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History and Epidemiology of Anabolic Androgens in Athletes and Non-athletes

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Abstract: The use of androgens, frequently referred to as anabolic-androgenic steroids (AAS), has grown into a worldwide substance abuse problem over the last several decades. Testosterone was isolated in the 1930s, and numerous synthetic androgens were quickly developed thereafter. Athletes soon discovered the dramatic anabolic effects of these hormones, and AAS spread rapidly through elite athletics and bodybuilding from the 1950s through the 1970s. However it was not until the 1980s that widespread AAS use emerged from the elite athletic world and into the general population. Today, the great majority of AAS users are not competitive athletes, but instead are typically young to middle-aged men who use these drugs primarily for personal appearance. AAS abuse has now become particularly prevalent in regions such as Scandinavia, the United States, Brazil, and British Commonwealth countries, but remains rare in countries such as China, Korea, and Japan – a pattern that reflects cultural differences in attitudes towards male muscularity.
1. Introduction

The anabolic androgens, commonly referred to as anabolic-androgenic steroids (AAS), are a family of hormones that comprises testosterone – nature’s original AAS, so to speak – together with hundreds of synthetic derivatives of testosterone developed over the last 75 years. All AAS possess both anabolic properties, causing muscle growth and fat loss, together with androgenic properties, which cause masculinizing effects such as beard growth, deepening of the voice, and masculinized secondary sexual characteristics. These properties have been observed since ancient times, because humans recognized that castration of young males could produce profound changes in body habitus, libido, and aggressiveness – suggesting that some chemical factor present in the testes was responsible for these features. However, the nature of this chemical factor remained speculative through the end of the 19th century.

In the 1870s, the renowned physician Charles Edouard Brown-Séquard began to experiment with injecting testicular extracts and other materials from young guinea pigs into aging dogs, hoping to witness a rejuvenating effect (Brown-Séquard, 1889). These experiments largely failed, although one appeared partially successful. Ultimately, Brown-Séquard resolved to experiment upon himself. Accordingly, the 72-year-old physician prepared an extract from the testicles of dogs and guinea pigs and self-administered six doses of this preparation subcutaneously over a span of two weeks. In a paper describing the experiment (Brown-Séquard, 1889), he writes that within two or three days he recovered levels of strength and endurance that he had not enjoyed for years. Prior to the injections, he wrote that he could work standing for only half an hour at a time before having to be seated. After the injections, to the astonishment of his assistants, he worked standing one day for three and one quarter hours, and still had enough energy to edit a manuscript for an hour and a half after dinner. Prior to the injections, by contrast, he had had no energy to do any work after dinner, and usually went promptly to bed. He even regained his ability to bound up and down flights of stairs – something he had not been able to do for 12 years.
Brown-Séquard’s report inspired widespread use of testicular extracts – the so-called Brown-Séquard elixir – throughout Europe and North America over subsequent decades. However, in a modern investigation that carefully duplicated Brown-Séquard’s published methods, the resulting extract proved to have testosterone concentrations that were four orders of magnitude below those required to produce a biological effect (Cussons, Bhagat, Fletcher, & Walsh, 2002). Thus, Dr. Brown-Séquard’s pioneering experiment, though based on sound scientific reasoning, has emerged as one of history’s most famous examples of the placebo effect.

2. The 1930s and 40s: the birth of AAS

Testosterone was ultimately isolated and described by German and Dutch chemists in 1935 (David, Dingemanse, Freud, & Laquer, 1935; Wettstein, 1935). Soon thereafter, Butenandt and Hanisch in Germany and Ružička and Wettstein in Switzerland (Butenandt & Hanisch, 1935; Ružička & Wettstein, 1935) published methods for the synthesis of testosterone – a discovery for which Butenandt and Ružička were awarded the Nobel Prize in Chemistry in 1939 (see Figure 1 for a chronology of the history of AAS from this date onwards). Over the next decade, numerous synthetic variations on the testosterone molecule quickly followed (Kopera, 1985; Pope & Brower, 2009), and by 1956 more than 200 AAS had been described (Nieschlag & Nieschlag, 2016).

In the early years, these newly discovered hormones were frequently prescribed by psychiatrists attempting to treat male “involutional melancholia” or the “male climacteric” (Altschule & Tillotson, 1948; Barahal, 1938; Danziger, Schroeder, & Unger, 1944; Davidoff E & Goodstone, 1942; Guirdham, 1940; Zeifert, 1942). For example, in a 1948 report from the present authors’ center, McLean Hospital in Massachusetts, USA, Altschule and colleagues (Altschule & Tillotson, 1948) reported the results of treatment with testosterone, usually at doses of 50 milligrams intramuscularly per day, in 28 men and 3 women, ranging in age from 31 to 74
years, suffering from various types of depressive disorders. Most were reported sufficiently improved to be discharged from hospital, although in many cases, these patients also received electroconvulsive therapy, a highly effective treatment for depression, thus confounding the results.

Also starting as early as the 1940s, AAS became used for a variety of medical purposes, such as in the treatment of hypogonadism (Nieschlag & Behre, 2012), certain types of anemia (Coletta, Esposito, & Palomby, 1961; Khalil & Ibrahim, 1962; Seip, 1961), and various other conditions (Gribetz, Sweet, Becker, Levitt, & Hodes, 1955; Nieschlag & Behre, 2012). Several of these medical indications for AAS use persist to the present day.

3. The 1950s to the 1970s: AAS propagate through elite athletics

Although the anabolic effects of AAS had already been demonstrated by Kochakian in the 1930s (Kochakian & Murlin, 1935; Kochakian, 1937), use of these drugs for muscle gains or athletic purposes evolved only gradually over the next decade. AAS received a boost in 1945 from the book “The Male Hormone” by the well-known writer Paul de Kruif (de Kruif, 1945), which mentions, among other things on the front cover, that testosterone “boosts muscle power.” It is rumored that by the late 1940s and early 1950s, the United States West Coast bodybuilding community had begun to discover AAS, and that the use of these drugs then spread quickly through the elite bodybuilding world (Baker, 2011). By the 1950s, on the East Coast, Dr. John Ziegler became an early champion of AAS use, and administered AAS to a number of world-class bodybuilding competitors (Baker, 2011; Fitzpatrick, 2002).

AAS soon entered other branches of athletics, with perhaps the first major example being use of AAS by the Russians at the 1954 Vienna weightlifting championships (Wade, 1972). Over the next decade, AAS use propagated rapidly through other sports, especially those requiring muscle strength, such as the shot put and other field events. In one of the darkest stories from this era, the German Democratic Republic (GDR) initiated a systematic
program of AAS doping for their Olympic athletes. Classified documents, obtained after the collapse of the GDR in 1990, showed that from 1966 onward, a vast program involving hundreds of physicians and other scientists worked on the development of AAS and administration of these drugs to thousands of athletes annually (Franke & Berendonk, 1997; Spitzer, 2006). Many of these athletes were girls and women who suffered substantial and sometimes irreversible masculinizing effects as a result of the androgenic effects of these compounds. This program allowed a country with a population of only 18 million to win 150 Olympic gold medals between 1960 and 1990.

The use of AAS was banned in the Olympics starting in 1967, but many athletes succeeded in avoiding detection over the ensuing years by discontinuing AAS use well in advance of the testing date, or by using a variety of other methods to foil detection techniques. Meanwhile, most of the general public, and even the great majority of the medical community, remained largely uninformed about these drugs and their remarkable effects. Indeed, in many studies of AAS conducted in the 1970s and even into the 1980s, the investigators failed to find a difference between AAS and placebo on various measures of strength or athletic ability (Casner, Early, & Carlson, 1971; Crist, Stackpole, & Peake, 1983; Golding, Freydinger, & Fishel, 1974; O'Shea & Winkler, 1970). Upon reanalysis, it is clear that many of these studies used doses of AAS far below those used by actual athletes, and frequently employed minimal training regimens that failed to take advantage of the anabolic effects of the drugs. As late as 1977, the American College of Sports Medicine (ACSM), in a position paper (American College of Sports Medicine, 1977), found “no conclusive evidence” that even extremely large doses of AAS could aid athletic performance. However, an influential 1984 review by Haupt and Rovere (Haupt & Rovere, 1984) carefully assessed the methodology of the various available studies and concluded that AAS, in adequate doses, and with appropriate training regimens, were indeed effective. By 1987, the ACSM retracted its earlier position and conceded that AAS were effective after all (American College of Sports Medicine, 1987). Even then, however, the ACSM
still exuded skepticism, stating that “this positive effect [of AAS] on strength is usually small and obviously not exhibited by all individuals.” Remarkably, it was not until 1996 that Bhasin and colleagues finally demonstrated in a rigorous fashion that supraphysiologic doses of testosterone were unequivocally effective for muscle gains (Bhasin et al., 1996).

The seminal paper of Bhasin et al. appeared as a lead article in the *New England Journal of Medicine* and has now been cited more than 700 times. Remarkably, this paper revealed what had already been common knowledge among elite athletes for nearly 50 years, and yet it was highly newsworthy to the medical community. The extraordinary time delay between initial “underground” recognition of the effects of AAS in the athletic community and the much later recognition of AAS effects by the medical community represents, in our opinion, one of the major embarrassments of modern medicine. The failure of physicians to recognize and acknowledge these effects are likely contributes to the scorn that many AAS users express towards the medical community, even to the present day (Dawson, 2001; Pope, Phillips, & Olivardia, 2000; Pope, Kanayama, Ionescu-Pioggia, & Hudson, 2004).

4. The 1980s and 1990s: AAS use spills into the general population

For decades, extending through the 1970s, AAS remained a well-kept secret of athletes, who fooled most of the general public and much of the medical community into believing that their stunning physiques and record-shattering performances were all a result of hard work and dedication. Finally, in the 1980s, the secrecy started to erode, and AAS began to spill out of the athletic world and onto the streets (Kanayama, Hudson, & Pope, 2008). Several factors converged to catalyze this process. First, the 1980s saw the appearance of the earliest “underground guides” on how to utilize and self-administer AAS. The earliest of these, the “*Underground Steroid Handbook*” by Dan Duchaine (Duchaine, 1981), appeared in 1981 and quickly sold hundreds of thousands of copies (Assael, 2007). It contained descriptions of most of the commonly used AAS, a discussion of side effects, instructions on how to combine
different AAS into “stacks” of drugs to be administered simultaneously, step-by-step details on how to perform self-injections, and dietary tips for maximum muscle gains. The 1981 edition was quickly superseded by several progressively larger and more sophisticated revisions over the next decade (Duchaine, 1983, 1988, 1991), all of which sold widely. Similar underground guides from other authors, such as Phillips’ Anabolic Reference Guide (Phillips, 1985, 1991), followed rapidly thereafter.

In the 1980s, AAS could be readily purchased with a doctor’s prescription in United States pharmacies. In American gyms, aspiring AAS users could easily obtain the names of local physicians who would readily write prescriptions for AAS, often for a cash price. Even without a prescription, possession or sale of AAS was only a misdemeanor in American law through the 1980s, and gym clients often spoke openly with each other about the drugs that they were using. Consequently, in the space of a decade, AAS use spread rapidly through rank-and-file gym clients throughout the United States. By the end of the 1980s, the typical AAS user was no longer an elite athlete, and indeed often not even a competitive athlete at all, but instead a young man in a local gym who simply wanted to get stronger and look more muscular.

The explosion of AAS use among rank-and-file gym clients was sufficient to arouse regulatory concern by the end of the 1980s. Accordingly, in 1990, the 101st United States Congress passed the Steroid Trafficking Act, reclassifying AAS as schedule III compounds under the jurisdiction of the Drug Enforcement Administration (DEA) (One Hundred First United States Congress, 1990). In the wake of this act, AAS use became more secret, but did not abate. Although the new law greatly reduced or eliminated the domestic manufacture of most AAS in the United States by the early 1990s, this effect proved to be largely futile, because the rise of the Internet made it possible to obtain AAS from numerous overseas countries by the mid-1990s. This phenomenon continues up to the present, with thousands of Internet vendors selling AAS from factories in China, Southeast Asia, former Eastern Bloc countries, and Latin America (Brennan, Kanayama, & Pope, 2013; Cordaro, Lombardo, & Cosentino, 2012; Pirola et
al., 2010). Although it is illegal for Americans to import these drugs, the huge volume of Internet sales has rendered interdiction extremely difficult, and consequently prosecutions are rare.

Also starting in approximately the 1980s, the use of AAS for personal appearance was greatly potentiated by a parallel development in the United States and other Western societies, namely an increasing attention to a muscular male body. Although the West has venerated male muscularity for centuries, from the statues of Greece and Rome to the gods of Scandinavia (Kanayama, Hudson, & Pope, 2012; Yang, Gray, & Pope, 2005), this tradition began to expand dramatically in recent decades (Pope et al., 2000). Hollywood movies such as Conan the Barbarian (1982) and Rambo II (1985), touting bodybuilder stars, became box office hits. Images of men in women’s magazine advertisements became progressively more likely to appear bare-chested or minimally clothed – a trend that accelerated particularly in the 1980s (Pope, Olivardia, Borowiecki, & Cohane, 2001). From the 1970s through to the 1990s, the male centerfolds in Playgirl magazine grew dramatically more muscular (Leit, Pope, & Gray, 2001). Even young boys’ action toys, such as G.I. Joe, sprouted larger and larger muscles over the same time span (Pope, Olivardia, Gruber, & Borowiecki, 1999). In 1964, when G.I. Joe was first introduced, he showed the muscular dimensions of an ordinary man; if he were enlarged to human size, his bicep would have been about 12.2 inches in circumference. By 1975, his bicep had increased to 15.2 inches; by 1992 it was 16.4 inches – close to the upper limit attainable by an average lean male weightlifter who has not used AAS. By 1998, the “G.I. Joe Extreme” action toy sported a bicep of 26.8 inches – beyond even the outer limits attainable by a lean human AAS user. Nowadays, young men growing up in Western societies are besieged with images of muscular male bodies, from action toys and cartoons in childhood, to magazine advertisements, television dramas, and Hollywood movies in adulthood, all extolling male muscularity. One can hardly pass the checkout counter at a modern pharmacy or convenience store without seeing a muscular male body (often achieved via AAS use) on a magazine cover. Very likely, one of the driving forces of this trend has been burgeoning advertising from
industries seeking to profit from men’s insecurities about their bodily appearance – especially the multi-billion-dollar nutritional supplement industry, and companies selling other products for muscle gains, fat loss, and fitness. For young men growing up in this climate, the appeal of AAS – drugs that are dramatically effective and with few serious short-term side effects – can become irresistible (Pope et al., 2000; Pope et al., 2014).

An interesting psychiatric correlate of these trends has been the rise of a disorder called “muscle dysmorphia” (Sreshta, Pope, Hudson, & Kanayama, 2016). This is a condition, primarily seen in males, where an individual perceives himself to be small and frail, even though he is actually large and muscular. By the 1980s, this condition was already familiar to weightlifters in the bodybuilding underground, who called it “bigorexia.” This term was derived from the term “anorexia nervosa,” in which individuals, typically young women, perceive themselves as fat even though they are actually lean or even emaciated. Thus “bigorexia” was effectively a reverse form of anorexia nervosa. The first scientific paper to describe this disorder, to our knowledge, appeared in 1993, and specifically referred to the condition as “reverse anorexia nervosa” (Pope, Katz, & Hudson, 1993). The authors described nine such cases among men evaluated in an interview study comparing 55 AAS users with 53 non-AAS-using weightlifters. All of the nine men described chronic preoccupations that they did not look sufficiently muscular. Many reported that they had declined invitations to go to the beach or go swimming, for fear that they would look too small if seen with their shirts off. Others reported wearing heavy sweat clothes even in the heat of summer to disguise their bodies, fearing that they would look too small. Interestingly, two of the nine men had experienced actual anorexia nervosa during adolescence, and had been converted to “reverse anorexia nervosa” later. All of the nine men were from the subgroup of 55 AAS users, and four of the nine reported that there reverse-anorexic symptoms had contributed to their decision to start using AAS.

The term “reverse anorexia nervosa” was replaced by the term “muscle dysmorphia” in 1997 (Pope, Gruber, Choi, Olivardia, & Phillips, 1997), in a paper suggesting that muscle
dysmorphia was fundamentally a form of body dysmorphic disorder in which the focus was on one’s muscularity as opposed to other aspects of bodily appearance. Over the subsequent 20 years, some 200 scientific papers have now appeared on the subject of muscle dysmorphia, including papers presenting various rating scales designed to diagnose the syndrome (Hildebrandt, Langenbucher, & Schlundt, 2004; Mayville, Williamson, White, Netemeyer, & Drab, 2002; Rhea, Lantz, & Cornelius, 2004), case-control studies comparing men with muscle dysmorphia versus comparison men (Cafri, Olivardia, & Thompson, 2008; Olivardia, Pope, & Hudson, 2000), and numerous papers describing the close association between muscle dysmorphia and AAS use (Cafri et al., 2005; Choi, Pope, & Olivardia, 2002; Hildebrandt, Schlundt, Langenbucher, & Chung, 2006; Kanayama, Barry, Hudson, & Pope, 2006; Kanayama & Pope, 2011; McCreary, Hildebrandt, Heinberg, Boroughs, & Thompson, 2007; Pope et al., 2005; Rohman, 2009). In 2013, muscle dysmorphia was specifically listed as a subtype of body dysmorphic disorder in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (American Psychiatric Association, 2013).

It should be noted that many forms of body dysmorphic disorder (e.g., concerns about thinning hair, facial features, etc.) may cause great distress, but do not commonly lead to serious dangers to physical health. By contrast, muscle dysmorphia may act as a gateway to AAS use, and also may tend to perpetuate AAS use in individuals who fear that they may lose muscular size (Kanayama, Brower, Wood, Hudson, & Pope, 2010), thus potentiating AAS dependence syndromes. AAS dependence, especially when continued for many years, may contribute to substantial physical morbidity and even mortality (Pope et al., 2014).

Although muscle dysmorphia has now become well-recognized as a risk factor for AAS use in young men, it should be noted that even lesser degrees of body image concerns have contributed to the rise in AAS use among non-athletes. Notably, these concerns tend to be concentrated in Western cultures (Pope et al., 2000), and are largely absent in East Asian cultures such as China, Korea, and Japan (Kanayama et al., 2012). In Confucian tradition, for
example, a masculine man is someone who has intellect, integrity, and force of character, but not someone who is particularly muscular (Yang et al., 2005). Thus, East Asian men rarely aspire to be massively muscular, and thus AAS use remains rare in East Asia. For example, in one 2009 study that administered questionnaires 118 Chinese male graduate students aged 21-38 in Beijing (Yang, Gray, Zhang, & Pope, 2009), not a single respondent reported that he had used AAS, nor did any respondent even know of an acquaintance who had done so, despite the fact AAS could be legally purchased without a prescription in China. By contrast a 2006 study in Norway – a country with a “strong man” tradition dating back to the Norse gods and the Vikings – found that 3.6% of male high school students had used AAS, and 28% of all students (both male and female) knew of at least one acquaintance who had used AAS (Pallesen, Josendal, Johnsen, Larsen, & Molde, 2006). This striking contrast speaks to the profound influence of cultural attitudes towards muscularity in the genesis of AAS use.

Returning to our chronological narrative, the 80s and 90s also saw the first prevalence studies attempting to assess the frequency of AAS use in student populations. In an influential early paper, Buckley and colleagues administered anonymous questionnaires to 3403 male 12th-graders in 46 American public and private schools. The investigators reported that 6.6% of respondents acknowledged use of “steroids,” with about 27% of steroid users stating that their principal reason for using “steroids” was to improve personal appearance, rather than for any competitive athletic purposes. Several other American prevalence studies soon followed (Adalf & G., 1992; Dezelsky, Toohey, & Shaw, 1985; Johnson, Jay, Shoup, & Rickert, 1989; Pope, Katz, & Champoux, 1988), with one study claiming a prevalence of “steroid” use as high as 11% in male high school students. The United States Monitoring the Future Survey began assessing “steroid” use among American high school students annually starting in 1991 (Miech, Johnston, O'Malley, Bachman, & Schulenberg, 2016), and the United States Centers for Disease Control and Prevention’s (CDC) Youth Risk Behavior Surveillance (YRBS) System assessed “steroid” use in American middle-and high-school students every second year, also starting in 1991.
Numerous other local surveys, administering anonymous questionnaires to smaller samples, also appeared starting in the 1990s (e.g., (DuRant, Rickert, Ashworth, Newman, & Slavens, 1993; Faigenbaum, Zaichkowsky, Gardner, & Micheli, 1998; McCabe, Brower, West, Nelson, & Wechsler, 2007; Middleman, Faulkner, Woods, Emans, & DuRant, 1995; Scott, Wagner, & Barlow, 1996; Yesalis, Barsukiewicz, Kopstein, & Bahrke, 1997).

In the above paragraph, we have deliberately used the word “steroids”, rather than AAS, to indicate that these surveys typically asked students about “steroid” use without clearly explaining that the question applied exclusively to anabolic-androgenic steroids, as opposed to corticosteroids. Also, most questionnaires failed to clarify that anabolic-androgenic steroids were illicit drugs, available only on the black market, that should not be confused with nutritional supplements or other legally available products. As a result of these and other factors, anonymous questionnaires have generated large numbers of false-positive responses for “steroid” use, leading to inflated estimates of the true prevalence of AAS use in student populations. In one of the most extreme examples of this phenomenon, the 2003 CDC YRBS survey claimed that 7.3% of seventh grade girls had used AAS (Centers for Disease Control and Prevention (CDC), 2004). However, in a recent analysis of data from nine studies comprising 3218 male AAS users, there were no cases where the respondent had begun AAS prior to the age of 13 – indicating that the true rate for seventh grade girls is almost certainly 0%. The reader is referred to detailed discussions of the methodology of anonymous surveys for a full exposition of these methodological flaws (Kanayama, Boynes, Hudson, Field, & Pope, 2007; Pope, 2005; Pope et al., 2014). A detailed recent analysis (Pope et al., 2014), combining prevalence information from multiple sources with careful attention to these methodological issues, has concluded that currently between 2.9 and 4.0 million American men have used AAS at some time in their lives as of 2014 and that the ratio of male to female users was about 50 to 1. The same analysis indicated that the incidence of new-onset AAS use has been relatively
constant over the years, with about 100,000 new AAS users being added in the United States annually.

International data suggest that widespread AAS use in general-population individuals began to appear in other countries about 5-15 years behind the United States. By the 1990s, prevalence studies had begun to document a substantial prevalence of AAS use among students in Canada (Melia, Pipe, & Greenberg, 1996), the United Kingdom (Williamson, 1993), Australia (Handelsman & Gupta, 1997), and Scandinavian countries (Kindlundh, Isacson, Berglund, & Nyberg, 1999; Lindstrom, Nilsson, Katzman, Janzon, & Dymling, 1990; Mattila, Parkkari, Laakso, Pihlajamaki, & Rimpela, 2010). After the year 2000, more extensive data began to appear from other countries, including especially continental Europe (Rachon, Pokrywka, & Suchecka-Rachon, 2006; Wanjek, Rosendahl, Strauss, & Gabriel, 2007) and Brazil (Abrahin, Sousa, & Santos, 2014; Fonseca, Galduróz, Noto, & Carlini, 2010; Galduróz, Noto, Nappo, & Carlini, 2005; Galduróz, Noto, Fonseca, & Carlini, 2004). Many additional epidemiologic studies have emerged from Scandinavian countries, where AAS use continues to be particularly prevalent (Hakansson, Mickelsson, Wallin, & Berglund, 2012; Hallgren et al., 2015; Kindlundh, Hagekull, Isacson, & Nyberg, 2001; Leifman, Rehnman, Sjoblohm, & Holgersson, 2011; Mattila, Rimpela, Jormanainen, Sahi, & Pihlajamaki, 2010; Nilsson, Baigi, Marklund, & Fridlund, 2001a, 2001b; Pallesen et al., 2006; Parssinen & Seppala, 2002; Swedish National Institute of Public Health, 2010).

5. The 21st century: AAS becomes a major world substance abuse problem

Today, AAS use has become widespread throughout the Western world and arguably represents the newest of the world’s major substance abuse disorders. Tens of millions of men, particularly in Scandinavia, the United States, British Commonwealth countries, and Brazil, together with lesser numbers in continental Europe, other Latin American countries, the Middle East, and Southeast Asia, have begun to experiment with these drugs (Sagoe, Molde,
Andreassen, Torsheim, & Pallesen, 2014). The great majority of these AAS users are ordinary rank-and-file male gym clients, most of whom are not using AAS for any competitive athletic purpose, but instead are using these drugs simply because they want to look bigger and more muscular. For example, in one recent international Internet survey study, 78.4% of 500 male AAS-using respondents were found to be noncompetitive bodybuilders or nonathletes (Parkinson & Evans, 2006). In another Internet survey, 70.4% of 506 male AAS users were classified simply as “recreational exercisers” (Ip, Barnett, Tenerowicz, & Perry, 2011). In a recent American study (Pope, Kanayama, & Hudson, 2012), 94 AAS users age 18-40, recruited by advertisements in gymnasiums, were asked on personal interview whether they had used AAS to improve their performance in a competitive sport. Only 6 (6%) responded that they had used AAS exclusively for competitive athletic purposes, with another 13 (14%) responding that they had used AAS partially for competitive athletics, and 75 (80%) of users responding that they had never used AAS for competitive athletics at all.

Despite these findings, most of the general public, and even the medical community, still erroneously regards AAS use as primarily a problem of doping among athletes. The much larger population of non-athlete AAS users remains largely underground and surprisingly undetected. Recent papers have suggested that there are several reasons for this. First, AAS use is typically a late-onset form of substance abuse. For example, a recent review (Pope et al., 2014) examined pooled data from five recent American studies, collectively assessing nearly 3000 AAS users, in which age of onset of AAS use was elicited. The investigators found that the median onset of first AAS use across the studies was about 22 years, with only 13.1% of AAS uses reporting that they initiated use by age 18, and only 2.2% starting by age 16. The same investigators also examined data from five additional international studies assessing age of onset of AAS use and found a similar age distribution. Thus, the typical AAS user, even when he is in the early stages of using AAS, is not a student, but instead a young adult, who is no longer under the surveillance of parents, teachers, or other supervisory individuals – and hence
goes undetected. It should be noted in passing that anonymous American high school surveys continue to imply that there are large numbers of teenage AAS users. However, as explained above, these surveys generally have yielded greatly inflated figures for teenage AAS use as a result of false-positive responses.

A second factor that obscures the true prevalence of AAS use is the secrecy maintained by most users. In particular, users rarely disclose their AAS use to physicians. In one study, 27 (56%) of 43 AAS users enrolling for research interviews reported that they had never disclosed their AAS use to any physician that they had ever seen (Pope et al., 2004). When it is considered that these particular men were sufficiently candid that they had volunteered to engage in an interview study in the first place, it follows that the overall population of AAS users is very likely even more secret than the sample interviewed in the study. The same study found that AAS users felt that physicians were well informed about the effects of tobacco and alcohol, less informed about the effects of illicit drugs, and by far the least informed about AAS. As these findings suggest, many AAS users continue to express contempt for the medical community – a phenomenon abundantly illustrated on AAS-associated Internet websites – and hence they have little motivation for disclosing their AAS use to professionals (Brennan et al., 2013). Moreover, because clinicians are often poorly informed about AAS use, they rarely inquire about it when seeing patients. For example, in one study of 223 consecutive men admitted to an inpatient substance-abuse program (Kanayama, Cohane, Weiss, & Pope, 2003), the investigators found that 29 (13%) reported a history of AAS use, but in only 4 of these 29 cases had AAS use been documented by the admitting physician. Several other publications have similarly emphasized the reluctance of AAS users to disclose their histories to health professionals (e.g., (Dawson, 2001; Kutscher, Lund, & Perry, 2002).

Third, AAS use remains undetected because these drugs rarely cause problems that cause users to come to emergency clinical attention. For example, for many years the United States Drug Abuse Warning Network (DAWN) tracked emergency room visits associated with
various forms of substance abuse (Substance Abuse and Mental Health Services Administration, 2016). The DAWN system was discontinued in 2011, but prior to this date, one could quickly ascertain the number of emergency room visits associated with, say, opiate overdoses, adverse reactions to cocaine or methamphetamine, severe alcohol intoxication, and other drug emergencies. However AAS, even when consumed in huge doses, rarely cause an acute medical emergency that precipitates an emergency room visit. Thus thousands of AAS uses may exist in a given community, yet remain almost entirely “under the radar,” in that clinicians hardly ever see them. And even when they users encounter clinicians, they generally do not disclose their AAS use in the first place. Moreover, it should be remembered that widespread general-population AAS use did not appear until the 1980s, and that the great majority of the world’s AAS users are under the age of 50 today. Thus, most of these men have not grown old enough to develop any major complications of long-term AAS use that might bring them to a doctor’s office, because the serious adverse effects of AAS – such as cardiomyopathy, atherosclerotic disease, and prolonged hypogonadism – rarely express themselves prior to middle-age (Pope et al., 2014). Thus, most community physicians have never treated an AAS user for a drug-related complication.

However, this situation may be poised to change, as the leading edge of the epidemiologic “bubble” of AAS users moves forward in time. The next decade will see substantial numbers of AAS users entering their 50s and 60s, and hence there may well be a marked increase in cardiac and neuroendocrine disease associated with these compounds, thus making them more familiar to ordinary clinicians.

Another feature of 21st-century AAS use – which may also bring more AAS users to the attention of ordinary physicians – has been the markedly increasing prevalence of individuals who have developed AAS dependence syndromes (Hildebrandt, Lai et al., 2011; Hildebrandt, Yehuda, & Alfano, 2011; Ip, Lu et al., 2012; Kanayama, Brower, Wood, Hudson, & Pope, 2009; Kanayama et al., 2010; Kanayama, Brower, Wood, Hudson, & Pope, Jr., 2009; Kanayama,
Hudson, & Pope, 2009; Pope et al., 2010; Wood, 2008). As far back as the late 1980s, early case reports and small case series had commented on AAS dependence syndromes (Brower, 1989; Brower, Blow, Beresford, & Fuelling, 1989; Brower, Blow, Young, & Hill, 1991; Brower, Eliopulos, Blow, Catlin, & Beresford, 1990; Hays, Littleton, & Stillner, 1990; Tennant, Black, & Voy, 1988), but it is not until recently that these dependence syndromes have become widely recognized and studied. Recently, an analysis of pooled data from 10 international studies has suggested that some 30% of AAS users may develop dependence – a prevalence much greater than that seen for most other dependence-inducing drugs (Pope et al., 2014). There are at least three separate pathways that likely contribute to the evolution of AAS dependence (Kanayama et al., 2010). First, as mentioned above in our discussion of muscle dysmorphia, AAS users may become “addicted” to maintaining the massive musculature that they have achieved, and may become upset or even panicky at the prospect of losing muscular size after discontinuing AAS. This attitude is reinforced within the AAS-using subculture, where a muscular bodily appearance may become a primary source of self-esteem (Blouin & Goldfield, 1995; Goldfield & Woodside, 2009; Kanayama et al., 2006; Sreshta et al., 2016). Second, AAS suppress the hypothalamic-pituitary-testicular axis, causing users to shut down their natural testosterone production (Coward et al., 2013; Kanayama et al., 2015; Rahnema, Lipshultz, Crosnoe, Kovac, & Kim, 2014; Tan & Scally, 2009). Thus, when users discontinue AAS, especially after prolonged use, they are thrown into a state of hypogonadism. Recent research has suggested that hypogonadism may persist for months or even years following cessation of prolonged AAS use (Boregowda, Joels, Stephens, & Price, 2011; Kanayama et al., 2015; Menon, 2003; Takayanagi et al., 2008; van Breda, Keizer, Kuipers, & Wolffensuttel, 2003). Hypogonadism is characteristically associated with loss of libido, impaired erectile function, decreased energy and enthusiasm, and in perhaps 10% of cases, marked depression (Allnutt & Chaimowitz, 1994; Brower, Blow, Eliopulos, & Beresford, 1989; Malone & Dimeff, 1992; Schmidt et al., 2004; Thiblin, Runeson, & Rajs, 1999). Thus, many individuals, after stopping AAS use, may resume
the drugs quickly in order to make the dysphoric feelings go away. This pathway to AAS dependence was recognized nearly 30 years ago by Kashkin and Kleber (Kashkin & Kleber, 1989), but only recently has the magnitude of this problem come to be appreciated (Coward et al., 2013; Kanayama et al., 2015; Rahnema et al., 2014; Tan & Scally, 2009). Third, AAS may cause dependence via their hedonic properties. Although AAS do not produce an acute “reward” of intoxication in the manner of classical drugs of abuse such as alcohol, opiates, or cocaine, there is no question that these drugs produce satisfying feelings of self-confidence, and even feelings of “invincibility” in a large number of users (Pope et al., 2014). Interestingly, it has recently been shown that male hamsters, when given the ability to inject themselves with AAS via a nose poke device, will self-administer AAS to the point of death (Peters & Wood, 2005; Wood, 2006, 2008). This phenomenon has been demonstrated even in studies where the animals are administering intracerebroventricular AAS – thus showing that the reinforcing effects of AAS use are attributable to the brain, rather than from a peripheral source such as, say, relief of muscle pain (Wood, Johnson, Chu, Schad, & Self, 2004). Given this “triple threat” of pathways to AAS dependence – body image concerns, neuroendocrine effects, and hedonic effects – it is perhaps not surprising that the 21st century has seen increasing attention to this problem.

Finally, the 21st century has also seen a striking proliferation of other appearance- and performance-enhancing drugs that are increasingly used in conjunction with AAS or in place of them. Some of these drugs, especially fat-burning agent such as clenbuterol, thyroid hormones, and amphetamines, were already popular in both bodybuilding and competitive athletic circles even before the 21st century (Pope et al., 2014). However, one of the most distinctive trends of the new century has been the rising use of human growth hormone (HGH), together with its daughter hormone, insulin-like growth factor 1 (IGF-I). These hormones were formerly very expensive, but are now cheaply available via the Internet from overseas manufacturers (Brennan, Kanayama, Hudson, & Pope, 2011; Gibney, Healy, & Sonksen, 2007; Holt &
Sonksen, 2008; Sagoe et al., 2015). One recent interview study found that 27 (27%) of 100 American AAS users also reported a history of using HGH and/or IGF-I (Brennan et al., 2011). Some debate persists as to whether these hormones, taken in markedly supraphysiologic doses, truly have anabolic properties, but there is little doubt that they will continue to enjoy great popularity among both athletes and nonathletes who are also using AAS (Gibney et al., 2007; H.G. Pope et al., 2014). Another hormone increasingly abused for “bulking up” is insulin, which is readily diverted onto the black market. Prior to 2000, insulin abuse by nondiabetic bodybuilders was very rare (Evans, 1997; Perry, Wright, & Littlepage, 1992), but recent surveys have reported insulin use in 5% to as much as 25% of AAS users (Baker, Graham, & Davies, 2006; Cohen, Collins, Darkes, & Gwartney, 2007; Hildebrandt, Langenbacher, Carr, & Sanjuan, 2007; Ip, Barnett, Tenerowicz, & Perry, 2012; Parkinson & Evans, 2006; Perry, Lund, Deninger, Kutscher, & Schneider, 2005). Newer appearance- and performance-enhancing drugs, such as selective androgen receptor modulators (SARMs), continue to come rapidly over the horizon (Krug et al., 2014; Thevis, Geyer, Kamber, & Schanzer, 2009; Thevis et al., 2015).

Although a detailed discussion of these many other drugs is beyond the scope of this paper, it is important to recognize that AAS increasing represent only one of many different classes of agents (albeit still the most important class) used by recreational bodybuilders and by athletes in the 21st century. Several recent papers have addressed this phenomenon of polypharmacy in greater detail (Dodge & Hoagland, 2011; Hildebrandt, Lai et al., 2011; Ip et al., 2011; Sagoe et al., 2015).

6. The future

There is nothing to suggest that the use of AAS, together with use of the many ancillary drugs described above, is likely to decline in the foreseeable future. It is a simple fact of biology that these drugs are highly effective, and they are readily obtainable legally in many countries, and illegally via the Internet and other black-market sources in countries where they are
prohibited. Despite substantial efforts at maintaining doping control among athletes and efforts at interdiction of AAS in the much larger numbers of nonathletes, there is little reason to suspect that legislative or enforcement attempts will markedly alter current trends. However, as the older members of the AAS-using population advance through middle age, it appears likely that we will see increasing recognition of the long-term adverse effects of these drugs, especially in the form of cardiomyopathy, atherosclerotic disease, and prolonged hypogonadism (Pope et al., 2014). It must be hoped that these developments will help to awaken both the drug-using community and the medical community to the severity of the problem, in a manner analogous to the way that the world has awakened to the dangers of cigarette smoking over the last several decades. To this end, it would seem important to aggressively pursue further research on the long-term effects of AAS and other performance-enhancing drugs, and to propagate this information as effectively as possible.
Legend for Figure 1: A timeline showing various events in the history of androgens from the 1930s to the present.
References


Fitzpatrick, F. (2002, October 20, 2002). Where steroids were all the rage: A doctor's curiosity and a businessman's love of weightlifting set off a revolution in York. *Philadelphia Inquirer*.


Highlights

• Before 1980, anabolic-androgenic steroids (AAS) were used primarily by elite athletes

• After 1980, AAS use spilled out of elite athletics and into the general population

• Now most AAS users are just recreational weightlifters and not competitive athletes

• Many of today’s AAS users take these drugs purely to enhance personal appearance

• Concerns about male body image have fueled the rise of AAS use in Western cultures