Nutrition Division, U.S. Army Research Institute of Environmental Medicine, Natick, Mass.

Dietary supplement use was assessed in three military populations—768 Army Rangers, 152 members of the Special Forces, and 315 officers at the Army War College. The Army Rangers are an elite unit of young enlisted volunteers (aged 23.6 ± 4.3 years). The participants' average time in the Army was two years; they are junior grade, low paid, and have extremely high physical job demands. The Special Forces are more mature than Rangers (aged 31.3 ± 6.1 years). They have about 10 years of experience in the Army, and experience high physical and mental job demands. Officers at the Army War College are at the middle-to-upper management level and have been selected for higher-level assignments. Their jobs have moderate physical demands and high mental demands, and the average age of these officers is 44. This study population included 284 males and 31 females.

Generally speaking, maintaining physical fitness and weight standards is an occupational requirement in the military. Failure to meet standards eventually leads to separation from the service, and in some units, advancement depends on maintaining a high fitness level. The following proportion of men engaged in aerobic exercise at least three times a week: 98.4% Rangers, 96.0% Special Forces, and 74.5% of male Army War College attendees. Strength training was performed at least three times a week by 45.3% of Rangers, 35.8% of Special Forces, and 33.6% of male attendees at the Army War College.

All three groups reported high levels of supplement use. More than 80% of Rangers, about 65% of Special Forces, 70% of male officers at the War College, and approximately 80% of female officers at the War College reported use of supplements at least once per week. The types of supplements consumed, however, varied by group.

Among Rangers, the 10 most frequently used supplements were carbohydrate-electrolyte drinks (70%), multivitamins (28%), creatine (23%), protein and amino acids (23%), sports bars (22%), antioxidants (20%), herbs (13%), androstenedione (8%), vitamin C (7%), and vitamin A (4%). Among Special Forces, the 10 most popular supplements were sports drinks (36%), multivitamins (32%), protein powder (16%), creatine (16%), sports bars (15%), vitamin C (11%), meal replacement drinks (9%), vitamin E (7%), antioxidants (6%), and androstenedione (6%).

Among male officers at the Army War College, the top 10 supplements were multivitamins (42%), vitamin E (25%), vitamin C (19%), sports drinks (11%), antioxidants (9%), B-complex (7%), garlic (7%), beta-carotene (6%), ginkgo biloba (6%), and calcium (6%). The proportion of women officers using supplements was higher than among men. The top 10 supplements used by female officers at the War College were multivitamins (53%), calcium (39%), vitamin E (36%), vitamin C (33%), antioxidants (23%), beta-carotene (19%), magnesium (15%), folate (15%), B-complex (14%), and B_6 (12%).

Not unexpectedly, the War College officers tended to take supplements for general health, while Rangers and Special Forces tended to consume supplements marketed for enhancement of physical performance. Survey questions on the reasons for consuming supplements confirm this pattern of use. Rangers and Special Forces reported using supplements for muscle or performance enhancement or to increase energy. The more mature soldiers from the War College and Special Forces were more likely to report taking supplements for general health effects.

In conclusion, elite Army populations consume high levels of nutritional supplements. Different elite Army populations have different patterns of supplement use depending on perceived need. Research to justify this level of supplement use is lacking.

<u>Patterns of Supplement Use among NCAA Student-Athletes:</u> Gary Green, M.D., Chair, NCAA Subcommittee on Drug Testing/Drug Evaluation, Los Angeles

Every four years the NCAA surveys student-athletes to evaluate the use of drugs (e.g., amphetamines, marijuana, cocaine), nutritional supplements, cigarettes, and alcohol. The surveys are sent to faculty representatives of each NCAA institution. The surveys are administered in a voluntary and confidential manner. They are distributed to all members of a particular team on the same occasion, and all surveys are collected over a one-month period to minimize influence by media events.

For the 2001 survey, 969 member institutions were asked to participate and 74% returned the survey. A total of 21,225 responses were collected (61% male, 79% white). The number of women participating in the survey has increased dramatically, from approximately 3,000 in 1982 to 8,000 in 2000. By division, about 41% of the returns were from Division I, 23% from Division II, and 35% from Division III.

Several questions were asked about supplement use—have you used nutritional supplements in the past 12 months, which supplements have you used, what are the reasons you use nutritional supplements, where do you usually get your nutritional supplements, what are your sources of information about supplements, when did you start using nutritional supplements, and what is the main reason you stopped using supplements?

Nutritional supplements were used by 29.2% of respondents in the past 12 months, 12.8% reported use then stopped, and 58.4% had not used supplements. Creatine was the most popular supplement (26%), followed by amino acids (10%), androstenedione (4%), chromium (4%), ephedra (3.9%), hydroxymethylbutyrate (HMB) (3%), and DHEA (1%).

Ephedrine use was first surveyed in 1997, and consumption increased from 3.5% to 3.9% over a four-year period. Ephedrine use decreased among men's sports but increased in women's sports, particularly where thinness is valued such as gymnastics. Among ephedrine consumers, 58% reported first use in high school.

Improving athletic performance and physical appearance were the primary reasons to use nutritional supplements (27%), followed by weight loss/weight gain and general health (20%), to prevent injury (9%), and to recover from illness or injury (6%). Among supplement users, 59% purchased them from retail stores, 9% obtained them from a friend or family member, 5% from strength coaches, 5% from coaches, 5% from athletic trainers, and 4% from a website or mail order. Information about supplements was most often obtained from a friend (14%), followed by a retail store (13%), nutritionist (12%), teammate or other athlete (12%), parent (9%), athletic trainer (8%), coach (7%), physician other than team physician (5%), and team physician (1%).

Supplement use typically began before college—57% in high school and 6% in junior high or earlier. Approximately 20% began use freshman year of college and 16% after freshman year. For intervention programs, it is important for the NCAA to partner with colleagues at NFHS. The earlier use of nutritional supplements is also mirrored by use of

other drugs. Except for cocaine, more than half the users of alcohol, marijuana, and smokeless tobacco reported first use in high school.

The following responses were recorded for the question, what is the main reason you have never used or have stopped using supplements: 40% no desire to experience the effects, 16% concerned about health effects, 10% didn't get the desired effect, 10% stated it was against their beliefs, 7% costs too much, 1% coach's rules, 1% fear of losing eligibility, and 0.3% fear of getting caught. It appears that interventions by coaches setting rules and fear of losing eligibility are largely ineffective.

In addition to surveying student athletes, a survey is conducted every two years among athletic directors. One question asked which supplement would result in a positive drug test by the NCAA? Androstenedione had the highest response (83%), closely followed by ephedrine (82%), 19-norandorstenedione (72%), creatine (11%), amino acids (8%), and glucosamine (8%). Creatine, amino acids, and glucosamine do not produce positive drug tests, but a significant number of trainers believed they did.

In summary, a significant portion of NCAA athletes uses supplements. Use of supplements often begins in junior high or high school. Better sources of information need to be made more available.

Patterns of Use: Elite Athletes: Ann Grandjean, Ed.D., Executive Director, Center for Human Nutrition, Omaha, Neb.

Nutrition and physical performance is very likely one of the oldest practiced subspecialties in nutrition. Vitamin supplementation by athletes has been an area of interest since the 1930s. The first reported use in the literature was for the 1939 Tour de France. Cyclists at the front of the pack said they performed better when they used vitamin supplements.

In 1982, data were collected on 69 Olympic athletes. Multivitamin/minerals were used by 92% of the athletes. Use of other supplements was dramatically lower—vitamins 38%, minerals 20%, multinutrient liquid/powder 10%, protein 6%, and yeast 2%.

For the 2000 Olympic summer games, the American had 602 team members. Dietary supplement data were collected for 592 athletes, which is currently undergoing analysis. Among the athletes who reported taking dietary supplements, 45% were female. Multivitamin/multiminerals were the most commonly consumed dietary supplement.

The reason for using sports supplements varies by age and skill level. The reasons given by high school students are for promoting growth, preventing illness, treating illness, enhancing performance, and muscle development. Male college athletes report using supplements to improve athletic performance, build muscle, increase energy/feel better, or prevent disease, their use was based on the recommendation of family member or friend, coach/trainer, or nutritionist/dietician. Among female college athletes, the top

reasons for use were; to prevent disease; to compensate for an inadequate diet; and to improve athletic performance. The most frequent reason given by Olympic athletes is to prevent illness. Getting sick before Olympic competition is a real threat to ending careers, hopes and dreams. Their use was based on the recommendation by family member or friend, coach/trainer, nutritionist/dietician, or by a physician/pharmacist.

What is the future of dietary supplements for performance enhancement? Dietary supplements have had an impact, but there will not be major changes ahead. Over the years, athletic performance in general tends to improve primarily because of changes in equipment and secondarily due to changes in training and conditioning. Use of banned substances will continue to be an issue. Removing ephedra from the dietary supplement market will not solve the problem. Changing regulations will not stop stimulant use; athletes will find a black market source if necessary. To change behavior, motivation for use must be understood.

Future research should include additional surveys, particularly to investigate reasons for use, to examine supplements that benefit the "weekend warrior" athletes, and to study differences between responders and nonresponders. Research should report the type of sporting event, level of athletic accomplishment, assessment measures used, and the degree of change needed for effect.

Discussion

Matt Strait (DEA): In Dr. Pope's surveys there was a subcategory of individuals who used these products for more than a year. Are there data that explain their fear of discontinuation or unwillingness to stop use?

Dr. Pope: Part of it is the lack of credibility of doctors among athletes. Doctors said testosterone didn't work and made themselves the laughing stock of the athletic community. Most users don't believe warnings from the official medical community.

Michelle Hoeferlin (Nestle): Are there any emerging trends in supplement use, general OTC use, or objectives that athletes are seeking.

Dr. Pope: Over the last three years, use seems fairly consistent. People currently using androstenedione, ephedra or creatine were using it two years ago. I don't see any big sellers on the horizon.

Dr. Grandjean: There are no big changes among Olympic and NCAA Division I athletes. However, the use of androstenedione has grown among people who work out in gyms.

Dr. Fourcroy (USADA): There are now reports of irreversible hypogonadal axis from long term anabolic steroid use. Dr. Pope, what was the source of anabolic steroids among gym users and what were the psychiatric consequences?

Dr. Pope: You're right, gonadal function does not always return to normal after anabolic steroid use. I am treating a 28-year-old patient who took anabolic steroids for a prolonged period and stopped use a year ago. He developed chronic depression but has responded well to antidepressants. His testosterone level is half the lower limit of normal range.

Christine Haller, M.D. (U. of Calif.): Is there an official Army policy for supplement use?

Dr. Lieberman: There are different policies for different services, all of which are similar to recommendations made by the American Dietetic Association.

Dr. Green: Would you comment on drug testing in the military.

Dr. Lieberman: Soldiers are required to undergo periodic random drug tests. If they are using illegal substances they are removed from the service and subject to criminal prosecution.

Dr. Tolliver (DEA): How important is labeling versus testimonials in magazines or on the Internet? Do you see more than oral dosage forms, such as sublinguals, buccal formulations, and sprays? Can you comment on the use of 5,alpha-andro-1-ine-3, 17-dione/diol?

Dr. Pope: A substantial number of consumers ignore the label. Many people take doses well in excess of label recommendations. There does not seem to be a lot of people using sprays or buccal formulations. The various forms of androstenedione, particularly combinations or cocktails, percolate through the gym world and will continue to do so.

Dr. Green: Consumers are clearly influenced by people other than health professionals. They get a lot of information from testimonials and what they hear in the gym. It's probably how they decide on dosage. Various types of formulations—nasal sprays, sublinguals, will probably increase in popularity.

Christina McIntyre (Virginia Tech): What has been the effect of NCAA bylaw 16.5.2.2?

Dr. Green: It has led athletes back to nutritionists and athletic trainers for nutrition advice.

Eugene Lambert (Covington & Burling): Dr. Lieberman, what do you know about the extent of supplement use among soldiers? Do they follow label recommendations?

Dr. Lieberman: The survey did not ask about adherence to label directions. Based on anecdotal conversations, in many cases instructions are ignored.

Gary Gottesman, M.D. (NIA): Is there data from the NCAA survey on how many people graduate or team success rate?

Dr. Green: There is a question about grade point average, but the analysis has not been completed.

Dr. Gottesman: Are there some schools that tend to use more supplements than others?

Dr. Green: Yes, and that's why the bylaw (16.5.2.2) was passed.

Ira Jacobs, Ph.D. (Defense and Civil Inst. of Environ. Med.): Are there any data on perceived effect of performance-enhancing products?

Dr. Pope: Our surveys asked people what they thought had happened. About half the creatine and androstenedione users felt they benefited. The majority of ephedrine users said they lost weight. All the anabolic steroid users reported benefit.

Dr. Grandjean: Benefit also depends on the level of athletic skill and whether the individual is a responder or nonresponder. For example, there is significant improvement with creatine among vegetarians.

Elements of Evidence Based Review: Mary Hardy, M.D., Cedars-Sinai Medical Center, Los Angeles

What kind of information is needed to make good clinical decisions and to guide patients? Information on risk, benefit cost, and, value of the therapy, along with placing the data into context.

Most herbal users do not indulge in monotherapy; 24% of users consume six or more herbs. Patients use multiple products, and the products often consist of formulas that contain multiple components. About 15% of pregnant women use one to eight herbs on a regular basis. About 50% of patients never reveal supplement use to their doctor, and 30% don't tell a pharmacist. Even in situations where patients receive a very strong message to stop or curtail herbal use, they still use these therapies. In a prospective study of 3,106 elective surgery patients, 22% were using herbs at the time of surgery. Most had been counseled to stop use of herbs, OTC medications and pharmaceutical drugs. At

least four or five herbs cause significant herb-drug interactions, and 21% of this group of herbal users was also taking prescription medications.

The public is concerned about safety; only 14% of consumers consider herbs very safe—a drop from 80% over two years. Many patients are concerned about side effects of herbs and are not getting the efficacy they expected. Consumers are also overwhelmed by too many choices at the store, and cost is a factor.

One of the major tools developed in the past 50 years is evidence- based medicine or the conscientious, explicit and judicious use of current best evidence in making decisions about patient treatment. The first randomized controlled trial was conducted in 1948 to test streptomycin for tuberculosis.

Evidence-based medicine is dependent on information. The first conventional place to find information is the biomedical literature using databases such as Medline. For complementary and alternative medicine (CAM) one of the biggest problems is finding the information. Approximately 50% of available literature is identified through a Medline search, but the number drops precipitously for CAM—17% for homeopathy, 30% for herbals such as ginkgo. There are 695 CAM journals worldwide, but Medline indexes just 10%. For ethnic based therapies, access to foreign journals is critically important. However, abstraction becomes very difficult for articles in languages other than English or European languages. Specialized searching strategies are necessary to identify literature that is not generally indexed.

Safety of herbal therapies is a major issue. There is an enormous amount of information on safety, but it is not well organized. Rich ethnobotanical and traditional use data are often available, along with data from animal studies, open-label trials, clinical trials, adverse event reports, post marketing surveillance and pharmacovigilence. For herb-drug interactions, 20% of the data comes from animal studies, which are difficult to generalize to a human population. Much of the information is theoretical, based on loose associations. There are some formal case reports, but very little clinical data and almost none from randomized controlled trials.

Consumers are not likely to report adverse events from herbal use. Based on several surveys, the percentage of adverse event reports for herbs was 4.3%. Of 19 reports, 15 were severe enough to stop herb use, and four required medical attention. None required hospitalization.

It is difficult to attribute causality using adverse event reports. It is difficult to find information on adverse effects due to the low sensitivity of MESH terms in searching databases. Information is often incomplete, such as the severity of the event, whether it was reversible, whether product use was related temporally to the event, or an alternate explanation was possible. Frequency of the event is important, but often impossible to calculate without knowing the denominator value.

The majority of clinical studies are woefully underpowered to detect rare events. To detect an event that occurs one in a thousand times would require 3,000 subjects. Most CAM studies have less than 150 subjects. Clinical trials have a limited duration, often not long enough to capture rare events. The study populations are highly selected, and the people at highest risk for adverse events are excluded form the trial. Study populations are not necessarily equivalent to the general population. Additionally, all observers—patients and clinical observers—are known to underreport adverse events. In spite of the limitations, randomized clinical trials are the only type of study able to attribute causality. Cohort studies generally are not constructed to determine causality. Case series or case reports cannot attribute causality unless the patient has been rechallenged.

A significant problem with CAM randomized controlled trials is the lack of specificity in the methods section. Often, the plant species is not described (i.e., genus and species names provided), method of product preparation is often missing, and the manner in which the product is obtained typically is not described. This lack of specificity is not tolerated for conventional clinical trials, and it should not be tolerated for CAM trials. Constructing adequate controls may also be difficult. Blinding may not be possible for some interventions.

The Cochran collaborative has begun to provide systematic reviews, and there is a control trials registry for CAM. In 1998, 3,500 randomized controlled trials had been identified. Nearly 40 reviews in CAM have been completed. There is some evidence of publication bias. Approximately 50% of randomized controlled trials presented at conferences are not published.

Stimulant and Thermogenic Ingredients
Moderator: Mary Hardy, M.D.

Acute Physical Performance Effects After Ingestion of Ephedrine or Ephedrine Combined with Caffeine: Ira Jacobs, Dr. Med. Sc., Chief Scientist, Defense and Civil Institute of Environmental Medicine, Toronto, Canada

A multi-centre international survey of more than 2,500 military special operations personnel showed that more than 60% used ergogenic aids. Research was conducted to clarify whether there was an empirical basis to contentions about the performance benefits of purported ergogenic aids, and to evaluate potential applications during military operations. At the time this research commenced there was no empirical evidence published documenting the effects on physical performance of combining caffeine with ephedrine. Thus, a systematic investigation was undertaken of the effects of these purported ergogenic aids on physical performance across a wide range of exercise intensities. The studies used pharmaceutical grade anhydrous caffeine and ephedrine hydrochloride.

It was clarified that the investigators do not advocate the use of caffeine or ephedrine by competitive athletes or anyone else because there may be health risks for individuals who have latent or known cardiovascular disease. However their research was directed at clarifying the potential performance benefits for individuals who are expected to be very fit and healthy or they would not be in the combat units to which they belong. The ethical considerations of "cheating" that are such a significant issue when it comes to the use of nutritional supplements by athletes have no relevance to applications for military personnel.

The first randomized controlled trial was a cycle ergometer test to exhaustion at a relatively high intensity of physical exertion—85% of maximum oxygen consumption (VO_2 max). Participants received 5 milligrams (mg) per kilogram (kg) bodyweight of caffeine, 1 mg/kg ephedrine, a combination of caffeine and ephedrine, or placebo (Metamucil). The time to exhaustion with placebo was 12.5 minutes. Caffeine or ephedrine extended the time to about 14 minutes, but the combination extended the time to 17.5 minutes. Such a magnitude of improvement in physical performance of this nature is normally only achieved after several weeks, if not months of physical training.

Additional trials were run with 20 subjects to gather information on ephedrine's effect on blood pressure and heart rate over 48 hours. The subjects ingested placebo, 375 mg caffeine, 75 mg ephedrine, or caffeine plus ephedrine. Ingesting a combination of caffeine and ephedrine did not change the blood clearance rates compared to ingesting caffeine or ephedrine alone. In all cases the plasma concentration peaked 1.5 to 2.5 hours after ingestion. All treatments increased systolic blood pressure when compared with a placebo trial. One hour after ingestion, blood pressure was significantly higher with ephedrine plus caffeine than for ephedrine alone. By three hours, the absolute systolic blood pressure for caffeine plus ephedrine was equal to that of ephedrine alone and both were greater than caffeine. By five hours, the effects had begun to dissipate. By eight hours, there was no difference from placebo. Heart rate response was similar for ephedrine plus caffeine and ephedrine alone. Both were significantly higher than caffeine alone and placebo. The effect was maintained up to 24 hours after ingestion.

The dose of the combination intervention (equivalent to 5 mg/kg caffeine and 1 mg/kg ephedrine) caused nausea in 20-25% of subjects when they were exercising. Several trials examined lowered doses of ephedrine and caffeine. A lower dose caffeine (4 mg/kg) and ephedrine (0.8 mg/kg) also increased time to exhaustion during high intensity aerobic exercise (from 16 min. during a control trial to 26 min. during the caffeine + ephedrine trial). There was no report of nausea and the ergogenic effects were maintained with the lower doses.

The next step was field-testing to demonstrate efficacy in a military setting. The test was a standard army fitness test, a 3.2-kilometer (km) "warrior run" in "light fighting order" (helmet, rifle, light backpack, wearing combat boots)

on two consecutive days. Ten subjects randomly received placebo on the first day and caffeine plus ephedrine on the second day or the reverse order; on another occasion the sequence of the intervention was reversed. Compared to placebo, the run time was reduced by about one minute with caffeine plus ephedrine. While the improvement was significant, it was a much lower relative magnitude than the improvement observed under laboratory conditions.

Another set of experiments examined the effect of caffeine and ephedrine on anaerobic power using the Wingate test. In this test, the subject sprints as hard as possible for 45 seconds on a cycle ergometer. Power output is recorded throughout the time period and as fatigue occurs the power output decreases progressively during a typical test. Sixteen males participated in a repeated-measures design trial where they received each of the following treatments: caffeine (5 mg/kg), ephedrine (1 mg/kg), a combination of caffeine plus ephedrine, or placebo. There was a statistically significant increase in the power output during the first 10 seconds of the Wingate test with ephedrine alone. However, the improvement was deemed to not be large enough to warrant further investigation.
Whereas the Wingate test was used to evaluate anaerobic power, the maximal accumulated oxygen deficit test was used to evaluate anaerobic capacity. Time to exhaustion was measured at a power output equivalent of 125% VO_2 max. Eight males received each of the treatments described above. The caffeine alone and combination of caffeine plus ephedrine had a statistically significant, but small, effect in increasing time to exhaustion during the anaerobic deficit test.

The effect of caffeine and ephedrine on muscle endurance during weight lifting exercise was also investigated. Thirteen males each ingested the following treatments: 4 mg/kg caffeine, 0.8 mg/kg ephedrine, caffeine plus ephedrine or placebo. For each subject, the one repetition maximum (RM) was established (i.e. the maximum weight that could be lifted once). The performance test consisted of three cycles of supine leg press at 80% 1RM until exhaustion, followed by bench press at 70% 1RM until exhaustion. For the leg press, only the first set of repetitions was affected, but the improvement was somewhat startling.
The mean number of repetitions for leg press was significantly higher after using caffeine plus ephedrine (19.8) or ephedrine alone (17.4) compared with placebo (14.0). It would take several weeks of training to accomplish this magnitude of improvement without the ingestion of the caffeine and ephedrine For the bench press, again only the first set of repetitions was significantly affected, and the improvement was smaller than for the leg press. The mean number of repetitions was 14.3 with caffeine plus ephedrine, 13.3 with ephedrine alone, 12.4 with caffeine alone, and 12.7 with placebo.

Because ephedrine and caffeine elevate metabolic heat production, there is a concern that this combination could impair tolerance time during exercise in the heat. To explore this possibility, 10 subjects exercised at 40°C, 30%

relative humidity for three hours, or until rectal temperature reached 39.3$_{o}$C or heart rate was 95% of maximal heart rate for three consecutive minutes. The oxygen uptake during the heat stress test was higher only for the caffeine (5 mg/kg) plus ephedrine (1 mg/kg) combination. Tolerance time and rectal temperature were not affected. The mean skin temperature was lower with the caffeine plus ephedrine combination, which explains why rectal temperature did not increase. The subjects were likely able to evaporate more sweat to balance the extra metabolic heat production. Although heat tolerance was not impaired in this experiment, the results suggest that the predisposition to heat illness may be a serious concern if exertion occurs in an environment where the ability to remove body heat is impaired, such as humid climates or when protective clothing is worn.

In summary, caffeine and ephedrine is considered to be an effective acute-use ergogenic aid that may be of benefit for certain types of military operations such as those requiring increased physical work capacity very quickly. Pharmaceutical grade ephedrine hydrochloride was used in these studies, and its
bioequivalence to nutritional supplements containing ephedrine alkaloids is unknown. Future research with ephedrine should examine health risks, optimal dosing, bioequivalence with nutritional supplements, stability of nutritional supplements, and possible drug interactions.

Acute Metabolic Responses to Synephrine-Caffeine Compared to Ephedrine-Caffeine: Luke Bucci, Ph.D.: Vice President of Research, Weider Nutrition International, Salt Lake City

Ephedra works by several mechanisms. It directly stimulates adrenergic receptors and enhances the body's production or output of epinephrine and norepinephrine. The user gets an adrenaline rush, or the equivalent of that feeling. For people who chronically use ephedra products, they like that rush and the mental effect. Previous studies for weight loss show that 40 mg per dose increases heart rate 7 beats per minute and systolic blood pressure by up to 5 millimeters (mm) of mercury (Hg). With chronic use, the cardiovascular response diminishes after two to four weeks. With a 24 mg-dose, heart rate increased by 4-6 beats per minute and systolic blood pressure increased by 2 mm Hg.

Other stimulants of interest are synephrine, green tea, guarana, quercetin, and yohimbe. Synephrine, from the plant *Citrus aurantium*, is a direct-acting alpha$_1$-adrenergic agonist and a weak beta-adrenergic agonist. The naturally occurring herb contains parasynephrine, while OTC products such as neosynephrine contain metasynephrine. The typical dose in traditional Chinese medicine (TCM) is 10 mg. It causes no significant increase in heart rate, blood pressure or respiratory exchange ratio (RER). It is generally recognized as safe (GRAS), based on its use as bitter citrus flavoring. Due to its bitter flavor, synephrine is usually combined with carbohydrates and protein.
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Green tea contains about 250 mg of caffeine per serving. It is a natural source of caffeine, and decaffeinated green tea can be used in placebo-controlled trials. The (-)-epigallocatechin-3-gallate (EGCG) polyphenolic component in green tea works synergistically with caffeine enhancing thermogenesis. Green tea also works synergistically with ephedrine. It inhibits phosphodiesterase at the adenosine receptor, which are the normal feedback mechanisms for epinephrine and norepinephrine.

Guarana is another herbal source of caffeine, containing about 50 mg per serving. It also inhibits phosphodiesterase and adenosine and works synergistically with ephedrine for metabolic thermogenic effects.

Yohimbe, from the plant *Pausinystalia johimbe*, contains yohimbine—an indolakylamine (12 mg per serving in standardized extracts). Yohimbine is an alpha$_2$-adrenergic receptor antagonist and may inhibit feedback regulation of epinephrine and norepinephrine. Human obesity studies using yohimbine as a single agent produced mixed results but appears safe up to 43 mg.

Quercetin is a flavonoid antioxidant commonly found in foods such as onions, wine, and apples. *In vitro* evidence suggests that it inhibits prostaglandin A1 for three to six hours. Potentially, quercetin could inhibit the effect of prostaglandins on the feedback inhibition of epinephrine and norepinephrine. It is an aspirin alternative for combinations with ephedrine and caffeine.

A study was conducted to compare the effect of synephrine-caffeine combinations with ephedrine-caffeine. The randomized, double blind, placebo-controlled crossover study involved 20 subjects (10 male, 10 female), 18-37 years of age. The subjects had a regular and consistent pattern of exercise three to five times per week and were screened for medical problems (e.g., hypertension). The study measured resting metabolic rate, so no exercise was involved. The subjects watched a bland video for three hours.

The resting metabolic rate or caloric expenditure was increased significantly by ephedrine-caffeine, but increased only at the last time point with synephrine-caffeine. The same pattern was observed with the respiratory exchange ratio. Compared with placebo, body core temperature significantly increased by 0.3-0.5^{o}C with both ephedrine and synephrine. Heart rate was increased 12% by ephedrine, but synephrine did not differ from placebo. Ephedrine increased mean arterial blood pressure by 6-8 mm Hg, but the effect with synephrine was smaller (3-5 mm Hg). A mood survey questionnaire showed that tension was increased with placebo, synephrine, and ephedrine. A feeling of vigor was improved in the synephrine group only. There were no differences between treatments for anger, depression or fatigue.

In summary, the resting metabolic rate increased significantly with ephedrine-caffeine, but not with synephrine-caffeine. More calories are burned with ephedrine plus caffeine. If the data are extrapolated to 24 hours, then the synephrine-caffeine also burned more calories than placebo. The respiratory exchange ratio is significantly lower with

ephedrine-caffeine, which means more fat is burned. The body core temperature was increased equivalently with each formulation (but not placebo), so there was thermogenic action. The ephedrine-caffeine combination increased heart rate by 12%; synephrine-caffeine did not change heart rate significantly. Ephedrine-caffeine elevated mean arterial blood pressure by 6-8 mm Hg; the effect by synephrine-caffeine was smaller (3-5 mm Hg).

In conclusion, a commercial ephedrine-caffeine product significantly increased metabolic rate, fat burning thermogenesis, heart rate, and blood pressure for three hours after ingestion, which is consistent with previous research. A synephrine-caffeine formulation significantly increased metabolic rate, thermogenesis, blood pressure and feeling of vigor for three hours after ingestion. The synephrine-caffeine formulation offered similar performance as ephedrine-caffeine products but had smaller cardiovascular effects. Synephrine-caffeine is a viable alternative to ephedrine-caffeine, but has enjoyed far less commercial success than ephedrine-caffeine products.

Hormone Products and Analytical Challenges
Moderator: Robert Wolfe, PhD

Analysis of Over-the-Counter Steroid Preparations: Gary Green, M.D., Department of Family Medicine, University of California at Los Angeles (UCLA)

A study was conducted recently by the UCLA Olympic Analytical Laboratory (*Clinical Journal of Sports Medicine*, 2001, 11: 254-259) to determine whether OTC steroid supplements sold in the Los Angeles area conform to the labeling requirements of DSHEA. According to DSHEA, a dietary supplement is considered misbranded if the label fails to list the identity and strength of the ingredients in the product.

For the study, 12 brands of dietary supplements were randomly selected from retail stores in the Los Angeles area and were analyzed by high-pressure liquid chromatography (HPLC). Only one of the 12 products was properly labeled. Brand 1 failed to list androstenedione as an ingredient; brand 2 listed 250 mg of androstenedione, but it contained 166 mg plus 10 mg of testosterone (not listed as an ingredient). Brand 3, which listed 100 mg androstenediol, contained 78 mg. Brands 4 and 5 had about half the dose purported on the label, while brand 6 was somewhat closer to the stated dose. The label on brand 7 matched the contents of the product. Brand 8 had 35 mg of androstenedione, but listed 50 mg. Brand 9 listed six steroids on its label; three of them were not detected and the others were found in relatively small quantities. Brand 10 did not contain one of the steroids listed on the label. Brand 11 contained about 70% of some ingredients. Brand 12 listed 50 mg androstenediol on the label, but actually contained 88 mg. In summary, nearly all the OTC steroids tested failed to conform to DSHEA labeling requirements.

Kamber *et al.* published a study examining nutritional supplements as a source of positive doping cases (*International Journal of Sport Nutrition and Exercise Metabolism*, 2001,

11: 258-263). They purchased 75 products from the Internet, including 17 prohormones (e.g., androstenedione, 19-norandrostenedione, DHEA), and analyzed the products for labeled content. Seven of the 17 (41%) prohormone products contained substances not listed on the label. In three brands, testosterone was detected. Several products contained steroids less than the stated amount or not present at all. All the mislabeled brands were from the United States and did not conform with DSHEA requirements.

Microcontamination is another problem, and Catlin *et al*. conducted a study to investigate trace contamination of OTC androstenedione and positive urine test results for a nandrolone metabolite (*JAMA*, 2000, 284: 2618-2621). A previous study had demonstrated that trace nandrolone metabolites were found in subjects given "pure" 100 mg or 300 mg androstenedione. Catlin *et al*. analyzed 100 mg commercial androstenedione capsules by liquid chromatography-mass spectrometry-mass spectrometry (LC-MS-MS) at a level of 0.001 purity. The product was found to contain an average of 7.6 micrograms (mcg) 19-norandrostenedione per capsule. To examine the possibility of positive doping results with such small amounts of 19-norandrostenedione, four male subjects were given 10 mcg of 19-norandrostenedione. Urine samples were collected over eight hours, and from zero to two hours there was a mean excretion rate of 17.2 nanograms (ng) per milliliter (mL) 19-norandrosterone (19-NA) and 5.2 ng/mL 19-noretiocholanolone (19-NE). All levels would have exceeded the IOC threshold of 2ng/mL for nandrolone metabolites.

None of these results should be surprising. In 1999, *Consumer Reports* tested 12 brands of echinacea and ginkgo and found lower levels than listed on the label. The problem is not limited to prohormones.

In conclusion, most U.S. purchased OTC steroids do not conform to DSHEA; the labels do not reflect the actual contents of the product. Studies using OTC steroids need to be analyzed carefully. OTC steroids present a major challenge for sports drug testing.

Discussion

Tim Maher, Ph.D. (Mass. College of Pharm. and Health Sciences): Is androstenedione contamination found in all samples? Are there samples with no contamination from norandrostenedione? Does contamination have to do with synthesis? For example, in China androstenedione is made by microbial processes.

Dr. Green: We have only studied a few samples, but 19-norandrostenedione is present. The question is a good one—is the contamination a result of the manufacturing process or was it present in the raw material? It appears that it might be a result of the synthesis process.

Jonathan Geiger, Ph.D. (U. of Manitoba): I'd like to reemphasize the importance of clinical testing to know what the product does in the human body. This level of testing is necessary to assure athletes that they won't test positive.

Dr. Green: It's a good point. Manufacturers following GMPs would find the products "pure" at 0.1% purity, but the IOC testing is more sensitive and detects much smaller amounts. It's not enough to chemically analyze the product in the laboratory; it has be ingested by athletes and analyzed.

Potential Beneficial Effects of DHEA in Humans: Wendy Kohrt, Ph.D., Professor of Medicine, Division of Geriatric Medicine, University of Colorado Health Science Center, Denver

DHEA (and its sulfur form, DHEA-S) is the most abundant steroid in human plasma. It is widely distributed in the body, and the highest concentrations are found in the brain. DHEA and DHEA-S are converted to androstenedione, then onto testosterone. Testosterone is then metabolized to dihydrotestosterone (DHT) or estradiol. DHEA-S serves as the precursor to about 50% of the androgens in adult men, and perhaps as much as 75% of active estrogens in premenopausal women and nearly all the estrogens in postmenopausal women. Typically, DHEA-S is measured in studies, as its concentration is much higher in serum than DHEA.

In humans, about 95% of secreted DHEA comes from the adrenal glands. In most animals, other than nonhuman primates, very little DHEA comes from the adrenals. Additionally, DHEA/DHEA-S concentrations are much higher in humans than animals. Unfortunately, this means there is not a good animal model to study DHEA. As animal data are presented, remember that the relevance to humans is unknown.

DHEA and DHEA-S are some of the best biological markers for aging. Levels begin to rise roughly at the time adrenal glands mature, generally, between ages 10-12 years. DHEA/DHEA-S levels usually peak about age 25, followed by a steady and precipitous decline. By age 65-75, circulating levels may be 20-30% of those from youthful years.

In rodents, DHEA is a potent anti-obesity agent. It is effective in minimizing excess fat accumulation in animal strains genetically predisposed to obesity. It is also effective when given after the accumulation of fat; it is effective in reducing fat mass. DHEA is also a potent anti-diabetogenic agent and enhances the glucoregulatory actions of insulin. In rabbits, it is also a fairly potent anti-atherogenic agent by diminishing atherosclerotic plaque.

A 1988 study in humans (*Journal of Clinical Endocrinology and Metabolism*, 1988, 66: 57-61) tested the effect of 1600 mg/day DHEA for 28 days in 10 men, aged 22-25 years. No side effects were noted, and androstenedione levels increased. There was a nonsignificant trend for an increase in free testosterone, and no significant change in estrogens. There was no significant change in total body mass, but the DHEA-treated

group had a 5 kg-increase in lean mass, countered by a decrease in fat mass. This decrease in fat mass over a four-week period would require an estimated 500 kilocalorie (Kcal) energy deficit per day, or an increase in energy expenditure. No effect on insulin action was observed in the study.

Using the same DHEA intervention, a follow-up study (*International Journal of Obesity*, 1990, 14: 457-463) examined the effect of DHEA in six obese men (body mass index = 28-38 kg/m^2). There was no change in body composition.

The effect of DHEA on resistance training in young men was also explored. Brown *et al.* (*Journal of Applied Physiology*, 1999, 87: 2274-2283) randomized 19 men (aged 19-29 years) to placebo or 150 mg DHEA per day following a dosing regimen of two weeks on, one week off, for eight weeks. They found a small but significant increase in androstenedione over the period of the study but no changes in total or free testosterone. The estrogen profile also remained unchanged, measuring estrone, estradiol, and estriol. There was a tendency for the DHEA-treated group to increase lean mass by about 30% and decrease fat mass. An estimated 50 subjects would be needed to demonstrate significant changes in body composition.

A number of studies have examined the effects of DHEA in older men and women. Villareal *et al.* (*Clinical Endocrinology*, 2000, 53: 561-568) conducted a three-month open-label study of oral DHEA replacement (50 mg/day) with 18 (10 women, 8 men) elderly subjects (aged 64-82 years). All the subjects had DHEA levels less than 20% of values in young people. The 50-mg dose brought the levels up to those of younger individuals. Encouraged by the results at the end of three months, the subjects agreed to stay on treatment for an additional three months. At the end of the six-month treatment period, there was a significant increase in lean mass that tended to be larger in women. There was also a significant decrease in fat mass—almost 1.5 kg over six months. Additionally, whole body and lumbar spine bone mineral density increased significantly; increases tended to be larger in men. The 3% increase in lumbar spine bone mineral density is equivalent to the response to estrogen among postmenopausal women. Total testosterone increased significantly in men and more than doubled in women; no changes in estrogen measures were observed. Insulin-like growth factor I (IGF-1) also increased significantly, which has been a consistent finding in many studies. IGF-1 is considered an anabolic agent in many animal models, as it stimulates muscle hypertrophy and bone hypertrophy.

In summary, there have been relatively few good controlled trials of DHEA supplementation or replacement in humans. The data currently available do not provide any evidence that DHEA enhances performance—either athletic performance in younger individuals or functional performance in older adults. There are intriguing data that suggest that DHEA supplementation in older adults with low DHEA levels could increase lean mass and decrease fat mass. Additional controlled trials are required to better understand DHEA's mechanism of action and sex- and age-specific responses to DHEA

supplementation. DHEA should be investigated as a potential therapy for female athletes with amenorrhea, disordered eating, and at high risk for osteoporosis.

Discussion

Robert Wolfe, Ph.D. (U of Texas): Do you think that DHEA inhibits the endogenous secretion of DHEA? If endogenous secretion is stopped, what happens when supplementation ceases?

Dr. Kohrt: I don't know of any studies that have evaluated that question. The response from 1600-mg doses does suggest that endogenous production may be shut down partially, but I'm not aware of any evidence for that.

Dr. Wolfe: Children who receive growth hormone go through a period of deficiency when growth hormone treatment is stopped. In these studies with hormone supplementation, it is worthwhile to look at the response when supplementation is stopped.

Dr. Bucci (Weider): We have done a case study of DHEA for five years, following serum hormone levels over that time period. When we start-stop, the levels return to the previous baseline. There may be an increase of metabolic pathways for disposal.

Muscle Building Nutritional Supplements—Is Androstenedione an Anabolic Steroid?
Greg Brown, M.S., Exercise Biochemistry Laboratory, Department of Health and Human Performance, Iowa State University, Ames

Androstenedione is purported to have its anabolic effects through conversion to testosterone. In 1962, Mahesh and Greenblatt found that 100 mg of androstenedione given to two women caused a significant (~ fivefold) increase in serum androstenedione and testosterone.

To determine whether acute androstenedione intake alters serum hormone concentrations in young men, King *et al*. randomized 10 untrained males to placebo or 100 mg androstenedione. Ingesting 100 mg androstenedione increased serum androstenedione concentrations 60 minutes after intake, and those concentrations remained elevated for six hours. Serum total and free testosterone concentrations did not differ between placebo and androstenedione groups.

The next question was whether chronic androstenedione intake enhanced gains in muscle size and strength during resistance training. Twenty untrained males (average age 23 years) were randomized to receive either placebo or 100 mg androstenedione three times a day for eight weeks. The subjects also participated in full body resistance training three days a week (80-85% 1RM). The subjects ingested the androstenedione or placebo in a two-week on, one-week off supplementation regimen. Serum hormones were measured

after each two-week supplementation period. Androstenedione had no effect on muscle strength, type II (muscle) fiber area, or lean body mass. Ingesting androstenedione did not change serum total or free testosterone at any time during the eight weeks of supplementation. Androstenedione supplementation did cause a significant decrease in high-density lipoprotein (HDL) cholesterol and significant increases in serum esterone and estradiol concentrations.

Other studies have similar findings. Rasmussen *et al*. (*Journal of Clinical Endocrinology and* Metabolism, 2000, 85(1): 55-59) found that 100 mg androstenedione supplementation did not increase serum testosterone concentration and muscle protein synthesis was not changed. A study by Leder *et al*. (JAMA, 2000, 283(6): 779-782) demonstrated that 100 mg androstenedione does not change serum testosterone concentrations, but a single dose of 300 mg androstenedione does cause a significant increase in serum testosterone. The significance of this increase appears to be due to two subjects who experienced tremendous increases in testosterone.

Serum testosterone concentrations did not change in a study of men between the ages of 30 and 60 years supplemented with 100 mg androstenedione three times a day. The estrogen response was similar to that found previously with young men. Androstenedione supplementation did increase serum free testosterone by about 40% in 30-, 40- and 50-year old men. It is not clear whether this increase would cause a physiological effect or enhance performance. Androstenedione supplementation also increased dihydrotestosterone (DHT) concentration about 80%.

In summary, chronic androstenedione supplementation of 100 mg three times a day did not enhance serum testosterone, muscle protein synthesis, or increase muscle mass and strength associated with resistance training. Chronic supplementation did increase serum DHT and serum estrogens, and decreased serum HDL-cholesterol. Lowered HDL-cholesterol can increase cardiovascular disease risk by 10-15%. Elevated estrogen levels have been associated with pancreatic cancer and gynecomastia. Elevated androstenedione levels are associated with prostate cancer, pancreatic cancer, and neural/behavioral changes. Elevated DHT has been linked to benign prostate hypertrophy and baldness.

Androstenedione has also been used in stacking formulas with herbal extracts. Various herbal extracts purport to inhibit enzymes related to DHT metabolism or inhibit estrogen formation, thereby changing the hormonal response to androstenedione supplementation. A study of androstenedione plus various herbal extracts (e.g. saw palmetto, chrysin, Tribulus terristris) did not prevent the formation of estrogens, increase serum testosterone levels, inhibit DHT formation, or enhance resistance training.

Future research should address the effect of larger doses of androstenedione, long-term health effects of chronic androstenedione supplementation, age-specific responses, and the effect of alternate modes of delivery. To the latter point, a preliminary study with a

sublingual dose of 20 mg androstenediol caused a significant increase in serum testosterone concentration.

Discussion

Dr. Fourcroy (USADA): There is no evidence that saw palmetto has any effect of 5-alpha-reductase or DHT. Do you know what Mark McGwire was taking and how much?

Mr. Brown: He was taking androstenedione. I don't believe the brand or dose was ever made publicly available.

Dr. Wolfe: Based on the results Mr. Brown presented, it looks like Mark McGwire's home run record may stand as testimony to a placebo effect.
The close relation between DHEA and androstenedione is obvious from the pathways that were shown, but data on opposing effects appear to be present. For example, DHEA showed a decrease in low-density lipoprotein (LDL) cholesterol, whereas androstenedione showed a decrease in HDL cholesterol. Any speculation on the differing effects?

Dr. Kohrt: There were many other variables. For example, in the DHEA study with older individuals, the subjects had low DHEA levels. The subjects in the androstenedione studies versus those in the DHEA studies also probably had very different lipid profiles.

Dr. Bucci (Weider): Dr. Green, do you know the number of androstenedione products that were tested?

Dr. Green: It was about half the products we could find commercially available in the Los Angeles area.

Dr. Bucci; Mr. Brown, did your subjects with elevated estrogen levels exceed the upper limit of the reference range for estrogen?

Mr. Brown: In the men, the estrogen levels ranged from mid-normal to high-normal values.

Dr. Yannicelli (Pharmavite): Do you think that DHEA might be used as part of an arsenal in treating osteoporosis in postmenopausal women?

Dr. Kohrt: There are no data from controlled trials of the effects of DHEA replacement in postmenopausal women. There are, however, two ongoing trials in this country—one in my lab and one in California. I think both trials are in the second year, so we should know more in about two years.

Dr. Yannicelli: Mr. Brown, in the study of androstenedione in men 30-60 years old, did you look at muscle strength as well? Has anyone titrated the dose of androstenedione to obtain a certain plasma concentration of testosterone and then look at muscle strength?

Mr. Brown: Muscle strength was not assessed in the trial with men 30-60 years of age. Regarding the dose-response effect, single 100-mg and 200-mg doses had no effect on testosterone. The single 300-mg dose did show a significant increase in testosterone. A study presented at the American College of Sports Medicine (ACSM) last year indicated that testosterone must increase 100% to affect muscle strength.

Dr. Tolliver (DEA): Mr. Brown, in your studies do you have a positive control? Have you taken a substance that is definitely known to be anabolic and looked at effects on muscle strength and mass?

Mr. Brown: We did not use a positive control. I think there is a study that used sublingual administration of testosterone, and there was a change in muscle strength.

Dr. Wolfe: We looked at muscle protein synthesis rate in response to injection with androstenedione and found no effect. With testosterone and oxandrolone, there was a significant effect on muscle protein synthesis, which over a month carried through to increase strength and function.

Dr. Tolliver: Wasn't the testosterone given by a route other than oral administration?

Dr. Wolfe: Yes, but the oxandrolone was given orally.

Dr. Tolliver: Oxandrolone is orally active and gets around the hepatic first-pass effect. It would be nice to see a study with a positive control, such as testosterone, given orally to compare substances that experience the hepatic first-pass effect.

Dr. Green: The limitations in the studies by Dr. King and Mr. Brown included using untrained subjects, and 1RM is not a good model for assessing strength. Also the doses were too small. One study has showed that supraphysiologic doses of a known anabolic agent, testosterone, were required to demonstrate significant increases in strength. Small doses of androstenedione are not going to show any significant effect.

Dr. Wolfe: The implication is that the methods used were insensitive to detecting change. That is not the case. With other hormones, such as IGF-1 and a variety of anabolic hormones, we have demonstrated an effect. The conventional dose of androstenedione does not have an effect.

Dr. Green: Why wouldn't you use trained individuals?

Mr. Brown: It is extremely challenging to find a group of trained individuals who are not taking supplements and who are at similar levels of training.

Dr. Green: Well, research is challenging.

Dr. Wolfe: Anabolic effects can be shown in the absence of trained individuals, such as a study of elderly subjects given testosterone once every two weeks to restore normal levels. There was no exercise program and muscle mass and strength increased.

Dr. Green: That's comparing apples and oranges. If you're investigating the effect of androstenedione in athletes, you need trained subjects.

Mel Williams, Ph.D. (Old Dominion U.): Given the potential health risks of androstenedione and possibly DHEA, is there any ethical consideration of doing research in humans?

Dr. Kohrt: Thus far, the adverse events reported in response to DHEA supplementation in young people or replacement in older people has been minimal. In older women, there is a decrease in HDL cholesterol that seems to be a fixed amount of 4-5 mg per deciliter (dL). It occurs early—in the first month or so—and does not continue to decline with further treatment. The masculinizing effects in women—increased facial hair and acne—seem to be the most frequently reported. Out of 100-200 subjects reported in various studies, there is probably less than handful of those reports. The ongoing studies will look for possible adverse outcomes, such as benign prostatic hypertrophy and prostate-specific antigen (PSA) changes in men and effects on the endometrium and breast cancer risk in women.

Mr. Brown: With androstenedione, the human subjects review board has required a lot of oversight. Patients were dropped from the study if certain indicators (e.g., blood chemistry values) reached an unhealthy level.

Dr. Williams: Have you done any research to determine if some of the effects are reversible after stopping supplementation?

Mr. Brown: We have not looked at that, and to my knowledge, no one else has.

Dr. Tolliver: Is there any research looking at the effect of androstenedione in women? Could androstenedione or DHEA reverse hypogonadism in men?

Mr. Brown: There is no published research that has examined androstenedione effects in women. We have just completed some pilot experiments on an acute hormonal response to androstenedione in women. Eight college-age women with normal menstrual status took 100-300 mg androstenedione. There was considerable increase in testosterone. There was also a study of DHEA for women with adrenal insufficiency, and they responded quite well.

Dr. Kohrt: A group at Massachusetts General has just finished some work in women; I understand it will be published in the next year.

Mark Thomas (Nat. Inst. of Allergy and Infectious Disease): There have been an increasing number of teens and even prepubescent males utilizing androstenedione. Have you found any additional side effects specific to these groups of people?

Mr. Brown: There is no research that I am aware of that addresses prepubescent males.

Creatine and Other Metabolic Intermediates
Moderator: Karl Friedl, Ph.D.

Creatine Supplementation in the 21st Century—What We Know and What We Don't Know: Jeff Volek, Ph.D., Human Performance Laboratory, Department of Kinesiology, University of Connecticut, Storrs

In the past few years, several surveys have examined the prevalence of creatine use among athletes. The data show that creatine is consumed by 16% of high school athletes, 14% of high school male athletes, 41-48 % of male and 4% of female Division I athletes, and 45% of Norwegian power athletes. Creatine sales have increased from $30 million in 1995 to $180 million in 1998.

Creatine is not a vitamin or mineral, and it is not a steroid. It is not an amino acid, peptide or protein. Creatine is a nonessential compound made in the body from amino acids, but does not contain any peptide bonds. Creatine is also obtained in the diet, primarily from meat. The body produces enough creatine, as vegetarians have normal levels. The recommended maintenance dose of creatine—2-3 grams (g) a day—is just slightly higher than levels obtained by diet. Creatine is not taken in pharmacological doses.

The main function of creatine is as a temporary energy buffer. It is an energy substrate that is used to rephosphorylate adenosine triphosphate (ATP) during high intensity exercise. The majority of creatine research in the 1990s concentrated on exercise performance in many different modalities, such as cycling, running, swimming, and endurance protocols. The majority of studies have shown an ergogenic effect on

performance during short duration, high intensity types of exercise. Typically, it provides a small improvement of 5-10%.

There are several reasons why some studies do not show a favorable effect from creatine supplementation. Many of the studies have inadequate statistical power. There is also considerable variability in muscle creatine concentrations in the normal population. It has been demonstrated several times that individuals with higher muscle creatine levels do not exhibit the same increase in muscle creatine using a standard loading protocol. Additionally, performance tests can be unreliable. If there is 15% variation in the measure, it may not be possible to detect a 5-10% improvement. Sometimes the wrong performance test is selected, such as testing subject isometrically in a dynamic resistance-training program.

Several studies have examined the effect of creatine on body composition. In acute studies (<7 days), body mass and total body water increase. The technology is not perfected, however, to know whether the water gain is intracellular or extracellular. Fat mass really does not change much. There is little convincing data that creatine affects lipid metabolism or lipolysis. The majority of chronic studies (>7 days) involved resistance training in conjunction with creatine supplementation. These studies have shown an augmented increase in body mass, lean body mass, and muscle fiber hypertrophy. Fat mass was not affected. Total body water tends to increase on an absolute scale, but relative to the increase in body mass it does not change much.

Several studies have examined metabolic changes with creatine supplementation. Skeletal muscle creatine content increases about 20-25% with a typical loading dose of creatine or smaller doses over a longer period of time. There appears to be a synergistic effect of creatine supplementation when combined with exercise or elevated insulin levels. This is typically achieved through a combination of carbohydrate ingestion and creatine. Some recent work with a three-day glycogen depletion/repletion protocol showed that muscle with increased creatine levels could store more glycogen. This indicates an interaction between phosphocreatine metabolism and carbohydrate metabolism in terms of glycogen storage.

There are mixed results on how creatine affects glycolysis in muscle and blood lactate accumulation—some studies show reductions; others enhanced blood lactate production, while some have no change. The conflicting results may be due to the lack of standardizing exercise intensity from pre- to post-testing. Creatine appears to have no effect on whole body protein synthesis, but instead a reduction in whole body protein catabolism, as measured by reduction in the appearance of leucine. Creatine also seems to increase the resynthesis of phosphocreatine during recovery from exercise, which can be a potential mechanism for the ergogenic effect observed during repeated bouts of exercise. Some recent work indicates an increase in glucose transporter isoform 4 (GLUT 4) concentrations in muscle during rehabilitation from disuse atrophy. Potentially, creatine could affect insulin sensitivity and serve as a treatment for diabetes.

In terms of cardiovascular effects, several studies show no effect on resting or exercise blood pressure, heart rate, or oxygen consumption. There is some evidence, based on a couple studies, that creatine supplementation decreases cholesterol and triglycerides, but these results have not been replicated. Hormonally, creatine has no effect on testosterone, cortisol, renin, angiotensin, or insulin. One study demonstrated an increase in growth hormone, but it has not been replicated. A slight increase in aldosterone has been observed with creatine supplementation.

The primary mechanism for creatine is related to energy dynamics. Increased free and phosphorylated creatine increases the storage of energy substrate, so one can exercise at a higher intensity for a longer period of time. Creatine provides a better match between ATP supply and demand. Other viable mechanisms involve cell swelling. Protein metabolism may be affected by changing the water content of the cell. A few studies have demonstrated a reduction in muscle relaxation time that could account for enhanced performance.

Abnormal side effects have not been reported in the literature. Extensive studies on creatine supplementation and kidney function in healthy subjects showed no adverse effects. Occasional gastrointestinal (GI) distress has been reported with large doses of creatine, but with lower doses distress occurs at the same frequency as placebo.

Few studies of creatine have been conducted with adolescent or elderly populations. One study with 17-year old swimmers showed a favorable effect, but there really are no data for adolescents. Elderly subjects have been used in a few studies, with mixed results. Creatine could be a potential therapeutic agent, especially with the loss in muscle mass and functional ability as people age. Creatine could be a valuable supplement for the elderly. The studies in women indicate that they respond similarly to men. Only one or two studies have been conducted with vegetarians, which show similar increases in performance and lean body mass as healthy omnivore populations.

An interesting turn in research is the effect of creatine in different disease states, especially patients with atrophy or muscle fatigue secondary to impaired energy production. Creatine may have potential therapeutic use. Animal models of Parkinson's disease have shown that creatine can prevent dopamine reductions. Other animal studies have demonstrated neuroprotective effects from hypoxia. Creatine has been shown to accumulate in the brain.

Future research should include pharmacokinetic studies to optimize dosing regimens. Additionally, a better understanding is needed to understand the reasons for variable responses to creatine. Long-term safety and studies in different populations are also important.

Safety and Efficacy of Beta-hydroxy-beta-methylbutyrate (HMB) in Augmenting Lean Tissue and Strength Gains with Resistance Training: Steve Nissen, Ph.D., Professor, Animal Science Department, Iowa State University, Ames

From a nutritional standpoint, to affect the net growth of muscle, protein synthesis must be increased or protein breakdown decreased. Protein synthesis is supported primarily by the supply of energy and amino acids, whereas protein breakdown is controlled by a myriad of factors, principally hormones.

HMB is produced from the amino acid leucine. It is used in the synthesis of cholesterol. Certain tissues like muscle require 100% *de novo* synthesis of cholesterol within the tissue. If the muscle is damaged, it must make cholesterol to repair the muscle membrane. One theory that explains the effect HMB is that in certain stressful conditions or other metabolic events when there is not enough cholesterol synthesized from endogenous sources, HMB provides a convenient source.

Nine human studies with HMB have been published since 1996. There were no negative results, but certainly quite a variation in response. As a group, however, the studies show that muscle mass increases 0.14% to 0.4% per week with HMB supplementation. Safety data are based on 3-12 weeks of supplementation. HMB was related to small decreases in systolic blood pressure (3 mm Hg), a 9% decrease in LDL cholesterol and no change in HDL cholesterol, no changes in blood hematology, and no negative effects on emotional profiles.

A recent meta-analysis (submitted for publication) examined a number of forms of supplementation and resistance exercise. The criteria for selecting studies for the analysis included placebo-control design, body composition data, minimum three weeks of supplementation, training period at least twice a week, and statistical information for calculation of effect size. More than 250 studies of creatine, HMB, chromium, androstenedione, DHEA, and protein were reviewed. Creatine had the greatest number of qualified studies (15) with a quality score of 37 (a score of 40 is considered exceptional). The nine HMB studies had a quality score of 35; 12 chromium studies scored 33; three androstenedione trials scored 32; two DHEA studies scored 24, and four studies with protein scored 27.

Based on the 37 studies in the meta-analysis, the lean tissue gain from exercise alone (placebo) is remarkably consistent—about 0.2% per week. The only supplements that had a significant effect on lean tissue gain were HMB and creatine. Both of these supplements approximately doubled the effect of exercise on lean body mass. HMB and creatine were also the only supplements that had a significant effect on muscle strength.

There appears to be less protein turnover with HMB supplementation. The limited data with older adults and women indicate that HMB is effective in these populations. Some preliminary data indicate that HMB improves immune function. It is also clear that HMB has no effect on lean body mass without exercise.

Muscle mass declines with age; it peaks in the mid-20s, and by age 75 the average loss is 20-25% of muscle mass. When the elderly get sick and lose 4-5 kg of lean muscle mass,

it increases the risk of death. Disease, such as AIDS and many stage II-IV cancers, can also cause wasting. There is preliminary evidence that HMB can slow protein breakdown.

A recently completed 12-week study of elderly adults in an assisted living setting examined the effect of a HMB mixture on lean tissue and mobility. The mixture contained 2 g HMB, 5 g arginine, and 1.5 g lysine taken once a day. The subjects did not exercise. The placebo group lost lean body mass, whereas the supplemented group experienced a net gain of about 1 kg over 12 weeks. Compared with placebo, the HMB mixture also improved mobility.

Studies conducted with AIDS and cancer patients used a different HMB mixture—3 g HMB, 15 g arginine, and 15 g glutamine in divided doses. HMB reversed wasting in each group. The AIDS study involved 36 subjects, supplemented over eight weeks. The placebo group lost 0.7 kg, and the HMB group gained 2.5 kg. The cancer study was also eight weeks and involved 40 subjects. The placebo group lost 1.1 kg, and the HMB group gained 1.4 kg. It appears the glutamine and arginine stimulate protein synthesis and HMB slows protein breakdown.

In summary, there is a scientific basis to support the effectiveness and short-term safety of creatine and HMB. Both of these compounds double the effect of exercise. Creatine and HMB are not highly lipid soluble, so it is unlikely they remain in the body for a long time. Chronic safety issues are not predicted based on current data, but long-term studies should be conducted.

Combining Compounds—The Pluses and Minuses of Stacking: Tim Maher, Ph.D., Professor, Massachusetts College of Pharmacy and Health Sciences, Boston

The biochemical disciplines of pharmacology and nutrition share many similarities, such as the study of biotransformation, absorption, distribution, metabolism, and excretion of a substance. In each discipline, while the study of individual compounds in isolation has helped to establish a basic understanding, more attention is being devoted to studying interactions of combinations of biologically active compounds. Additionally, the study of combinations of nutraceuticals, sometimes called "stacking," has become very important.

When compounds combine and interact in a complex biological system, a number of possible scenarios may result such as additivity (1 + 1 = 2), synergism (1 + 1 >2), potentiation (1 + 0 >1), and antagonism (1 + 1 = 0). To demonstrate synergism requires testing of multiple doses. Potentiation means that one of the substances has no activity itself, however, when combined with the active compound produces a greater than expected response. This is often the result of changes in elimination, distribution or metabolism. Antagonism occurs when compounds interact in such a way that prevents one from producing its full response. It can be functional, dispositional, or receptor-mediated.

The proper design and analysis of experiments that investigate the interaction between two or more compounds is much more complex than that for an individual agent. Techniques such as isobolographic analysis while much more time consuming and costly are needed to accurately describe interactions between compounds. Isobolographic analysis is a technique that utilizes multiple doses in combination that aims to produce the same effect and help in determining whether combinations are additive, subadditive or supra additive.

There are many types of interactions—food-food, drug-drug, supplement-supplement, food-drug, drug-supplement, and food-supplement. Tetracyclines compete for absorption with calcium and magnesium in dairy products. Lipid-containing foods enhance the absorption of griseofulvin, an antifungal agent. Some statins interact with grapefruit juice To produce as much as a 15-fold greater area under the curve of the concentration-time response. A recent paper in *New England Journal of Medicine* (2001, 345(25): 1809-1817) reported that ibuprofen and aspirin interact in a subadditive or antagonistic manner. Ibuprofen has some anti-platelet activity mediated by a different mechanism, which potentially interferes with aspirin's anti-platelet activity. Few people would have suspected that two compounds, which inhibit platelet aggregation, could produce a subadditive interaction.

A therapeutic example of stacking is the use of various compounds to treat different types of cancer. It is very common and typical to use drug combinations in chemotherapy or in combination with radiation and surgery. Drugs with unique mechanisms of action are used to attack aberrant cells via different pathways.

The sympathomimetics amphetamine, ephedrine and phenylpropanolamine each interact with presynaptic terminals and cause a release of norepinephrine to produce a response. Compared to a saline control, each of these compounds decreases food intake. Tyrosine supports catecholamine synthesis. When tyrosine is combined with such sympathomimetics, it enhances the effectiveness of these compounds in decreasing food intake. Tyrosine also potentiates the analgesic activity of opioids such as morphine. Tyrosine, however, does not potentiate the respiratory depressant effects of opioids.

In testing a number of different dietary supplement products, a wide variety of content is found. With ephedrine, different isomers have different pharmacological effects. It is difficult to design experiments examining interactions of compounds when the contents of the test products are not known definitively. Future research should include rigorous quantitative studies to confirm suspected synergistic or potentiating activity. Safety and efficacy must be monitored (e.g., blood pressure, gastric effects, respiratory depression), and uniformity of test articles must be insured. Finally, compounds must be tested in real-life use patterns, such as with the recent report involving aspirin and ibuprofen.

Discussion

Karl Friedl, Ph.D. (Army Operational Medicine Research): It has taken 20 years just within the Department of Defense (DoD) studying one compound—caffeine—for the Institute of Medicine to issue recommendations on use of this substance. We cannot wait another 20 years for the next substance. A focused research agenda is needed to develop conclusions for the public. We cannot continue to throw out caveats for endless research. The public needs conclusions and recommendations.

Dr. Strait (DEA): Was HMB over represented in the meta-analysis?

Dr. Nissen: I don't think HMB was over represented; the selected studies fit the criteria.

Participant: Were the studies with the HMB mixture with arginine and lysine designed to rule out the possibility that the mitigation of wasting was simply due to improvement of energy balance—perhaps by the use of placebo or dietary controls?

Dr. Nissen: There were no dietary controls. We used the traditional dietary recall, which is not very sensitive. But there weren't any changes per se in dietary intake. One study was done institutionally and all the meals were eaten in the same dining hall.

Participant: What about the placebo, was it balanced in energy?

Dr. Nissen: A proper placebo is tough anytime nitrogen is added to the diet. We used a combination of five nonessential amino acids, including alanine, serine, glutamic acid.

Dr. Wadler (NYU School of Medicine): HMB is a wonderful example of what's wrong with DSHEA. HMB came to market in the mid- to late 1960s based on 28 individuals taking two different doses for a maximum of three weeks. Thereafter, it became a big seller. When it came to market, the only publication was an abstract presented at ACSM, which was not peer reviewed. My concern is the process. Compare that with a drug and the requirements with respect to safety and efficacy. A dietary supplement product will appear on the shelf and it will be widely marketed based on little data. Six of the nine HMB studies were since 2000, yet this substance has been on the market a number of years. It speaks to the flaws in DSHEA, that a product with virtually zero human safety studies is widely sold.

Dr. Nissen: Your point is well taken. HMB has some history behind it from animal studies. There were two human safety studies, which were not published, prior to its commercial availability.

Participant (NIH): Arguably, the most important muscle in the body is the heart. If the ventricular wall were enlarged, it could decrease ventricular volume and decrease ejection fraction. This would result in decreased blood and oxygen delivery to an already increased peripheral muscle mass. This might help explain some of the nonresponders.

Dr. Volek: I don't think that the heart muscle accumulates creatine. One study did look at cardiac function tests, including ejection fraction, after a loading dose of creatine. There was no effect. Additionally, there has been no effect on blood pressure or heart rate.

Dr. Fourcroy (USADA): What is the excretory pathway for creatine? I would assume the bulk of the activity is intra-mitochondrial. How does it get into the mitochondria?

Dr. Volek: Creatine is not located in the mitochondria; it is in the cytosol, primarily in muscle cells. As to excretion, it is a nonenzymatic reaction. Creatine and muscle are degraded to creatinine at a fairly constant rate and then excreted in the urine.

Dr. Geiger (U. of Manitoba): Creatine is found in the mitochondria. In fact, in terms of neuroprotective actions of creatine, the effects are thought to be mediated in the mitochondria, because creatine kinase is part of the mitochondria permeability pore.

Dr. Volek: I am aware of the creatine shuttle between the mitochondria and the sites of action on myosin ATPase, but I was not aware that creatine was actually stored in the mitochondrial matrix.

Dr. Pope (McLean Hospital): Has the HMB meta-analysis been published?

Dr. Nissen: It has been submitted.

Dr. Strait: Did the meta-analysis attempt to qualify or disqualify any particular methods for increases in lean mass versus strength?

Dr. Nissen: We included every method for lean mass. We used any exercise data for strength.

Dr. Strait: What was the reason for using lysine and arginine in the HMB mixture?

Dr. Nissen: Lysine appears to be a limiting amino acid in older people, and there is a theoretical lysine-arginine antagonism.

Dr. Friedl: Is there an approach to model combined effects?

Dr. Maher: As with Dr. Jacobs work with caffeine and ephedrine, when a response is observed, the next step is to vary the doses to determine whether lower doses are effective. People don't often consider lowering the dose in combinations. That's the advantage in cancer chemotherapy cocktails—lower doses give the desired effect with less toxicity.

Dr. Volek: Just a comment on the technologies available to measure changes in lean tissue and changes in total body water. My understanding is that using deuterium is the gold standard for measuring body water. There is an error in that measurement of ±1 liter. Combined with the fact that muscle is about 80% water, it is difficult to distinguish between true increase in lean tissue versus increases in intracellular-extracellular water.

Challenges Facing Sports Medicine Health Professionals
Moderator: Jonathan Geiger, Ph.D.

Nutritional Challenges for High Performance Athletes: Peter Lemon, Ph.D., Professor and Weider Chair, University of Western Ontario, London, Ontario

Several factors affect the dietary needs of athletes such as exercise type, intensity and duration; continuous versus intermittent exercise; rest and recovery time between sessions; degree of training; exercise environment (e.g., temperature and humidity); age; and gender. Energy intake differs strikingly between men and women. In general, when men exercise there is a substantial increase in energy intake in response to increased training expenditure. In contrast, women often fail to compensate for increased energy demands. A study of 16 university-aged elite female rowers examined the effect of caloric supplementation on performance. For 19 days, the women consumed a carbohydrate- or fat-based supplement that supplied 940 kilojoules (kJ) per day. Performance was measured using the 2000-meter (m) ergometer-rowing test before and after supplementation. Both supplements improved performance time. The results, however, demonstrated that the women had insufficient energy intake, and the addition of calories, regardless of source, improved performance.

Carbohydrate is another important energy source. Scandinavian studies from the 1960s showed that time to exhaustion increased when muscle glycogen levels are increased. A performance-based study with eight subjects demonstrated benefit of acute carbohydrate supplementation. The subjects were randomized to receive a placebo or carbohydrate drink, then they performed a time trial after 50 minutes of intense exercise at 80% VO_2. The carbohydrate drink led to a 6.5% improvement in performance. In a similar test, the effect of acute fluid intake was tested. The subjects consumed either 200 mL (low intake) or 1330 mL of fluid (high intake). High fluid intake improved performance by 6.5%.

Tarnopolosky *et al*. (*Journal of Applied Physiology*, 1992, 73(5): 1986-1995) compared the effect of protein supplementation on sedentary controls versus strength athletes. Protein synthesis was measured before and after 13 days of three daily dietary protein intakes—0.9 g/kg, 1.4 g/kg, and 2.4 g/kg. Among sedentary controls, increased protein intake did not alter protein synthesis. Among the strength athletes, protein synthesis significantly increased when intake increased from 0.9 to 1.4 g/kg. At higher intakes, there was no further increase in protein synthesis. The results indicate that supplemented protein intake may be beneficial only at certain levels.

The timing of supplementation also appears to be important. Rasmussen *et al.* (*Journal of Applied Physiology*, 2000, 88(2): 386-392) investigated the effect post exercise supplementation on muscle protein synthesis. Six subjects consumed a 500 mL drink containing 6 g amino acids and 35 g sucrose or a placebo drink 0-1 hour, 1-2 hours, 2-3 hours, or 3-4 hours after exercise. When the drink was consumed 1-2 hours after exercise there was a threefold increase in leg muscle protein synthesis compared with placebo.

The enhanced effect was not observed at the other time intervals. A similar study by Esmarch *et al.* (*Journal of Applied Physiology*, 2001, 535(Pt. 1): 301-311) examined the chronic effect of supplement timing on leg (quadriceps femoris) cross-sectional area and strength among 13 elderly men who participated in a 12-week resistance-training program. One group of subjects received a 420 kJ supplement (10 g carbohydrate, 7 g protein, 3.3 g fat) immediately after a weight training session, and another group received the same supplement two hours after training. A significant increase in leg cross-sectional size was observed only in the group that received the supplement immediately after each training session. A similar effect was seen with muscle strength. Both groups benefited from supplementation, but greater improvement was observed in the group that consumed the supplement immediately after exercise.

An eight-week study investigated the effect of creatine and protein on strength training and muscle size in young men. For muscle strength, the number of leg press repetitions at 80% 1RM was measured before and after the supplementation period. The following data were collected:

	Protein	Creatine	Protein + Creatine
Presupplementation	7.7 leg repetitions	11.9 reps	10.0 reps
Postsupplementation	23.9 leg repetitions	29.8 reps	40.0 reps

All three groups experienced significant improvement, but the combined protein and creatine supplement provided greater benefit than protein or creatine alone. The data below demonstrate similar effects, although not as definitive, on the effect on lean body mass:

	Protein	Creatine	Protein + Creatine
Presupplementation	66.4 kg	69.0 kg	68.1 kg
Postsupplementation	67.6 kg	70.7 kg	70.8 kg

Welle *et al.* (*American Journal of Physiology*, 1995, 268(3 Pt 1): E422) compared myofibrillar protein synthesis in nine young (22-31 years) with nine older (62-72 years) subjects. Protein synthesis in older subjects was significantly below that of younger subjects. Nutrient supplementation and training might reduce the age effect and benefit older individuals in terms of functional capacity.

Several challenges remain. For athletes, the challenge is determining what products and foods to take. For scientists, the challenge is to provide objective data, but funding is inadequate to provide this information. Industry is challenged by the lack of credibility, and regulators are challenged by safety and quality control issues. One solution to these challenges is greater partnership between industry and scientists. A percentage of industry sales could be placed in a research fund. The fund could support more laboratories for the collection of unbiased data, which in turn would provide credible information for industry marketing.

Challenges Facing Sports Medicine Professionals and Sport Organizations: Andrew Pipe, M.D., Chair, Canadian Centre for Ethics in Sport, Ottawa, Ontario

Caring for athletes is a unique responsibility. Those who care for athletes must understand that these individuals are their patients first and athletes second. The sports physician serves as an advisor and confidante and an advocate for the health of the athlete and well being of the sport. The sports physician has responsibilities to the patient, sport, and sports community and supports the pursuit of excellence by fair and ethical means. As a consequence, the sports physician fulfills the traditional role and responsibilities of the physician—safeguarding health and treating illness and injury. Superimposed on that role, however, are responsibilities that relate to the education of the athlete and provision of science-based advise and counseling to optimize performance.

Athletes are vulnerable. They are open to exploitation, and are often offered substandard or unconventional approaches to care. They can be treated as commodities, whose performance ultimately secures the advancement of others—coaches, administrators, or other team officials. For many athletes, nutrition is not a scientific discipline, but a religion. There are very real challenges in discussing changes in nutritional regimens with athletes who have fixed ideas about what constitutes appropriate nutrition.

The use of supplements raises a number of questions. Is there evidence of need? Is there evidence of benefit? Is there potential for harm, including dependency? Dependency also includes feeding a mindset among athletes that in order to compete and succeed they must consume a flotilla of various supplements and preparations. Performance enhancers could include supplements that correct deficits (e.g., iron) and replace fluids, carbohydrates, carbohydrate-electrolyte solutions, caffeine and creatine. An unpublished study (Corrigan and Kazlauskas) examined supplement use by athletes competing in the 2000 Sydney summer Olympics. The declaration of supplement and medication use was analyzed among 2,758 athletes tested for drugs during the course of the Olympics. Of that group, 2,167 (78%) declared use of a supplement or medication, and 569 declared no use. Among users, 542 took more than five products a day, and one athlete took 26 different products.

Considering the findings of Corrigan and Kazlauskas, the numerous examples of unequivocal malnutrition in elite sport are ironic. Elite female figure skaters are frequently undernourished and often poorly hydrated, which places them at risk for delayed physical development, menstrual irregularities, poor bone health, and suboptimal performance. Malnutrition may be the result of insufficient calories, fluids, calcium or iron.

Supplement products are aggressively marketed to athletes. These products come from a largely unregulated industry, and at times reflect the triumph of marketing over science. Problems include impurity or contamination, label claim not matching product content, and variability of content. These problems have profound implications on the risk of athletes testing positive for banned substances. How does one minimize the risk? In

light of these problems, the only sure way that athletes can avoid testing positive is to shun dietary supplements.

In the 1994 Commonwealth Games in Victoria, British Columbia, a weightlifter asked the international anti-doping organization if it would be permissible to take a product called Nature's Nutrition Formula One. Careful review of the product contents found no banned substances, but the athlete was cautioned that there was no guarantee of the product's safety. The athlete won a medal but was disqualified 36 hours later when three different sympathomimetics were detected. Subsequent analysis of the product disclosed that these compounds were in all of the analyzed samples.

Adverse effects of ephedra have been documented in case reports. In one example, a 41-year old woman experienced spasm of the coronary artery, subsequently placing her in a vegetative state. The coronary angiogram showed no evidence of coronary artery disease. Haller and Benowitz (*New England Journal of Medicine*, 2000, 343 (25): 1833-1838) reported similar findings. They reviewed 140 reported adverse reactions and attributed 10 deaths and 13 permanent disabilities to ephedra. They stated "The risks of taking ephedra alkaloids as a dietary supplement…are difficult to justify because the alkaloids have no demonstrated benefit. People who take these products to increase their exercise capacity…place themselves at risk without a substantial likelihood of benefit."

In Canada, every elite athlete receives written information regarding supplement use and drug testing. There are also meetings with all the national teams at training sites to provide specific advice about nutritional supplement use. In the months before Olympic games, letters are sent to the presidents of all national sport organizations and team physicians advising them of potential hazards associated with supplement use. When an Olympic team arrives at an Olympic site, there is a personal interview to carefully document supplement and medication use. The lack of assurances about the quality, content, and purity of supplement products places significant burdens on sport organizations. There is a growing frustration with the failure of the dietary supplement industry to regulate itself and with the failure of regulatory authorities to regulate this industry.

The current environment is characterized by various vacuums of knowledge and a regulatory hiatus. One way to respond to the challenges posed by this environment is to attempt to address or redress our ignorance and attempt to regulate these products in manners that are appropriate.

<u>Working with the Nutraceutical Industry for the Benefit of the Athletic Community:</u>
Grant Pierce, Ph.D., National Centre for Agri-Food Research in Medicine, St. Boniface Hospital Research Centre, Winnipeg, Canada

For the purpose of this presentation, nutraceuticals are defined as any extract (from plant or animal material) that has health-related benefits beyond those obtained from normal nutritional means (e.g., elk antler velvet, tribulus). Nutraceuticals are an acceptable

method of aiding athletic performance (directly and indirectly), but they can also present problems such as compromising health and inducing positive doping tests.

What steps are necessary to address dietary supplement issues scientifically? First, the industry must attend to problems with quality control. Secondly, researchers must conduct well-controlled clinical trials to determine whether nutraceuticals can influence athletic performance and drug tests. Industry and the research community can work in partnership to address these issues.

CV Technologies is a nutraceutical company located in Edmonton, Canada, and has produced a ginseng extract—Cold-F/X—with documented immune boosting effects on colds and influenza symptoms. Members of the Edmonton Oilers Hockey Club have used cold-F/X routinely since 1997 to enhance training by reducing the number of colds and influenza. However, during the 1998-1999 season, players who were candidates for Olympic teams stopped taking Cold-F/X due to concerns that the product might produce a positive doping test results. The purpose of the scientific study was to examine if ingestion of 400 mg/day ginseng root extract—Cold-F/X—had any effect on doping control urinalysis.

Male and female subjects enrolled in the Cold-F/X study met the following inclusion criteria: normal and healthy by medical history, amateur high performance athlete currently training and competing in Manitoba, between the ages of 18-25 years, willing to comply with protocol requirements for urine sampling, and written informed consent. Exclusion criteria included (1) use any herbal supplements during the study, (2) use any IOC banned substances during the study, (3) history of positive doping control urinalysis, and (4) pregnancy. The subjects (20 female, 19 male) received 200 mg capsules twice a day for 28 days.

Urine samples were collected under strict IOC guidelines with a certified doping control officer as a chaperone. Urinalysis was performed at an IOC accredited testing facility and screened for approximately 200 banned substances within the categories of stimulants, beta-agonists and blockers, narcotic analgesics, anabolic agents, diuretic agents, local anesthetics, masking agents, and peptide hormones. All subjects were found to have acceptable levels/undetectable levels of all tested substances. There were no positive tests. Cold-F/X does not contain any IOC banned substances, and ingestion of the product does not induce the generation of any IOC banned substance over a 28-day ingestion period. The conclusions are limited to the study duration and only apply to the Cold-F/X ginseng preparation. Validity may change if product quality changes.

The Cold-F/X study is an example of how industry can benefit from supporting research. This type of testing is important for three communities—athletes, regulatory bodies, and industry. This type of study allows athletes the confidence to use the product without fear of unknown and unwanted effects, such as positive doping tests. Regulatory bodies, such as IOC and WADA, have some basic information to respond to inquiries from athletes on product safety and to an athlete's claim regarding doping analysis results. For

industry, the study results can be used as a marketing tool to promote the use of their product as healthy, safe, and legal athletic supplement.

Challenges in Providing Timely/Credible Information to Athletes, Coaches, Parent and Health Professionals about Substance Use: Jonathan Geiger, Ph.D., Director, Division of Neuroscience Research, St. Boniface Research Centre, Winnipeg, Canada

Individuals use, misuse, and abuse pharmaceutical products, dietary supplements, and illegal drugs for a variety of reasons—to promote health, prevent disease, enhance performance, alter body composition, and level the playing field. This presents challenges to many communities. Researchers need more funding to study these substances and behaviors; regulators need information to make good decisions; educators struggle with effective messaging; industry must make a profit without forfeiting strong quality control measures; athletes want to excel in a fair and equitable manner; coaches also want to excel, but some do so at any cost; and parents are often clueless regarding substance use.

Elite athletes represent a minuscule market share for the industry, but they have a disproportionately large influence over marketing. On the negative side, athletes who test positive are blaming the supplement industry—legitimately or illegitimately—for their positive results. This produces damaging media reports, which harms the industry. Solutions to this problem include stricter regulations, proper labeling, identification of steroid hormone precursors, and timely, credible information that athletes understand. Athletes also need more harmony between health professionals—nutritionists, pharmacists, pharmacologists, and physicians. Dieticians will often tell athletes—all you need is food. Pharmacists will say take anything, because their pharmacies make more money be selling supplements. Few pharmacology programs offer course material on drugs and supplements used in sport. So, the message athletes receive is disharmonious.

The Dietary Supplement Education Alliance (DSEA) appears to be putting the "E" (education) back in DSHEA. On paper, its mission looks very good. The Alliance wants to promote science and convey a positive message. In reality, DSEA just wants to flood the media with positive messages to counteract the negative stories that are continually reported. This is a bad idea. The Alliance doesn't have enough money for this tactic. The money DSEA is spending should be spent on self-regulation, cleaning up products, and fixing the problems. Instead, DSEA is trying to manipulate the symptom, and the symptom is bad press and bad publicity. The strategy is ill conceived, and hopefully industry won't buy into it.

In Canada, the Centre for Substance Use in Sport and Health (SUSH) was created through federal funding to provide an educational model on substance use. The message remains consistent, regardless of the audience's age or level of education—"Just Say Know." It is best for people to know the positive and negative effects of a substance in order to make an informed decision. There are no scare tactics. Programs that stress scare tactics simply do not work. The literature says that informed decision making starts

in the fifth grade, so the SUSH program begins with youth, but can be used for all age groups.

A number of groups and individuals promote the concept of drug-free sport or a drug-free workplace. This message doesn't work. We want people to use drugs when needed, such as aspirin for headaches. There are appropriate substances and appropriate times to take these substances. Drug-free sport is not an achievable goal, and the message does not withstand scrutiny. Drug education programs should advocate honoring the rules of sport and the rules of law. These rules can be quite different from one another, although frequently are used interchangeably. The terms "legal" and "illegal" are often misused as synonyms of "banned" and "restricted." Additional components of a drug education program include the extent to which substances affect health and performance, the medical side effects and financial costs of taking substances, and acknowledging social pressures and helping to build self-confidence.

The SUSH core approach has seven elements—(1) fair play—ethics and rules of sport, (2) legal and illegal substances—the rules of law, (3) performances enhancing products and dose (e.g., performance enhancing at low dose but performance degrading at high dose), (4) health benefits, (5) medical side effects, (6) safety for oneself and others, and (7) financial considerations—cost of the product and impact if the product causes a positive doping result.

The solution to challenges presented by sports supplements is three-pronged. The information upon which decisions are made must be the best available. Education goes beyond just providing information, and we must insure effective education. Lastly, athletes must be assured that the substances they take are effective and safe.

Discussion

Todd Crowley, J.D. (Weider): I had hoped to hear a discussion of ethical versus unethical use of performance-enhancing products. For example is it unethical for a fitness enthusiast to take 3,000 mg of vitamin C per day to reduce muscle soreness? Does the answer change for an elite or professional athlete? The debate should not be whether DSHEA is good or bad, but instead focus on the ethics of taking performance-enhancing products. The problems with dietary supplements can be addressed within the framework of the law. A substance is adulterated if it contains an ingredient not listed on the label, and FDA can seize adulterated products. If FDA doesn't enforce the law, there is no consequence for these companies to stop such practices. One of the hallmarks of DSHEA is providing more information to the American public in order to make informed decisions. If you tell young men that androstenedione increases estrogen, they will stop using it. Lastly, let's stop lumping together all dietary supplements and supplement companies. There are good companies that sell properly labeled products.

Let's not get rid of an entire industry because of some bad players. Let's get rid of the bad players using the current framework of the law.

Dr. Pipe: The decision as to whether a substance is banned is arbitrary. Erythropoietin is banned, but sleeping in an altitude house is not. Lists of banned substances are constantly evolving and changing. Most, if not all, federations make allowances for therapeutic exemptions for legitimate medical conditions that require otherwise banned medications.
It seems that industry would move rapidly and effectively to confront the issue that undermines the whole nature of the industry—quality. The public is left to guess at the reasons for the industry's inertia, indifference or intransigence, which has precluded that activity from taking place. To say that there is a wholesale attempt to eliminate an industry is to grossly misinterpret the arguments that were advanced.

Dr. Geiger: There is an ethical component to the industry. CV Technologies had a good chemical footprint of their product, but wanted to make sure that athletes did not test positive. They funded a study conducted by an independent laboratory. The information was a return on their investment. The industry should use this as an example to get out ahead of the regulatory train that could bring unwanted changes.

Ms. McIntyre (Virginia Tech): I think it's also important to consider who delivers an educational message. Athletes who are successful and "clean" are effective.

Dr. Geiger: In Canada, we have an organization called the EsteemTeam. One member is Lisa Ling—she lives in Washington, D.C, and she is in the audience. Members of the team present a goal-setting speech to elite athletes.

Dr. Bucci (Weider): I've tried to talk with the U.S. Olympic Committee about their laboratories testing Weider supplements, and each time the door is slammed in my face. It's very disappointing to discover that our anti-doping agencies have no interest in working with supplement manufacturers.

Dr. Geiger: Our Centre is certainly interested in working with any company that wants to further research. It is beneficial for all parties.

Dr. Bucci: How much did the Cold-F/X study cost?

Dr. Pierce: It depends on how many substances are tested for and the length of the study.

Dr. Pipe: It is important to know that the IOC accreditation process mandates that laboratories will not do testing for other accredited anti-doping agencies. In Canada, we have a provision in our contract with the IOC accredited laboratory that allows for the conduct of appropriate research studies.

Dr. Pierce: CV Technologies could not approach the IOC laboratory directly. Our Centre is unbiased; it has nothing to gain from the results of the study. It is essential that there be a third party positioned at arm's length from the industry and the testing laboratory.

Shawn Talbot, Ph.D. (Pharmanex): Pharmanex is a sponsor of the 2002 Games and also ran into resistance from U.S. drug testing organizations. Luckily, Pharmanex received some help from Canada. During this conference we have heard calls for the industry to clean up its act. The industry is diverse with disparate agendas. Instead, would it not be valuable for health professionals and regulators to identify companies that are trying to do it right—with proper research and testing?

Dr. Pierce: One way to do that is to support research to confirm the quality of the products. Secondly, the regulations have to be enforced.

Closing Remarks: Paul Coates, Ph.D., Director, Office of Dietary Supplements, NIH

Dr. Coates thanked all the speakers, particularly Dr. Gary Green for his three-part presentation. He also thanked the participants for generating an enthusiastic discussion and identifying research needs. For ODS, the main outcome of the conference will be developing an appropriate research agenda. Educational efforts must be based on solid information, and ODS and its partners hope to contribute to that information.