vesicula per duo peculiaria foramina sease exonerare intra urethram, distincta ab iis per quae materia seminalis è vasis deferentibus excidit. Ad excercitandam in demortuorum cadaveribus penis erectionem hoc instrumentum quoque aptissimum est, nam immisso liquore per Arteriam Hypogastricam ad corpora nervosa excurrentem statim erigitur Penis, idque magis vel minus prout majori vel minori vi liquorem in corpora nervosa propuleris". GRAAF R. de, *Tractatulus de usu Siphonis in Anatomia.* In: *Opera Omnia*. Lugduni Batavorum, Officina Hackiana, 1677.

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TRANSFORMING THE TESTICLE: SCIENCE, MEDICINE AND MASCULINITY, 1800-1950

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SUMMARY

The article explores episodes of the history of the discovery of function and actions of testicle - focusing first on their transformation from a quasi - mystical organ of virility to chemical factory secreting substances essential to physical and psycological attributes of masculinity; then showing how the powers of the testicular secretions were soon seen to extend for beyond the narrowly sexual sphere.

In his encyclopaedic history of endocrinology, Victor Medvei describes the testicle as *'the oldest key to the endocrine treasure trove'*[1]. But although the testes had always been associated with virility, it was only during the nineteenth century that its purely sexual actions were established as being distinct from and independent of its reproductive functions. This paper explores episodes of this complicated history, focusing first on the transformation of the testicles from a quasi-mystical organ of virility to a chemical factory secreting substances essential to physical and psychological attributes of masculinity and then showing how the powers of the testicular secretions were soon seen to extend far beyond the narrowly sexual sphere.

The functions of the ovary, too, were elucidated roughly during the same period but along substantially different tracks. The ovary, as I have argued elsewhere, was harnessed to diverse clinical theories and procedures long before any clear know-

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ledge of its endocrine importance had been acquired. This theme is virtually absent from the history of testicular research. The functions of the testicle were identified along rather more predictable paths of research, which, however, received a massive boost from the rejuvenation mania of the 1920s[2].

John Hunter: Gonadal Sympathies

The importance of the testes for the maintenance of the male sexual characters was known even to Aristotele. Castration, he had observed, resulted in the loss of masculine attributes. As far as systematic, *experimental* investigations of the issue are concerned, however, the story begins with John Hunter (1728-1793).

Hunter, of course, was not working within today's endocrinological paradigm. In his time, as C. Barker Jørgensen has pointed out, the body was supposed to be regulated and its organs connected by a range of *sympathies*, rather than by nerves or circulating hormones[3].

Only rather incomplete accounts remain of Hunter's experiments on the gonads. He seems to have relied greatly on transplantation experiments to determine their functions. That method would remain central to research on the gonads well into the modern era and some of Hunter's eighteenth-century experiments strike one as forerunners of those common in the early 1900s. Unfortunately, he did not publish a detailed account of the one that would become most famous. In this, he transplanted the testis of a cock *'into the belly of a hen'*, possibly expecting, Jørgensen speculates, *'a more or less complete sex reversal'*. That did not, of course, occur, leading Hunter to regard the experiment as a failure. It was Hunter's rather dramatic expectation that may have blinded him to the possibility that the transplanted hens, although they had not miraculously changed into cocks, did develop a mixture of male and female secondary sex characters such as masculinized combs and wattles, results commonly obtained in similar experiments conducted during the 1920s[4].

Even if Hunter had noted these changes, they would not have suggested a humoral mechanism of gonadal action on the sex characters. For Hunter as well as his contemporaries, distant ac-

tion within the body was brought about by sympathies animated by the vital principle. Whether those sympathies were channelled through the nerves or the blood was not an important issue. At a more mundane level, Hunter was less of a natural philosopher than a surgeon. Like many of his contemporary surgeons, he was primarily interested in exploring the *'possibilities of severing and reuniting parts of the body'*[5]. In their investigations of the links between the sex glands and the secondary sex characters, early-nineteenth-century scientists did not move very far beyond Hunter. Indeed, as Jørgensen emphasises, the influence of the testicles on sexual characters was universally acknowledged but the nature and mechanisms of that influence were either ignored or admitted to be unknown[6].

Arnold Adolf Berthold and Early Humoral Theories

In 1849, the Göttingen physiologist Arnold Adolf Berthold (1803-1861) published a brief paper (which had been preceded by a preliminary communication on the same topic) describing the results of his experiments on six young, castrated cocks[7]. Two of the cocks were left castrated and developed into capons. *'They were not aggressive'*, observed Berthold,

> *"they fought with other cockerels rarely and then in a half-hearted manner, and they developed the monotone voice of the capon. Comb and wattles became pale and developed but slightly; the head remained small"*[8].

In two other animals, one testis had been removed, while the other, separated from its attachments, was left lying loose in the abdominal cavity. The last two animals in the series had beren castrated completely but then re-implanted with one testis each on their intestines. The four animals in the second and third groups developed into normal, sexually differentiated cocks:

> *"they crowed lustily, often engaged in battle with each other and with other cockerels, and showed the usual reactions to hens. Their combs and wattles developed as in normal fowls"*.

When the testicular graft was removed from one of the third group, however,

"the fowl began to emit the typical voice of the capon, it no longer showed interest in hens, nor would it battle with other cockerels; in fact it remained at a distance from them and showed the nature of a true capon"[9].

It was clear from these results that the testicles were essential to the development and maintenance of masculine sexual characters. But how was that testicular influence mediated? Autopsies had revealed that the transplanted testes in the experimental animals had permanently lost their original nervous connections – and yet, the animals had remained fully masculine. It followed, therefore, that the masculinizing effects of the testes must be mediated through the blood. Berthold did not speculate on the nature of this blood-mediated influence. It is likely that his chief interest was not so much to elucidate the functions of the testicle but to investigate whether testicles could be successfully transplanted. Indeed, in his tabulation of the results of his experiment, the first item stated:

"The testes belong to the transplantable organs; they may become reattached after removal from the body; actually one may transplant them from one animal to another, and the attachment may occur at the original site of removal or in an entirely foreign location..."[10]

He also announced that he was planning to replicate Hunter's experimental transplantation of testicles from a cock to a hen, although there is no record that he ever performed this experiment[11].

Whatever Berthold's own interests, however, his experiments were hailed by later scientists as revolutionary[12]. In his own time, however, they did not have much impact. Berthold's colleague, the well-known physiologist Rudolph Wagner tried to replicate the experiment without any success. Towards the end of the century, several other scientists tried their hand at testicular transplantation but they, too, failed. The failure to replicate Berthold's findings left the questions hanging, which stimulated a young physiologist of Vienna, Arthur Foges, to launch yet another attempt at their replication in 1897. Operating on 3-5-week-old cocks, Foges conducted thirty-three castrations but could remove all testicular tissue only in eight cases. Berthold's

chosen animal, Foges discovered, was extremely difficult to castrate because it frequently possessed functional bodies of testicular tissue in addition to the testicles proper. Incomplete castration did not seem to interfere with the development of male secondary sex characters – sexual development was only impeded if the remnant of the testicle fell below a certain critical mass and if the animal was not old enough to have developed some male characters before the operation. Foges also attempted to transplant testes from one cock into another: whether or not the recipient still had its own testicle, the graft failed.

Even his few successes, however, illuminated the nature of the specific influence of the gonads on the development of the secondary sex characters. Some of the secondary sex characters, Foges established, were undoubtedly independent of gonadal influence. Castration led to caponisation (which began quickly after the operation) but never to feminization. The cocks could still crow, although they did not usually do so. Far from being timid, they fought constantly among themselves and also with normal cocks and hens. Their combs differed from those of normal cocks but also from those of hens. This was an important point. Ever since British naturalist William Yarrell (1784-1856), it had been accepted that castrated male animals became feminine in appearance and behaviour[13]. Even Charles Darwin, citing Yarrell, had asserted that the castrated male animal took to *"sitting on eggs, and will bring up chickens"*[14]. This proved, Darwin had claimed, that

"the secondary characters of each sex lie dormant or latent in the opposite sex, ready to be evolved under peculiar circumstances"[15].

August Weismann had accepted Darwin's hypothesis, adding that

"men who have been castrated in their youth retain a high voice like that of the other sex, and the beard does not become developed"[16].

Foges's study demonstrated that these views were inaccurate[17]. His findings were soon accepted by most scientists and in 1910, Artur Biedl declared that

"observation of man and of animals of widely different species shows, beyond any manner of doubt, that castration does not impart characteristics peculiar to the opposite sex, and that transformation into the heterosexual type [i.e. feminization in males or masculinization in females] is never observed"[18].

Much, of course, remained to be clarified about the differences between the consequences of pre-pubertal and post-pubertal castration but one point, at least, was clear: the testicles were essential to the development of full masculinity but a male deprived of them did not develop physical characteristics that were fully feminine.

The Consolidation of Humoral Theories

The elaboration of modern concepts of testicular endocrinology was greatly dependent upon the elucidation of testicular histophysiology. It was Franz Leydig (1821-1908) who, in 1850, had identified that the testicles comprised at least two distinct groups of cells: the sperm-producing cells and the interstitial cells that came to known as Leydig cells[19]. There were other cell-groups of histological importance (such as the cells of Sertoli) but physiologically, the two former groups seemed to be most relevant.

Initially, it was widely believed that the function of the Leydig cells was to process nutritional material for the production of spermatozoa. Soon, however, it was noticed that the destruction of the sperm-producing cells – as seen naturally in undescended testes – did not interfere with the development of the secondary sexual characteristics. Similar findings were obtained after experimental destruction of the germinal tissue, as in the work of Julius Tandler and Siegfried Grosz, both of Vienna. Tandler and Grosz had irradiated the testes of roebucks with x-rays. The animals showed none of the typical changes associated with castration, such as the loss of antlers. The internal secretions, thus, could be assumed to have remained undisturbed. On histologic examination, the irradiated testes showed a loss of generative tissue but conservation of the interstitial cells. The conclusion, therefore, was that the generative tissue played no role in the internal secretory activity of the testes and the virilizing substances of the testicle must be produced by the hitherto underestimated Leydig cells[20].

The experiments of Pol André Bouin (1870-1962) and Paul Ancel (1873-1961), anatomists at the University of Nancy and then at Strasbourg, provided the most persuasive evidence: they ligated the vas deferens, thereby causing pressure atrophy of the generative tissue. The interstitial cells survived and the experimental animals showed no loss of masculine sexual characters. In other experiments, they showed that if a rabbit was castrated unilaterally and its vas on the other side resected, there was no diminution in sexual activity. When the remaining testicle was examined, however, the generative tissue had degenerated completely while the interstitial cells had multiplied luxuriantly. Moreover, cryptorchid animals, although infertile, were never deficient in masculine sexual characters. It was clear, therefore, that the sexual characters and the sexual instinct of the male depended entirely on the interstitial tissue[21].

Brown-Séquard and the Apotheosis of the Testicle

Although the human testicles never experienced the kind of reckless clinical manipulation that the human ovaries underwent, the saga of testicular research did have its own clinical dimension. From the late nineteenth century, the gland had become a clinical superstar. This prominence was entirely due to the efforts of the eminent French-American-Mauritian physiologist Charles-Edouard Brown-Séquard (1817-1894). Brown-Séquard had impeccable credentials as a scientist as well as an endocrine researcher. In 1856, he had shown, through a series of experimental removals of the adrenals, that those glands were essential to life[22]. This early work was all but obscured by his later research on the testicles. In 1889, he created an international sensation by announcing to an august assembly that he had rejuvenated himself physically as well as mentally by injections of the testicular extract of dogs and guinea pigs. This claim was widely criticised, especially by later generations of endocrine scientists: Herbert Evans, memorably, condemned Brown-Séquard and other exponents of glandular rejuvenation for afflicting endocrinology with *'obstetric deformation in its very birth'*[23].

Contrary to that view, Brown-Séquard's claim and his subsequent efforts to substantiate it, as Merriley Borell has shown, stimulated a great deal of original research on the nature and functions of the internal secretions and not simply those of the testes. At the same time, Brown-Séquard inaugurated a golden age of organotherapy during which the medical marketplace was flooded with extracts and various preparations of virtually every organ – from the brain to the ovaries, from the testicles to the spleen – which were prescribed for virtually every conceivable disorder that did not respond to orthodox treatment.

> *"Organotherapy, opotherapy, or the Method of Brown-Séquard as it was often called, came* - says Borell - *to be the therapeutic hope of physicians from Cleveland to Bucharest"*[24].

These products, of course, were obtained from animals and varied quite astronomically in quality and purity. Even the purest were not necessarily of any therapeutic use. But many practitioners and not a few patients *perceived* them to be useful and such perceptions helped establish endocrinology as a new science with some of the basic principles of which the general population quickly became familiar. The vogue for organotherapy focused medical attention on the internal secretions to an unprecedented degree and as Borell has emphasized, it was no coincidence that effective thyroid and adrenal extracts were obtained as early as the 1890s. Interest in rejuvenation and other supposedly miraculous clinical powers of testicular extracts did not diminish either. The endocrine glands were now central to medical research as well as medical practice. The testicles could only gain from this new fascination with endocrinology.

The Decade of the Testicle

It was during the 1920s that physiological and clinical research on testicular functions came together in what, for a time, seemed to be a spectacularly successful synthesis. One can hardly think of another era when one bodily organ featured so consistently and so prominently in the world's news as well as in the specialist medical press. From *Good Housekeeping* to *Medizinische Klinik*, there was no escape from the latest news and de-

bates on the secretory functions of the testicle. This worldwide interest had been sparked by recent claims that different kinds of medical manipulation of the testicle could result in physical and mental rejuvenation. It seemed that the holy grail chased by Brown-Séquard and his followers (not to mention hundreds of quacks since the dawn of humanity) had at last been found[25].

A comprehensive cultural and medical history of the rejuvenation craze of the 1920s has yet to be written. As far as the testicle was concerned, two very different figures were of central importance: the surgeon Serge Voronoff of Paris and the physiologist Eugen Steinach of Vienna. Voronoff originated the notorious *'monkey-gland'* transplantation, in which testicular tissue from chimpanzees was transplanted into aging men rich enough to afford the operation[26]. Steinach's method was much simpler: he claimed that a simple vasectomy, by destroying the germinal tissue freed up space for the proliferation of the hormone-producing interstitial tissue. The secretion of higher quantities of sex hormones led to the natural, lasting rejuvenation of the individual. Voronoff, on the other hand, did not believe that the many positive results his patients reported were due to any proliferation of the interstitial cells. He argued, instead, that the epithelial cells of the seminiferous tubules in the graft underwent transformation into reticulated tissue, the secretions of which were responsible for the positive results[27].

Now, none of these techniques for rejuvenation proved to be viable in the long run and their popularity in the short term was attributed by opponents to the gullibility and suggestibility of aging men. At the same time, however, they were also considered by many doctors and numerous laypeople, to be safe as well as effective. It is also worth noting that modern hormonal replacement therapy (which is used, of course, primarily on menopausal women but is increasingly being offered, with far less scientific accreditation, to elderly men) operates on principles that are far more complex than Steinach's or Voronoff's but still tolerably similar in the fundamental assumption that the sex hormones are essential for the maintenance of health, well-being, libido and general vitality. Although operations for rejuvenation went out of vogue in the 1930s, it would be a mistake to assume that this as-

sumption perished with them. The availability of potent, standardised sex hormones in the 1930s ensured that the basic goals of the operation could continue to be pursued without surgery. Let us, therefore, end our explorations with a quick look at the dawn of what may be called the second golden age of testicular organotherapy, albeit an organotherapy that was now standardised, rationalised and based on demonstrable physiological evidence.

The most secret quintessence of life

A fervent lay admirer of Steinach's work once declared that after conquering the problem of rejuvenation through surgery for men, Steinach had distilled *'the very essence of Eve'* in his potent extract of female sex hormones, which was marketed by Schering-Kahlbaum under the name of Progynon[28]. Paul de Kruif echoed this colourful locution in 1945 when he proclaimed that the elaboration of demonstrably effective testicular extracts and hormones in the 1930s constituted the discovery of *'the most secret quintessence of life'*[29]. Physiologist Alan Parkes was more sober but no less exultant when he saluted the *'spectacular chemical and physiological advances'* achieved between 1929 and 1935, leading to the identification and characterization of *'the chief naturally occurring oestrogens and androgens, as well as progesterone'*, together with the discovery of the *'hypophysial, placental and endometrial gonadotrophins'*. It was, simply, *'the heroic age of reproductive endocrinology'*[30].

Ever since Brown-Séquard, commercial preparations of testicular extracts had, of course, been widely available. They were prescribed by innumerable clinicians but few, if any, were accepted as active in *physiological* terms by medical scientists. Even the most genuine testicular extracts could never be effective except in enormous doses because the active hormone is contained within the gland in minute amounts: the factory, as American sexologist Harry Benjamin put it pithily, was not the storehouse (as opposed, for instance, to the thyroid, which was both, thereby ensuring that physiologically active thyroid extracts had been far easier to obtain[31].) The whole saga of the extraction of the active male sex hormone, in fact, turned on the discovery of sources richer in it than testicular tissue itself.

In Brown-Séquard's day, the efficacy of an extract was judged purely by clinical effects. By the 1930s, a more precise criterion had been introduced. In order to be considered potent, a testicular extract had to pass the capon comb test, i.e. it had to stimulate the growth of the shrunken comb and wattles of a castrated cock. Once the injections were stopped, the comb and wattles had to shrink again. The first testicular extract to pass this test had been obtained by Lemuel McGee and Fred Koch from bull testicles at the Department of Physiological Chemistry, the University of Chicago. The extract appeared to be non-toxic but its chemical nature remained impenetrable – Koch and Gallagher weren't even sure whether their extract had one active principle or more and declined to suggest a name for the extract. *'Too often'*, they declared righteously,

> *"a name gives a false sense of security as regards the purity of the product, a fact we wish to emphasize, for it is our firm opinion that the extract is as yet grossly impure..."*

An even greater obstacle to clinical use was the low yield: in order to obtain the *'minimal daily dose'*, one needed forty-three grammes of frozen bull testicle[32]!

By now, however, it had been found that what was already being called the male hormone was present in the blood of cocks[33]. It, therefore,

> *"seemed logical to conclude that since the male hormone is in the blood, it would probably also be found in urine"*[34].

German scientists had already announced that male and female urine contained chemicals that stimulated the development, respectively, of the male and female secondary sex characters. Male urine, therefore, was well worth exploring as a source of the male hormone. This was done by the vitamin pioneer Casimir Funk and his American associate Benjamin Harrow, who obtained the extract by evaporating the filtrate obtained from the urine by alcoholic precipitation and later by extraction with chloroform. The extract – or sometimes, concentrated urine itself – was tested by the capon comb test: *'in every*

instance injections caused the masculinising effect'[35]. One *'cock unit'* of the male hormone, which Funk and Harrow soon referred to as *'testiculin'*, was that amount which, *'when injected daily into each of 6 castrated cocks, will give an average increase in comb of 10 mm. in 10 days'* – this amount could be obtained from 75 cc of a young man's urine[36].

Finally, in 1931, Adolf Butenandt in Germany obtained a crystalline substance from 25,000 litres of male urine, which he called androsterone *'in the belief that it was the essential male hormone'*[37]. By 1934, Leopold Ruzicka in Zurich had synthesized androsterone from cholesterol and the pharmaceutical industry's interest in sex hormones reached fever-pitch. The next year, Ernst Laqueur and his team in the Netherlands, funded by Organon, obtained a crystalline form of active male hormone from the testicle, to which they gave, according to Alan Parkes, *the dreadful name "testosterone"*[38]. Butenandt and a colleague, funded like Steinach in earlier years by Schering, synthesized testosterone in 1935, narrowly beating Ruzicka (sponsored by Ciba) to it[39]. The synthetic hormone was quickly introduced to clinical medicine, in the form of injections (testosterone propionate was the most favoured injectable, but there were others), pellets for subcutaneous implantation and, subsequently, tablets of methyl testosterone for oral use[40].

Once these products had reached the market, they were applied with enthusiasm to a dizzying range of clinical conditions. Impotence, predictably, was a popular indication but sadly for many, testosterone, in spite of the high hopes associated with it, proved to be of no use in the treatment of functional impotence[41]. Its use in male infertility, too, was doomed to failure because it was found to cause azoospermia by depressing the release of the hypothalamic releasing factor that ultimately controls sperm production[42]. (Recently, however this effect has led to serious proposals supported by sophisticated research for the use of androgens as male contraceptives[43]).

The efficacy of the androgens in increasing muscle mass, promoting a general sense of well-being and relieving a host of age-related frailties quickly led to their use in a condition labelled male climacteric. A detailed history of this concept can-

not be provided here, but even a cursory look at the many articles published on it in the 1940s would show us that the spirit of Steinach, if not his operation, was alive and well in the 1950s[44]. Not every doctor, of course, believed in the male menopause. In Britain, endocrinologist Raymond Greene dismissed the symptoms as *'more easily explicable by arterial degeneration or by plain boredom and dissatisfaction'*. But even a skeptic like Greene had to acknowledge that the administration of androgens in such cases to be occasionally justifiable ... there is no doubt that in the man whose testicular function is failing, albeit physiologically, the male hormone may have a noticeably tonic effect, increasing the patient's energy and sense of well-being. It is perhaps to the good that the effect on potency is slight or absent. Sexual potency depends upon a chain of which the endocrine function of the testicles is but one link. A man is not old because his testicles are failing: they are failing because he is old[45].

HRT for ageing men never took off in a big way but the idea has never gone away. Doctors on the fringes of the profession use it widely already and many speculate that the pharmaceutical industry, lured by the profitability of such treatments, might push for the introduction of large-scale male HRT, eventually making it part of legitimate medical practice[46].

One early use of testosterone proved dramatically useful and was accepted universally. This was for the treatment of eunuchoid boys suffering from failure of the Leydig cells to secrete adequate amounts of testosterone. Administration of testosterone produced marked benefits – although not the reversal of infertility – and the child showed the characteristic changes of puberty[47]. The only harmful effect noted by a British consultant was *'the excessive sexual activity of the eunuch to who a too high dosage is given'*. He added, however, that the effect was transient *'and the eunuch does not mind much'*[48].

Was the male hormone used only for sexual disorders in the early years of androgen treatment? Far from it. There were several non-sexual indications that might strike us today as wrong, ludicrous or ludicrously wrong: angina pectoris, for instance, or benign prostatic enlargement, or depression. More importantly,

it was appreciated quite early that the sex hormones were really growth hormones[49].

> *"Concentration upon the growth factor of the anterior pituitary, which is at present rarely of clinical value, has deflected attention from the fact that testosterone is a potent stimulus to growth of many tissues of the body, especially of the muscles, of the hair and, until the union of the epiphyses which it hastens, of the bones"*,

observed Raymond Greene[50].

Nor, of course, was androgen secretion a monopoly of the male. By 1940, it had been noticed, with not a little amazement, that both sexes secreted ample quantities of male and female hormones. Controversies raged over the origin and significance of the *'crossed'* hormones[51]. *"It is not known"*, one clinician wrote, summing up the uncertainties,

> *"whether the androgens which have been isolated from the ovary and from the adrenal cortex are natural hormones of these organs or are simply excretion products of ovarian and adrenocortical steroid metabolism which happen to be androgens by an accident of nature'"*.

The uncertainties of origin and doubts about function notwithstanding, clinicians were not slow to use crossed hormones in treatment. Although the use of *'female'* hormones in men was not embarked upon very swiftly, plenty of uses were found quite quickly for androgens in women. As an authoritative 1947 survey put it:

> *"For approximately a decade androgens have been utilized as therapeutic agents in women. The too rigid early concept of androgens as male hormones seemed at first to lend merely an academic interest to their application to women; but with the growing awareness that they were capable of profoundly altering the sexual physiology of women their potential value as therapeutic agents began to be appreciated"*[53].

Androgens interfered with menstruation and caused a number of virilizing effects, such as acne, hirsutism, enlargement of clitoris and deepening of the voice. All of these were dependent upon the dose and duration of treatment and on individual susceptibility. Except for the voice changes, however, they disappeared – even if slowly – after cessation of treatment[54]. The masculinizing effects, therefore, were serious but not serious enough to rule out androgen treatment in women.

Perhaps surprisingly, androgens were first found useful in combating the vasomotor and psychological symptoms associated with the menopause. Although the oestrogens were obviously useful in treating those symptoms, they sometimes led to uterine bleeding. In such cases, androgens alone or in combination with oestrogens were of great value. How exactly they countered menopausal symptoms (including postmenopausal osteoporosis) was mysterious but everybody agreed that they were effective[55]. Just as the removal of the ovaries had been found to stop intractable uterine bleeding (whether purely *'functional'* or associated with fibromyomas) in the late nineteenth century, androgen treatment was found useful for the same conditions in the mid-twentieth[56]. The male hormones, it was suggested, acted like *"a* medical curettage *achieved by the inhibition of ovarian hormonal activity via the pituitary"*[57]. Since androgens suppressed menstruation, they were also found useful in endometriosis and pelvic inflammatory diseases associated with dysmenorrhoea and even pre-menstrual tension[58].

In the course of androgen therapy in women, *"the unexpected observation was made that they appreciably enhanced libido"*[59]. The mechanism, once again, was unknown but it was suspected that the male hormones increased the sensitivity and vascularization of the external genitals. Their enlarging effect on the clitoris was especially striking and they were soon being recommended for the treatment (preferably *"by the gentle inunction of an androgenic ointment"* on the clitoris) of frigidity due to clitoral insensitivity[60]. The enhancement of female desire, needless to say, was not a comfortable topic for doctors of the mid-twentieth century. *"It should be borne in mind"*, warned the 1947 review mentioned previously,

> *"that the effect on libido may not be desirable in all instances, since increased libido without normal channels for satisfaction may become a serious individual problem and lead to psychic trauma"*[61].

Above all, however, androgens were found useful in the treatment of pelvic and breast cancer in women. Although they did not reverse or even halt the neoplastic process, they were impressive in causing weight gain, reduction of discomfort and improvement in subjective well-being, especially in cases with painful metastatic deposits in the bones[62]. The androgens were not, of course, first-line therapy in cancer but they had significant palliative potential – in this, they again reinforced the nineteenth-century conviction that certain inoperable cases of cancer in the female might be palliated by the removal of the ovaries. The so-called 'male' hormone was not only of use in boosting masculinity but in countering femininity – androgen treatment made oophorectomy unnecessary, allowing clinicians to achieve similar, if not identical ends by less invasive means.

Writing in 1943, the American physician Gerald J. Newerla observed that although the testis was

> *"the first gland subjected to animal experimentation ... approximately a century – from 1848 until 1935 – was needed before the androgenic hormone was isolated and synthesized in pure crystalline form. This fact is still more surprising when comparison is made with the internal secretions of other glands, such as the thyroid, the parathyroid, the pancreas and the adrenals, whose endocrine activity was not suspected until much later, yet whose active principles were isolated chemically, and even synthesized, much earlier than were those of the testis"*[63].

Once they were available, however, the androgens immediately entered clinical practice and not always in the most expected ways either. To appreciate some of the historical reasons for these uses, we need to be aware of apparently unrelated contexts such as the vogue for oophorectomy in the late nineteenth century or that for surgical rejuvenation in the early twentieth. It is important, no doubt, to avoid overestimating those contexts but to write the history of sexual endocrinology without incorporating them is to risk distortion of the historical origins of the whole enterprise.

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11. See BERTHOLD A. A., *Über die Transplantation der Hoden*. Nachrichten von der Georg August Universität und der königliche Gesellschaft der Wissenschaften zu Göttingen, 19 February 1849, pp. 1-6.
12. FOGES A., *Zur Lehre von den secundären Geschlechtscharakteren*. Archiv für die gesammte Physiologie 1903; 93: 39-58, 39.
13. YARRELL W., *On the Influence of the Sexual Organ in Modifying External Character*. Journal of the Proceedings of the Linnean Society (Zoology) 1857; 1: 76-82, p. 81. On Yarrell, see FORBES T. R., *William Yarrell, British Naturalist*. Proceedings of the American Philosophical Society 1962; 106: 505-15.
14. DARWIN C., *The Variation of Animals and Plants under Domestication*. 2nd edn., 2 vols New York, Appleton, 1897, 2, pp. 26-27.
15. *Ibid.* 2, p. 27.
16. WEISMANN A., *The Germ-Plasm: A Theory of Heredity*. NEWTON W. (translated by), *Parker and Harriet Römfeldt*. New York, Scribner's, 1893, pp. 358-59.
17. Foges had been preceded by SELLHEIM H., *Zur Lehre von den sekundären Geschlechtscharakteren*. Beiträge zur Geburtshilfe und Gynäkologie 1898; 1: 229-55. Sellheim's views, however, were based on even fewer experiments than those of Foges.
18. BIEDL A., *The Internal Secretory Organs*, p. 378.
19. LEYDIG F., *Zur Anatomie der männlichen Geschlechtsorgane und Analdrüsen der Säugethiere*. Zeitschrift wissenschaftl. Zool. 1850; 2: 1-57.
20. TANDLER J. and GROSZ S., *Untersuchungen an Skopzen*. Wiener klinische Wochenschrift 1908; 21: 277-82, pp. 281-82.
21. Bouin and Ancel published extensively on the subject between 1903 and 1926. See the following examples: BOUIN P. and ANCEL P., *Recherches sur les cellules interstitielles du testicule des mammifères*. Archives de zoologie expérimentale et générale, 4th ser. 1903; 1: 437-523; ANCEL P. and BOUIN P., *Recherches sur le rôle de la glande interstitielle du testicule: Hypertrophie compensatrice expérimentale*. Comptes rendus hebdomadaires des séances de l'Academie des Sciences 1903; 137: 1288-90; ANCEL P. and BOUIN P., *L'apparition des caractères sexuels secondaires est sous la dépendance de la glande interstitielle du testicule. Ibid.* 1904; 138: 168-70; and ANCEL P. and BOUIN P., *Les cellules séminales ont-elles une action sur les caractères sexuels? Discussion et nouvelles recherches*. Comptes rendus hebdomadaires des séances et mémoires de la Societé de Biologie 1923; 75: 175-78. On their work, see KLEIN M., *Ancel, Paul Albert*. Dictionary of Scientific Biography 1970; 1: 152-53; KLEIN M., *Bouin, Pol Andre. Ibid,* 1970; 2: 344-46; and KLEIN M., *Sur les interférences des scien-*

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22. See ROLLESTON H. D., *The endocrine organs in health and disease with an historical review*. London, Oxford University Press, 1936, pp. 28-29, 319-21.
23. EVANS H., *Present Position of Our Knowledge of Anterior Pituitary Function*. Journal of the American Medical Association 1933; 101: 425-32, p. 425.
24. BORELL M., *Brown-Séquard's organotherapy and its appearance in America at the end of the nineteenth century*'. Bull. Hist. Med. 1976; 50: 309-20, p. 310.
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26. See HAMILTON D., *The monkey-gland affair*. London, Chatto and Windus, 1986.
27. The same effects, Voronoff claimed, occurred after the Steinach operation, although Steinach, by concentrating on the degeneration of the germinal elements that occurred during the first few months after the operation, had missed the later regeneration of the germinal cells and their conversion into reticulated, secretory tissue. See THOREK M., *The Human Testis*. Philadelphia, Lippincott, 1924, pp. 51-54.
28. See VIERECK G. S., *Glimpses of the great*. New York, Macaulay, 1930, p. 264.
29. DE KRUIF P., *The Male Hormone*. Garden City, NY, Garden City Publishing, 1945, p.188.
30. PARKES A. S., *The rise of reproductive endocrinology, 1926-1940. Proceedings of the Society for Endocrinology*. Journal of Endocrinology, 1966; 34: ix-xxxii.
31. GALLAGHER T. F., and KOCH F. C., *The testicular hormone*. Journal of Biological Chemistry 1929; 84: 495-500; and BENJAMIN H., *The latest endocrine advance: the male hormone. Preliminary communication with remarks on hormone isolation in general*. Medical Journal and Record 1930; 131 no 11: 545-48, on p. 545.
32. See GALLAGHER T. F. and KOCH F. C., *The testicular hormone*. Journal of Biological Chemistry 1929; 84: 495-500, pp. 496, 497.
33. The quotation is from FUNK C., HARROW B. and LEJWA A., *The male hormone*. American Journal of Physiology, 1930; 92: 440-49, p. 440, who clarified that by the phrase *"the male hormone, all we mean to imply ... is that we have an extract which influences the growth of comb and wattles, and this extract, for purposes of convenience, we designate the «male hormone»"*. See *ibid*. p. 441.
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35. See FUNK C. and HARROW B., *The male hormone*. Proceedings of the Society for Experimental Biology and Medicine 1928-29; 26: 325-26, p. 326.
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