

*·Editorial·*

## Hormones and sport: physiology, pharmacology & forensic science

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Sport is probably the most ubiquitous voluntary human social activity. Defined as the playing of competitive games according to rules, sport forms a microcosm of human society that combines playfulness (“homo ludens”), healthfulness, competitiveness and showiness into a rich amalgam that illustrates the best and worst (with much in between) about organized human social activities. It ranges widely to celebrate achievement in fame and fortune through competitive success and co-operative efforts, to foster socialization by the bonding experiences of team-spirit in childhood and youth, to providing the most popular mass entertainment and to create vignettes of the worst excesses of human avarice, cheating and violence. Sport also ranges from the lows of defeat and disappointment, to the highs of a “personal best” that is within anyone’s reach and to the most profound accomplishments of world records; from the most solitary of personal struggles to the most public of popular entertainment. A modern version of Shakespeare’s “all the world’s a stage” might nowadays be recast more widely as “all the world’s a stadium”.

For society at large, sporting champions are widely admired heroes whose skill, triumphs and rewards through fair and honest effort provide stellar inspiration and aspirational goals for a worthy and successful life. It is no coincidence that the fastest route out of impoverished minority ghettos of the modern metropolis is through sporting success. However, the means of achieving success in sport and the lauded status of champions may fall into conflict, principally through cheating. Rules of fair and honest play are intrinsic to sport and cheating fundamentally breaches those rules, whether it is by match fixing, using illegal equipment or drugs. Cheating is a deliberate dishonesty, destroying fairness and perpetuating a social and/or commercial fraud on other players and watchers of sport. The temptations of fame and fortune lead some competitors to a greed-fuelled, win-at-all-costs approach. Discarding fairness, simply doing to others what one accepts done to themselves, as naïve niceties and abandoning the ethical mandate of honest effort within the rules, degrade the lofty goals of sporting contest turning it into the sociopathic quest of merely not getting caught or a staged and cynical farce like television wrestling.

Fairness, as a subjective judgment, is inherently an elastic concept. It is, at the very least, influenced by prevailing cultural beliefs and prejudices of the times and thereby its standards may change over time. For example, a century ago the contemporaneous social values dictated that sportsmen were expected to compete on the basis of “natural talent” for the love of the sport whereas the use of systematic training and being paid were considered an “ungentlemanly” approach, an affront to the dignity of any self-respecting athlete. Similarly, in 1912 Baron Pierre de Coubertin, the founder of the IOC, thought that the participation of women in Olympic games was “Impractical, uninteresting, ungainly ... – and improper”. Social pressures and the tide of political fashions dictate that such attitudes can change, surprisingly quickly considering the usually glacial timescale of cultural practices. Hence, coaching, professionalism and women’s participation have for decades been among the fundamentals of any modern elite competitive athletic program.

The modern concept of fairness in sport has dictated making exceptions to the idealized goal of open competition for all. These exceptions are justified as enhancing rather than detracting from the fairness of elite sports competition. The most prevalent of these special provisions is gender separation in sports. At the 2008 Beijing Olympics, strict gender separation applies in 24 of 28 distinct Olympic sports so that only 10 out of 302 events are open for mixed, non-segregated competition. A few events are restricted to men (baseball, boxing, Greco-Roman wrestling) or women (rhythmic gymnastics) but fully integrated events are held only in equestrian and synchronized swimming, although badminton and sailing run both mixed as well as segregated competitions. The usual rationale for such near universal sex segregation is the gender dimorphism of physique and strength. This segregation into separate but equal competitions aims to allow women a chance to win in events where the hormonally determined superiority of men in height, weight and strength would make it otherwise virtually impossible for women to win against men. This interpretation is supported by the historical record as, despite progressive improvement by both adult male and female athletes in all sports, the gender gap in championship performances at all levels of sport remains largely undiminished. The wide acceptance of gender segregation transformed into a quasi-automatic tenet perhaps explains anomalies such as its (mis)application to events wherein success depends on non-physical skills such as accuracy in hitting targets or board and card games. The only other stratification supported in elite sports is that of weight classes in power sports (boxing, judo, wrestling, taekwondo, weightlifting) although similar power events (throwing, sprinting) in athletics

are not segregated by weight class. Nor are sports stratified by height classes even when tall stature is a clear physical advantage as in basketball.

The biological basis for gender segregation in sports is the consequence of long-term endogenous androgen exposure of men after puberty. In non-contact sports, elite performance, as reflected in championship records, does not differ systematically by gender in childhood but diverges between men and women from the chronological age of puberty onwards. Throughout life women maintain circulating testosterone levels unchanged from those of children whereas during puberty males experience an increase in testosterone production rate of ~30-fold reflected in ~20-fold increase in circulating testosterone levels. Given Nature's clue, it was only logical that in trying to supercharge sports performance, attention soon turned to hormones, androgens in particular. It may also have been encouraging that androgens are the only class of human steroid hormones free of known spontaneously occurring clinical overdose syndrome. Yet growth at puberty in females also markedly improves sports performance indicating that the hormonal events entrained by puberty are not solely attributable to increased androgen exposure. Clearly both skill as well as non-androgen dependent changes in physique (including musculature and the growth of the skeletal fulcrum) create performance advantages in sport.

The identification of androgens as ergogenic (performance enhancing) agents dates back to almost the identification of testosterone as the major mammalian androgen in the mid 1930's. The recognition of superior male athletic capabilities is ancient and the attribution to a secretion of the testis dates back to Berthold's mid-19th Century experiments using John Hunter's 18th Century technique of testis transplantation to show testes at any anatomical location were necessary and sufficient to maintain cock combs. This conceptual landmark, often misattributed to Brown-Sequard whose aqueous extracts of testis contained no testosterone [1], confirmed long-held beliefs that the testis was responsible for creating and maintaining masculine physique. The development of synthetic androgens, mostly during the pharmaceutical boom of the immediate post-war decades, provided the means and while the Cold War provided the opportunity for drug cheats to establish a systematic foothold in elite sports. This quasi-infectious epidemic eventually became entrenched because there existed sufficient susceptible individual hosts although modern analytical scientific forensic detective work has closed off most effective opportunities for drug cheating. The effectiveness of the bans on androgen doping are often and easily underestimated. In-competition testing has virtually eliminated this form of cheating for all marketed or known androgens which are detected by highly sensitive mass spectrometry for often months after last administration. Among those intent on persisting to try androgen doping, this has led to increasing indirect and less effective approaches which have also been in turn progressively discovered and neutralized. The term "designer androgen" has two distinct connotations—one refers to the legitimate pharmaceutical development of the first non-steroidal androgens [2] and the second to the illicit development of undetectable androgens for sports doping [3]. The dynamism and success of the forensic science underlying the detection and effective combating of hormone abuse in sports has led to a sad irony that progress in the illicit sphere, introduction of new androgens rapidly followed by detection and banning, outpaces the speed of progress in the licit realm of drug registration. While elite competition is mostly free of hormone abuse, out of competition testing and detecting and deterring the more devious forms of hormone abuse will require ongoing vigilance.

In this special section of the Journal celebrating the 2008 Beijing Olympics, invited authors focus on the cutting edge issues in hormones and sport. The first section reviews the contemporary understanding of the physiological and pharmacological basis of hormones as determinants of muscle function and sports performance. Dr Bhasin's group highlight lessons arising from their landmark clinical studies which proved that athletes abusing androgens were correct in ascribing benefits to high dose androgens at a time when the prevailing evidence-based belief among medical scientists was that supraphysiological androgens had no ergogenic effects in healthy, eugonadal men [4]. Bhasin showed memorably that the androgen dose-response relationships with muscle size and strength runs linearly well beyond the eugonadal ranges and, in passing, that meta-analysis is no substitute for high quality evidence. Dr Zitzmann [5] reviews the evidence that genetic influence on tissue androgen sensitivity via the single well established functional genetic polymorphism in androgen action, the CAG triplet repeat in the androgen receptor, might influence muscle mass and performance. Drs Ehrnborg and Rosén [6] consider the background and physiology underpinning the belief that GH is a hormone of abuse in sports. Reviewing critically the limited evidence, they conclude there is no convincing evidence that GH is ergogenic, consistent with the naturally occurring clinical GH overdose syndrome (acromegaly) that produces muscular weakness, rather than enhanced strength.

The second section examines the history and present status of the fight for fairness in sport now guided by the World Anti-Doping Agency (WADA). Dr Fitch, a sports physician with decades of experience in elite sports and doping, reviews the history of androgen abuse and its detection over recent Olympics as part of the evolving organized fight against hormone doping [7]. Drs Barroso, Mazzoni and Rabin [8] from WADA highlight the key priority

issues and challenges being tackled in WADA's leadership of the quietly successful but ongoing fight against sports doping. They confirm that hormone abuse remains a troublesome problem as hormones remain the most potent and frequently detected drugs in sport. Drs Handelsman and Heather [9] review the current challenges in androgen doping with emphasis on designer androgens, indirect androgen doping and the potential application of in vitro androgen bioassay to detecting novel unknown androgens. Drs Nelson and Ho [10] review the background and current progress in implementing the two leading approaches for tests to detect GH doping. These are the direct GH isoform test, a sensitive test with a relatively brief detection window, and the more recent indirect GH marker approach which aims to extend the detection window with recent promising findings. Based on his clinic's extensive experience in management of transgender, Dr Gooren [11] considers the issues of gender verification focusing on the vexed but rare issue of the transgender athlete's participation in gender segregated sport, again reflecting wider social issues in miniature. He raises the interesting issue whether long-term endogenous androgen exposure leaves a physical imprint that persists despite subsequent cross-hormonal treatments and conversely whether a genetic female taking male androgen doses can compete fairly in female (or male) events.

Finally, thanks are owed to the journal staff, authors and reviewers who have contributed to the value of the Journal's special section on Hormone and Sport marking the 2008 Beijing Olympics.

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