The concept of some special substance that can turn a male child into a man and also control sexual performance has been an enigma for many centuries. Farmers of antiquity had always known that castrated pigs, bullocks and cockerels would fatten up, and would become less aggressive. It was also realised for centuries that the testes were involved in some way with masculinity in humans. Removal of the testes in a prepubertal boy stopped the onset of puberty, with consequent failure to develop secondary sexual characteristics, diminished sex drive and loss of fertility. Although removal of the testes after puberty caused sterility, it did not necessarily remove desire or the ability to get an erection, as the inhabitants of a caliph’s harem guarded by his postpubertal eunuchs often found to their satisfaction. Paradoxically, failing sexual powers may well come with age, but a man can still be fertile.

**DISCOVERY OF TESTOSTERONE**

Desperately trying to restore their failing ability, men would try many weird and wonderful substances, potions and techniques. In 1771, the English surgeon John Hunter first showed the masculinising effects of transplanting a cock’s testicles into a hen.\(^1\) Unfortunately, he did not publish his results widely and it was not until 70 years later that the German scientist Arnold Berthold repeated the experiment, publishing the results.\(^2\) He showed that the testicles produced an important substance affecting masculinity.

Figure 1. Crystalline testosterone (© Pasieka/Science Photo Library)

John Tomlinson outlines the history of testosterone, from the early experiments demonstrating its masculinising effects to the modern-day use of testosterone for treatment of hypogonadism.

As a result of this work, much effort over the next century went into trying to isolate the mysterious substance involved. The vogue of transplanting monkeys’ testes into humans continued from the late 19th century to the early 20th century. Even now, especially in some Asian countries, substances such as rhinoceros horn and mandrake root are ground up and taken as an aphrodisiac. The scientific search for the elusive substance ended when testosterone was discovered and isolated in the pre-war period between 1920 and 1939.

*John Tomlinson died suddenly on 11 June 2012 (see obituary on page 41).*
The discovery of testosterone is remarkable in that it was announced in the same year, 1935, by three European scientists working independently. Ernst Laqueur, a scientist with Organon in Amsterdam, first isolated and synthesised this elusive substance, naming it testosterone in May 1935, three months ahead of a German scientist, Adolf Butenandt, working with Schering in Berlin. His paper was published in August, a week ahead of that of Ružička, a Yugoslavian chemist with Ciba in Zurich. The last two received the Nobel Prize for their work in 1939.

Soon, implants of pure crystalline testosterone became available (Figure 1). Although oral treatment with methyl testosterone was also obtainable, it was unpopular in the UK because of toxic hepatic side-effects (although it is still available in the USA). For almost 60 years, pellets of subcutaneous crystalline testosterone were the only satisfactory, long-acting form of testosterone. However, this treatment did not catch on, first because of the cloud hanging over it caused by the deleterious effects of methyl testosterone, and second because pharmaceutical companies felt that there was no financial benefit in pursuing further research. Patients with a low testosterone level were considered to be low priority, as hypogonadism was not (then) considered to be life-threatening. This changed when work to find a male contraceptive began and the long-term effects of hypogonadism became apparent.

**HYPOGONADISM**

In a healthy man, the production of testosterone diminishes gently as he ages, with the level of free testosterone in a 70-year-old being two-thirds that of a 25-year-old. Many men put their waning interest in sex or loss of sex drive quite correctly down to the fact that they are just growing older and are quite content as they are. However, in an increasingly large number of men, this gentle fall in testosterone production can accelerate well before expected, sometimes even in their late 50s and early 60s (Boxes 1 and 2). There can be a series of seemingly unconnected and rather nebulous symptoms, such as excessive fatigue and a decrease in sex drive; some men become quite distressed at the loss of their familiar, early-morning drive; some men become quite distressed. Depression can be marked and may become quite severe. This often leads to the patient being mistakenly treated with antidepressants, which only worsens the sexual problems and does not sort out the real difficulty of testosterone deficiency. It is only much later, with long-standing androgen deficiency, that there are obvious physical changes, such as testicular atrophy, sparse body hair, gynaecomastia and osteopenia.

There are also marked but variable mood changes, with the family noticing much greater irritability and bad temper in an otherwise placid man (the ‘Victor Meldrew’ signs). Depression can be marked and may become quite severe. This often leads to the patient being mistakenly treated with antidepressants, which only worsens the sexual problems and does not sort out the real difficulty of testosterone deficiency.

**BOX 1. Causes of testosterone deficiency**

**PRIMARY CAUSES**
- Genetic (Kleinfelter’s or Kallman’s syndromes) – rare

**SECONDARY CAUSES**
- Advancing age, usually >65 years
- Diabetes and the metabolic syndrome (Box 2), which, with central obesity, insulin resistance, dyslipidaemia, hypertension and hypogonadism, is a warning of possible future cardiovascular problems
- Testicular trauma: after torsion, orchidectomy, a road accident or war injuries
- Body trauma: after a major operation or heart attack
- Infections: mumps/orchitis, glandular fever, especially after puberty, hepatitis, sexually transmitted infections and HIV/AIDS
- Other hormonal causes: pituitary tumour (prolactinoma), long-term steroids, and other drugs such as cannabis, ketoconazole, which inhibits testosterone production in the testes and adrenals, and spironolactone, an androgen antagonist
- Chemotherapy and radiotherapy, especially to the pelvis
- Excessive exercise

**BOX 2. Features of the metabolic syndrome**
- Obesity
- Raised blood pressure
- Low testosterone
- Diabetes with a glucose level >6mmol/l
- Low high-density lipoprotein cholesterol (<1.15mmol/l)
- Raised triglycerides (>1.9mmol/l)
- Raised C-reactive protein (>8mg/l)
Interestingly, the symptoms are similar to those of the menopause, although for a man there is not a ‘pause’ in the physical sense like menstruation in a woman, and so the ‘male menopause’ and the ‘andropause’ are semantically inaccurate. As these symptoms are rather nebulous, a careful history and examination should be carried out, including a rectal examination to rule out an overt carcinoma of the prostate. Most patients and many doctors dislike this examination, but it is essential, especially if there is the possibility of replacement testosterone being considered. A diagnosis of hypogonadism should not be made without biochemical confirmation (Box 3).3

MANAGEMENT OF TESTOSTERONE DEFICIENCY

Does gonadal deficiency matter? For very many men, the answer is a resounding ‘Yes’ and current medical thinking is in agreement. A low testosterone level (and consequent erectile dysfunction) is a predictive marker for those who are at high risk of cardiovascular events, morbidity and mortality.6

Unfortunately, many doctors are still concerned that giving testosterone causes cancer of the prostate, even though there has been no evidence for this.6 No association has been found between the risk of prostate cancer and serum concentrations of testosterone, but the story has become confused because adding testosterone aggravates the growth and spread of an already existing carcinoma. It is therefore mandatory to check the prostate-specific antigen (PSA) in any man about to start on replacement (not supplementary) testosterone, within three months of starting, six months later and then every 12 months while on replacement, which is generally for life. If the PSA rises by >1.4ng/ml in any one year after starting testosterone therapy, the patient should have a urological check, and close surveillance in the future.

The normal testosterone range is 12–35nmol/l (350–985ng/dl). The international recommendation is that a testosterone level of 8nmol/l or less should be treated, and >12nmol/l does not need to be treated.9 If the level is 5.5nmol/l or less, the prolactin level should be checked. A level between 8 and 12nmol/l should be repeated and an empirical, monitored trial of replacement for three months should be given (Box 4). The aim of treatment should be a total testosterone of at least 15nmol/l to ensure symptomatic improvement.11

BOX 3. Blood tests required to confirm hypogonadism³

- Testosterone (mid-morning sample)
- Sex hormone-binding globulin
- Follicle-stimulating hormone
- Full blood count including haematocrit
- Fasting lipids
- Fasting glucose
- Thyroid function
- Prostate-specific antigen (mandatory)

BOX 4. Normal and abnormal testosterone levels

- Normal range: 12–35nmol/l
  - young adults can have a level well over 20nmol/l
- Hypogonadism: <8nmol/l
  - replacement testosterone required (any age)
- Doubtful hypogonadism: 8–12nmol/l
  - retest with a mid-morning specimen and, if still low, give a three-month trial of testosterone replacement (test prostate-specific antigen first)

BOX 5. Testosterone preparations

ORAL
- Testosterone undecanoate (Restandol), 40mg capsules in oily solution, four times a day with a fatty meal

BUCCAL
- Testosterone (Striant SR), adhesive buccal tablet, 30mg every 12 hours (can fall off)

INTRAMUSCULAR
- Testosterone enanthate, non-proprietary injection, 250mg every two to three weeks
- Oily testosterone undecanoate (Nebido) 1g every 10–14 weeks
- Sustanon 250mg/ml (mixture of three testosterone compounds), 1ml every two to three weeks
- Testosterone propionate (Virormone), 50mg/ml, 1ml two to three times a week

IMPLANT
- Testosterone (crystalline) pellets, 200mg x 6 approximately every four to six months

TRANSDERMAL
- Gels: Testim, Testogel and Tostran containing testosterone in an alcoholic gel, 5mg rubbed in daily
The major role of replacement therapy is to replace testosterone levels to as close to physiological concentration as possible. There are five different types of testosterone preparation: oral, buccal, intramuscular, implant and transdermal (Box 5).

The most popular (and economical in time) preparations tend to be an injection, usually a long-acting one, or a gel, as they do not have the see-saw effects of the older preparations.

Testosterone replacement leads to improved wellbeing and mood within three to six weeks, with a maximum effect in 18–30 weeks. Sexual interest reappears within three to four weeks, though maximum benefits take longer. Early-morning erections can return quickly, but can take up to six months; there are fewer hot flushes and minimal sweating, as well as enhanced effectiveness of PDE-5 inhibitors. It is impressive and satisfying to see the effects on a man’s quality of life within three weeks, in one who thought enjoyment of life had come to an end. However, it is obvious that hypogonadism is an underdiagnosed condition and men with hypogonadism may present to a range of medical specialities and medical professionals who need to be more aware of the syndrome.

‘Just why substitution of testosterone is withheld [by doctors] is not clear. However, the better the general effects of testosterone on wellbeing, mood, bone, muscle, and blood are understood, the more testosterone replacement will be considered.’

Declaration of interests: none declared.

REFERENCES