Testosterone Prohormone Supplements

GREGORY A. BROWN[1], MATTHEW VUKOVICH[2], and DOUGLAS S. KING[3]

[1]Human Performance Laboratory, University of Nebraska at Kearney, HPERLS Department, Kearney, NE; [2]Human Performance Laboratory, South Dakota State University Department of HPER, Brooking, SD; and [3]Exercise Biochemistry Laboratory, Department of Health and Human Performance, Iowa State University, Ames, IA

ABSTRACT

BROWN, G. A., M. VUKOVICH, and D. S. KING. Testosterone Prohormone Supplements. *Med. Sci. Sports Exerc.*, Vol. 38, No. 8, pp. 1451–1461, 2006. Testosterone prohormones such as androstenedione, androstenediol, and dehydroepiandrosterone (DHEA) have been heavily marketed as testosterone-enhancing and muscle-building nutritional supplements for the past decade. Concerns over the safety of prohormone supplement use prompted the United States Food and Drug Administration to call for a ban on androstenedione sales, and Congress passed the Anabolic Steroid Control Act of 2004, which classifies androstenedione and 17 other steroids as controlled substances. As of January 2005, these substances cannot be sold without prescription. Here, we summarize the current scientific knowledge regarding the efficacy and safety of prohormone supplementation in humans. We focus primarily on androstenedione, but we also discuss DHEA, androstenediol, 19-nor androstenedione, and 19-nor androstenediol supplements. Contrary to marketing claims, research to date indicates that the use of prohormone nutritional supplements (DHEA, androstenedione, androstenediol, and other steroid hormone supplements) does not produce either anabolic or ergogenic effects in men. Moreover, the use of prohormone nutritional supplements may raise the risk for negative health consequences. **Key Words:** ANDROSTENEDIONE, ANDROSTENEDIOL, DHEA, NUTRITIONAL SUPPLEMENTS, TESTOSTERONE, ESTRADIOL

Dehydroepiandrosterone (DHEA), androstenedione, androstenediol, and similar testosterone precursor steroid hormones are marketed as prohormone nutritional supplements (frequently referred to as "andro" supplements). Proponents allege that these supplements are converted to testosterone or testosterone analogs and augment the adaptations to resistance training. In 1998, the use of androstenedione by Mark McGwire, who at the time was the home run record holder in Major League Baseball, stimulated extensive media attention and dramatically increased the sales of androstenedione (18,72). At that time, however, the safety and efficacy of prohormone supplements as ergogenic aids was largely unknown.

The Anabolic Steroid Control Act of 1990 (21 USCS Section 802) defined anabolic steroids as "…any drug or hormonal substance that promotes muscle growth in a manner pharmacologically similar to testosterone…" Because the efficacy of androstenedione and related compounds in promoting muscle growth was unknown, these compounds were not classified as anabolic steroids and could be purchased legally as dietary supplements. Recently, concerns over the safety of androstenedione use prompted the United States Food and Drug Administration to ban androstenedione sales and request that Congress classify androstenedione as a controlled substance (62). The Anabolic Steroid Control Act of 2004 (21 USCS Section 802, amended) amended the original act, redefining anabolic steroids as "…any drug or hormonal substance, chemically and pharmacologically related to testosterone (other than estrogens, progestins, corticosteroids, and dehydroepiandrosterone)…" Thus, a compound can now be classified as an anabolic steroid despite having no demonstrable anabolic effect. This act classifies androstenedione and 17 other steroids as controlled substances. As of January 2005, these substances cannot be sold without prescription.

Given the stated concerns over the safety and efficacy of androstenedione use, a review of the current state of scientific knowledge regarding androstenedione use is appropriate. This review focuses primarily on the safety and efficacy of androstenedione but also discusses DHEA, androstenediol, 19-nor androstenedione, and 19-nor androstenediol supplements.

SECRETION AND INTERCONVERSION OF ANDROGENIC PROHORMONES

Steroid hormones are synthesized from cholesterol (Fig. 1) and contain 17–21 carbon atoms connected in four rings of

Address for correspondence: Douglas S. King, Department of Health and Human Performance, 248 Forker Building, Iowa State University, Ames, Iowa 50011; E-mail: dsking@iastate.edu.
Submitted for publication June 2005.
Accepted for publication March 2006.

0195-9131/06/3808-1451/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/01.mss.0000228928.69512.2e

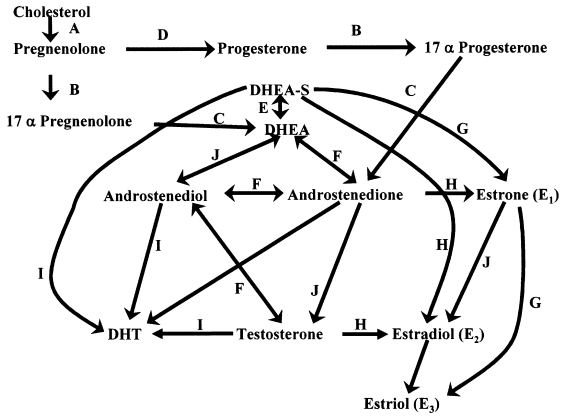

FIGURE 1—Interconversions of testosterone precursors, testosterone, estrogens, and inactive steroid hormones. A, cholesterol side chain cleavage; B, 17α hydroxylase; C, 17,20 lyase; D, 3β hydroxysteroid dehydrogenase type 1; E, DHEA sulfotransferase; F, 3β hydroxysteroid dehydrogenase; G, 16α hydroxylase; H, P450 aromatase; I, 5α reductase; J, 17 β-hydroxysteroid dehydrogenase.

five to six carbon atoms, with a few carbon atoms projecting from the cyclopentanoperhydrophenanthrene nucleus. Based on International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology standards, steroid hormones are given systematic names based on the position of the carbon atoms relative to the nucleus, as well as being given stereoisomer names if the groups are bound to asymmetric carbon atoms below the plane of the bond (α) or above the plane (β). Additionally, steroid hormones are given their class names based on their activity, such as estrogens, which maintain the size and function of the female reproductive tract, whereas androgens maintain the size and function of the male reproductive tract. The prohormones androstenedione, androstenediol, and DHEA are considered to be androgens only to the extent that they can be converted to the more potent and physiologically significant steroid hormones testosterone and dihydrotestosterone (DHT).

Dehydroepiandrosterone (3β-hydroxy-5-androsten-17-one; DHEA) is formed from 17-hydroxypregnenolone and serves as a precursor to androgens and estrogens. The normal male produces 15 $mg \cdot d^{-1}$ DHEA and has a normal serum DHEA concentration of 7–31 $nmol \cdot L^{-1}$ (49). Secreted from the adrenal cortex, DHEA can be converted *in vivo* to many different hormones, including testosterone, androstenedione, androstenediol, or estradiol (30). Because of its precursor function and its conversion to other hormones, DHEA has been advertised as a "master hormone" capable of many benefits, including memory enhancement, libido restoration, ergogenic aid, diabetes prevention, and weight loss.

Androstenedione (androst-4-ene-3, 17-dione) is a steroid hormone formed from 17-hydroxyprogesterone or from DHEA. The normal male synthesizes approximately 1.4 $mg \cdot d^{-1}$ of androstenedione and has a serum androstenedione concentration of approximately 3–10 $nmol \cdot L^{-1}$ (32). Androstenedione is secreted primarily from the adrenal gland and is converted to testosterone through the action of 17β hydroxysteroid dehydrogenase (17βHSD) (41), estrogens through aromatase (52), or DHT through 5α reductase (46). These conversions occur primarily in skeletal muscle, adipose tissue, skin, and the prostate gland (30).

Androstenediol (4-androstene-3β, 17β-diol) is similar to androstenedione in that it is formed from DHEA, secreted from the adrenal gland, and converted to estrogens through aromatase (52), or DHT through 5α reductase (46). Conversion of androstenediol to testosterone, however, is via the action of 3β hydroxysteroid dehydrogenase (3βHSD) (33). These conversions also occur primarily in skeletal muscle, adipose tissue, skin, and the prostate gland (30). Normal secretion rates and serum concentrations for androstenediol in humans have not been established.

In addition to androstenedione and androstenediol, there are other similar prohormones, such as 19-nor androstenedione and 19-nor androstenediol, which are chemically identical to androstenedione and androstenediol, except that these substances lack a carbon atom in the 19th position of the molecule (63,64); these prohormones are marketed as ergogenic aids that are converted to testosterone or testosterone analogs. Indeed, the Drug Enforcement Agency indicates that at least 10 different "andro" prohormones are marketed as nutritional supplements (25).

EFFECTS OF PROHORMONE SUPPLEMENTATION

Acute Effects of Androstenedione Intake in Men

Serum androstenedione concentrations. In men, serum androstenedione concentrations are increased up to sevenfold above baseline and remain elevated for > 6 h after ingesting 100–300 mg of androstenedione (4,16,24,39,44,55), indicating that a considerable amount of the ingested androstenedione escapes hepatic catabolism. Interestingly, Beckham and Earnest (4) observed that the acute serum androstenedione response to ingesting 200 mg of androstenedione is markedly attenuated after 28 d of androstenedione ingestion, suggesting that chronic intake of androstenedione results in either reduced absorption, enhanced clearance, or enhanced catabolism of the ingested androstenedione with prolonged androstenedione intake.

Serum testosterone concentrations. One of the primary marketing claims for androstenedione, based on a German patent application (31), is that 50 mg of androstenedione increases serum testosterone concentrations by 40–83% within 15 min of intake, whereas 100 mg increases serum testosterone by 111–237%. These claims, however, have been invalidated by numerous scientific investigations.

In the first systematic investigation on the effects of androstenedione ingestion in men (aged 19–29 yr; mean = 23 yr), a single 100-mg dose of androstenedione did not increase serum free or total testosterone concentrations during the 6 h after intake (39). Others have also reported that serum testosterone concentrations are not increased in

men aged 20–40 yr after ingesting 100 mg of androstenedione (Fig. 2) (2,16,44,55).

Although 100 mg of androstenedione is the dose frequently suggested by manufacturers, it is likely that athletes are using much larger doses. Earnest et al. (24) reported that 200 mg of androstenedione in men aged approximately 24 yr increases ($P < 0.05$) the serum testosterone area under the curve by approximately 15% during the 90 min after ingestion. The serum testosterone concentrations in this investigation, however, were not significantly higher at any time point following ingestion of androstenedione. It appears that the values reported for the area under the curve apparently included the area attributable to baseline serum testosterone concentrations, which were slightly higher in the group of subjects ingesting androstenedione. Furthermore, those investigators (4) later reported that a 200-mg dose of androstenedione does not acutely raise serum testosterone concentrations in men.

Leder et al. (44) observed that a single 300-mg dose of androstenedione increased ($P < 0.05$) serum testosterone concentrations by approximately 34% during the 8 h after intake in men aged 20–40 yr. Considerable variations were seen in these data, however, and two subjects exhibited large increases in serum testosterone (33 nmol·L^{-1}) after intake of 300 mg of androstenedione (Fig. 2), whereas the remaining 12 men had only a very small increase in serum testosterone.

The causative factors determining why some people are androstenedione "responders" and some "nonresponders" have not been characterized. A possible explanation for the phenomenon of responders and nonresponders to androstenedione intake may be reduced hepatic uptake and clearance of the supplement in responders, which allows for greater peripheral conversion of androstenedione to testosterone; however, this has not been investigated. Body composition may influence the hormonal response to androstenedione intake because excess adipose tissue enhances aromatase activity (26). However, we have observed that body fatness is not correlated to the androgen or estrogen response to androstenedione intake in young men (16,39). Finally, we have observed that men > 30 yr exhibit a greater testosterone response to androstenedione than do younger men (13,14,16,39), indicating that age and basal serum testosterone concentrations may influence the response to androstenedione intake. Further research to identify factors that influence the hormonal response to androstenedione intake is warranted.

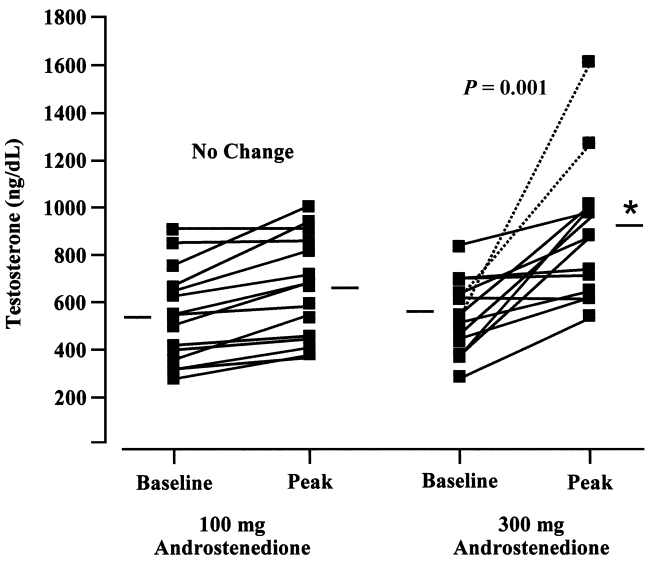

FIGURE 2—Dose–response effects of androstenedione ingestion on serum testosterone concentrations in men. The horizontal lines represent the mean baseline and peak hormone levels. Two additional men who received the 300-mg·d^{-1} dosage had serum testosterone levels above the upper limit of normal on day 1. To convert values for testosterone to nanomoles per liter, multiply by 0.0347. *Asterisk* indicates $P < 0.001$ vs baseline by the paired *t*-test. Reprinted with permission from Leder, B. Z., C. Longcope, D. H. Catlin, B. Ahrens, D. A. Schoenfeld, and J. S. Finkelstein. Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 283:779–782, 2000. Copyright © 2000 American Medical Association. All rights reserved.

Serum estradiol concentrations. In men, androstenedione intake acutely increases serum estradiol concentrations in a dose-dependent manner (16,39,44). For example, Leder et al. (44) observed a 42% increase (from 15 pmol·L^{-1} at baseline to a peak of 23 pmol·L^{-1}) in the serum estradiol area under the curve during the 8 h after intake of 100 mg of androstenedione and a 128% increase (peaking at 27 pmol·L^{-1}) after intake of 300 mg of androstenedione (Fig. 3). Although these were large increases in serum estradiol concentrations, they remained within the normal physiological range. Interestingly, Ballantyne et al. (2) observed that serum estradiol concentrations are elevated after resistance exercise only in a supplemented state. This finding suggests that physical activity may enhance aromatase activity or the increased peripheral blood flow because physical activity delivers more substrate to the tissues containing aromatase.

Serum gonadotropin concentrations. Cybernetics is the study of the communication and control of regulatory feedback in systems. The endocrine system is regulated through a complex series of negative and positive feedback and feed-forward processes, through which a change in the plasma concentration of one hormone may alter production of the same or other hormones by inhibiting or stimulating hormone-producing enzymes and secretion of hormones from a target gland. For instance, elevations in serum testosterone concentrations can result in decreased hypothalamic section of gonadotropin-releasing hormones, which can reduce pituitary secretion of the gonadotropin-luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (6) and result in reduced testicular spermatogenesis and testosterone formation (30). The use of testosterone precursors and the concomitant increases in the plasma concentrations of these weak androgens may, in theory, provide negative feedback to the hypothalamic–pituitary–adrenal–testicular axis. Furthermore, increased plasma concentrations of weak androgens may inhibit steroidogenic enzymes, altering not only androgen, but also estrogen formation and secretion (54). These changes may have a negative influence on spermatogenesis and

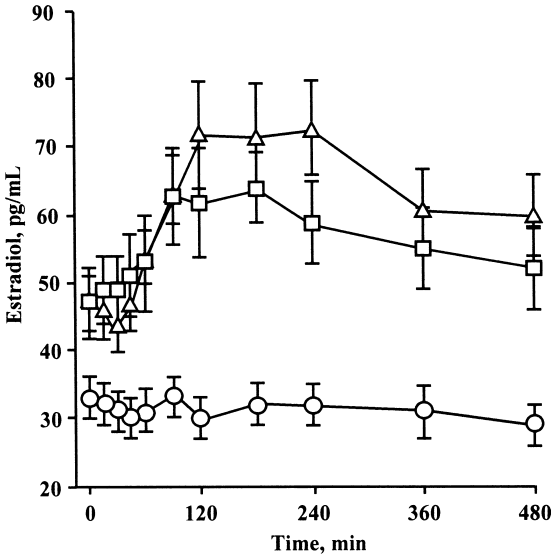

FIGURE 3—Dose–response effects of androstenedione ingestion on serum estradiol concentrations in men. Reprinted with permission from Leder, B. Z., C. Longcope, D. H. Catlin, B. Ahrens, D. A. Schoenfeld, and J. S. Finkelstein. Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 283:779–782, 2000. Copyright © 2000 American Medical Association. All rights reserved.

the plasma concentration of the more physiologically potent hormone testosterone.

The effects of androstenedione intake on spermatogenesis and reproductive function have not been investigated. Ballantyne et al. (2) reported that ingesting 100 mg of androstenedione caused an 70% increase in serum LH concentrations, which would stimulate hypothalamic–pituitary–adrenal–testicular function. These results are difficult to explain because there was no concomitant increase in serum testosterone. However, the majority of studies indicate that serum LH (16,39,55) and FSH concentrations (16,39) do not change following androstenedione intake, suggesting that no negative or positive feedback occurs to the hypothalamic–pituitary–adrenal–testicular regulation of testosterone production with the doses of androstenedione studied.

Other hormones. Together, the studies clearly show that doses < 300 mg of androstenedione do not acutely increase serum testosterone concentrations in men 20–40 yr of age (2,4,9,16,24,39,44,55), and that doses > 300 mg of androstenedione may increase serum testosterone concentrations only in certain individuals (34,44). These findings are in agreement with those suggesting that the primary fate of ingested androstenedione is conversion to inactive substances such as conjugated testosterone, androsterone, and etiocholanolone (21,42). Indeed, as much as 89% of orally administered androstenedione may be catabolized into inactive substances before it can enter the peripheral circulation (32), and 98% of testosterone formed from orally ingested androstenedione undergoes hepatic breakdown (32), suggesting that either very large doses, or modes of delivery that bypass digestion and hepatic filtration, are necessary for androstenedione intake to increase serum testosterone concentrations.

The preferential conversion of androstenedione to estrogens and DHT is not surprising because the characteristics of the enzymes involved in the interconversion of androstenedione favor the formation of these hormones. The Michaelis constant for the aromatization of androstenedione (Km = 25 nmol·L^{-1}) (26) favors the production of estrogens compared with the 17βHSD conversion of androstenedione to testosterone (Km = 1500 nmol·L^{-1}) (54). The enzyme kinetics for 5α-reductase (Km = 180 nmol·L^{-1}) also favor the conversion of androstenedione to DHT (68). These data suggest that, although larger doses of androstenedione may increase serum testosterone concentrations, still larger increases would occur in serum estrogens and DHT.

Androstenedione intake with herbal enzyme inhibitors. Because of the numerous fates of ingested androstenedione, and the finding that androstenedione does not increase serum testosterone concentrations, formulations have been made with the intent of limiting the fate of ingested androstenedione to testosterone by including herbal extracts that inhibit aromatase and 5α reductase. Therefore, we studied the effect of the intake of 100 mg of androstenedione combined with 50 mg of DHEA, 180 mg of saw palmetto extract, 100 mg of indole-3-carbinol, 310 mg of chrysin, and 250 mg of Tribulus terrestris, a formulation intended to block aromatase, and 5α reductase, thus trapping androstenedione into the 17β HSD pathway. This formulation did not increase serum-free and total testosterone concentrations for 6 h after intake (16), indicating that herbal extracts do not alter the fate of ingested androstenedione.

Effects of Chronic Androstenedione Intake in Men

Serum testosterone concentrations. Prolonged ingestion of androstenedione in doses of 50 mg b.i.d. for 12 wk (67), 100 mg q.d. for 1 wk (44), 100 mg b.i.d. for 12 wk (9), 200 mg q.d. for 4 wk (4), 100 mg t.i.d. for 4 (13,14) or 8 wk (16,39), or 300 mg q.d. for 1 wk (44) does not increase serum total testosterone concentrations in men. We have observed, however, that ingesting 100 mg of androstenedione t.i.d. for 28 d increases serum-free testosterone concentrations by 40% in 28 older (30–59 yr; mean = 42 ± 1.6 yr) men (13,14) (Fig. 4), and the increases in free testosterone were related to basal serum-free testosterone concentrations. Serum-free testosterone concentrations decline in men 1.2%·yr^{-1} after age 30 (29). The older subjects (30–59 yr; mean = 42 ± 1.6 yr) who exhibited increased serum-free testosterone concentrations in response to androstenedione intake (13,14) had lower free testosterone concentrations than did the younger subjects (19–29 yr; mean = 23 ± 0.8 yr) who did not exhibit changes in serum-free testosterone concentrations (16,39). Together, these data indicate that basal serum testosterone concentrations influence the effects of androstenedione ingestion. Supporting this hypothesis, Jasuja et al. (34) reported nearly twofold increases in serum testosterone concentrations in hypogonadal men during 12 wk of ingesting androstenedione

(1500 mg·d^{-1}). Together, these findings suggest that androstenedione ingestion can promote increases in serum-free testosterone concentrations only in men with low serum-free testosterone concentrations. Alternatively, the elevated serum-free testosterone concentrations may be caused by reduced sex hormone–binding globulin (SHBG) concentrations (34,44), which may result in an uncoupling of SHBG from testosterone to bind to the other steroid hormones.

Serum estrogens and DHT. Although prolonged androstenedione intake in men does not uniformly increase serum testosterone concentrations, serum estrogen concentrations are increased by prolonged androstenedione intake (9,13,14,16,39,44). Ingesting androstenedione also increases serum DHT concentrations in men (13,14). The significant elevations in serum estradiol and DHT with prolonged androstenedione intake in men are in agreement with the previously mentioned observations that the enzymatic activities (e.g., Km) of aromatase (26) and 5α-reductase (68) favor converting androstenedione to estradiol and DHT, respectively, rather than to testosterone.

Androstenedione intake and resistance training. Only a few studies have examined the effects of androstenedione ingestion on the adaptations to resistance training. Taking 50 mg b.i.d. for 12 wk in trained men aged 40–60 yr (67), 100 mg b.i.d. for 12 wk in untrained men aged 35–65 yr (9), or 100 mg t.i.d. for 8 wk in untrained men aged 19–29 yr (16,39) does not augment the changes in muscle strength, muscle mass, muscle fiber size, or loss of body fat (Fig. 5) observed with strength training. For example, in untrained young (22.6 ± 0.8 yr) men, we (39) observed a mean increase of 31% in 1RM with exercise in both placebo and androstenedione groups, whereas we (16) observed a mean increase of 31% in the placebo group and a 26% increase in the group ingesting a supplement containing daily doses of 300 mg of androstenedione, 150 mg of DHEA, 750 mg of tribulus terrestris, 625 mg of chrysin, 300 mg of indole-3-carbinol, and 540 mg of saw palmetto. Rasmussen et al. (55) reported that *in vivo* muscle protein synthesis is not increased (Fig. 6) by androstenedione intake despite an approximately 700% increase in serum androstenedione concentrations, which further demonstrates that androstenedione intake does not increase muscle strength or size.

In contrast to the previously mentioned studies demonstrating that ingestion of androstenedione in doses of 50–300 mg·d^{-1} in normal men is not anabolic, Jasuja et al. (34) recently observed that ingesting a 1500-mg·d^{-1} dose of androstenedione for 12 wk in hypogonadal men increased fat-free mass by 6%, muscle strength in bench press by 9%, and serum testosterone concentrations from 4 to 9 nmol·L^{-1}. In comparison, 10 wk of 100 mg·wk^{-1} testosterone enanthate in hypogonadal men increased serum testosterone from 2.5 to 17.7 nmol·L^{-1}, fat-fee mass by 9%, and bench press strength by 22% (7). Finally, resistance training alone for 10 wk would be expected to increase lean body mass by 3% and bench press strength by

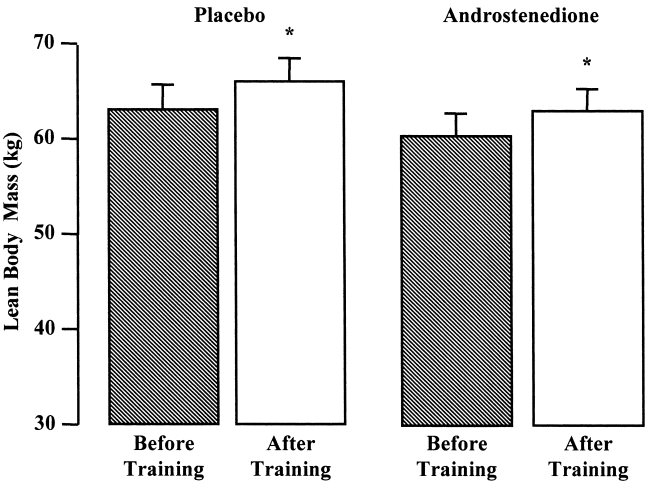

FIGURE 5—Lean body mass before and after 8 wk of resistance training combined with androstenedione (100 mg t.i.d.) or placebo supplementation. Supplements were administered during weeks 1–2, 4–5, and 7–8. Data are means ± SE for $N = 10$. * Significantly different from before resistance training (main effect; $P < 0.05$). Reprinted with permission from King, D. S., R. L. Sharp, M. D. Vukovich, et al. Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. *JAMA* 281:2020–2028, 1999. Copyright © 1999 American Medical Association. All rights reserved.

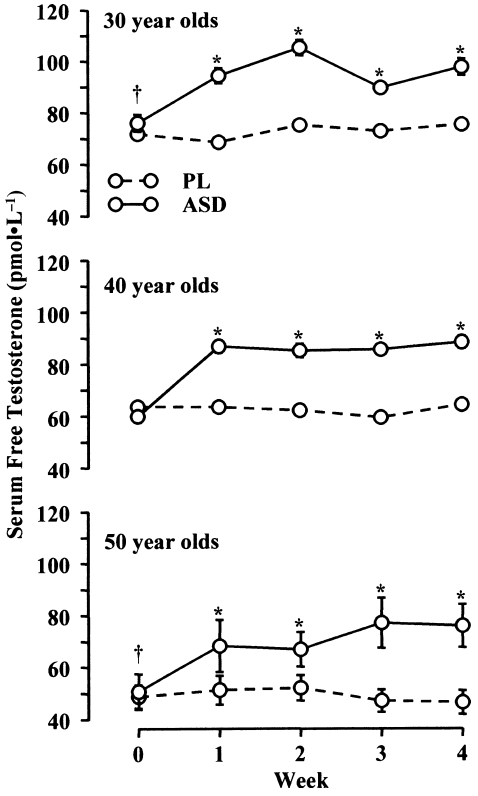

FIGURE 4—Serum-free testosterone concentrations during 4 wk of androstenedione supplementation in men 30–56 yr of age. * Significantly different from week 0 (main group effect, $P < 0.05$). † Those 50 yr of age differ from those 30 yr of age (main effect, $P < 0.05$). Reprinted with permission from Brown, G. A., M. D. Vukovich, E. R. Martini, et al. Endocrine responses to chronic androstenedione intake in 30- to 56-year-old men. *J. Clin. Endocrinol. Metab.* 85:4074–4080, 2000. Copyright © 2000 The Endocrine Society. All rights reserved.

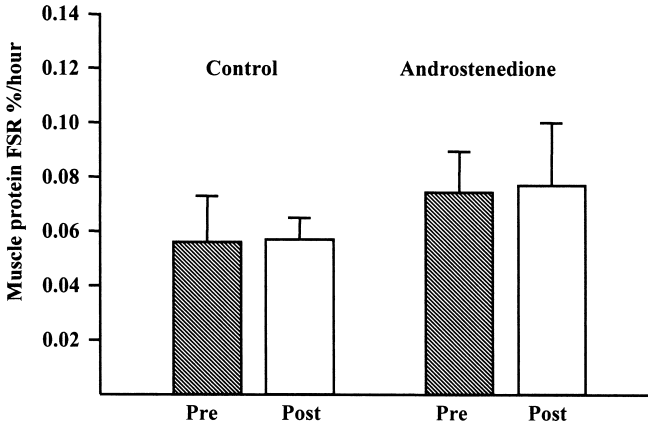

FIGURE 6—Muscle protein fractional synthetic rates of control and androstenedione treatment groups. Subjects were studied twice in the postabsorptive resting state. Pre, initial study; post, second study (5 d after ingestion of 100 mg·d^{-1} androstenedione for the androstenedione treatment group). No differences were detected between the control group and the treatment group or between pre and post values. Reprinted with permission from Rasmussen, B. B., E. Volpi, D. C. Gore, et al. Androstenedione does not stimulate muscle protein anabolism in young healthy men. *J. Clin. Endocrinol. Metab.* 85:55–59, 2000. Copyright © 2000 The Endocrine Society. All rights reserved.

9% (6). Therefore, although androstenedione may provide some remediation for the loss of strength and muscle mass in hypogonadal men, the anabolic effects of androstenedione intake are much less than those of testosterone supplementation and only slightly higher than those achieved with resistance exercise alone.

Androstenedione and muscle growth. Vierck et al. (65) observed that cells incubated in androstenedione concentrations of 1.75 pmol·L^{-1} to 1.75 μmol·L^{-1} do not exhibit increased satellite cell proliferation or differentiation, suggesting that androstenedione does not promote growth in muscle cells. Increased satellite cell proliferation or differentiation, however, is only one of the several possible pathways that stimulate muscle growth (56). Conversely, Jasuja et al. (34) have recently reported that androstenedione concentrations of 10 nM to 100 μmol·L^{-1} binds to the androgen receptor, induces androgen receptor nuclear translocation, and increases muscle cell MHCII myotube area and upregulation of MyoD protein *in vitro*, suggesting that androstenedione promotes muscle cell growth. Because the normal serum androstenedione concentration in men is 3–10 nmol·L^{-1} (29), and serum androstenedione concentrations with androstenedione intake have been reported as high as 70 nmol·L^{-1} (55), it is possible, although not demonstrated *in vivo*, that androstenedione may promote myogenesis.

Acute Effects of Androstenediol Intake in Men

Serum testosterone concentrations. Although it has been reported that 15% of androstenediol (compared with 5% of androstenedione) is converted to testosterone *in vitro* (8), serum testosterone concentrations were not changed within 90 min after ingesting 200 mg of androstenediol in young (23 yr) men (24). Although serum testosterone concentrations were not changed in the 90 min after oral intake of 200 mg of androstenedione or androstenediol (24), we have observed (11) that sublingual administration of 21.4 mg of androstenediol combined with 3.7 mg of androstenedione causes a 110% increase in serum testosterone 1 h after intake, and serum testosterone concentrations remain 40% above baseline 3 h after intake. These findings are consistent with the findings that digestion and hepatic breakdown remove most of an ingested androgen (32) because sublingual delivery bypasses digestion and hepatic metabolism. Although the sublingual androstenediol product we investigated contained both androstenediol (21.4 mg per tablet) and androstenedione (3.7 mg per tablet), the increased serum testosterone concentrations likely resulted from the androstenediol contained in the tablet because the serum testosterone concentrations were significantly elevated at 30 min after intake, whereas serum androstenedione concentrations were not elevated at this time. Furthermore, we have observed that increases in serum androstenedione concentrations of a magnitude greater than those observed following use of the sublingual androstenediol do not increase serum testosterone concentrations in men (16,39). Although it may be tempting to suggest that sublingual androstenediol increases serum testosterone concentrations, whereas sublingual androstenedione does not, the use of sublingual androstenedione has not been investigated.

Serum estradiol concentrations. Advertisements claim that androstenediol is not converted to estrogens. We have observed, however, that serum estradiol concentrations are acutely elevated 80% by a 21.4-mg dose of sublingual androstenediol (11). Therefore, it appears that use of androstenediol increases serum estrogen concentrations.

Chronic Effects of Androstenediol Intake in Men

Endocrine effects. To date, only two published reports have appeared on the endocrine responses to prolonged androstenediol intake. Broeder et al. (9) observed that 100 mg of androstenediol b.i.d. for 12 wk did not alter serum testosterone concentrations but did increase serum estradiol concentrations. We have observed that when men 30–59 yr of age ingest a product designed to prevent conversion of androstenediol to estradiol or DHT containing 300 mg of androstenediol, 480 mg of saw palmetto, 450 mg of indole-3-carbinol, 300 mg of chrysin, 1500 mg of gamma-linolenic acid, and 1350 mg of Tribulus terrestris per day for 28 d, serum total testosterone concentrations did not increase, whereas serum-free testosterone was elevated 37%, serum estradiol was elevated 86%, and serum DHT was elevated 57% (15). These findings are similar to those observed with 100-mg t.i.d. androstenedione intake (13,14), suggesting that the serum testosterone, estradiol, and DHT responses to oral androstenediol intake do not differ from those of androstenedione.

Androstenediol and resistance training. To date, only one study has examined the effects of androstenediol intake on the adaptations to resistance training. Broeder

et al. (9) reported no difference in the adaptations to resistance training (e.g., increased muscular strength and muscle mass, reduction of fat mass) in men aged 35–65 yr who ingested 100 mg of androstenediol b.i.d. or placebo during 12 wk of high-intensity resistance training. Although more studies are needed to confirm these findings, the similar endocrine responses in initial studies to androstenediol and androstenedione (e.g., no change in serum testosterone concentrations and similar magnitude of elevation in estradiol concentrations) suggest that androstenediol does not possess anabolic properties.

Acute Effects of DHEA in Men

In men aged 20–70 yr, ingestion of 50–100 mg of DHEA increases serum DHEA from normal concentrations of 7–31 $nmol \cdot L^{-1}$ and DHEA-S from normal concentrations of 2–10 $\mu mol \cdot L^{-1}$ up to sevenfold and increases serum androstenedione concentrations approximately fourfold, but serum testosterone and DHT concentrations are not changed (1,17,49,50,71). In older men (50–70 yr), ingesting 50–100 mg of DHEA elevates serum estradiol concentrations by 24–39% to the upper normal physiological range (1). Thus, ingestion of DHEA increases only weak precursor hormones, with little to no increase in more potent androgens or estrogens.

Chronic Responses to DHEA Intake in Men

Prolonged ingestion of DHEA in doses ranging from 50 to 1600 $mg \cdot d^{-1}$ in men aged 20–65 yr produces dose-dependent increases in serum DHEA, DHEA-S, and androstenedione. No concomitant increase is seen, however, in serum testosterone or DHT (17,49–51,53,71). In men, the fate of ingested DHEA is unclear. Labrie et al. (40), however, observed that a transdermal 20% DHEA solution was converted primarily to biologically inactive steroids, further indicating that DHEA intake does not promote physiologically meaningful changes in men.

In an early study, ingested DHEA appeared to have great potential as an ergogenic aid when Nestler et al. (53) observed, in young men who consumed 1600 $mg \cdot d^{-1}$ DHEA for 28 d, that body fat (measured using skinfolds) was decreased by 31%. In contrast, Welle et al. (69) observed that the intake of 1600 $mg \cdot d^{-1}$ DHEA for 4 wk did not alter energy or protein metabolism, body weight, or two indices of lean body mass (total body water and total body potassium), suggesting that DHEA does not promote loss of body fat.

Wallace et al. (67) reported no differences in the gains in strength or lean mass in older (48 yr), experienced male weight lifters who ingested a placebo or 50 mg DHEA b.i.d. We have observed, in young, novice weight lifters. no differences occurring in the gains in strength or lean mass to ingesting 50 mg of DHEA t.i.d. or placebo (17). Together from these studies, it appears that DHEA does not promote fat loss or muscle gain or augment adaptations to resistance training in healthy men.

Responses to Prohormone Intake in Women

Androstenedione intake in women. At least 200,000 women in the United States alone have used or are using androstenedione (37). As in men, androstenedione intake in women causes a large increase in serum androstenedione concentrations (10,38,43). In contrast to men, androstenedione intake in women increases serum testosterone concentrations (3,10,38,43,48). The magnitude of the effect of androstenedione intake on serum testosterone concentrations in women is unclear because of very limited research and discrepant findings. Mahesh and Greenblatt (48) reported that serum testosterone concentrations were increased 16 $nmol \cdot L^{-1}$ 1 h after intake of 100 mg of androstenedione. The small sample size ($N = 2$) and uncertain age and reproductive status of the subjects, as well as the unknown purity of the ingested androstenedione, make interpretation of these data problematic. We have observed increases in serum testosterone of 4.3 and 8.2 $nmol \cdot L^{-1}$ (from normal values of 1 $nmol \cdot L^{-1}$) 1 h after intake of 100 and 300 mg of androstenedione, respectively, in young (22 yr) women (10). Leder et al. (43) administered 50 and 100 mg of androstenedione to older (47–64 yr) women and observed that serum testosterone concentrations were increased by 2.1 and 3.5 $nmol \cdot L^{-1}$ 1 h after intake, respectively. Recently, Kicman et al. (3,38) administered 100 mg of androstenedione to young women (20–32 yr) and observed a very large (25 $nmol \cdot L^{-1}$) increase in serum total testosterone 1 h after intake. Kicman et al. (38) used a formulation of androstenedione ground and triturated with lactose to aid dispersion. Because this formulation resulted in serum androstenedione levels approximately sixfold higher than those observed by us (10) or Leder et al. (43), the differences in the serum testosterone response in these studies may be caused by the processing of the androstenedione. Although the magnitude of the increase in serum testosterone concentrations observed in women remains unclear, it is clear that ingesting androstenedione increases serum testosterone concentrations in women.

In women, 50 and 100 mg of androstenedione intake does not change serum estradiol concentrations (10,43), but a significant, acute increase is seen in serum estradiol concentrations after intake of 300 mg of androstenedione (10). These observations differ from those on men demonstrating increased serum estradiol concentrations after 100–300 mg of androstenedione (2,16,44,55). The tissue distribution and activity of enzymes responsible for interconversions of androgens and estrogens is different in male and female primates (41). For example, the 17 βHSD activity for the formation of testosterone from androstenedione is higher in female rhesus monkeys for both skeletal muscle (37.8 vs 8.4 $pmol \cdot mg^{-1} \cdot h^{-1}$) and adrenal tissue (254.4 vs 124.2 $pmol \cdot mg^{-1} \cdot h^{-1}$) (41). These findings are consistent with the increase in serum testosterone concentrations observed in women and are in line with previous observations that women rely more on the peripheral conversion of androstenedione to testosterone (32), whereas men rely primarily on the aromatization of androgens for estrogen synthesis (47).

Although no data exist on the effects of prolonged androstenedione or androstenediol intake in women, the change in the hormonal milieu resulting from prohormone use in women may cause masculinizing effects along with other negative changes in health, such as heart disease (60).

DHEA Intake in Women

In women, ingesting DHEA increases serum DHEA, androstenedione, testosterone, and DHT concentrations for 8 h in a dose-dependent manner (48,51,71). For instance, ingesting 50 mg of DHEA causes a peak increase in serum testosterone 100% above baseline (71), whereas 400 mg of DHEA increases serum testosterone by 236% (51). These elevations in serum androgens are not accompanied by elevations in serum estrogens (51,71), which is consistent with the suggestion that DHEA is an important testosterone precursor but not an important estrogen precursor in women (45).

Chronic intake of DHEA in women increases serum testosterone concentrations. Chronic DHEA intake is also associated with insulin resistance, increased incidence of acne, facial hair, and other symptoms of hirsuitism (49–51).

Other Prohormone Supplements

It is purported that 19-nor androstenediol and 19-nor androstenedione convert to the potent anabolic steroid nandrolone. A paucity of data is found on the hormonal response to ingestion of the 19-nor testosterone prohormones. Van Gammeren et al. (63,64) observed that the adaptations to resistance training are not augmented in experienced weight lifters taking these prohormones in doses of up to 334 $mg \cdot d^{-1}$, which suggests that the 19-nor testosterone precursors do not cause a meaningful change in the anabolic hormones in the body.

HEALTH RISKS OF PROHORMONE USE

The altered hormonal milieu caused by prohormone intake (e.g., elevated serum androstenedione, estradiol, and DHT concentrations) is similar to the hormonal milieu observed in men with gynecomastia (5), prostate cancer (28), testicular cancer (22), and pancreatic cancer (27). In addition, this hormonal profile is similar to the hormonal profile used experimentally to induce benign prostate hypertrophy in dogs (70). No documented cases exist of these endocrine-related diseases caused by prohormone supplementation.

Prolonged ingestion of androstenedione or androstenediol reduces HDL-C levels within 1 wk of use (9,13–16,34,39); it is unknown how long recovery from this side effect takes. Reduced high-density lipoprotein C (HDL-C) levels have been associated with an increased risk for heart disease (59). Although no documented cases exist of heart disease caused by prohormone supplementation, reduced HDL-C levels are associated with an increased risk of heart disease.

In rats, androstenedione has been found to hypertrophy the areas of the brain that regulate aggression (66), suggesting that prolonged androstenedione use can have negative psychological effects such as "roid rage". It has also been speculated that intake of androstenedione in young people can cause premature closure of the epiphyseal plates because of its stimulatory effects on osteoblast activity (44), although premature closure of the epiphyseal plates would likely be caused by the conversion of androstenedione to estradiol (19). Lastly, case studies indicate that androstenedione intake can cause priapism (35) and reproductive dysfunction in males (57).

Although the use of prohormones may predispose the user to the abovementioned negative health consequences, use of androstenedione does not appear to alter liver function, as indicated by unchanged serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), glutathione (GSH), glutathione S-transferase (GST), total microsomal P450, nuclear DNA damage, and lipid peroxidation (8,13–17,23,39,58).

DETECTION OF PROHORMONE USE

Although it has been repeatedly demonstrated that prohormone supplementation does not provide an ergogenic benefit, prohormones are widely used (37), and their use is prohibited by numerous sports organization, including the National Football League and the International Olympic Committee. Because detection of banned steroid (e.g., androstenedione, androstenediol) use is one of the primary deterrents, it is important to be able to accurately detect the use of androstenedione and related compounds in athletes. Currently, no well-accepted technique exists for detecting prohormone supplement use.

The testosterone:epitestosterone (T:E) ratio is the standard technique used for detecting exogenous steroid use. However, the T:E ratio is not a reliable indicator of androstenedione use because some subjects experience T:E ratios above the allowed threshold (61) and others do not (12,20,21). Furthermore, many androgenic supplements are contaminated with hormones, caffeine, ephedrine or other banned substances not listed on the product label (20,36). Although the sale of androstenedione has been banned, effectively detecting and deterring prohormone use may be problematic. Indeed, detecting and deterring prohormone use may require the adoption of new testing procedures, such as analysis of the carbon mass ratio or 6α-hydroxyandrostenedione (21).

FUTURE RESEARCH ISSUES

Although the current ban on prohormone sales as nutritional supplements makes studying these compounds difficult, there are still a number of issues regarding the efficacy and safety of prohormone supplement use that may warrant investigation. Although we think it is unlikely, it is possible that doses of prohormones higher than those previously studied may increase muscle size and strength. One area of interest is dose responsiveness, comparing the acute and chronic endocrine response to

doses ranging from as little as 50 mg to as high as 2000 mg, which covers the range of the "manufacturer-suggested" doses as well as doses that have been anecdotally reported to have been used by weight lifters. These studies should assess changes in serum androgen and estrogen levels as well as plasma lipids to assess possible long-term health consequences. Another possible area of study is to investigate the influence of timing of testosterone precursor intake relative to exercise and meals. It would be interesting to determine how long the change in serum lipids and hormones last after long-term testosterone precursor intake has been discontinued.

Because no large scale trials have been conducted on the effects of prohormones in women or men across age or racial groups, our knowledge in this area is limited. Women may experience ergogenic effects from testosterone precursors because of the gender differences in testosterone formation and the differences in steroidogenic enzyme activities and distribution.

In addition to ingesting testosterone precursors, these substances have been sold in spray, cream, and sublingual forms that bypass first-pass hepatic catabolism and may be more effective at altering the endocrine milieu than orally ingested forms. Studies on the acute and long-term efficacy of alternative modes of testosterone precursor administration would enhance our understanding of the efficacy of these products as ergogenic or medicinal substances.

SUMMARY

Intake of 100- to 200-mg doses of androstenedione or androstenediol, or up to 1600 mg of DHEA, does not increase serum testosterone concentrations in men, except for a minor increase in serum-free testosterone in those with low serum testosterone concentrations. A single dose of 300 mg of androstenedione may increase serum testosterone in some, but not most men. If prohormones are administered in a manner that bypasses digestion and hepatic catabolism (e.g., sublingually) serum testosterone concentrations are elevated in men, although the impact of this increase in serum testosterone on muscle size and strength is unknown. The use of prohormone supplements in women is associated with increases in serum testosterone concentrations, with potential masculinizing effects. The change in the hormonal milieu following prohormone supplement use can cause serious side effects, including heart disease and cancer, although these health effects have not been systematically evaluated. DHEA, androstenedione, androstenediol, nor androstenedione, and nor androstenediol do not enhance the gains in muscle size or strength observed with strength training alone, although use of prohormone nutritional supplements can cause an athlete to fail a drug test.

In summary, there appears to be little or no benefit in using prohormone nutritional supplements. Therefore, the use of any prohormone supplement should be discouraged by athletic trainers, coaches, educators, researchers, and physicians. As noted earlier, the sale of testosterone precursor supplements has been banned. The U.S. Food and Drug Administration, however, appears to have based this decision primarily on the conclusion that "androstenedione, if given in sufficient quantities and for sufficient duration, is likely to cause androgenic (and thus anabolic) effects" (62), despite evidence to the contrary. Furthermore, the recent classification of androstenedione and related compounds as anabolic steroids may give the impression that testosterone precursor supplements are indeed anabolic, with the unintentional consequence of encouraging testosterone precursor use.

REFERENCES

1. ARLT, W., J. HAAS, F. CALLIES, et al. Biotransformation of oral dehydroepiandrosterone in elderly men: significant increase in circulating estrogens. *J. Clin. Endocrinol. Metab.* 84:2170–2176, 1999.
2. BALLANTYNE, C. S., S. M. PHILLIPS, J. R. MACDONALD, M. A. TARNOPOLSKY, and J. D. MACDOUGALL. The acute effects of androstenedione supplementation in healthy young males. *Can. J. Appl. Physiol.* 25:68–78, 2000.
3. BASSINDALE, T., D. A. COWAN, S. DALE, et al. Effects of oral administration of androstenedione on plasma androgens in young women using hormonal contraception. *J. Clin. Endocrinol. Metab.* 89:6030–6038, 2004.
4. BECKHAM, S. G., and C. P. EARNEST. Four weeks of androstenedione supplementation diminishes the treatment response in middle aged men. *Br. J. Sports Med.* 37:212–218, 2003.
5. BERKOVITZ, G. D., A. GUERAMI, T. R. BROWN, P. C. MACDONALD, and C. J. MIGEON. Familial gynecomastia with increased extraglandular aromatization of plasma carbon-19-steroids. *J. Clin. Invest.* 75:1763–1769, 1985.
6. BHASIN, S., T. W. STORER, N. BERMAN, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N. Engl. J. Med.* 335:1–7, 1996.
7. BHASIN, S., T. W. STORER, N. BERMAN, et al. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *J. Clin. Endocrinol. Metab.* 82:407–413, 1997.
8. BLAQUIER, J., E. FORCHIELLI, and R. I. DORFMAN. In vitro metabolism of androgens in whole human blood. *Acta Endocrinology (Copenh)* 55:697–704, 1967.
9. BROEDER, C. E., J. QUINDRY, K. BRITTINGHAM, et al. The andro project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. *Arch. Intern. Med.* 160:3093–3104, 2000.
10. BROWN, G. A., J. C. DEWEY, J. A. BRUNKHORST, M. D. VUKOVICH, and D. S. KING. Changes in serum testosterone and estradiol concentrations following acute androstenedione ingestion in young women. *Horm. Metab. Res.* 36:62–66, 2004.
11. BROWN, G. A., E. R. MARTINI, B. S. ROBERTS, M. D. VUKOVICH, and D. S. KING. Acute hormonal response to sublingual androstenediol intake in young men. *J. Appl. Physiol.* 92:142–146, 2002.
12. BROWN, G. A., M. D. VUKOVICH, and D. S. KING. Urinary excretion of steroid metabolites after chronic androstenedione ingestion. *J. Clin. Endocrinol. Metab.* 89:6235–6238, 2004.
13. BROWN, G. A., M. D. VUKOVICH, E. R. MARTINI, et al. Endocrine responses to chronic androstenedione intake in 30- to 56-year-old men. *J. Clin. Endocrinol. Metab.* 85:4074–4080, 2000.
14. BROWN, G. A., M. D. VUKOVICH, E. R. MARTINI, et al. Effects of androstenedione-herbal supplementation on serum sex hormone

concentrations in 30- to 59-year-old men. *Int. J. Vitam. Nutr. Res.* 71:293–301, 2001.
15. Brown, G. A., M. D. Vukovich, E. R. Martini, et al. Endocrine and lipid responses to chronic androstenediol-herbal supplementation in 30 to 58 year old men. *J. Am. Coll. Nutr.* 20:520–528, 2001.
16. Brown, G. A., M. D. Vukovich, T. A. Reifenrath, et al. Effects of anabolic precursors on serum testosterone concentrations and adaptations to resistance training in young men. *Int. J. Sport Nutr. Exerc. Metab.* 10:340–359, 2000.
17. Brown, G. A., M. D. Vukovich, R. L. Sharp, T. A. Reifenrath, K. A. Parsons, and D. S. King. Effect of oral DHEA on serum testosterone and adaptations to resistance training in young men. *J. Appl. Physiol.* 87:2274–2283, 1999.
18. Brown, W. J., M. D. Basil, and M. C. Bocarnea. The influence of famous athletes on health beliefs and practices: Mark McGwire, child abuse prevention, and androstenedione. *J. Health Commun.* 8:41–57, 2003.
19. Bulun, S. E. Clinical review 78: aromatase deficiency in women and men: would you have predicted the phenotypes? *J. Clin. Endocrinol. Metab.* 81:867–871, 1996.
20. Catlin, D. H., B. Z. Leder, B. Ahrens, et al. Trace contamination of over-the-counter androstenedione and positive urine test results for a nandrolone metabolite. *JAMA* 284:2618–2621, 2000.
21. Catlin, D. H., B. Z. Leder, B. D. Ahrens, C. K. Hatton, and J. S. Finkelstein. Effects of androstenedione administration on epitestosterone metabolism in men. *Steroids* 67:559–564, 2002.
22. Chang, S. S., B. Ivey, J. A. Smith, B. J. Roth, and M. S. Cookson. Performance-enhancing supplement use in patients with testicular cancer. *Urology* 66:242–245, 2005.
23. Colker, C. M., J. Antonio, and D. Kalman. The metabolism of orally ingested 19-nor-4-androstene-3, 17-dione and 19-nor-androstene-3, 17-diol in healthy, resistance-trained men. *J. Strength Cond. Res.* 15:144–147, 2001.
24. Earnest, C. P., M. A. Olson, C. E. Broeder, K. F. Breuel, and S. G. Beckham. In vivo 4-androstene-3, 17-dione and 4-androstene-3 beta, 17 beta-diol supplementation in young men. *Eur. J. Appl. Physiol.* 81:229–232, 2000.
25. Fomous, C. M., R. B. Costello, and P. M. Coates. Symposium: conference on the science and policy of performance-enhancing products. *Med. Sci. Sports Exerc.* 34:1685–1690, 2002.
26. Forney, J. P., L. Milewich, G. T. Chen, et al. Aromatization of androstenedione to estrone by human adipose tissue in vitro. Correlation with adipose tissue mass, age, and endometrial neoplasia. *J. Clin. Endocrinol. Metab.* 53:192–199, 1981.
27. Fyssas, I., K. N. Syrigos, M. M. Konstandoulakis, et al. Sex hormone levels in the serum of patients with pancreatic adenocarcinoma. *Horm. Metab. Res.* 29:115–118, 1997.
28. Geller, J. Rationale for blockade of adrenal as well as testicular androgens in the treatment of advanced prostate cancer. *Semin. Oncol.* 12:28–35, 1985.
29. Gray, A., H. A. Feldman, J. B. McKinlay, and C. Longcope. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *J. Clin. Endocrinol. Metab.* 73:1016–1025, 1991.
30. Grifin, J. E., and S. R. Ojeda. In: *Textbook of Endocrine Physiology*, 5th ed. New York: Oxford University Press, pp. 228–233, 2004.
31. Hacker, R., and C. Mattern. Androstenedione Patent Application (Germany). Arrowdeen Ltd. DE 42:14953, 1995.
32. Horton, R., and J. F. Tait. Androstenedione production and interconversion rates measured in peripheral blood and studies on the possible site of its conversion to testosterone. *J. Clin. Invest.* 45:301–313, 1966.
33. Inaba, M., and T. Nakao. Conversion of 4-androstenediol and 5-androstenediol to testosterone, and conversion of dehydroepiandrosterone to 4-androstenediol by rat testis in vitro. *Endocrinol. Jpn.* 13:160–172, 1966.
34. Jasuja, R., P. Ramaraj, M. R. Phong, et al. Delta-4-androstene-3, 17-dione (4-androstenedione) binds androgen receptor, promotes myogenesis in vitro, and increases serum testosterone levels, fat-free mass, and muscle strength in hypogonadal men. *J. Clin. Endocrinol. Metab.* 2004.
35. Kachhi, P. N., and S. O. Henderson. Priapism after androstenedione intake for athletic performance enhancement. *Ann. Emerg. Med.* 35:391–393, 2000.
36. Kamber, M., N. Baume, M. Saugy, and L. Rivier. Nutritional supplements as a source for positive doping cases? *Int. J. Sport Nutr. Exerc. Metab.* 11:258–263, 2001.
37. Kanayama, G., A. J. Gruber, H. G. Pope Jr., J. J. Borowiecki, and J. I. Hudson. Over-the-counter drug use in gymnasiums: an underrecognized substance abuse problem? *Psychother. Psychosom.* 70:137–140, 2001.
38. Kicman, A. T., T. Bassindale, D. A. Cowan, S. Dale, A. J. Hutt, and A. R. Leeds. Effect of androstenedione ingestion on plasma testosterone in young women; a dietary supplement with potential health risks. *Clin. Chem.* 49:167–169, 2003.
39. King, D. S., R. L. Sharp, M. D. Vukovich, et al. Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. *JAMA* 281:2020–2028, 1999.
40. Labrie, F., A. Belanger, L. Cusan, and B. Candas. Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: intracrinology. *J. Clin. Endocrinol. Metab.* 82:2403–2409, 1997.
41. Labrie, F., V. Luu, S. X. Lin, et al. The key role of 17 beta-hydroxysteroid dehydrogenases in sex steroid biology. *Steroids* 62:148–158, 1997.
42. Leder, B. Z., D. H. Catlin, C. Longcope, B. Ahrens, D. A. Schoenfeld, and J. S. Finkelstein. Metabolism of orally administered androstenedione in young men. *J. Clin. Endocrinol. Metab.* 86:3654–3658, 2001.
43. Leder, B. Z., K. M. Leblanc, C. Longcope, H. Lee, D. H. Catlin, and J. S. Finkelstein. Effects of oral androstenedione administration on serum testosterone and estradiol levels in postmenopausal women. *J. Clin. Endocrinol. Metab.* 87:5449–5454, 2002.
44. Leder, B. Z., C. Longcope, D. H. Catlin, B. Ahrens, D. A. Schoenfeld, and J. S. Finkelstein. Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 283:779–782, 2000.
45. Longcope, C. Dehydroepiandrosterone metabolism. *J. Endocrinol.* 150 Suppl:S125–S127, 1996.
46. Longcope, C., and S. E. Fineberg. Production and metabolism of dihydrotestosterone in peripheral tissues. *J. Steroid Biochem.* 23:415–419, 1985.
47. Longcope, C., T. Kato, and R. Horton. Conversion of blood androgens to estrogens in normal adult men and women. *J. Clin. Invest.* 48:2191–2201, 1969.
48. Mahesh, V. B., and R. B. Greenblatt. The in vivo conversion of dehydroepiandrosterone and androstenedione to testosterone in the human. *Acta. Endrocrinol.* 41:400–406, 1962.
49. Morales, A. J., R. H. Haubrich, J. Y. Hwang, H. Asakura, and S. S. Yen. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin. Endocrinol. (Oxf)* 49:421–432, 1998.
50. Morales, A. J., J. J. Nolan, J. C. Nelson, and S. S. Yen. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J. Clin. Endocrinol. Metab.* 78: 1360–1367, 1994.
51. Mortola, J. F., and S. S. Yen. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. *J. Clin. Endocrinol. Metab.* 71:696–704, 1990.
52. Nelson, L. R., and S. E. Bulun. Estrogen production and action. *J. Am. Acad. Dermatol.* 45:S116–S124, 2001.
53. Nestler, J. E., C. O. Barlascini, J. N. Clore, and W. G. Blackard. Dehydroepiandrosterone reduces serum low density

lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. *J. Clin. Endocrinol. Metab.* 66:57–61, 1988.
54. OSHIMA, H., D. F. FAN, and P. TROEN. Studies of the human testis. Properties of delta-5-3beta and 17beta-hydroxysteroid dehydrogenases in the biosynthesis of testosterone from dehydroepiandrosterone. *J. Clin. Endocrinol. Metab.* 40:573–581, 1975.
55. RASMUSSEN, B. B., E. VOLPI, D. C. GORE, and R. R. WOLFE. Androstenedione does not stimulate muscle protein anabolism in young healthy men. *J. Clin. Endocrinol. Metab.* 85:55–59, 2000.
56. RENNIE, M. J., H. WACKERHAGE, E. E. SPANGENBURG, and F. W. BOOTH. Control of the size of the human muscle mass. *Annu. Rev. Physiol.* 66:799–828, 2004.
57. RITTER, R. H., A. K. CRYAR, and M. R. HERMANS. Oral androstenedione-induced impotence and severe oligospermia. *Fertil. Steril.* 84:217, 2005.
58. SAHU, S. C., P. P. SAPIENZA, R. L. SPRANDO, et al. Hepatotoxicity of androstenedione in pregnant rats. *Food Chem. Toxicol.* 43:341–344, 2005.
59. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA* 269:3015–3023, 1993.
60. TOSCANO, V., R. BALDUCCI, P. BIANCHI, et al. Two different pathogenetic mechanisms may play a role in acne and in hirsutism. *Clin. Endocrinol. (Oxf)* 39:551–556, 1993.
61. URALETS, V. P., and P. A. GILLETTE. Over-the-counter anabolic steroids 4-androsten-3, 17-dione; 4-androsten-3beta, 17beta-diol; and 19-nor-4-androsten-3, 17-dione: excretion studies in men. *J. Anal. Toxicol.* 23:357–366, 1999.
62. US FOOD AND DRUG ADMINISTRATION. FDA White Paper: Health Effects of Androstenedione. http://www.fda.gov/oc/whitepapers/andro.html. Accessed on March 7, 2006.
63. VAN GAMMEREN, D., D. FALK, and J. ANTONIO. The effects of supplementation with 19-nor-4-androstene-3, 17-dione and 19-nor-4-androstene-3, 17-diol on body com-position and athletic performance in previously weight-trained male athletes. *Eur. J. Appl. Physiol.* 84:426–431, 2001.
64. VAN GAMMEREN, D., D. FALK, and J. ANTONIO. Effects of norandrostenedione and norandrostenediol in resistance-trained men. *Nutrition* 18:734–737, 2002.
65. VIERCK, J. L., D. L. ICENOGGLE, L. BUCCI, and M. V. DODSON. The effects of ergogenic compounds on myogenic satellite cells. *Med. Sci. Sports Exerc.* 35:769–776, 2003.
66. VILLALBA, C., C. J. AUGER, and G. J. DE VRIES. Androstenedione effects on the vasopressin innervation of the rat brain. *Endocrinology* 140:3383–3386, 1999.
67. WALLACE, M. B., J. LIM, A. CUTLER, and L. BUCCI. Effects of dehydroepiandrosterone vs androstenedione supplementation in men. *Med. Sci. Sports Exerc.* 31:1788–1792, 1999.
68. WEISSER, H., and M. KRIEG. Kinetic analysis of androstenedione 5 alpha-reductase in epithelium and stroma of human prostate. *Steroids* 62:589–594, 1997.
69. WELLE, S., R. JOZEFOWICZ, and M. STATT. Failure of dehydroepiandrosterone to influence energy and protein metabolism in humans. *J. Clin. Endocrinol. Metab.* 71:1259–1264, 1990.
70. WINTER, M. L., M. C. BOSLAND, D. R. WADE, R. E. FALVO, M. NAGAMANI, and J. G. LIEHR. Induction of benign prostatic hyperplasia in intact dogs by near-physiological levels of 5alpha-dihydrotestosterone and 17beta-estradiol. *Prostate* 26:325–333, 1995.
71. YEN, S. S., A. J. MORALES, and O. KHORRAM. Replacement of DHEA in aging men and women. Potential remedial effects. *Ann. N. Y. Acad. Sci.* 774:128–142, 1995.
72. YESALIS, C. E. III Medical, legal, and societal implications of androstenedione use. *JAMA* 281:2043–2044, 1999.