The Canary and the Bone: A Darwinian Lecture on Erectile Dysfunction

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Abstract

Erectile dysfunction (ED) is one of the most common impairments in sexual function seen in males. The pathogenesis of ED is commonly attributed to a complex interaction of biological, psychological and social factors. The high prevalence of ED and its impact on male sexual function require further explanation from an evolutionary perspective, as one might expect the forces of natural selection to reduce ED frequency over generations. This chapter explores the Darwinian perspective of ED and highlights the importance of sexual selection

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and the loss of the penile bone, the *baculum*, as contributing to the presence and persistence of ED in human males. This chapter unravels the complexity of the evolutionary basis of ED, examining the hypothesis that the loss of baculum has generated ED, which serves, like the *canary in the coalmine*, as an early marker of general health. Thus, the inability to achieve and/or maintain an erection adequate for the fulfillment of sexual intercourse might act as a "fuse" for species preservation. Similarly to how fuses burn in a car to prevent more extensive damage, ED would develop in men who harbor other concurrent conditions, or exposed to accumulation of several risk factors of various origin, as a measure to prevent "damage" to the species as a whole. This mechanism would favor reproduction of healthier men, while at the same time reducing the risk of transmission of harmful genes to subsequent generations. The implications of this hypothesis are explored, as well as the importance of modern medicines targeting the phosphodiesterase 5 enzyme in overcoming the evolutionary handicap of ED.

Keywords
Erectile dysfunction · Evolution · Darwin · Baculum · Systems sexology · Handicap, PDE5i

1.1 Introduction: Dissecting Erectile Failures

Erectile dysfunction (ED) is defined as the *recurrent and persistent inability to achieve or maintain an erection firm enough for satisfactory sexual intercourse* in the presence of proper erotic stimuli [1]. According to the recent Italian Society of Andrology and Sexual Medicine (SIAMS) guidelines on ED, the condition may be classified based on the severity of symptoms (subclinical, mild, moderate, and severe) [2]. **Subclinical ED** (SED), identified through strict and well-defined major and minor criteria, is the pathological burden of men who are not affected by 'clinical' ED but experience inconsistent, situation-, partner-, and mood-related difficulties with erection or reduced penile hardness, which can inconstantly interfere with penetration [3]. When these definitions are considered, the prevalence of ED and SED is high among the male population. Analyses of the global epidemiology of ED show that the condition is prevalent across countries [4, 5]. While SED has been recently observed in 4.4% of 11,200 patients attending an outpatient andrological centre [6], the overall estimated prevalence of ED varies considerably, depending on the study and the methods used to define ED and to measure this phenomenon, with estimates ranging from 3% to 76.5% [7]. A summary of the prevalence of ED across nations is presented in Table 1.1.

It is thought that cases of ED are increasing over time, reflecting a growing burden of the condition in modern society [9]. Incidence increases have been noted in the literature, particularly in recent decades, which may reflect changes in the recognition of ED following the introduction of successful pharmacological options to manage this condition in the late 1990s [10]. Rising ED rates may reflect a genuine growth in male sexual dysfunction cases over time, as well as increased public

Table 1.1 Prevalence of ED across eight nations in men aged 18 years or older and 40–70 years of age [8]

Nation	Population	Prevalence of ED (%)
Brazil	≥18 years 40–70 years	37.2 42.1
China	≥18 years 40–70 years	41.6 47.4
France	≥18 years 40–70 years	44.9 47.8
Germany	≥18 years 40–70 years	44.9 46.1
Italy	≥18 years 40–70 years	48.6 52.2
United Kingdom	≥18 years 40–70 years	42.6 42.6
United States	≥18 years 40–70 years	42.0 46.1

awareness of these issues [9]. However, the global burden (i.e. the total number of patients with SED and ED) is expected to increase considerably with time due to the ageing population and the rise in the rates of ED seen across nations, where population growth and lifestyle factors linked to ED are notable, such as in China [11].

One of the key trends in the prevalence of ED is its association with age [12], with a considerable increase in men older than 40 years. The Massachusetts Male Aging Study [13] found that the self-reported prevalence of ED in men aged 40–70 years was 52% (17.2% mild, 25.2% moderate and 9.6% severe), while within this age group, there was a threefold increase in prevalence between men aged 40 and 70 years. A follow-up in this population over an average of 8.8 years found that the annual incidence of ED increased by decade, with 12.4 cases per 1000 man-years in those aged 40–49 years, 29.8 for men aged 50–59 years and 46.4 for men aged 60–69 years [14]. Another large survey conducted in a German cohort of 8000 men aged 30–80 years reported an overall prevalence of ED at 19.2%, increasing from 2.3% at 30 years of age to 53.4% at 80 years of age [15]. These findings are supported by more recent data on the association between age and ED [16, 17].

It is important to consider that the prevalence of ED may be underestimated in available literature due to factors such as male privacy, reluctance to discuss the condition or social and cultural beliefs influencing attitudes towards sexual function and behaviour [4]. In addition, while age is strongly associated with ED, the condition also occurs in younger age groups of men [18]. Although not demonstrated yet, SED could be expected to more typically affect young populations, being a bona fide prodromic stage of clinical ED [3]. Hence, while age is likely to have an important influence on erectile function, one must consider that with increasing age, there is also a higher likelihood of health risk factors, chronic conditions and comorbidities that may influence the potential for ED, which may also be present in a smaller proportion of younger men [4, 16]. Indeed, it has been noted that the risk of ED sharply increases with the accumulation of comorbidities [16]. The risk factors underlying SED and ED will be considered later in this chapter.

Due to the high prevalence of ED, this condition is one of the most commonly managed impairments of sexual function in clinical practice. Indeed, the impact of ED on sexual performance is widely recognised [19]. Erectile function is essential for successful copulation, and the development of ED may lead to poor sexual performance [20]. In addition, ED can have profound effects beyond its biological impact on sexual performance, influencing psychological health, social well-being and other important outcomes from a holistic care perspective [21]. Indeed, it has been noted that patients with ED experience a greater burden of psychological and relational symptoms than the healthy population, along with lower health-related quality of life and impairments in daily activities and occupational function [21]. These consequences are noted in Fig. 1.1. Men with ED need treatment approaches that take into account their personal experiences and preferences [22]. Hence, it is important that this highly prevalent condition, which is associated with a range of challenges and needs, should be considered a key focus of sexual medicine.

1.2 Erectile Dysfunction from the Bio-Psycho-Social Model to the Systems Sexology and the Darwinian Perspective

To better understand the major clinical aspects of ED, a new concept needs to be introduced to amplify and extend the well-known bio-psycho-social (BPS) model [24] into a more complex one we call *systems sexology* (SS), mimicking the well-known paradigm of systems medicine (SM) [25]. As an SM, SS takes into account two major aspects: the first is the role of lifestyle in the developmental origins of health and diseases [26, 27]. The second is the ability to understand the deep interactions between the four systems that shape sexual health in general and erectile health in particular: the system of the mind, the system of experience, the system of political and economic choices and, last but definitely not least, the system of the body [28]. Interestingly, these systems must be considered, not necessarily as ED aetiologies, since a direct causative relationship is not always demonstrable in medicine based on evidence, but rather as risk factors for both subclinical and clinical erectile failure.

It is a typical way of reasoning in the light of the SS to admit an inverse *butterfly effect* as that occurring between the political lack of adherence to the green economy, the consequent increase of pollution, the presence of microplastics and endocrine disruptors in the environment, and, finally, reproductive and sexual consequences such as hypogonadism, morphological genital alteration, and ED in a single individual [29]. Similarly, states and political and religious powers supporting negationists and anti-vaccine groups, thus hastening the spread of the virus, could be considered risk factors for the sexual long-COVID, peculiarly represented as ED, occurring during and after complex COVID diseases [30, 31]. Finally, it is a typical lesson from SS to admit that the large majority of ED risk factors are related to behaviours, acted out, or endured, producing various degrees of inflammation at tissue level which may produce endothelial dysfunction as seen in virtually all cases of ED [32]. More insights on the new SS model can be found in the Chap. 7 of this book.

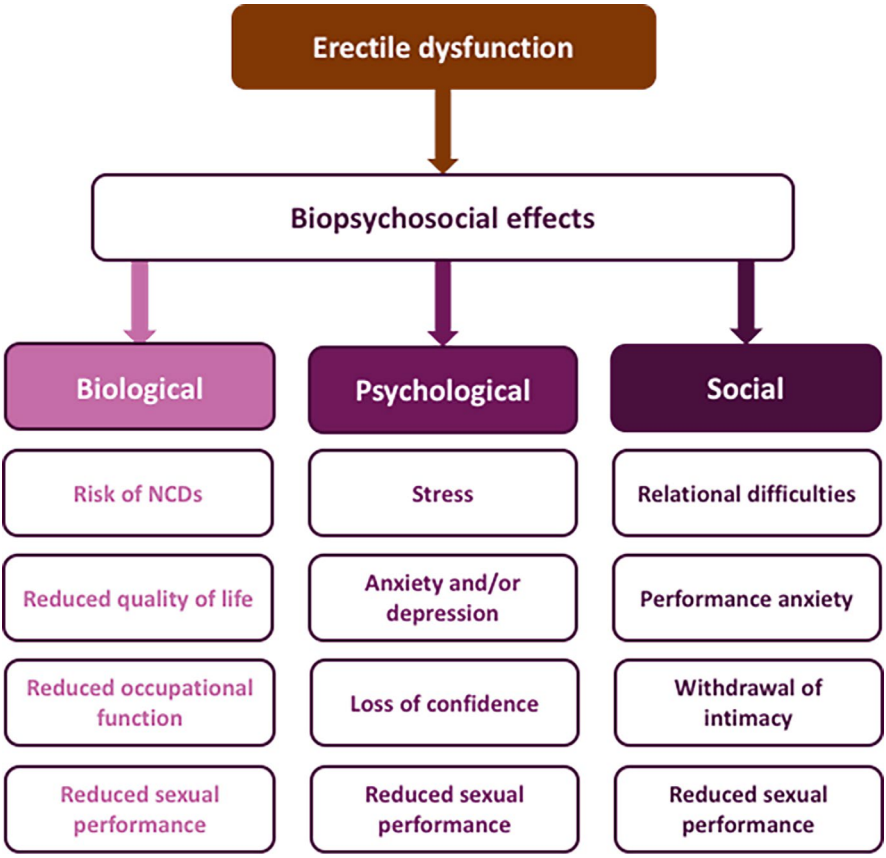

Fig. 1.1 Impact of ED on patients, considering biological, psychological and social risk factors [21, 23]

Having represented some aspects of the complexity of the ED mechanisms, it is now time to introduce another unusual way to understand this frequent and multifaceted sexual symptom: the *Darwinian perspective*. One of the most striking features of the high prevalence of ED is how contradictory this may be seen within the context of evolutionary biology. Charles Darwin's by natural selection [33] emphasises the survival of the fittest within a species, with fitness denoting the probability that a characteristic will be reproduced. How do we reconcile the high prevalence of ED with the evolutionary imperative of survival of the fittest according to the Darwinian dogma? Moreover, in species that sexually reproduce through copulation, coitus should be particularly protected to increase the chance of reproduction, which is more important for the survival of the **selfish gene** than for the survival of the individual itself [34, 35]. But, apparently, this does not seem to be the case for humans. The next paragraphs of this chapter seek to explore this issue by analysing the evolutionary basis of sexual functioning, drawing an evaluation of ED through an evolutionary lens with an unusual focus on the loss of the penis bone as a key

factor in ED prevalence in humans, thus attempting an evolutionary explanation for ED risk factors, and finally proposing the implications of a neo-Darwinian perspective of ED for its prevention and effective treatment.

1.3 Evolutionary Basis of Sexual Functioning

It is accepted that both human and animal anatomy and physiology are influenced by the mechanism of survival of the fittest or, in other words, by the **natural selection** [36]. The underlying principle of natural selection is that the survival and reproduction of individuals and, thus, of species depend on the differences in phenotype [33]. Traits that are linked to anatomical, biological, physiological and behavioural phenotypes may be selected over generations when they facilitate individual advantages and individual survival or those of the species. Typically, the selection of traits is more likely when species are adapted to their environments [36]. However, other important traits may also be selected based on the particular preference of mating partners.

Sexual traits (frequently also identified as 'sexual ornaments') are often subject to an ontogenetic force that is at least comparable to that of the mentioned natural selection: **sexual selection**, a form of selection that is representative of the reproductive success of individuals and of the final survival of species [37]. While natural selection is linked to the overall struggle for survival and includes elements of reproduction, sexual selection is focused on mate choices and strategies, successful copulation, the production of offspring, and reproductive advantage, which are key drivers of selection, even where no physical advantage is apparently evident.

One example of sexual selection can be seen in the peacock's tail feathers (train), where extravagant displays of eyespot feathers play a role in attracting a mate. As Darwin—probably the greatest proto-sexologist ever—genially hypothesised in his second book, *The Descent of Man* [37], the evolution of the peacock's train occurred as a result of female preference to mate with males with this phenotype. It was not until more than a century later, in 1991, that evidence supporting this theory emerged in scientific literature, showing that females approach multiple males prior to mating but invariably select the male with the greatest number of eyespots on his train [38]. Further evidence showed that mating success was associated with the presence of these eyespots (when removed, mating success was reduced) [39]. The peacock's tail is a typical sexual ornament used for **intersexual competition**, i.e. typically in the heterosexual setting, to obtain the sexual attention of certain individuals [40].

The question remains as to why a female should choose a male based on this phenotypic trait when it does not necessarily confer any direct advantage from a reproductive standpoint. Indeed, the peacock's train does not contribute towards protection from predation, paternal care or any other physical benefit that may have a practical advantage for survival. Conversely, the larger the train of the peacock, the more likely that the male is vulnerable to predation [41]. As with most sexual traits, the peacock's train size is an evident handicap that should have disappeared according to natural selection if another driver, sexual selection, does not support its maintenance and development in the species. The **Theory of Handicap**, based on

the Handicap Principle, postulates that sexual traits are, in the majority of cases, handicaps that represent a phenotypic condition, which may provide support for sexual selection (Box 1.1).

Box 1.1: The Handicap Principle

The handicap principle is the disputed but robust hypothesis proposed by the Israeli biologist Amotz Zahavi in 1975 [42–44]. Key elements of the theory are noted below. Interestingly, the theory was later supported by game theory models and successfully applied to several human contexts [45].

1. Secondary sexual characteristics are **costly** signals.
2. Sexual traits must be **reliable** as they cost the signaller resources that individuals with less of a particular trait could not afford.
3. Individuals of greater biological fitness signal this through handicapping behaviours or morphological traits that **lower overall fitness**.
4. Sexual traits selected through Darwinian sexual selection work as conspicuous consumption, signalling the **ability to afford to squander a resource**.
5. The receivers select signals indicating quality because inferior-quality signallers are unable to produce such **wastefully extravagant signals**.
6. A sexual signal is reliable if the **cost** to the signaller of producing it is proportionately lower for higher-quality signallers than for lower-quality ones.
7. A handicapping sexual trait delivers the hidden message that the carrier or signaller **survived *despite* the handicap**, thus showing great fitness and, finally, better genes.

Phenotypic strength or quality is a key factor that infers genetic quality, which should be favoured in a mate according to the selective pressures of evolution [46]. In this example, it is hypothesised that the peacock's train may be an honest signal of phenotypic quality: peacocks with the highest phenotypic individual quality can survive the physical imposition of a large train, but those with low phenotypic quality cannot [41]. Therefore, the peacock's tail is potentially an important phenotypic signal of genetic quality; only the fittest (or the strongest, smartest or luckiest, according to different perspectives) can afford to maintain an elaborate train for attracting females. In other words, if a certain peacock survived despite the evident handicap of his long and coloured tail, which makes the individual more prone to predation, the individual is likely to carry better genes compared to others with a humbler (and safer) tail.

The potential for traits/ornaments that are prone to sexual selection to signal underlying phenotypes is an important concept when applied to other facets of sexual functioning, including ED. Erectile function may be considered an important phenotypic trait that not only facilitates successful reproduction but may also signal wider attributes of the male. The ability to maintain an erection is crucial to sexual

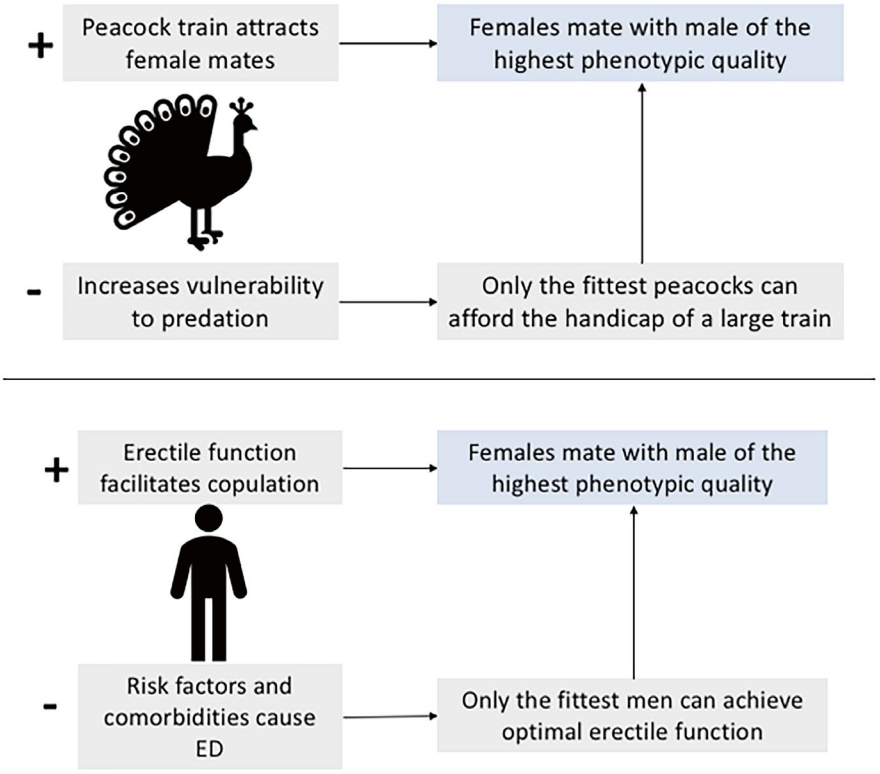

Fig. 1.2 Conceptual diagram of male-mating strategies from an evolutionary perspective. This figure illustrates how male-mating strategies, such as the peacock train and erectile function in humans, necessitate the fitness of the males due to the potential vulnerability imposed by these mating strategies

reproduction, and this is compromised in patients affected by ED. Importantly, ED is more common in those with a range of health conditions and with a high risk of future conditions that may be indicative of poor phenotypic quality [47]. Therefore, **ED may be defined as a condition-dependent phenotypic trait, whose expression is linked to the health of the individual** [48] (Fig. 1.2).

To further explore this hypothesis, the remainder of this chapter considers how ED may be viewed through an evolutionary lens in relation to the loss of the baculum and the risk factors that underlie the development of ED in humans.

1.4 Understanding Erectile Dysfunction Through an Evolutionary Lens: The Baculum

The **baculum,** or **os penis**, is a penile bone found within the distal half of the penis in the vast majority of mammals (Fig. 1.3) [49]. The baculum is formed through the ossification of the distal region of the corpora cavernosa and is located above the

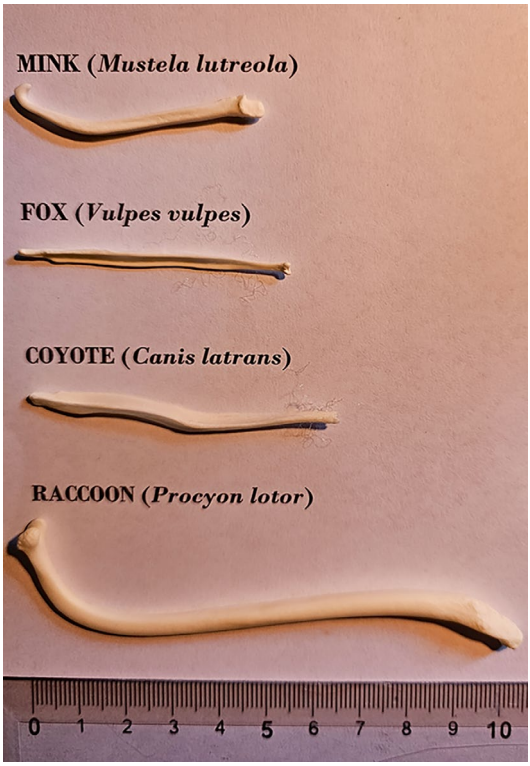

Fig. 1.3 Baculi from different mammals (EAJ's collection). The ruler is in centimetres. Note the difference in dimension and shape. (Figure reproduced with permission from EAJ)

urethra [50]. The baculum has been described across numerous mammalian orders, including in primates [51]. However, it is notably absent in humans, but chimpanzees, our closest relative, still possess a baculum [52]. In many species, the baculum is hypothesised to play an important role in reproductive success [53].

The baculum, in animals where it is present, i.e. the majority of mammals, is governed by a voluntary skeletal, muscular apparatus known as the **retractor penis** [54]. In Fig. 1.3, the insertional groove can be easily identified in the penis bones. The mechanism through which the baculum operates reflects a key role in providing a simple and affordable supportive structure for erection, rather than relying on the rigidity of the soft tissue of a reproductive organ, governed by a complex and aleatory psychoneuroendocrine and vascular mechanism. When required during sexual activity, muscular contraction facilitates the protrusion of the baculum into the penile sheath [49]. This leads to the stiffening of the erect penis and facilitates copulation. The baculum may be beneficial in a reproductive context, not only in helping the rigidity of the erection during penetrative intercourse but also in maintaining and supporting erection during sexual performance, particularly in species with prolonged intromission [53, 55]. In addition, the baculum has been hypothesised to play a role in reducing sperm competition, with the morphology and length of the baculum correlated with paternity in some species [53, 56]. It has also been suggested that the baculum may serve to orient the female towards a specific male partner and, at the same time, cause damage to the female reproductive tract to

prevent subsequent mating with another potential partner [53, 57]. It may also stimulate female ovulation or implantation in some species, with baculum length tending to increase in species with induced ovulation [57]. The baculum may also be seen as a signal of male quality, with morphology and length providing a phenotypic marker of fitness [53], perhaps—we can hypothesise—useful for intrasex and/or intersex competition.

While there are several hypotheses over the exact benefits of the baculum and the mechanisms through which it facilitates reproductive success, it is evident that species with a baculum have this structure as an aid to reproduction and do not rely solely on the engorgement of the penis with blood to allow erectile function. However, the evolutionary profile of the baculum's morphology and function suggests that the penile bone may have undergone variations and adaptations corresponding to environmental and sexual selection pressures. These pressures may have impacted its morphology as well as its presence.

The evolutionary history of the baculum in primates suggests that this structure has been gained and lost over many lineages [53, 58, 59]. It has been suggested that the baculum has been gained at least nine times and lost at least ten times throughout mammalian evolution [53]. As with genital morphology, it has been suggested that the shape of the baculum is dependent on sexual selection [49]. Notably, the evolutionary history of the baculum also reveals considerable variation in the morphological characteristics of this bone [58]. Experimental data have also supported the role of sexual selection in the determination of baculum morphology. For instance, the modification of the sexual selection processes in populations of house mice led to changes in baculum morphology. Specifically, when post-copulatory sexual selection pressure was artificially increased, after 27 generations, mice showed significant thickening of the baculum compared to those in populations where enforced monogamy was established (thereby reducing sexual selection pressure) [58].

These findings support the idea that sexual selection and associated pressures may influence the evolution of the baculum. The assumption follows that populations where sexual selection pressure is high, including those with seasonal mating and in polygamous systems, will be subject to stronger evolutionary forces [49]. Conversely, where sexual selection pressures are low and monogamy prevails, evolutionary forces may be less relevant in influencing baculum morphology and preservation. This explanation is not entirely applicable to humans, a species we might define as **monogamous-unfaithful**. Indeed, monogamy gives humans the enormous adaptive advantage of being able to support fragile and immature children. These advantages may have the same specific adaptive weight as those produced by renewed genetic opportunities obtained from extra-pair mating. As a result, since the vector of monogamy is equally and oppositely powerful to that of infidelity, humans are the only animals fully endowed with free will in their sexual choices, despite being largely influenced in these by the four systems explored by the SS, the systems of the mind, experience, society, and, of course, the body. Moreover, in humans, the substantial **loss of oestrus** and the **concealment of ovulation**—two critical and specific sexual functions—have shaped human sexual behaviour as it appears nowadays [60].

Between primates, humans are almost unique in having lost the baculum during differentiation from common ancestors. The exception seems to be the *Ateles*, a genus of New World monkeys (platyrrhines) that also lack a baculum [61]. The absence of the baculum in *Ateles* represents a separate evolutionary path from humans, who are Old World primates (catarrhines). This implies that baculum loss occurred in a few primate lineages, not only in the human lineage, allowing us to suggest that platyrrhines are perfect animal models to study ED and male peripheral reactions instead of rodents, which are unfortunately largely used in the scientific literature for both erection and ejaculation studies.

A few theories have been proposed to explain the loss of the baculum in humans as a result of sexual selection. Some of these posit that the loss of the baculum is a means for females to evaluate male health [35] and that it may have occurred in response to decreased post-copulatory competition and increased monogamy, which require shorter intromission [62]. Additionally, the tactile stimulation hypothesis proposes that the female choice for tactile stimulation and the possibility of enjoying a larger range of copulatory positions facilitated a boneless penis [63]. Other theories hypothesised the advantage in preventing the risk of penile blunt trauma associated with upright posture and a possible role in intrasex competition [52]. These theories are summarised in Fig. 1.4.

Collectively, these theories provide a basis for explaining how changes in mating systems may have reduced the need for the baculum while also highlighting how sexual selection processes may be influenced by baculum loss.

The presence of baculum in ancestral primates suggested that the *os penis* first arose at the time of the split of non-placental/placental mammals and the most recent common ancestor of primates and carnivores [49]. Examining the symplesiomorphy—i.e. how an ancestral characteristic is shared by all members of a clade, including both genders of a species—early analyses showed that the female

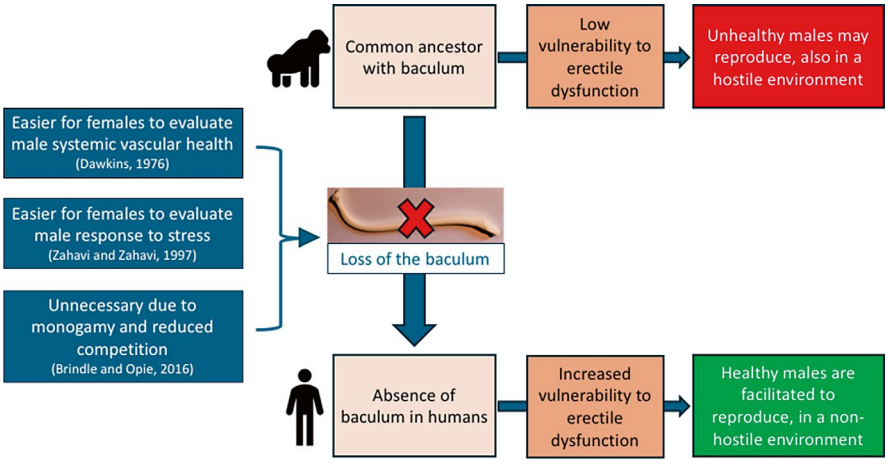

Fig. 1.4 Overview of theories for baculum loss in humans, with supporting evidence/studies and with the modified Dawkins's adaptive theory. (Adapted from Smith and Hechtel [62])

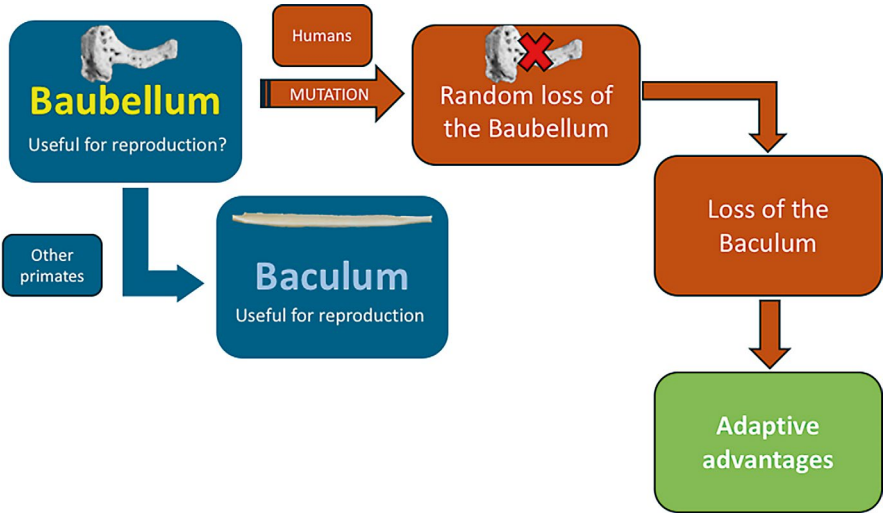

Fig. 1.5 The Jannini theory of baubellum-baculum. For the ontogenesis of virtually all male dimorphic genital tissues, an undifferentiated/female template is needed. Just as the clitoris is the anatomical and functional model on which the penis is formed during prenatal ontogenesis, so the baubellum is be considered the template of the baculum. Nevertheless, being apparently non-essential to reproduction, the baubellum has been lost in some primates. The random disappearance of the baubellum's template caused the loss of the baculum, which generated unexpected advantages in some species, like humans

counterpart of the baculum, the **os clitoris** or **baubellum**, has been lost more frequently during evolution. In particular, among 163 studied species, apparently 29 have a baculum but not a well-developed baubellum [64]. However, a more recent phylogenetic analysis, confirming the baculum/baubellum homology, found that for each baubellum, a baculum was invariably present [61].

The latter evidence may not help solve the conundrum. The baubellum may be hypo- or non-functional with respect to reproduction itself and thus randomly lost over time, but why is the baculum also lost despite its important role in protecting the erection needed for the survival of species? As with other genital tissues, the baculum is the modification of the baubellum occurring during ontogenesis in the presence of masculinity-driving genes and hormones. The absence of a clear-cut utility in non-matriarchal species (where clitoral exhibition may help gain an alpha rank) may have led to the disappearance of the baubellum, which in turn drove the loss of the baculum. Interestingly, this generated gender-specific consequences (Fig. 1.5).

We may hypothesise here that the loss of the baubellum in women may have increased the chances of having a **female orgasm**, a function poorly studied and perhaps rarely and questionably observed in animals. Although in some species the baubellum seems related to the stimulus of ovulation [65], the coitus for several female animals is frequently painful instead of pleasurable. The absence of the bone in the human clitoris, coupled with the replacement of a potentially painful baculum

by softer tissues, may have facilitated the emergence of the human clitoral orgasm [66].

However, a major adaptive advantage of the disappearance of the baculum could be hypothesised in the males of our species. We may theorise that this mutation played and plays an important feature not only in how females evaluate the fitness of males from an evolutionary perspective, as suggested by Dawkins [35], but also in producing an efficient and powerful **adaptive mechanism** that makes copulation possible only for psychologically, relationally and physically healthy individuals acting in a non-stressing environment. In fact, after losing the baculum during evolution, human male erectile function was no longer a voluntary action [2]. The pivotal machinery for developing and sustaining an erection in humans relies on factors such as the presence of an efficient tunica albuginea, the activity of a healthy endothelium, and the relaxation of **smooth muscle cells** within the cavernous tissue, allowing for an increased input and a decreased output of blood to and from the corpora cavernosa, leading to increased blood pressure in the penis [67]. While Dawkins put forth the handicap theory of baculum loss, which allows females to evaluate males' fitness, specifically for vascular health, it is important to add here that, in humans, reproduction is not only based on female choices and that erectile function does not only represent a vasculogenic process nor just a physical one. Erectile function in humans is influenced by a complex interplay of factors, including environmental, psychological, relational, endocrinological, neurological and vascular [2]. The voluntary control of erectile function, if any is maintained at all, may have a greater negative influence on function rather than a positive one [48]. Therefore, understanding ED as a signal of health and male response to stress—both related to health and environmental factors—may be a more rigorous hypothesis, reflecting the diverse factors that influence erectile function.

The core of our hypothesis is that the loss of the "useless" baubellum and, consequently, of the baculum, has generated a mating strategy according to which the healthiest individuals (not necessarily and exclusively those selected by the partners) are facilitated in reproduction, consistent with the principle of the reproduction of the fittest (healthiest), and finally solving the *Darwinian paradox* of the loss of a very strong support to the reproductive power, such as is the penile bone. The absence of the baculum produces a detrimental effect on an individual (as an unfitting person may fail to reproduce), but it may also possibly confer an overall great advantage by accelerating the evolution of the human species. This is exactly what happens in animal societies dominated by alpha females and/or males (wolves, lions, deer, etc.), where (almost) only the alpha individual reproduces while all other animals with lower individual characteristics are condemned to being unable to pass on their genes to future generations [68, 69]. In the case of these **intrasexual** (i.e. agaist the individuals of the same sex) **competitions**, the selection for reproduction of more fitting individual characteristics compared to others weaker is probably lower with respect to that expressed by the modulation obtained with a more comprehensive selection generated by the 'absolute' environmental, intrapsychic, relational and biological health (Fig. 1.6).

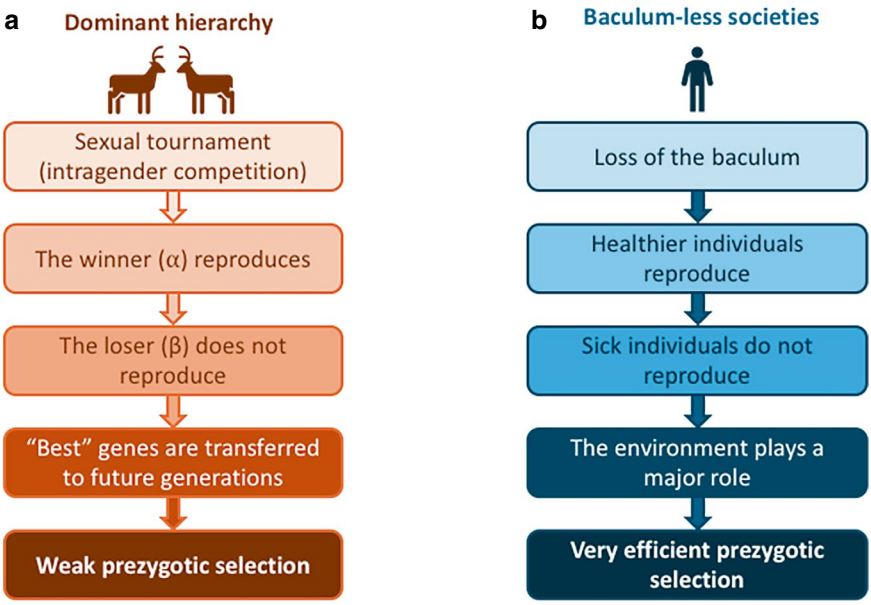

Fig. 1.6 Comparison between two prezygotic selection strategies. Ethologically, an animal society is based on a *dominant hierarchy* (**a**), where members interact to create a ranking system, in which a dominant higher-ranking individual is called the 'alpha' and submissive, lower-ranking individuals are referred to as 'beta'. One of the advantages of these hierarchies is that rather than fighting each time they meet, individuals of the same sex establish a relative rank, with alpha individuals often having the right to mate. This strategy should select for good genes, but in reality, it is potentially effective only in relation to another individual (in this case, the loser in the sexual tournament). The disadvantage is that a very large number of individuals do not reproduce. Conversely, in *baculum-less societies* (**b**), reproduction is possible and easy in several healthy individuals within a healthy environment. While the first strategy is 'relatively' efficient, the second one is 'absolutely' more efficient for selecting more fitting individuals and healthier pups

This hypothesis can be further supported by evaluating the role of evolution in relation to **risk factors** for ED, illustrating the importance of baculum loss as a mechanism through which erectile function serves as a signal for phenotypic quality.

1.5 Evolutionary Explanations for ED Risk Factors

The development of ED and the risk factors associated with this condition have been extensively studied across populations [23, 70, 71]. Risk factors for ED may be categorised to align with the complex aetiological drivers of the condition, including systemic biological factors and relational and intrapsychic factors [2]. A summary of the key risk factors for ED is presented in Table 1.2.

From a biological perspective, risk factors for ED tend to reflect advancing age, the influence of lifestyle factors or the presence of a hostile environment, producing distress in individuals [2]. Advancing **age** is one of the clearest risk factors for ED,

Table 1.2 Summary of key risk factors for ED

Category/type of risk factor	Risk factors
Lifestyle	Smoking Obesity Physical inactivity Excessive alcohol and drug consumption
Systemic	Organ and system insufficiency and failure (lung, kidney, etc.) Cancer Other systemic diseases (e.g. genetic and autoimmune diseases, infections, etc.)
Cardiovascular	Hypertension Cardiovascular disease
Metabolic	Type 2 diabetes mellitus, gout, etc.
Hormonal/endocrine	Hypogonadism Hyperprolactinemia and other pituitary disorders Hyperthyroidism and hypothyroidism Cortisol disorders
Neurological	Spinal cord injury Epilepsy Specific neurological conditions (multiple sclerosis, Parkinson's disease)
Urological	Lower urinary tract symptoms (LUTS) and chronic prostatitis *Induratio penis plastica* Penile structural abnormalities
Iatrogenic	Drugs interfering with testosterone activity and metabolism Anti-psychotics or antidepressants Pelvic surgery
Psychiatric, psychological and relational	Affective disorders (depression, anxiety, etc.) Psychoses Negative education and experiences Low self-esteem or confidence Relational difficulties (poor communication, impaired couple fitness)
Sexual	Hypoactive sexual desire disorder Ejaculatory disorders (LCEE, loss of control of erection and ejaculation) Partner sexual disorders Infertility (infertosex syndrome) Couplepause/doublepause

Note that the anti-erectile mechanism of action of these risk factors is, in the large majority of cases, acute or subacute *inflammation* and that the specific lesion of the *endothelium*, in general, and that of the corpora cavernosa, in particular, is a consequence of inflammation [2, 72]

with an increase in the prevalence of ED seen in older men [23]. It could be noted here that having an older father in a wild environment may reduce the chances of offspring survival. Indeed, it is to be noted that the majority of ED risk factors accumulate with time or are more likely to affect older men. In fact, particularly in older populations, the development of chronic disease or comorbidities can lead to an increased risk of ill health, suggesting that there are advantages to reducing reproduction in these older age groups to ensure the genetic fitness of future generations. However, as noted previously, age alone may not be the full story in explaining the

increased likelihood of ED with advancing years. Indeed, **lifestyle**-related risk factors accumulate over time and become more likely in age groups where ED is common [2]. These lifestyle factors are diverse and include smoking, obesity, physical inactivity and the consequences of disease processes, such as hypertension, metabolic syndrome, diabetes mellitus and psychiatric neurological, endocrine, cardiovascular, toxicological and systemic conditions (e.g. respiratory and oncological diseases)—all meeting the definition of **chronic non-communicable diseases** (NCDs) [2]. Interestingly, parasites, viruses and bacteria may also be linked, directly or indirectly, to ED. A common factor seen in communicable diseases and NCDs is **inflammation**, the mechanism of action of endothelial failure, which is considered the most frequent reason for erectile weakness or impairment [73]. In other words, the loss of the baculum has favoured the survival of species with the best fitness, where only healthy individuals can successfully and reliably achieve an erection and thus, by means of copulation, reproduce.

Intrapsychic and **relational** risk factors have also been identified in relation to ED [2]. Intrapsychic factors underscore the proposed importance of the link between biological and psychological functions during sexual performance. Specifically, negative attitudes or experiences related to sexual performance may interfere with cues for sexual arousal, linking psychological/cognitive processes impacting biological mechanisms [23]. Low self-esteem, sexophobic education, negative experiences, egodystonic sexual orientation, gender issues in homo−/bi−/transphobic environments, depression, anxiety and psychoses may all potentially contribute towards negative perceptions of sexual performance, failure prevision, avoidance of sexual activity and loss of sexual intimacy, finally resulting in ED [72, 74]. In other words, only individuals psychologically and psychiatrically healthy may copulate and reproduce, thanks to the loss of the baculum. Interestingly, relational dynamics may also contribute to the negative cycle of psychological influence on erectile function, with partner expectations, judgment, lack of communication or relationship satisfaction potentially contributing to ED [75]. When there are existing physiological risk factors for ED, this may heighten the potential for intra-psychic and relational risk factors to influence future sexual performance [23]. In other words, only individuals in a fitting relationship (i.e. in a congruous erotic setting) may be facilitated to copulate and reproduce, again thanks to the loss of the baculum.

This hypothesis is made—apparently—fragile by the possible (although unlikely) presence of an erection in, for example: (i) gender violence (i.e. in the absence of relational health), (ii) in depressed/anxious/psychotic people (i.e. in the absence of intrapsychic health), (iii) in highly stressful conditions, such as famine, epidemy, or war (i.e. in the absence of environmental health), (iv) in initial stages of performing wrong and unhealthy lifestyles (i.e. in absence of correct behaviours), (v) in the initial stages of communicable or NCDs (i.e. in the absence of full biological health). However, it should be considered a biological and reproductive advantage should never work in 100% of the cases. It has been, in fact, demonstrated that mate preference tends to a steady state, or equilibrium, when the benefits of mate choice are sufficiently large relative to the cost of choice [76]. Furthermore, we have to note that in all of the above-mentioned extreme situations, achieving an erection is

much more difficult than under normal, healthy conditions and that the hypothesised mechanisms, to properly work, should just (strongly) favour more fitting individuals and settings.

One could also argue, against this explanation, that ED appears to be associated with diseases characteristic of modern society [52]. But this argument seems fragile, given that virtually all diseases, even those that characterize archaic human life, such as infections and trauma, can be important risk factors for ED. Vice versa, the **handicap** (working as an advantage) **of the loss of the baculum** increased its selective power with the rise of more complex diseases, related to modern lifestyles, such as NCDs, *bona fide* much less present in primitive societies.

Another comparison with the female counterpart may help thrust the hidden benefits of baculum loss, further supporting our hypothesis. This can be achieved by comparing the mechanisms that regulate oogenesis in human females and those that produce ED in males [77]. For instance, females are born with a finite number of oocytes, which are typically released during monthly ovulatory cycles, from puberty to menopause. Consequently, once oocytes are depleted, the age at which a female can reproduce is naturally determined, avoiding risks of pregnancy and childbirth in older age groups. The prevalence of ED in men without a baculum is dramatically age-dependent; this characteristic reduces the menace of high-risk pregnancies with increased prevalence of dangerous mutations and also reduces the possibility of a too late parenthood for effective care of the typically immature offsprings of the human species. In other words, since men do not experience the same mechanisms as menopause, which exerts a highly effective **pre-gametic** blockade, the decline in testosterone and the difficulty in achieving and maintaining an erection, typical of the so-called andropause, counteract the aforementioned (over)production of spermatozoa throughout a man's life through a mechanism we might define as **pre-copulatory**. But there is more. When focusing on the monthly ovulatory cycle, it is notable that successful ovulation depends on the environment and health, with environmental stressors and ill health potentially causing ovulation to cease. This may be further viewed as an efficacious protective mechanism (again, far from acting 100% of the time) against reproduction during periods of distress in the environment or during poor individual/couple/species health conditions. Having to target only one egg cell per month, this gear is particularly effective in reducing, if not inhibiting, ovulation, fertilization, implantation, pregnancy and even puerperium in the presence of hostile or risky environments and psychological, relational and physical problems. However, it cannot have the same efficiency in males, who are capable of continuously producing a huge amount of sperm from puberty through to old age [78]. In other words, as above mentioned, blocking one single egg per month (or interrupting a fragile pregnancy or puerperium) is much easier than blocking millions of spermatozoa produced by the testes. Therefore, both pre- and post-zygotic interference-from the environment and from psycho-relational and physical events-on females, aims at facilitating reproduction under optimal conditions, a strategy which cannot be applied to males with the same efficiency. A completely pre-zygotic and pre-coital selection mechanism is required, as provided by the loss of the baculum (Fig. 1.7).

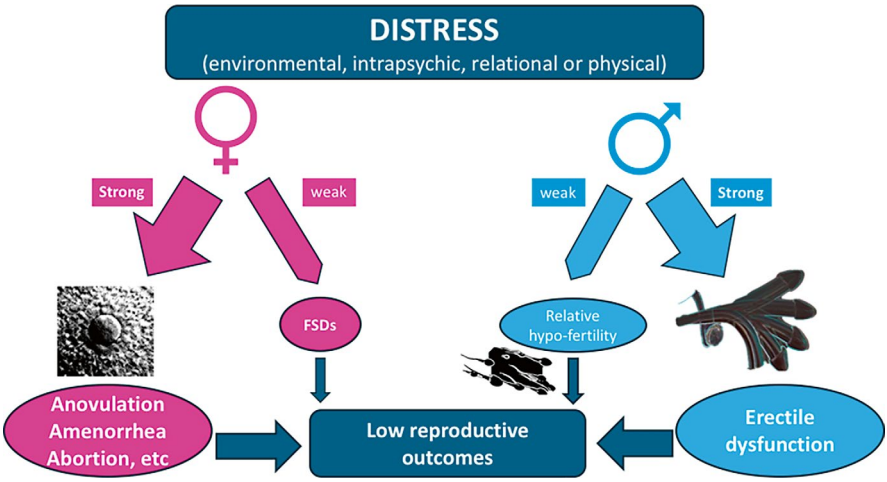

Fig. 1.7 Gender differences in the effect of distress on reproduction. The same di-stressor produces two strong effects in females (from anovulation to abortion) and males (erectile dysfunction), with two mechanisms quite efficient in blocking reproduction, as the arrow sizes indicate. Conversely, the reproductive output itself is *relatively* less dramatically and less universally affected by distress-induced female sexual dysfunction (FSD) and by the effect on spermatogenesis

One may argue that psychological and physical diseases, environmental toxins and distress also affect spermatogenesis. This is true as the same mechanisms act very negatively on females by producing several female sexual dysfunctions (FSDs). However, both pathological processes are characterised by low efficiency in blocking the reproductive output. Distress-induced, communicable-disease-induced and NCD-induced complete azoospermia is rare, or non-existent (in contrast to oligospermia) [79], and distress-induced, communicable disease-induced and NCD-induced FSDs certainly produce a barrier to reproduction [80], but no one is per se able to efficiently fully block it [81]. Anovulation/abortion and non-baculum-dependent ED, as on-off systems, appear much more efficient.

1.6 Other Advantages of the Loss of the Baculum

When considering the ancestral versus the modern environment, it is important to note how priorities in sexual performance and the need for the baculum may differ in modern men compared with ancestors and other species. For instance, the need for a quick erectile and ejaculatory process is recognised as important in ancestral hominids and in other species, and the baculum may facilitate a quick ejaculation (*coitus citus*. Lat: coitus as fast as possible) [82]. This reflects the advantage of speed in depositing semen to impregnate the mate, thus achieving the potential for reproduction [83]. This may be particularly advantageous where pressures exist in the environment, such as sexual selection pressures (other mates) or the risk of predation, which favours a reduction in the time spent copulating [83].

In contrast, bonds and relationships from the prehistory of *homo sapiens* reflect different values and approaches to mating than the behaviours seen in polygamous species with high sexual selection pressure [84]. This echoes changes over time and within the species, such as long-term mating strategies, female choice and empowerment in partner selection, value placed on monogamy, and low sexual selection pressure from other mates in the post-copulatory period [84]. Furthermore, the need for rapid ejaculation following the initiation of sexual intercourse is no longer considered essential or favourable. This reflects the aim of human sexuality as one oriented toward pursuing pleasure and heightening the enjoyment of the partner, requiring men to control their ejaculation [83]. Hence, cultural forces have reduced the importance of speed during reproduction, which may also reflect evolutionary adaptations to human relationships and society over time.

1.7 Implications for Treatment and Prevention: Inhibiting Type 5 Phosphodiesterase as the New Baculum

A range of factors contribute to the development of ED in humans, including biological, environmental, relational and intra-psychic. This constellation of factors may be seen, to varying degrees, in all patients presenting with ED, highlighting the multifactorial nature of this clinical condition. An understanding of these factors and how they relate to lifestyle choices provides an opportunity for the prevention of ED as well as the targeted management of the condition when it presents.

The **prevention** of ED at the population level is vital from a public health perspective. The consequences of ED on individuals and partners/relationships can be profound and can impact not only sexual performance but also wider well-being. However, it is particularly important to consider the prevention of ED as being justified, considering that ED can be an early signal of poor health. Preventative strategies targeting lifestyle risk factors have the potential to not only reduce the likelihood of ED but may also confer wider benefits for human health, including reduction in cardiovascular risk, as explored in Chaps. 2 and 5. The importance of ED prevention and treatment in the context of 'diabesity' (Chap. 3), psychological conditions (Chap. 4) and endocrine disorders (Chap. 6) will also be considered.

Once ED presents, effective treatment is crucial to minimise the impact of the sexual symptom. Historically, treatment options for ED were limited to and relied mainly on aphrodisiacs or alchemical practices, with **psychotherapy** later introduced as a therapeutic approach in the early twentieth century [4]. In the 1970s, an alternative to psychotherapy was the use of exogenous **androgen therapy** [85]. In the 1980s, malleable penile implants and inflatable **prostheses** were introduced [86]. While these devices and prostheses remain in use today, non-invasive strategies remain more desirable for the majority of men affected by ED. It was only in 1998 that the first approved pharmacological approach to managing ED was introduced to practice in the form of oral tablets of **sildenafil** citrate, a powerful and well-tolerated phosphodiesterase type 5 (PDE5) inhibitor [87, 88]. Consequent to their introduction in practice, PDE5 inhibitors (PDE5i) have become the most common intervention for ED and are recommended as first-line therapy, regardless of

the underlying cause, when the removal of the contributing risk factor is impossible or insufficient to restore erectile function [2, 89]. An overview of contemporary treatment options for ED is presented in Table 1.3.

The development of PDE5i for use in managing ED is one of the most widely known instances of serendipitous discovery in modern times. This class of drugs was initially developed to treat angina by promoting smooth muscle relaxation, but patients were observed to develop nocturnal and spontaneous erections during evaluation [90]. These effects led to a change in focus towards the use of PDE5i in sexual medicine and the management of ED. The mechanism of action of PDE5i involves the amplification of the **nitric oxide** (NO) - **cyclic guanosine monophosphate** (cGMP) pathway [91, 92]. This pathway includes the production of NO in nerve endings and vascular endothelial cells in response to physiological sexual stimulation. NO is, in turn, responsible for increasing cGMP, a regulatory of calcium channels, leading to the closure of these channels and a decrease in intracellular calcium. This results in smooth muscle **relaxation** and the vasodilation of the

Table 1.3 Overview of the treatment options for ED [2]

Therapeutic intervention	Details
Aetiological approaches	
Lifestyle modification	Healthy diet/Mediterranean diet to prevent or manage obesity, metabolic syndrome, and diabetes mellitus Physical activity to reduce weight or prevent obesity and diabesity Smoking and other drug cessation Moderation in drinking alcohol
Aetiological therapies	Addressing or reducing the sexual impact of the underlying risk factor (e.g. curing cancer or renal failure, etc.)
Hormonal therapies for endocrine conditions	Testosterone replacement therapy in hypogonadism Targeted management of pituitary, thyroid and adrenal dysfunctions
Psychological therapies	Counselling Psychoanalysis to be considered where other approaches have failed
Symptomatic approaches	
Oral pharmacological agents	Oral PDE5i as a first-line option for managing ED in all eligible patients, both in the traditional film-coated pills or in the newer orodispersible films that specifically respect patient intimacy
Psychotherapies	Sex therapy (e.g. cognitive-behavioural therapy to be integrated with other psychotherapeutic interventions and lifestyle changes)
Intra-urethral or intra-cavernosal administration of vasoactive substances	Alprostadil in men where PDE5 inhibitors are contraindicated, not tolerated or ineffective
Physical therapies	Vacuum devices may be considered where pharmacological options are contraindicated or not effective Low-intensity shockwaves
Surgical therapies	Penile prostheses must be considered where other options are contraindicated or not effective

Note the distinction between aetiological (when the underlying risk factor is specifically addressed and possibly cured) and symptomatic (when the therapy aims to reduce the impact of the symptom on the sexual and relational quality of life of the couple) approaches

arteries in the penis, leading to the engorgement of the corpus cavernosa with blood, i.e. the **erection**. The PDE5i specifically act by competitively inhibiting the "erectolytic" PDE5 enzyme, which is responsible for the breakdown of cGMP into GMP. Sildenafil thus promotes erection and penile hardness stabilizing the effects of cGMP, such as smooth muscle relaxation and enhanced penile blood flow [90].

1.8 Conclusion: The Loss of the Baculum and the Canary in the Coal Mine

The genial neo-Darwinian scientist John Burdon Sanderson Haldane (1892–1964) first intuited that thalassemia (and, later, sickle cell anaemia), a severe genetic blood disease, was much more prevalent where malaria was also present, prompting the hypothesis that mutations in carrier families likely persisted because they offered some protection against malaria in these malaria-endemic geographies [93]. In this case, a severe individual handicap (i.e. the genetic disease leading to various acute and chronic complications, several of which have a high mortality rate) remains in the population because it confers an immediate advantage in the survival to a mosquito-borne, lethal infectious disease such as malaria.

Similarly, the persistent and sexually selected disappearance of the baculum, despite the evident handicap affecting the ability to copulate and thus to reproduce, produced the advantage of selecting more healthy *carriers of genes* in a healthier environment coupled with a more fitting partner, which may have powerfully boosted human evolution. This perfectly fits the criteria of the handicap theory mentioned above.

We suggest here that ED is a signal of poor phenotypic quality and, as such, reflects the pressures of evolutionary sexual selection in humans. The development of ED may be a sensitive and early marker of wider disease processes and vulnerabilities that are less desirable in mates and subsequent offspring. *The loss of the baculum gave rise to ED*, a symptom that is probably rare, if not virtually unknown, in the animal kingdom and transformed ED itself into the **best biomarker** able to early predict, as this book largely demonstrates, virtually all external and internal factors discouraging reproduction. We can easily infer here that the loss of the baculum played a major and unique role in accelerating the entire process of human evolution by facilitating and selecting, through a strong and efficient *pre-zygotic mechanism*, the reproduction of individuals displaying vascular, endocrine, neurological, immunological, oncological, systemic, toxicological, psychiatric, environmental, intrapsychic and relational health. No one human symptom could be considered as powerful as ED as an early biomarker of general and environmental health—hence the perfect *canary in the coalmine*.

The growing role of lifestyle factors in the population's overall health and wellbeing, including their key contribution to the development of communicable- and NCDs, may be linked to the rising prevalence of ED. It could be, therefore, imagined that a "prehistoric" or at least "pre-industrial" life might have been advantageous from a sexual and reproductive perspective. However, this is not the case, because there is another aspect to consider. Thanks to advances in modern

medicine, humans fortunate enough to live in affluent regions of the planet now enjoy better overall health than ever before. At the same time, they enjoy an incredible ability to address sexual symptoms (in the case of men, primarily thanks to the *Viagra Revolution*), despite the growing burden of chronic diseases in society, particularly impacting older age groups. Thus, recent advances in healthcare have enabled better management of the negative effects of modern lifestyle risk factors, just as they have led to an increase in the average human lifespan and associated expectations of health and well-being in old age, including sexual function.

The burden of ED largely affects older populations as a result and imposes fragility on the male sexual physiology in this age group. There is a need to consider expectations of sexual function and pleasure in patients affected by ED, independent of age, to support the delivery of individualised and holistic care according to the lesson of the new SS model (Chap. 7). The treatment of ED is therefore crucial, and there is a need for PDE5i to overcome the "advantageous" fragility of male sexual physiology, which is, after the loss of the baculum, a major sexually selected impediment to reproduction. These drugs are invaluable in improving erectile function and overcoming this evolutionary obstacle [48].

But all these achievements would not be possible without the loss of a little penile bone thousands of years ago and the serendipitous discovery of revolutionary pharmacological support just 30 years ago.

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References

1. Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, Moreira ED, et al. Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med. 2010;7(4 Pt 2):1598–607.
2. Corona G, Cucinotta D, Di Lorenzo G, Ferlin A, Giagulli VA, Gnessi L, et al. The Italian Society of Andrology and Sexual Medicine (SIAMS), along with ten other Italian scientific societies, guidelines on the diagnosis and management of erectile dysfunction. J Endocrinol Investig. 2023;46(6):1241–74.
3. Jannini EA, Lenzi A, Isidori A, Fabbri A. Subclinical erectile dysfunction: proposal for a novel taxonomic category in sexual medicine. J Sex Med. 2006;3(5):787–94.

4. Mazzilli F. Erectile dysfunction: causes, diagnosis and treatment: an update. JCM. 2022;11(21):6429.
5. Owen CK, Khalafalla K, Wang R. Value of phosphodiesterase 5 inhibitors as a combination therapy for treating erectile dysfunction: a literature review. UroPrecision. 2024;2(1):9–15.
6. Burgio G, Giammusso B, Calogero AE, Mollaioli D, Condorelli RA, Jannini EA, et al. Evaluation of the mistakes in self-diagnosis of sexual dysfunctions in 11,000 male outpatients: a real-life study in an andrology clinic. J Clin Med. 2019;8(10)
7. Kessler A, Sollie S, Challacombe B, Briggs K, Van Hemelrijck M. The global prevalence of erectile dysfunction: a review. BJU Int. 2019;124(4):587–99.
8. Goldstein I, Goren A, Li VW, Tang WY, Hassan TA. Epidemiology update of erectile dysfunction in eight countries with high burden. Sex Med Rev. 2020;8(1):48–58.
9. Pozzi E, Capogrosso P, Boeri L, Cazzaniga W, Matloob R, Ventimiglia E, et al. Trends in reported male sexual dysfunction over the past decade: an evolving landscape. Int J Impot Res. 2021;33(6):596–602.
10. Schouten BWV, Bohnen AM, Groeneveld FPMJ, Dohle GR, Thomas S, Bosch JLHR. Erectile dysfunction in the community: trends over time in incidence, prevalence, GP consultation and medication use – the Krimpen study: trends in ED. J Sex Med. 2010;7(7):2547–53.
11. Wang W, Fan J, Huang G, Zhu X, Tian Y, Tan H, et al. Meta-analysis of prevalence of erectile dysfunction in mainland China: evidence based on epidemiological surveys. Sex Med. 2017;5(1):e19–30.
12. Romanelli F, Sansone A, Lenzi A. Erectile dysfunction in aging male. Acta Biomed. 2010;81(Suppl 1):89–94.
13. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. J Urol. 1994;151(1):54–61.
14. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol. 2000;163(2):460–3.
15. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the "Cologne male survey". Int J Impot Res. 2000;12(6):305–11.
16. Pellegrino F, Sjoberg DD, Tin AL, Benfante NE, Briganti A, Montorsi F, et al. Relationship between age, comorbidity, and the prevalence of erectile dysfunction. Eur Urol Focus. 2023;9(1):162–7.
17. Nicolosi A, Moreira ED, Shirai M, et al. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology. 2003;61(1):201–6.
18. Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M, et al. The multinational men's attitudes to life events and sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin. 2004;20(5):607–17.
19. Pastuszak AW. Current diagnosis and management of erectile dysfunction. Curr Sex Health Rep. 2014;6(3):164–76.
20. Latini DM, Penson DF, Colwell HH, Lubeck DP, Mehta SS, Henning JM, et al. Psychological impact of erectile dysfunction: validation of a new health related quality of life measure for patients with erectile dysfunction. J Urol. 2002;168(5):2086–91.
21. Jannini EA, Sternbach N, Limoncin E, Ciocca G, Gravina GL, Tripodi F, et al. Health-related characteristics and unmet needs of men with erectile dysfunction: a survey in five European countries. J Sex Med. 2014;11(1):40–50.
22. Jannini EA, Droupy S. Needs and expectations of patients with erectile dysfunction: an update on pharmacological innovations in phosphodiesterase type 5 inhibition with focus on sildenafil. Sex Med. 2019;7(1):1–10.
23. Allen MS, Walter EE. Erectile dysfunction: an umbrella review of meta-analyses of risk-factors, treatment, and prevalence outcomes. J Sex Med. 2019;16(4):531–41.

24. Nimbi FM, Galizia R, Rossi R, Limoncin E, Ciocca G, Fontanesi L, et al. The biopsychosocial model and the sex-positive approach: an integrative perspective for sexology and general health care. Sex Res Soc Policy. 2022;19(3):894–908.
25. Federoff HJ, Gostin LO. Evolving from reductionism to holism: is there a future for systems medicine? JAMA. 2009;302(9):994–6.
26. Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin Reprod Med. 2009;27(5):358–68.
27. Mollaioli D, Ciocca G, Limoncin E, Di Sante S, Gravina GL, Carosa E, et al. Lifestyles and sexuality in men and women: the gender perspective in sexual medicine. Reprod Biol Endocrinol. 2020;18(1):10.
28. Jannini EA. Introduction: history of sexual medicine. In: Bettocchi C, Busetto GM, Carrieri G, Cormio L, editors. Practical clinical andrology. Cham: Springer International Publishing; 2023. p. 1–12.
29. Cripps SM, Marshall SA, Mattiske DM, Ingham RY, Pask AJ. Estrogenic endocrine disruptor exposure directly impacts erectile function. Commun Biol. 2024;7(1):403.
30. Sansone A, Mollaioli D, Ciocca G, Colonnello E, Limoncin E, Balercia G, et al. "Mask up to keep it up": preliminary evidence of the association between erectile dysfunction and COVID-19. Andrology. 2021;9(4):1053–9.
31. Sansone A, Mollaioli D, Limoncin E, Ciocca G, Bắc NH, Cao TN, et al. The sexual long COVID (SLC): erectile dysfunction as a biomarker of systemic complications for COVID-19 long haulers. Sex Med Rev. 2022;10(2):271–85.
32. Jannini EA. SM = SM: the interface of systems medicine and sexual medicine for facing non-communicable diseases in a gender-dependent manner. Sex Med Rev. 2017;5(3):349–64.
33. Darwin C. On the origin of species. None. London: John Murray; 1859.
34. Hamilton WD. The genetical evolution of social behaviour. II. J Theor Biol. 1964;7(1):17–52.
35. Dawkins R. The selfish gene. 1st ed. New York: Oxford University Press; 1976.
36. Hosken DJ, Stockley P. Sexual selection and genital evolution. Trends Ecol Evol. 2004;19(2):87–93.
37. Darwin C. The descent of man, and selection in relation to sex. London: John Murray; 1871.
38. Petrie M, Tim H, Carolyn S. Peahens prefer peacocks with elaborate trains. Anim Behav. 1991;41(2):323–31.
39. Petrie M, Halliday T. Experimental and natural changes in the peacock's (Pavo cristatus) train can affect mating success. Behav Ecol Sociobiol. 1994;35(3):213–7.
40. Buss DM. The evolution of desire: strategies of human mating, vol. 40. 1st ed. Basic Books; 1995. p. 711.
41. Kane SA, Wang Y, Fang R, Lu Y, Dakin R. How conspicuous are peacock eyespots and other colorful feathers in the eyes of mammalian predators? PLoS One. 2019;14(4):e0210924.
42. Zahavi A. Mate selection - A selection for a handicap. J Theor Biol. 1975;3(1):205–14.
43. Zahavi A. The cost of honesty (further remarks on the handicap principle). J Theor Biol. 1977;67(3):603–5.
44. Zahavi A, Zahavi A. The handicap principle: a missing piece of Darwin's puzzle. 1st ed. New York: Oxford University Press; 1997.
45. Grafen A. Biological signals as handicaps. J Theor Biol. 1990;144(4):517–46.
46. Heywood JS. Sexual selection by the handicap mechanism. Evolution. 1989;43(7):1387–97.
47. Li L, Zhang Y, Ma M, Liu F, Shang Y, Yuan Q, et al. Does erectile dysfunction predict cardiovascular risk? A cross-sectional study of clinical characteristics in patients with erectile dysfunction combined with coronary heart disease. Front Cardiovasc Med. 2024;11:1341819.
48. Cellerino A, Jannini EA. Why humans need type 5 phosphodiesterase inhibitors. Int J Androl. 2005;28(Suppl 2):14–7.
49. Brindle M, Opie C. Postcopulatory sexual selection influences baculum evolution in primates and carnivores. Proc Biol Sci. 1844;2016:283.
50. Herdina AN, Nugraha TP, Semiadi G, Haase A, Lina PHC, Godlevska L, et al. Bat development: interspecies differences in baculum ossification patterns. FASEB J. 2016;30(S1)

51. Carosi M, Scalici M. Baculum (*os penis*). In: Bezanson M, MacKinnon KC, Riley E, Campbell CJ, Nekaris KAI, et al., editors. The international encyclopedia of primatology. Wiley; 2016. p. 1–5.
52. Jakovlić I. The missing human baculum: a victim of conspecific aggression and budding self-awareness? Mamm Rev. 2021;51(3):454–64.
53. Schultz NG, Lough-Stevens M, Abreu E, Orr T, Dean MD. The baculum was gained and lost multiple times during mammalian evolution. Integr Comp Biol. 2016;56(4):644–56.
54. Pérez W, Vazquez N, Ungerfeld R. Gross anatomy of the male genital organs of the pampas deer (Ozotoceros bezoarticus, Linnaeus 1758). Anat Sci Int. 2013;88(3):123–9.
55. Dixson AF. Baculum length and copulatory behavior in primates. Am J Primatol. 1987;13(1):51–60.
56. Ramm SA. Sexual selection and genital evolution in mammals: a phylogenetic analysis of baculum length. Am Nat. 2007;169(3):360–9.
57. Larivière S, Ferguson SH. On the evolution of the mammalian baculum: vaginal friction, prolonged intromission or induced ovulation? Mamm Rev. 2002;32(4):283–94.
58. Simmons LW, Firman RC. Experimental evidence for the evolution of the mammalian baculum by sexual selection. Evolution. 2014;68(1):276–83.
59. Martin RD. The evolution of human reproduction: a primatological perspective. Am J Phys Anthropol. 2007;Suppl 45:59–84.
60. Barash DP, Lipton JE. The myth of monogamy: Fidelity and infidelity in animals and people. 1st ed. New York: W. H. Freeman; 2001.
61. Spani F, Morigi MP, Bettuzzi M, Scalici M, Gentile G, Carosi M. The ultimate database to (re) set the evolutionary history of primate genital bones. Sci Rep. 2021;11(1):11245.
62. Smith TC, Hechtel L. Erectile dysfunction and the baculum. Evol Med Public Health. 2019;2019(1):147–8.
63. Cormier LA, Jones SR. The domesticated penis: how womanhood has shaped manhood. 1st ed. University Alabama Press; 2015.
64. Lough-Stevens M, Schultz NG, Dean MD. The baubellum is more developmentally and evolutionarily labile than the baculum. Ecol Evol. 2018;8(2):1073–83.
65. Pavlicev M, Zupan AM, Barry A, Walters S, Milano KM, Kliman HJ, et al. An experimental test of the ovulatory homolog model of female orgasm. Proc Natl Acad Sci USA. 2019;116(41):20267–73.
66. Jannini EA, Rubio-Casillas A, Whipple B, Buisson O, Komisaruk BR, Brody S. Female orgasm(s): one, two, several. J Sex Med. 2012;9(4):956–65.
67. MacDonald SM, Burnett AL. Physiology of erection and pathophysiology of erectile dysfunction. Urol Clin North Am. 2021;48(4):513–25.
68. Cowlishaw G, Dunbar RIM. Dominance rank and mating success in male primates. Anim Behav. 1991;41(6):1045–56.
69. Owens D, Owens M. Social dominance and reproductive patterns in brown hyaenas, Hyaena brunnea, of the central Kalahari desert. Anim Behav. 1996;51(3):535–51.
70. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med. 2007;120(2):151–7.
71. Glina S, Sharlip ID, Hellstrom WJG. Modifying risk factors to prevent and treat erectile dysfunction. J Sex Med. 2013;10(1):115–9.
72. Dewitte M, Bettocchi C, Carvalho J, Corona G, Flink I, Limoncin E, et al. A psychosocial approach to erectile dysfunction: position statements from the European Society of Sexual Medicine (ESSM). Sex Med. 2021;9(6):100434.
73. Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. Heart. 2003;89(3):251–3.
74. Ciocca G, Di Stefano R, Collazzoni A, Jannini TB, Di Lorenzo G, Jannini EA, et al. Sexual dysfunctions and problematic sexuality in personality disorders and pathological personality traits: a systematic review. Curr Psychiatry Rep. 2023;25(3):93–103.
75. Ciaccio V, Di Giacomo D. Psychological factors related to impotence as a sexual dysfunction in young men: a literature scan for noteworthy research frameworks. Clin Pract. 2022;12(4):501–12.

76. Pomiankowski A, Iwasa Y. Runaway ornament diversity caused by Fisherian sexual selection. Proc Natl Acad Sci USA. 1998;95(9):5106–11.
77. Gofrit ON. The evolutionary role of erectile dysfunction. Med Hypotheses. 2006;67(5):1245–9.
78. Sharma R, Agarwal A, Rohra VK, Assidi M, Abu-Elmagd M, Turki RF. Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring. Reprod Biol Endocrinol. 2015;13:35.
79. Lenzi A, Lombardo F, Salacone P, Gandini L, Jannini EA. Stress, sexual dysfunctions, and male infertility. J Endocrinol Investig. 2003;26(3 Suppl):72–6.
80. Davis SR. Sexual dysfunction in women. N Engl J Med. 2024;391(8):736–45.
81. Stuppia L, Franzago M, Ballerini P, Gatta V, Antonucci I. Epigenetics and male reproduction: the consequences of paternal lifestyle on fertility, embryo development, and children lifetime health. Clin Epigenetics. 2015;7:120.
82. Jannini EA, Simonelli C, Lenzi A. Sexological approach to ejaculatory dysfunction. Int J Androl. 2002;25(6):317–23.
83. Jannini EA, Lombardo F, Lenzi A. Correlation between ejaculatory and erectile dysfunction. Int J Androl. 2005;28(Suppl 2):40–5.
84. Apostolou M. Sexual dysfunctions in men: an evolutionary perspective. Evol Psychol Sci. 2015;1(4):220–31.
85. Langarizadeh MA, Salary A, Tavakoli MR, Nejad BG, Fadaei S, Jahani Z, et al. An overview of the history, current strategies, and potential future treatment approaches in erectile dysfunction: a comprehensive review. Sex Med Rev. 2023;11(3):253–67.
86. Trost L, Hellstrom WJG. History, contemporary outcomes, and future of penile prostheses: a review of the literature. Sex Med Rev. 2013;1(3):150–63.
87. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil study group. N Engl J Med. 1998;338(20):1397–404.
88. Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU Int. 2005;96(3):257–80.
89. Mulhall JP, Giraldi A, Hackett G, Hellstrom WJG, Jannini EA, Rubio-Aurioles E, et al. The 2018 revision to the process of care model for evaluation of erectile dysfunction. J Sex Med. 2018;15(9):1280–92.
90. Andersson KE. PDE5 inhibitors – pharmacology and clinical applications 20 years after sildenafil discovery. Br J Pharmacol. 2018;175(13):2554–65.
91. Corbin JD. Mechanisms of action of PDE5 inhibition in erectile dysfunction. Int J Impot Res. 2004;16(Suppl 1):S4–7.
92. Jannini EA, DeRogatis LR, Chung E, Brock GB. How to evaluate the efficacy of the phosphodiesterase type 5 inhibitors. J Sex Med. 2012;9(1):26–33.
93. Hedrick PW. Resistance to malaria in humans: the impact of strong, recent selection. Malar J. 2012;11:349.