Drugs and ergogenic aids to improve sport performance

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The use of biochemical aids to enhance athletic performance has a long history. In our current sporting culture we attempt to divide these between the accepted legal ‘ergogenic aids’ and the unacceptable performance-enhancing ‘drugs’. It is unclear whether this distinction would have been made 2000 years ago when Pliny the Elder reported the effects of Horsetail juice on performance. Interestingly, the sporting ergogenic effects of horsetail haven’t passed the test of time. In the middle ages its astringency, due to its high silica content, made it ideal for scouring pewter and wooden kitchen utensils. The juice’s current ergogenic properties are more refined, its main use being in bath and shower products where a ‘natural conditioning effect’ is required. Perhaps more controversially, hidden amongst his 600 books, Claudius Galen, the 2nd century Greek physician to the gladiators, mentioned the positive effects of eating herbs, mushrooms and testicles. Galen believed that the right testicle was hotter and purer than the left, though whether this led to differential performance-enhancing effects was not rigorously tested.

We shouldn’t think that modern people are unusual in being obsessed with winning at all costs. Philostratos’s (200 AD) view of the Ancient Greeks was that “They made war training for sport and sport training for war.” He was less impressed with his generation of sportsmen who “spent too much time eating, drinking and fornicating instead of actually training”. This was reflected in their poor choice of ergogenic aids. Although the ancient Spartan athletes trained on a meat-full diet of bulls, oxen, goats and deer, athletes of his generation ate white bread, poppy seeds, fish and pork [1]. They treated sports

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as “more of a hobby than a way of life”. Grumpy old men are clearly not a modern phenomenon!

Clearly, if not actually preparing for war, the modern elite athlete in no way treats sport as merely a hobby. So have we biochemists advanced beyond Pliny, Galen and Philostratos in our understanding of how biochemicals can enhance sport performance? That is the aim of this book. It brings together nine international experts to discuss the use of legal and illegal chemicals in a wide range of sporting endeavours. It focuses on the underlying biochemical mechanisms, but of course in the light of the relevant physiology and sport performance.

So what can biology tell us about the possibility of enhancing sporting performance? The ‘disposable soma’ theory of aging [2] suggests that throughout most of human evolution people have lived short lives due to predation, accident or disease. So there has been no evolutionary selection pressure to prevent aging. This gives hope as it suggests that genetic or chemical manipulation has a lot of evolutionary space to work in, anti-aging treatments may not be competing with millions of years of natural selection. One can take a similar evolutionary perspective to look at areas of sport performance most likely to be enhanced by drugs. It has been suggested that, compared with other mammals, humans are poor runners; the argument being that the evolution of our brains enabled us to use tools rather than our bodies to hunt. Our ability to run could therefore be seen as a side effect of selection for upright walking. On the surface this suggests that there is a lot of capacity to improve over evolution as selection has not acted primarily on speed or endurance running for some time. Can drugs therefore be the ‘evolutionary’ tools to enhance performance? At least when it comes to endurance running, recent anatomical and anthropological studies suggest that this argument may not be strong. We have several adaptations for running: these include long, springy legs and big, muscular buttocks, while our relatively hairless bodies and ability to sweat profusely prevent us from getting overheated [3]. Throughout human history, and until recently in some cultures [4], man has hunted prey by running alone. This strategy of ‘persistent hunting’ involves targeting one animal and tracking it exclusively, usually starting in the hottest part of the day. As long as the same animal is hunted the human will generally win, even if it has to take over a day. The same skills can be seen when humans race animals competitively. Once you get to distances of the marathon and beyond humans outperform other species (e.g. dogs, horses), which are far faster over shorter distances.

This would imply that drugs would be more likely to succeed in short, power events; and indeed most drugs are targeted in this arena. However, the ‘success’ of erythropoietin and blood doping reveals that human evolution is not completely optimized for endurance sports performance (Chapter 5). Maybe given the dangers to the circulation of high (50%) resting haematocrits obtainable by erythropoietin administration, it is perhaps not surprising that evolution has not yet gone down this route.

One problem when studying the mechanism of action of ergogenic aids in sport is the difficulty of undertaking scientific studies under ‘field conditions’.
It is notoriously easy to find conditions where you can show differences as great as 10% in the laboratory, that if transferred to a sport would make someone a world beater. However, even though, in real events, the difference between winning and losing is often measured in fractions of a percentage, laboratory protocols do not always translate to an obvious performance benefit. Translating between the laboratory and the field is clearly not a trivial process. It is difficult to control for all the other factors that affect an elite athlete, such as, for example, diet and training regime. There is also an assumption that the biochemical mechanisms underpinning a performance enhancement in the average athlete are the same as in the elite athlete. This is not an unreasonable assumption, but it is an assumption nevertheless.

An additional problem when studying the effects of illegal drugs on sport performance is the difficulty in reproducing the ‘experimental regime’ used by athletes. Naturally, even more so than for ergogenic aids, these are kept secret. Although a major breakthrough in understanding came with the detailed records of East Germany’s ‘successful’ drug programme [5], we do not really know what current athletes are taking. It is likely that the doses and/or mixtures of these drugs would not be ethical to reproduce in a human laboratory study or even in an animal model. Unfortunately it is impossible to use elite athletes in such studies as even volunteering for a legitimate study would disqualify them from competition. These uncertainties may be at the root of the apparent anomaly where the WADA (World Anti-Doping Agency) has been desperate to develop tests for human growth hormone yet the scientific evidence that it improves performance is weak at best (see Chapter 6). Or, of course, the athletes could be wasting their money and risking their reputation for nothing!

A quick look at the internet will reveal a range of drug cocktails that would be impossible to study scientifically, even if it were ethical. My particular favourite is the use of DNP (dinitrophenol). This is a mitochondrial uncoupler that allows enhanced oxygen consumption with no ATP production, essentially converting fat oxidation directly into heat throughout the body. It was marketed as a wonder slimming drug in the early part of the 20th century, with probably over 100 000 people being treated in the 1930s. It is one of the few drugs that undoubtedly reduces body mass, predominantly fat, with no change in diet required [6]. Unfortunately, the therapeutic window is small and the effect of an overdose is a dramatic reduction of the body’s ATP which is potentially catastrophic. DNP had the honour of being the first drug to be banned by the newly formed US FDA (Food and Drug Administration) in 1938. Still it is a very useful drug for a ‘sport’ that is concerned about visible fat, but not athletic performance. Enter body-building (www.steroid.com/DNP.php):

“If you screw up using it, you may go blind, or end up in the hospital on an ice bed receiving ice-water enemas as the doctors frantically try to make the temperature of your yellow and sweaty body go back down. And no, I’m not joking. On the positive side, very few people have died...
from DNP use, although it remains a distinct possibility, as some DNP related fatalities have been reported”.

and

“Don’t get me wrong, not everyone feels like total garbage on DNP, but it’s by far the most common side effect I’ve heard of, next to bad breath. No, really. Oh, and I almost forgot yellow(ish?) sweat and body odor that’s brutal. Then there’s this weird taste in your mouth. On the bright side, we’re talking about fat loss of almost a half a kilogram per day (1 lb/day), when DNP is properly used.”

A key area which we address only tangentially in this book is the psychology of sports performance. It is probable that for many athletes taking a special pill or having a magic injection, in and of itself, enhances performance whatever the nature of the compound taken [7]. There is presumably no greater placebo effect than knowing you have a biochemical inside track over your opponents. It is a logical impossibility to develop a drug to mimic the placebo effect, against what would you test it? But could a drug be developed to amplify the placebo effect? (Un)fortunately not enough is known about the precise pathways involved in the brain. However, one area of sports neurochemistry that is garnering a lot of attention at present is the idea that our brains signal that we are tired before the maximal physiological end-point, presumably to preserve longer-term function. We therefore might be able to overcome this chemically in order to improve performance by providing a drug to overcome this brain fatigue message. These points are peripherally addressed by Beneke (Chapter 2), Nicholas (Chapter 4) and Cooper (Chapter 5). Although an interesting idea, without understanding the mechanism of fatigue it is hard to see how to overcome it biochemically. It is probable that the effects of stimulants (see Chapter 7 by Jones) on non-elite athletes are mediated in part by this kind of method, making ‘ordinary’ athletes work through pain and tiredness, but it is not clear that this works for elite athletes who have presumably trained, or been selected, to overcome these problems. One interesting, and very specific, biochemical theory (discussed in Chapters 4 and 5) that branched-chain amino acids could overcome ‘central fatigue’ by enhancing tryptophan transport across the blood–brain barrier seems to have fallen by the wayside despite interesting initial findings.

Before we can understand in detail how ‘drugs’ and ‘ergogenic aids’ can enhance performance maybe we have to first understand and define what we mean by these two terms? For performance-enhancing drugs this is almost an impossible task. One might think that a glance at the WADA prohibited list would make this obvious. Everything on this list is a drug and everything is not a legal ergogenic aid. Of course this is what athletes have to do. But it is not always clear what the rationale behind the list is. The WADA code defines a doping violation as “the presence of a prohibited substance or its metabolites or markers in an athlete’s bodily specimen”. This of course is legalese to allow the absolute primacy of the WADA list of prohibited substances. To get on
the WADA list a drug, or method, needs to fulfill two out of three criteria:
(i) be potentially performance-enhancing; (ii) be harmful to health; and (iii) be
against the “spirit of sport”. This includes such well-defined ideas as “fun and
joy”, “character and education” and “community and solidarity”.

As ever with definitions most would agree with the extremes. Taking a
glucose drink during a marathon only fulfills (i) but the use of injecting ana-
bolic steroids or high dose erythropoietin fulfills (i), (ii) and (iii). However,
things get blurred at the edges. So apart from adding new compounds, the
list is also revised from year to year; this is especially true with regards to
stimulants where some, notably pseudoephedrine, that were once banned are
now legal. Historically, doping agencies seem to have a bias against injectable
compounds, possibly because of the link to the illegal street drugs which are
used by the general population, some of which appear on the list despite hav-
ing no known performance-enhancing effects [presumably via fulfilling criteria
(ii) and (iii)]. For similar reasons cannabis is on the banned list, though the
evidence of enhanced performance is slim to none. Maybe it fails the “fun and
joy” criteria?

Maybe we, as biochemists, are given a hard time by WADA? Any form
of artificial technology can be used to enhance your body’s performance
as long as you don’t eat, drink or inject it. So it is okay to breathe hypoxic
gases, live in a low-oxygen tent or climb a mountain, but injecting erythro-
poietin to get exactly the same effect puts you on the banned list. However,
if the compound at any point in its life enters the food chain naturally then
it is an ergogenic aid and it is perfectly legal to ingest as many pills as you
like, creating levels difficult to obtain naturally. Creatine comes to mind as
an example of this. More intriguingly caffeine (see Chapter 8) was banned,
then set to a specific limit, bizarrely above the level that was performance-
enhancing, and then removed from the list. So now it is fine to have a cof-
fee before you run, unless of course you are a horse. The rationale here, one
assumes, is that caffeine is now considered a normal part of a human’s diet,
but not of a horse’s. We could carry on ad infinitum. It is clear that organiza-
tions like WADA have an almost impossible task of pleasing everyone, even
before trying to develop tests for new drugs (see Chapter 10). However, at
least the current annually updated list has the benefit of clarity. Now that we
have a (sort of) definition of the difference between a drug and an ergogenic
aid, the next thing we need to do before looking at biochemical mechanism is
to understand what are the limits of human performance. This is the topic of
Chapter 2 (Beneke and Böning) where it is argued that the limits of perfor-
mane are multifactorial. However, the classical distinction between the aerobic
(alactic) and anaerobic (lactic) systems is still a useful concept, with short
high-power events requiring predominantly phosphocreatine and glycolysis
for energy metabolism, while longer events require a greater contribution
from the mitochondrial respiratory chain. Indeed when it comes to illegal
performance-enhancing drugs it is clear that the most successful classes of
compounds (anabolic steroids, erythropoietin) very clearly address one or other of these pathways. However, there is complexity overlying this simple idea. It is likely, as with metabolic pathways, that it will be beneficial to address multiple control points simultaneously. Perhaps this underlies the reported use of erythropoietin among top sprinters? It is concluded that, although performance-enhancing drugs work, the issue with regards to the legal ergogenic aids is much less clear. The main use of biochemistry to enhance sports performance legally may not be in cleverer use of nutritional aids, but instead in understanding the basic mechanisms of fatigue and using this information to tailor training programs.

The next two chapters focus on the use of legal ergogenic aids that assist energy metabolism before (Spriet et al., Chapter 3) or during (Nicholas, Chapter 4) a race. Pre-event oral ingestion of carnitine, creatine and bicarbonate have all been touted as enhancing performance during exercise (Chapter 3). The simple response to whether these work is yes but …, no but … maybe but … in that order. Carnitine can in principle enhance long-chain fatty acid entry into mitochondria and buffer the exercise-induced increases in acetyl-CoA during exercise. However, it seems impossible to alter muscle cytoplasmic carnitine levels by taking pills. Instead intravenous infusions are required with co-administration of insulin. Whether this improves performance is still unclear and perhaps a moot point, given that the use of insulin is banned anyway. Creatine is more promising. There is good evidence that muscle levels respond to oral dosing and that this results in improved performance in sports that require short-term sprints (hence its somewhat controversial use by a number of top football and rugby clubs). It may also help with improving muscle mass during a resistance-exercise programme by currently unclear mechanisms (see also Chapter 5). The use of bicarbonate or citrate is more equivocal. Both affect plasma bicarbonate levels and therefore can potentially buffer pH changes during exercise. But potential performance benefits are frequently offset by side effects, vomiting and diarrhoea not being conducive to top athletic performance.

Perhaps the clearest example of a performance-enhancing, completely legal, nutritional aid appears in Chapter 4. The use of added carbohydrate-electrolyte solutions during endurance exercise has a sound biochemical basis and good experimental evidence base. It is hard to envisage anyone winning a marathon now only taking water on-board during a race and the remaining arguments are about fine details, not about whether these drinks affect performance.

Although Nicholas shows that carbohydrate supplementation is key to maintaining a supply of glucose for the mitochondria, events at the other end of the mitochondrial electron chain are equally, if not more, important. After all, these events are not called aerobic for no reason. Cooper (Chapter 5) discusses the importance of oxygen delivery to mitochondria. The evidence that this is limiting to endurance sports performance is overwhelming.
Increasing the blood oxygen content can be achieved legally by altitude training or hypoxic tents, though there is controversy about the optimal methodology required. When it comes to illegal performance-enhancing in aerobic sports, the granddaddy of methods is blood doping, using your own or someone else’s blood. The new kid-on-the-block is of course, erythropoietin, which controls red blood cell production. However, interestingly, with the recent enhancements in erythropoietin testing, blood doping has been making a comeback. Given the obvious and significant performance-enhancing benefits involved it is probable that this field will be a battleground for athletes and doping control for the foreseeable future.

Moving away from endurance events into the world of power sports, Chapters 6 (Tipton and Ferrando) and 7 (Wackerhage and Ratkevicius) explore the use of legal and illegal methods to improve the muscle mass, and hence power, available to athletes. Tipton describes the complex interplay between nutrition and exercise required to enhance muscle protein synthesis and inhibit protein breakdown. Intriguingly, although it is clear that banned anabolic steroids have a strong effect, there is no good evidence that natural steroid precursors such as androstenedione or dehydroepiandrosterone can promote a muscle mass increase during exercise. Androstenedione in particular was widely used in sports, especially in major league baseball, until banned by the US government in 2004. Intriguingly the two compounds of most concern to WADA, insulin and growth hormone, do not appear to stimulate muscle protein synthesis in laboratory studies. Wackerhage and Ratkevicius describe in detail the signalling pathways underpinning the control of muscle protein synthesis. Not surprisingly the list of compounds on this pathways reads like a doper’s handbook including insulin, growth hormone, insulin-like growth factor-1 and mechano-growth factor. Owing to the complexity of these pathways it would seem that it would be difficult to develop genuinely new drugs to target them, that do not have detrimental side effects on other signalling pathways. This seems to be the case on the activation side increasing muscle mass where knockouts of the key regulator, mTOR (mammalian target of rapamycin), show a number of effects outside the muscle. Perhaps the most intriguing recent discovery, however, is the myostatin pathway, which seems to rather specifically control the inhibition of increases in muscle mass. Myostatin knockout mice have a greater than 200% increase in muscle mass. And extreme muscling in cows and some humans has been linked to specific mutations in myostatin. This seems as close as possible to single gene control of a pathway and it is not surprising that inhibition of myostatin, either chemically or genetically, is a new frontier in searching for effective drugs to aid performance in power sports.

From World War II onwards amphetamine and its derivatives have been in widespread use by soldiers on all sides. So it is perhaps not surprising that the first drugs to be tested for in sport in modern times, and probably the first to be used, were stimulants. These were in common use in the 1950s and still account for over 10% of positive drug tests. Although the basic mechanism of stimulant
function is known, the fine details of how this might affect sport performance is unclear. This is perhaps the area where the most confusion exists with regards to drug testing. Pseudoephedrine is legal and ephedrine is banned. Yet current evidence suggests that, if anything, pseudoephedrine may be the more ergogenic. Athletes have been banned for taking the decongestant l-methamphetamine, whereas it is only the d-isomer that is the stimulant. However, even then there is little evidence that stimulants such as d-methamphetamine or cocaine are performance-enhancing. Although for obvious reasons there are limited recent studies on the ergogenic effects of cocaine, study in this area does have a long history. Sigmund Freud, in 1884 [8], reported the effects of cocaine on a number of disease and healthy states. An avid self-experimenter, Freud noted the effects of taking the drug:

“I took for the first time 0.05 g of cocaine and a few moments later I experienced a sudden exhilaration and feeling of ease”

Freud believed he was stronger on cocaine. Laudably, and perhaps surprisingly to our 21st century view of Freud, he didn’t believe everything his mind was telling him and decided with regard to these observations to “render them objective through measurements”. Hence he published the first paper demonstrating increases in grip strength after acute cocaine administration using a handgrip dynamometer [9]. But these studies haven’t stood the test of time [9]. It is likely that, as Freud himself noted, the effects are strongest when the subjects are at their weakest; any ergogenic effect on an athlete primed for competition will therefore be negligible.

Returning to current practice, the best stimulant for sport seems to be caffeine, which is proven to improve short-term high-intensity exercise; though the caveat here is that caffeine is far and away the best-studied stimulant making it easier to find the optimum dosing regime. It is looking like we need to revisit the biochemistry in some detail to see whether we can unravel the link between stimulants and performance. This is the purpose of Chapter 8 (Jones). Stimulants enhance neurotransmitter function generally by enhancing the persistence of catecholamine neurotransmitters. However, caffeine is a direct adenosine receptor antagonist. We now know a lot more about the wide range of biochemical pathways perturbed by caffeine in vitro. It seems likely that the dominant ergogenic effect in vivo is by adenosine receptor blockade which would be consistent with its increased efficacy compared with amphetamine-based stimulants. However, given the range of possible pathways Jones outlines, we should be cautious in these conclusions.

There is no doubt which area of illegal sport performance enhancement most captures the imagination of the media, public and sports governing bodies. The ability to alter your genes to create ‘superhumans’ is tied up with a whole panoply of mythical and racial imagery. Bizarrely, despite the historically over-inflated claims of gene therapy for curing disorders that affected only a single gene, the possibility of genetically enhancing humans to improve sport performance is nowhere near as far-fetched as it once appeared. Two facts
contribute to this concern. First there is the realization after the Balco (Bay
Area Laboratory Co-operative) and THG (tetrahydrogestrinone) scandal [10]
that athletes and coaches are putting resources into developing genuinely new
compounds and doping methods, rather than just ‘borrowing’ drugs originally
intended for medical research. Secondly, as outlined by Harridge and Velloso
in Chapter 8 many of the genes/proteins which are involved in determining
key components of athletic performance have been identified. Better (or worse)
still, naturally occurring mutations in humans as well as gene-transfer experi-
ments in adult animals have shown that altered expression of these genes can
indeed affect physical performance. Whether it be insulin-like growth factor
1, Akt or myostatin for increasing muscle mass, erythropoietin or VEGF
(vascular endothelial growth factor) for enhancing oxygen delivery or PGC1α
[PPAR (peroxisome-proliferator-activated receptor) γ co-activator] or PPARδ
for increasing type I fibre content, it seems increasingly likely that in the next
5–10 years it will be possible to enhance sport performance genetically. In the
prescient words of James Watson with regard to the human genome project, we
now have “a giant resource that will change mankind, like the printing press”.
Certainly it looks like sport will not be exempt from this change.

So where does this all leave the drug testers? Cowan (Chapter 10) runs a
WADA-accredited laboratory and illustrates the recent scientific successes that
have facilitated the control of doping in sport. Certainly with regards to small
metabolites, the advance of analytical techniques means that, given enough
resources, random out-of-competition testing is likely to eventually catch all
athletes using banned drugs. A problem relates to new compounds that have
not been tested before, as was shown with THG it required a ‘mole’ at Balco to
send the compound to a laboratory for its identification and to enable a test to
be subsequently developed. Blood and gene doping are far more problematic;
their solution is likely to require additional ways of looking at doping control,
moving from using reference populations alone to individual reference values,
in the form of ‘athlete’ passports.

History tells us that the search for new ergogenic aids, drugs and doping
methods will continue apace. Indeed this is one of the few biochemistry lec-
ture courses we teach where, in order to ask the students to keep abreast with
new discoveries, we can just ask them to follow the media. The underlying
biochemistry that underpins these developments is being increasingly well-
characterized. Hopefully this book will give students and researchers the tools
to understand the latest developments for years to come.

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