ON THE CONTRARY **Tony Delamothe**

Monkey business

Why is it easier to believe in the effects of testosterone than it is to show them?

If ever there was a hormone whose discovery was a foregone conclusion it was testosterone. Almost a century before the steroid was isolated Arnold Berthold showed that transplanting testes into castrated roosters restored their characteristically rooster-like behaviour.[1] After this, trapping the essence of masculinity in a bottle was only a matter of time. Time and, for Adolf Butenandt, 25 000 L of urine donated by a Berlin police barracks.[2] From this he extracted 50 mg of androsterone and went on to synthesise testosterone and win the Nobel prize for chemistry in 1939.

Between Berthold and Butenandt, however, came the neurologist Charles-Édouard Brown-Séquard. At the age of 72 he delighted the world by announcing that he had rejuvenated himself by injecting aqueous extracts of testes from freshly killed guinea pigs and dogs. A placebo effect, say modern killjoys—little hormone would have dissolved in water. Nevertheless, soon many doctors were treating their male patients with organ extracts.[1]

In the 1920s the surgeon Serge Voronoff became famous for transplanting monkey glands into his patients, even influencing the manager of Wolverhampton Wanderers to foist the procedure onto his players.[3] Wolves had a few great seasons (almost their last), but it transpired that transplanted glands were rapidly rejected, leaving only scar or inflammatory tissue.[4]

Soon after Butenandt's isolation of testosterone came implants and short acting injections that really did work. The question then, as now, was who should get them? There's no doubt that hypogonadal men should and that men who are merely feeling a bit out of sorts should not. But lots of grey areas—such as men who are a bit hypogonadal and who are feeling a bit out of sorts—remain. To catch up with current thinking I booked my free place on a recent Bayer HealthCare seminar entitled "Restore the Man."

Brown-Séquard and Voronoff would have recognised the focus of this event: the older man. Testosterone concentrations fall progressively with age, so a proportion of older men will predictably have testosterone concentrations below the normal range of healthy young men. It seems a bit harsh to turn an age related phenomenon into a disease, but that's what's happened. These older men risk being labelled as having "late onset hypogonadism" or "age associated testosterone deficiency syndrome," so it's important to know where to set the threshold. The best attempt has emerged from the European Male Ageing Study (EMAS), which has defined the syndrome of late onset hypogonadism as a combination of sexual symptoms and testosterone level.[5] But it's still a bit of a mess. As the authors point out, "The prevalence of even the most specific sexual symptoms of androgen deficiency was relatively high among men with unequivocally normal testosterone levels." Their criteria give a prevalence of late onset hypogonadism of 0.1% in men aged 40-49 years, 0.6% in those aged 50-59, 3.2% in those aged 60-69, and 5.1% in those aged 70-79.

This gives a rough estimate of the size of the market for testosterone replacement therapy, but no one can quite forget what happened with hormone replacement therapy in women. If treatments for prostate cancer seek to drive testosterone levels to zero, what would the effect of testosterone supplements be in men whose age puts them at the highest risk of developing prostate cancer? The position of speakers at the meeting varied from "it might be all right" to the more bullish. What's needed now is a large randomised controlled trial of testosterone in men who fit the EMAS criteria for late onset hypogonadism. But it will require steady nerves.

Meanwhile, another purported effect of testosterone is back in the spotlight: aggression. Here the evidence for a connection is far from clear cut. Summarising what was known in 1993, Gail Vines wrote: "In humans, just as in monkeys and mice, most attempts to link testosterone levels to aggression have failed."[1] Twenty years later David Benatar can find plenty of assertions of a connection in the literature but no convincing proof.[6]

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What's drawn recent attention to testosterone's aggressive potential is a study published in 2008,[7] which is now the centrepiece of a book.[2] It reports endogenous steroids in 17 male traders working over eight consecutive business days in the City of London. One key finding was that a trader's morning testosterone level predicted his day's profitability. Much about masculinity, aggression, competitiveness, and risk taking has been read into this single finding.

To someone used to reading research in regular medical journals, its presentation comes as a shock. The only testosterone value to appear anywhere in the paper was the mean testosterone of all the estimations performed on all the participants during the study. The outcome of interest was trading returns on days when traders' morning testosterones were above and below their median levels. I can tell you that the P value for this comparison was 0.008, but nothing else. The findings were featured in every financial newspaper and magazine and may explain why testosterone "has become Wall Street's drug of choice as traders seek a competitive edge in the face of job cuts," as the *Financial Times* put it.[8]

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ETHICS MAN **Daniel K Sokol**

A passion for accuracy

A cursory glance at doctors and others at the peak of their profession reveals that attention to detail binds them all

When I was called to the bar, my father gave me a beautiful wooden box, within which were inscribed the words of Hardy Cross Dillard, once dean of the University of Virginia Law School and later a judge at the International Court of Justice in the Hague. The text described the perfect lawyer, and one sentence read, "He is endowed alike with legal imagination and a passion for accuracy."

Even a cursory glance at people at the peak of their discipline reveals that a passion for accuracy, or attention to detail, binds them all. Although not enough to achieve success, it is a necessary component of it. The chess legend Gary Kasparov spent so much time analysing the games of his opponents before tournaments that a rumour emerged that he had a team of grandmasters conducting research on his behalf. Michael Jordan was known in his pre-National Basketball Association days for spending more time practising on the basketball court than any of his peers. The elite group of three star Michelin chefs, though widely different in style, share an almost obsessive concern for perfection. Fyodor Uglov, a surgeon renowned for his flawless technique, sutured 400 rubber gloves to improve his skills in anastomosis. It is a safe bet that all the medallists at the forthcoming Olympic Games, from archery to wrestling, will owe their triumph in part to a phenomenal attention to detail.

A passion for accuracy goes hand in hand with patience and persistence. Albert Einstein once said, "It's not that I'm so smart. It's just that I stay with problems longer." The challenge is staying focused for long periods when the task is dull. I can only imagine that studying the intricacies of the law of indirect tax is as soul sapping as studying the complex anatomy of the foot, but sadly there is no shortcut to mastering the subject. This is why William Osler considered the master word in medicine to be . . . "work."

Patience and persistence require time, and a key concern with the reduction in doctors' working hours brought about by the European Working Time Directive is that they will no longer have the time to develop an eye for detail.

A passion for accuracy is also needed for the practice of medical ethics. In my teaching I tell students that good ethics starts with good facts. Although on occasion decisions cannot wait and must be made with limited information, most of the time there are opportunities to gather more facts and reduce the role of conjecture. In medicine, too, there are times when attention to detail is inappropriate. Harvey Cushing, the father of modern neurosurgery, was a slow and meticulous surgeon, but his precision was unhelpful when transposed to a busy military hospital in war torn France. The historian Michael Bliss compared Cushing at the casualty clearing station to a master chef working at McDonald's. Nevertheless, in normal circumstances attention to detail is beneficial. This is why it is risky for professionals, including doctors and lawyers, to give advice in so called "kerbside" or corridor consultations. The account of the problem is likely to be one sided and incomplete. The spectre of negligence looms ominously behind such requests.

In the United Kingdom professional medical ethicists are rare birds who seldom make decisions that directly affect patients. In recent years an increasing number of clinical ethics committees have appeared in UK hospitals. This is a welcome development. Yet, looking back on my days sitting on these committees, I am concerned that, although well meaning and able, our advice to clinicians was based on partial information. With luck, we would receive a short summary of the case, drafted by the requesting clinician, hours before the meeting. Occasionally the clinician would attend and briefly present the case. We never had the other side of the story, at least no more than the clinician's account of it; nor were we ever shown the patient's medical notes.

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In such cases the risk of a biased presentation is significant. Deliberately or otherwise, the presentation may be structured in a way that favours the answer sought. There is no such thing as a neutral description of the facts of an ethical problem. What is said, and left unsaid, how it is told, in what order, by whom, what is emphasised and downplayed—all these affect the listener, even if only subliminally.

This unstructured approach is in contrast to that of the research ethics committee on which I sit, where we receive detailed protocols days in advance, spend hours reading over them, and prepare questions for the researcher. There is an uncomfortable asymmetry between the rigour expected of research ethics committees and clinical ethics committees, yet the advice of the second type can also, if acted on, affect patients. What is the quality assurance of clinical ethics committees—or indeed of medical ethicists such as myself? Anyone reading this article could call him or herself a medical ethicist and set up a consultancy service.

If I were the chairman of a clinical ethics committee or a hospital manager, I would ask myself this question: if someone issued a claim of negligence against a recommendation of the committee, what would the forensic examination of the decision making process reveal? Could we show a thorough attention to detail?

A passion for accuracy is not only a necessary element of great clinicians and committees: in each case it confers the added advantage of legal protection.

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