Use and Misuse of Hormones in Sport

It has been reported that Lionel Messi reached the pinnacle of his career with the help of growth hormone (GH) but this was ‘treatment’ not ‘doping’. He was diagnosed with GH deficiency when an 11 year-old schoolboy and through his brilliance at soccer earned enough to cover its substantial cost (1). Growth hormone is probably the most anabolic hormone known; it stimulates longitudinal bone growth in children and muscle, bone and soft-tissue growth in adults. It works in harmony with sex steroids in building and maintaining a healthy lean body but unlike sex-steroids, is powerfully lipolytic. Its use in elite sports is allowed provided it is used to treat a known medical condition and has been approved *a priori* by a Therapeutic Use Exemption from the appropriate Sports Federation.

Its first misuse in sport was documented in 1982 by Dan Duchaine in the 1st edition of his ‘Underground Steroid Handbook’ an 18-paged cyclostyled newsletter for US bodybuilders. He rated GH highly as the newest and most powerful anabolic agent ‘on the block’. When Ben Johnson won the 100 metres in the 1984 Olympic Games and admitted taking both anabolic steroids and GH (2), word quickly spread around the athletic community but did not reach adult endocrinologists; at this point Growth hormone was considered exclusively the domain of paediatricians. It was not until 1989 that the first peer-reviewed papers appeared showing GH’s powerful anabolic and lipolytic effects in adults with GH deficiency (3;4). Demonstrating performance-enhancing effect in athletes to the levels of certainty used in science is fraught with all sorts of difficulty; it is much easier for an athlete to test a range of potential ‘Performance-Enhancing Drugs (PEDs)’ using a ‘trial of one’ paradigm rather than the necessary but cumbersome ‘double-blind randomised controlled trial (RCT)’ approach. This is the main reason why athletes have always been ahead of the ‘anti-dopers’, even when a forensic analytical test may be available, which was not the case with GH. Despite these challenges, one large well-designed and executed (but possibly under-powered) RCT of GH in amateur athletes showed a small but significant enhancement of sprinting ability (0.4 sec in 100 metre race), enough to make the difference between winning a Gold Medal or no medal (5).

So great was the demand for GH on the black-market that stocks of GH in pharmacies and warehouses and even trucks on the road were specifically targeted (6). The International Olympic Committee (IOC) recognised this as a growing problem and recruited one of us (PHS) in 1993 to join their Medical Commission to advise and help find a solution to the growing GH problem. Growth hormone and its releasing substances, as proteins and peptides, presented a new class of doping agent for the IOC laboratories who were not suitably equipped to tackle this new class of PEDs. The IOC understandably were impatient and wanted a test for GH ‘now’ but had difficulty in accepting that any useful test could only come from research and that, if they wanted a test, they needed to commit $$ to this research. Eventually, after successful lobbying, the European Union included drug abuse in sport in their BIOMED2 Research call and we were successful with a proposal for a multi-national ‘GH-2000’ Project (BMH4 CT950678) involving medical scientists from UK, Sweden, Denmark and Italy in partnership with the two GH manufacturers Novo Nordisk and Pharmacia; the IOC laudably joined the project matching the EU financial contribution. After three years the project successfully presented a ‘biomarker’ test based on measuring insulin-like growth factor-I (IGF-I) and amino-terminal pro-peptide of type III collagen (P-III-NP) to the EU & IOC in March 1999. The hope was to establish the test for the Sydney Olympic Games in September 2000, when the necessary blood samples were collected, but it was not until the 2012 London Olympic Games that WADA adopted the GH-2000 ‘biomarker’ test. Some of this delay was due to the change of governance from the IOC to the World Anti-Doping Agency (WADA) and consequent delays before WADA became effective. The net result was that the biomarker test was ‘on ice’ for 3 years (7).

The possibility of an alternative approach detecting administration of recombinant GH (rhGH) – the ‘isoform’ method removed the focus from support of the indirect biomarker approach. This method has the advantage over the biomarker method of ‘directly’ identifying the use of rhGH, but depends on being able to measure a hormone whose concentration in blood varies 100 fold and rhGH has a very short half-life. Nevertheless, using monoclonal antibodies it was possible to prove that rhGH was present in blood and that the normal pituitary-derived physiological GH isomers were suppressed. WADA introduced the ‘isoform test’ at the Athens Olympic Games in 2004 (8). Because of the short half-life, the isoform test has a very short ‘window-of-opportunity’ as the blood sample must be drawn within 24 h of the last rhGH injection, whereas the biomarker method can detect GH misuse for several weeks after its last administration. This advantage was demonstrated at the London Paralympic Games when two athletes missed by the isoform test were caught by the biomarker test. The biomarker test has a further advantage over the isoform test in being able to detect misuse of (cadaveric) pituitary-derived GH (undetectable in the isoform test) and IGF-I (9) and likely also GH-releasing substances such as GH-releasing hormone (GHRH), GH releasing peptide (GRP 1-6) that are now directly measurable in urine using mass spectrometry (10). Unfortunately, technical development issues, failure of commercial assays and increasing needs to have knowledge of large ‘control’ cohorts have all delayed the roll-out of the biomarker method by WADA but these issue are now resolved and ‘roll-out’ to WADA laboratories is now in process.

Knowledge about the misuse of GH is unreliable as our intelligence is largely based on hearsay and anecdotes as testing for GH has been limited but it appears to be particularly popular in sprint and power sports, usually in combination with anabolic steroids.

Doping is not confined to young athletes and there is concern about GH misuse in ‘Masters’ events, Gary Player being convinced of its misuse in golf (11). Three RCTs have shown that GH has potential performance-enhancing effects in older men and women. Its effects are augmented by sex-steroids (12-14). It seems that the athletes again are leading the field in hormone research!

Everyone wants to see drug-free sport but never has the reputation of sport been as tarnished as it is now. What needs to be done? Anti-doping budgets must be increased by Sports Federations, WADA and IOC and this should be divided equally between ‘testing’ and ‘research’. Out-of-competition testing should be ‘targeted’ and increased to at least match in-competition testing. Research should be better funded and should focus on refining existing tests and introducing new ones.

1133 words and 14 references

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Authors:

Peter H Sonksen1 OBE MD FRCP FFSEM (UK)

David Cowan2 OBE FKC

Richard I G Holt3 PhD FRCP

1. Emeritus Professor of Endocrinology St Thomas’ Hospital and King’s College, London; Visiting Professor Southampton University phsonksen@aol.com
2. Director, Drug Control Centre, King’s College, London david.a.cowan@kcl.ac.uk
3. Professor in Diabetes & Endocrinology, University of Southampton R.I.G.Holt@soton.ac.uk