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Congenital absence of vas deferens: anatomical and embryological inputs from a series of autopsies reported in Europe throughout the 18th and 19th century.

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ABSTRACT

Congenital absence of the vas deferens (CAVD) is a syndrome with a heterogeneous presentation: bilateral (CBAVD) or unilateral (CUAVD), complete or partial and associated or not with other anomalies of the male urogenital system. A turning point came in 1968 when CBAVD was associated with cystic fibrosis and its *CFTR* gene mutations. Genetic studies then revealed that a minority of CBAVD but a majority of CUAVD are *CFTR*-independent. In the literature, reference is classically made to 2 sources from the 18th and 19th century: Hunter (1755) and Reverdin (1870). This scarcity prompted us to look for additional observations of CAVD. By a meticulous bibliographical search, we identified a corpus of 10 European observations (8 CUAVD and 2 CBAVD) some of them richly illustrated. They were collected between 1755 and 1876 throughout adult men autopsies. We also provided their primary and unambiguous sources. Analysis of the reported data revealed some interesting facts: both CBAVD cases were unlikely linked to cystic fibrosis and half of CUAVD cases were associated to an ipsilateral kidney absence, suggesting a *CFTR*-independent pathophysiology. Moreover, the anatomical details of the anomalies raise interesting embryological questions we have tried to address in the light of current data. This work made it possible to identify new historical sources dealing with male genital tract pathologies. It sheds light on the origins of andrology and opens up interesting prospects for research and education in the field.

INTRODUCTION

Congenital absence of the vas deferens (CAVD) has a variety of clinical presentations, depending on whether it is bilateral (CBAVD) or unilateral (CUAVD), complete or partial, and associated or not with other anomalies of the male urogenital system (1,2). CBAVD is usually discovered in adult males either as part of a routine evaluation for cystic fibrosis (CF) or another *CFTR* gene-related condition, or during the investigation of isolated infertility with obstructive azoospermia. Diagnosis of CAVD is based on a succession of clinical and spermiological examinations with a prominent role for ultrasonography (2–4). Its prevalence in men is estimated at 0.1% (1, 2). However, this figure is probably underestimated, as unilateral forms in fertile, asymptomatic men are generally not diagnosed (1). A major issue, that stems from CAVD diagnosis, is whether the patients carry or not CF-causing alleles, requiring then *CFTR* testing and genetic counselling (recently, other genes like *ADGRG2* has been addressed (5)). However, no genetic diagnosis could be made for up to 20% of CBAVD and 70% of CUAVD (1,4). These non-*CFTR* CAVD often present a solitary kidney suggesting an early organogenesis trouble involving Wolff's duct (1) and may constitute a specific syndrome. In the uro-andrology literature, two historical vignettes are classically reported about CAVD: that of Hunter, a Scottish surgeon of the 18th century which described the first CBAVD and that of Reverdin which stated the first association of CUAVD and ipsilateral kidney absence in 1870. However, the exact date of Hunter's discovery varies from article to article: 1755 (1, 6), 1737 (7) or even 1775 (8). This scarcity of CAVD historical vignettes and their inaccuracies are probably linked to a problem of identifying the sources (9). This prompted us to clarify the early historical background of CAVD and to identify the available original sources from the 18th and 19th century.

METHODS

We performed a comprehensive historical review of the English and French medical literature using PubMed from inception, Google Scholar and Google Books using the terms: vas + deferens + congenital + absence. The initial search identified articles and textbooks whose references were systematically tracked (upstreaming of bibliographical channels) leading to a collection of books and articles spanning the 18th and 19th century (secondary sources). The search strategy and its results are summarized in Figure 1. We identified and compiled a selection of 10 cases that were regularly cited by different authors and went back to their primary sources which were unambiguously identified (primary sources).

RESULTS

We identified ten primary sources and built up a corpus of 10 fully accessible observations. They range from 1755 to 1876 and come mainly from Paris and London (Table 1). All are autopsy descriptions of adult males aged between 20 and 81. If causes of death were reported, they were mainly infectious. Eight CUAVD were described, against only 2 CBAVD. For CUAVD, abnormalities were predominantly on the left. The testes were usually normal and present in the scrotum. The epididymis was most often abnormal, with an absence of the body and tail; the head was present, sometimes distended by an accumulation of secretions. VD absence took two forms: complete or partial. The latter case was more frequent with the central portion (iliac) being more often absent. The distal (retrovesical) or proximal (epididymo-testicular) segments were sometimes preserved. The seminal vesicles were rarely present and normal. When the distal segment of the CD was missing, they were systematically absent (reported as Godart's rule). In 4 cases, the kidneys and ureters were absent (always on the left). In the other cases, it is not clear whether the kidneys were present or had not been explored. CBAVD (cases 1 and 9) were reported on adults in London. Testis were normal and epididymis were often limited to their sole heads. VD presented various absence profiles. Strikingly, seminal vesicles were present but abnormal. Some of the observations were accompanied by illustrations, sometimes of high quality (Figure 2).

In order to carry out a more detailed and quantitative analysis of the cases, we reported their anatomical descriptions as a diagram (Figure 3). For epididymis, the heads were always present but bodies and tails were absent in 72% of cases (8/11). Regarding vas deferens, the proximal segments (ET and RT) were absent in 75% (9/12) of cases whereas the distal segment (RV) was absent in only 50% (6/12). Seminal vesicles were respectively abnormal and absent in 42% (5/12) and 25% (3/12) of cases. In order to suggest an embryological origin, we have gathered cases in three groups according to the extent of their anomalies. Group I comprises cases with only epididymis/vas deferens absences but normal seminal vesicles (cases 4L, 6L and 2R). Group II includes those with additional seminal vesicles anomalies (1R, 1L, 3L, 9R, 9L) and Group III those with confirmed ipsilateral kidney absence (cases 7L, 8L and 10L). There are two points of interest: if kidney is absent so is the ipsilateral seminal vesicle and both CBAVD cases belongs to Group II with abnormal seminal vesicles. Case 5L could not be attributed to one of these three groups because of absent kidney but present seminal vesicle.

DISCUSSION

In recent literature, there are very few historical vignettes of CAVD, and some are inaccurate. We have undertaken a search for sources by examining the English and French medical literature of 18th and 19th century as exhaustively as possible and found ten unambiguous historical sources of CAVD. Most likely, these are the oldest cases ever reported. In passing, we have completed and corrected the previous collection of 7 CAVD cases of this period published by Nelson in 1950 (19). We have identified three new cases, all French (cases 5, 7 and 10; Table 1).

Regarding CBAVD cases, one can note the scarcity of their reporting (2 cases only in 122 years, both in the London area). Hunter and Little described robust men with normal male attributes, and normal testis containing spermatozoa. They were not homozygous for CF-causing alleles since both died in their adulthood. Indeed, CF was only identified in 1938 and its diagnosis was made postmortem on infants of less than 18 months (20). These men probably had a *CFTR*-independent CBAVD or isolated CBAVD. Renal status could have provided genetic clues but it was not reported (Table 1). However, autopsies described in great details anatomical anomalies of both epididymides, VD and seminal vesicles and the later were present in a rudimentary form. These details could be interestingly compared with current imaging data from CBAVD patients. Regarding CUAVD cases of our series, they were more frequent and more scattered in Europe (Paris, London, Torino, Leiden). In all cases, testes were present (no cryptorchidism) and mostly normal with sperm production. However, the fertility of these men was not reported. Autopsies provided a precise description of missing VD segments (Figure 1). In 1860, Godard (14) was the first to identify that seminal vesicles were systematically absent when the VD retro-vesical segment was missing (Godard's rule). In half of cases (4/8), all from Paris, ipsilateral kidney was absent but this frequency is probably skewed by the lack of reporting. As discussed above for CBAVD, these unilateral cases are likely *CFTR*-independent. Of interest, when reported, renal absence coincided with that of seminal vesicles. Analysis of these cases and their authors' comments in their historical context is interesting because it allows us to go back to the origins of the uro-andrological knowledge. All authors identified that despite the lack of excretory function by CAVD, testes remain normal and continue to produce sperm. Testes and epididymides remnants (mostly the head) retain a reabsorption capacity to cope with the obstruction. This observation opened the way to animal experimentations in

France and England (14, 15, 21, 22) and it would be interesting to search a link with further works on vasectomy.

Another subject on which there was consensus was the embryological origin of VD defects. To understand the scope of reported anomalies, it is worth keeping in mind a few stages of the male genital tract development. As reported by classical embryology sources (23), both the urinary and genital systems derive from the intermediate mesoblast and the urogenital sinus and develop closely together. At WG3, the intermediate mesoblast generates two longitudinal structures parallel to the embryo's median axis, each comprises two regions: the nephrogenic cord and the genital crest. The first will give rise to the three consecutive embryonic kidneys in a temporal and cranio-caudal sequence: pronephros, mesonephros and metanephros. The later is the precursor of the testis and will receive the primordial germ cells of epiblastic origin. During WG3, the nephrogenic cord separates into two structures: the mesonephros with mesonephrotic tubules (ventral) and a solid cellular cord (dorsal). This mesenchymal cord grows and progresses caudally under the ectoderm to fuse with the wall of the cloaca. During its progression, the nephrogenic cord undergoes a mesenchymal-epithelial transition with the formation of a central lumen. It will be then known as the Wolffian duct (*Ductus mesonephricus*). However, its caudal part remains of mesenchymal nature and will play an important role in kidney formation. Any impairment or lesion at this level may cause renal agenesis. Hence, unilateral renal agenesis is often associated with ipsilateral urogenital anomalies affecting structures derived from the Wolffian ducts (24). Around day 28 (WG4), two structures appear under the action of reciprocal inductive signals: a metanephrotic mesoderm that forms caudally of the metanephros from the intermediate mesoderm, and facing it, the ureteric bud (UB) which is an outgrowth that emanates from the distal part of the Wolffian duct. Each UB enters the adjacent metanephrotic blastema leading to the development of the metanephros or definitive kidney. Between WG4 and 6, the WD are incorporated by extrophy into the posterior wall of the developing bladder. This process leads to the formation of the bladder trigone and to the separation of the UB apertures (upper part of the trigone) from those of the WD (lower part of the trigone at the level of the pelvic urethra). A dynamic view of this complex process can be seen here (<https://embryology.ch/fr/organogenese/systeme-urinaire/popup/t5vessie.html>). Until WG7, the genital tract is made up of two systems of paired ducts with the same appearance, whatever the sex. Then, under the influence of the sex-determining region of the Y chromosome (SRY), a genetic cascade induces the development of undifferentiated gonads to the testis. At WG8, fetal Leydig cells begin to secrete testosterone

which induces the genital system differentiation towards the male side while the paramesonephrotic Müllerian ducts regress under the effect of the Sertolian AMH. Between WG8 and WG12, the paracrine action of testosterone induces WD differentiation into 3 organs: the epididymis, the vas deferens and the seminal vesicles. Although contiguous, these derivatives depend on local epithelial-mesenchymal interactions and differ in morphology and gene expression (25,26). The WD need testosterone to remain and differentiate since any abnormality in hormone production or in androgen receptors cause them to regress (26,27). At WG9, the cranial part of both WD degenerates, leaving behind the epididymal appendixes whereas the portion adjacent to the future testis will differentiate into a convoluted duct, the epididymis. In the upper part, called the head of epididymis (*Caput epididymis*), the mesonephrotic tubules facing the rete testis will give rise to the future efferent ducts (28). Below the head, the epididymis body elongates and becomes strongly circumvented (29). The WD portion beneath the testis becomes the epididymis tail and downstream most of the WD differentiates into a muscular-epithelial spermatic duct, the vas deferens (30). At WG10, both WD give rise to an excrescence just before their apertures into the pelvic urethra: the seminal vesicles (31). The upstream portions of WD form the ampullas and those between the seminal vesicles and the prostatic urethra are called ejaculatory ducts. Their openings arrive at the *colliculus seminalis* on both sides of that of the prostatic utricle (a short remnant of the Müllerian ducts). At the same stage, thanks to signals from the surrounding mesenchyma and above all that of local dihydrotestosterone production, the prostate begins its development from endodermal buds that emerge from the pelvic urethra. Later during pregnancy, both testes migrate caudally into the scrotum and pull along the epididymis and the scrotal part of the vas deferens.

The distinct origins of the testis and the head of the epididymis compared to that of the rest of the epididymis and the VD were well known in the 19th century allowing some authors to throw lights upon the anatomical conditions of CAVD cases (17). From our side, we took advantage of this compilation of very first cases of CAVD and their detailed autopsic description to go beyond the historical analysis. Namely, we tried to quantify the Wolffian derivatives anomalies (Figure 3). The most frequently absent structures (around 75%) were epididymis body and tail and proximal (ET, RT) portions of the VD. Seminal vesicles were mainly present (9/12) but more often abnormal (5/9) whereas the RV portion of the VD is the less abnormal or absent (6/12). In order to get further insight into the possible embryological origin of the anomalies, we have grouped the cases into specific clusters taking in account the rostro-caudal development of the Wolffian derivatives. Hence, group I includes cases with only

epididymis/vas deferens absences but normal seminal vesicles. This means that WD development has passed the WG10 when seminal vesicles appear. Since the maintenance or regression of the Wolffian duct and its derived organs are androgen-dependent, the first hypothesis is that anomalies (namely aplasia) may be linked to a local or more and less extended failure of the androgenic signal upstream the seminal vesicles. However, a trouble in epithelial-mesenchymal interactions cannot be excluded (25-27). The presence of the ipsilateral kidney has not been reported, but it is reasonable to suggest that it is present. Group II comprises cases with additional seminal vesicles anomalies suggesting a trouble in epithelial-mesenchymal interactions (that ensures WD patterning) before or around the WG10 and androgenic signals (that ensures persistence). From our point of view, it is difficult to make an assumption about the presence of the ipsilateral kidney. Group III is of particular interest because it gathers the highest possible number of anomalies (Figure 3). It is the result of our efforts to identify new CUAVD cases. The combination of renal agenesis and that of seminal vesicles is typical of an early (WG4) and distal WD anomalies affecting the UB (24). These anomalies may also affect patterning and/or persistence of the other WD derivatives explaining their absence. Case 5L could not be attributed to one of these three groups because of a paradoxical phenotype (absent kidney but present seminal vesicle). It may be an isolated kidney aplasia after the UB induction associated to a VD aplasia. To confirm the usefulness of this clustering and the associated hypotheses, other cases of CAVD need to be analysed. This will be the subject of further work. Besides embryological and anatomical inputs, this work sheds light on the clinical intuition and reasoning of some authors like Gosselin and Godard (14, 15) which can be considered as pioneers in andrology. They were able to identify from the various pathological pictures and animal experiments that the testicle has two quite distinct functions: reproduction and virilization (testosterone had not been yet discovered). Godard noted and regretted that no information on the genital functions of the subjects could be gathered. Despite this, the two French authors draw the correct conclusions as to the patients' potential fertility. Bilateral damage to the spermatic ducts will not affect "*their virile faculty*" in the sense of sexual drive, erection and ejaculation (Gosselin) or their ability to have sexual intercourse (Godard), but they will lose "*their fertilizing power*" (Gosselin) and will have no children (Godard). Both authors believe that if the damage is unilateral, with the opposite side normal and healthy, "*it brings no apparent disorder*" (Gosselin) and "*the man will enjoy all his faculties*" (Godard). We recently confirmed that intuition by showing that 42% of men with CUAVD were not azoospermic and had children (32). Beyond andrological interest and by reaching primary sources of CAVD cases, the present work provides various clarifications and is of historical interest. The first case

of CBAVD is indeed Hunter's in 1755. Little confirmed in his own report of 1873 that he did not find any case before nor after that one. The first case of CUAVD could be that of Brugnone in 1786. The first one with confirmed absence of kidney could be that of described by Cusco in 1842 (and reported by Godard in 1860). We are thus correcting previous inaccurate assertions. This issue is mainly due to the use of imprecise secondary sources (9). However, we remain cautious in asserting the primacy of these three CAVD cases as wisely recommended by Mudry and Jackler (9). We scanned primary and secondary sources, mainly in French and English, citing each other and thus providing a certain level of confidence. Nevertheless, we did not meet nor specifically researched potential German medical sources addressing CAVD during this period.

Reporting historical medical records provides an underrated contribution to the medical knowledge provided a careful and critical analysis. It has been helpful for clarifying the nosology of certain pathologies such as Alzheimer disease that could be distinguished from senile dementia (33, 34). Thus, in the setting of CAVD, if we assume that CUAVD with ipsilateral kidney absence is a potential syndrome, the first historical series of cases was recognized in Paris between 1842 and 1876 (14, 16, 18). Further research is required to explore this syndromic hypothesis.

We have identified the first cases of CAVD described in the 18th and 19th century and unambiguously traced them back to early European sources at the interface of urology and andrology. We think that such systematic approach extended from inception to present days may shed light on clinical stratification and pathophysiological processes of CAVD. This may contribute to a better management of infertile couples and genetic counselling prior to conception. More broadly, this work underlines the importance of exploring socio-cultural and historical inputs to andrology (35).

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Table 1: Cases description and primary sources details.

Case	Year	Defect type ^a	Patient's age	Testis	Epididymis	Vas deferens	Seminal Vesicles	Kidney	Author	Location	Language	Ref
1	1755	Bi	adult	both normal	R: entirely ^b present L: head present	R: I to RV present L: entirely present	both abnormal	nr	Hunter	London	English	10
2	1786	U, R	26-27	normal	head present	RV present	present	nr	Brugnone	Torino	French	11
3	1813	U, L	adult	normal	entirely present	ET present	rudimentary	nr	Bosscha	Leiden	Latin	12
4	1840	U, L	71	abnormal	nr	I to RV present	present	nr	Paget	London	English	13
5	1842	U, L	45	small	entirely present	ET present	absent	absent	Cusco	Paris	French	14 ^c
6	1847	U, R	20 - 25	normal	head present	ET and RV present	present	nr	Gosselin	Paris	French	15

7	1859	U, L	37	normal	Head present	none	absent	absent	Godard	Paris	French	14
8	1870	U, L	old	normal	head present (cysts)	none	absent	absent	Reverdin	Paris	French	16
9	1873	Bi	40-50	both normal	R: head present L: head present	R: RV present L: none	both rudimentary	nr	Little	London	English	17
10	1876	U, L	81	normal	head present	none	absent	absent	Mayor	Paris	French	18

a, of the vas deferens; b, entirely present = head + body + tail; c, Cusco discovered his case in 1842 and communicated it to Godard which reported it in his own book (14). Abbreviations: Bi, bilateral ; ET, epididymo-testicular ; I ; iliac ; L, left, nr ; not reported ; R, right ; RV, retrovesical ; U, unilateral

Legend Figure 1: Diagram of the search strategy for secondary and primary historical sources for CAVD cases.

In a first step, we retrieved the secondary sources (white boxes) in PubMed and Google Scholar/Books using the indicated keywords. We identified Nelson's article (19), 5 books in English and 6 books in French. Then, we screened their texts and bibliographies to identify the CAVD cases. We retrieved 10 primary sources (grey boxes) reporting CAVD cases: the 7 classical ones that we confirmed and corrected and 3 new ones. We reported the comprehensive books' references in the supplemental document (SD1).

Legend Figure 2: Adaptation of the panel XII of Godard's book of 1860 – Case 7 (14).

Captions have been enlarged and colored for greater legibility and their corresponding text translated and integrally reproduced below. The book is freely accessible on: <https://books.google.fr/books?id=mQKvZMjRFUYC&hl=fr&pg=PP1#v=onepage&q&f=false>

Fig.1: a- bladder seen from its posterior surface, b- right ureter, c- right vas deferens, d- right seminal vesicle, e- left lobe of the prostate arrested in its development (sic), f- right lobe of the prostate, g- membranous portion of the urethra. Fig.2: a- section of the left lobe of the prostate, section of the right lobe of the prostate, c- orifice of the prostatic utricle into which the right ejaculatory duct opened. Fig.3: a- left testicle, b- left epididymal head (body and tail are absolutely missing), c- left spermatic cord. Fig.4: a- right testicle, right epididymis, c- right vas deferens, d- right spermatic cord.

Legend Figure 3: Diagram of the testis, internal male genital tract and kidneys reported in each case.

The upper panel (*Reference*) represents normal anatomy with the presence of the testis, complete epididymis and vas deferens, normal seminal vesicle and present kidney. The lower panel (*Cases*), describes schematically the anomalies and/or absences of each case. The last column indicates the number of absent or abnormal Wolffian derivatives (x/6) for each case. The last line sums up the number of anomalies or absence of each structure (except for testis for more simplicity). We called this representation *Godard's Diagram*. Abbreviations: B, body; Bi, bilateral; ET, epididymo-testicular; H, head; IP, iliac and pelvic; K, kidney; L, left; R, right; RV, retrovesical; SV, seminal vesicles; Ta, tail; Te, testis; Wd; Wolffian derivatives.

Figure 1

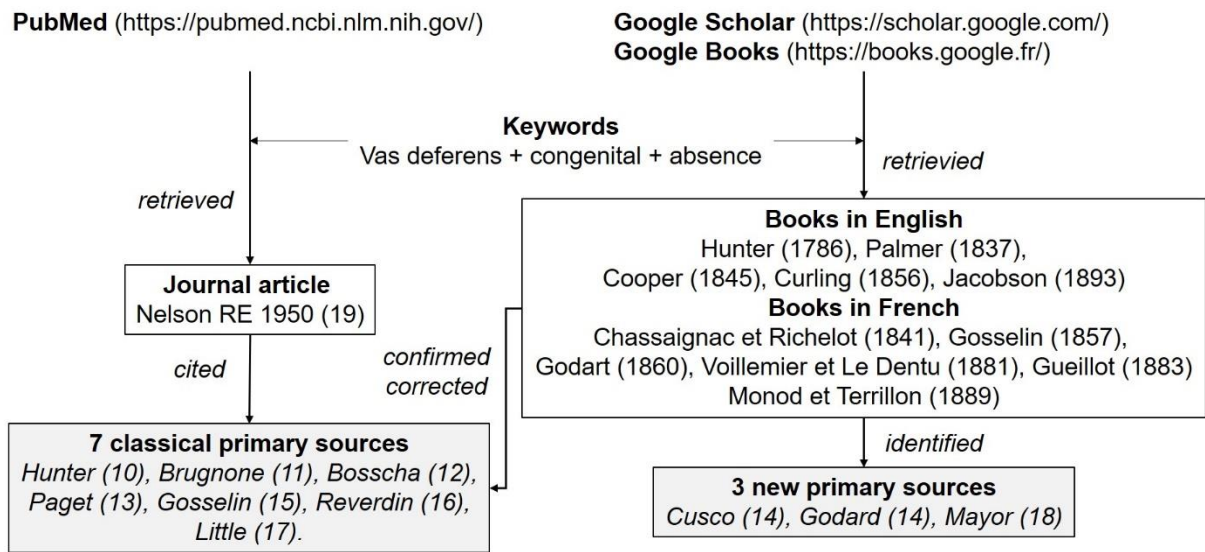
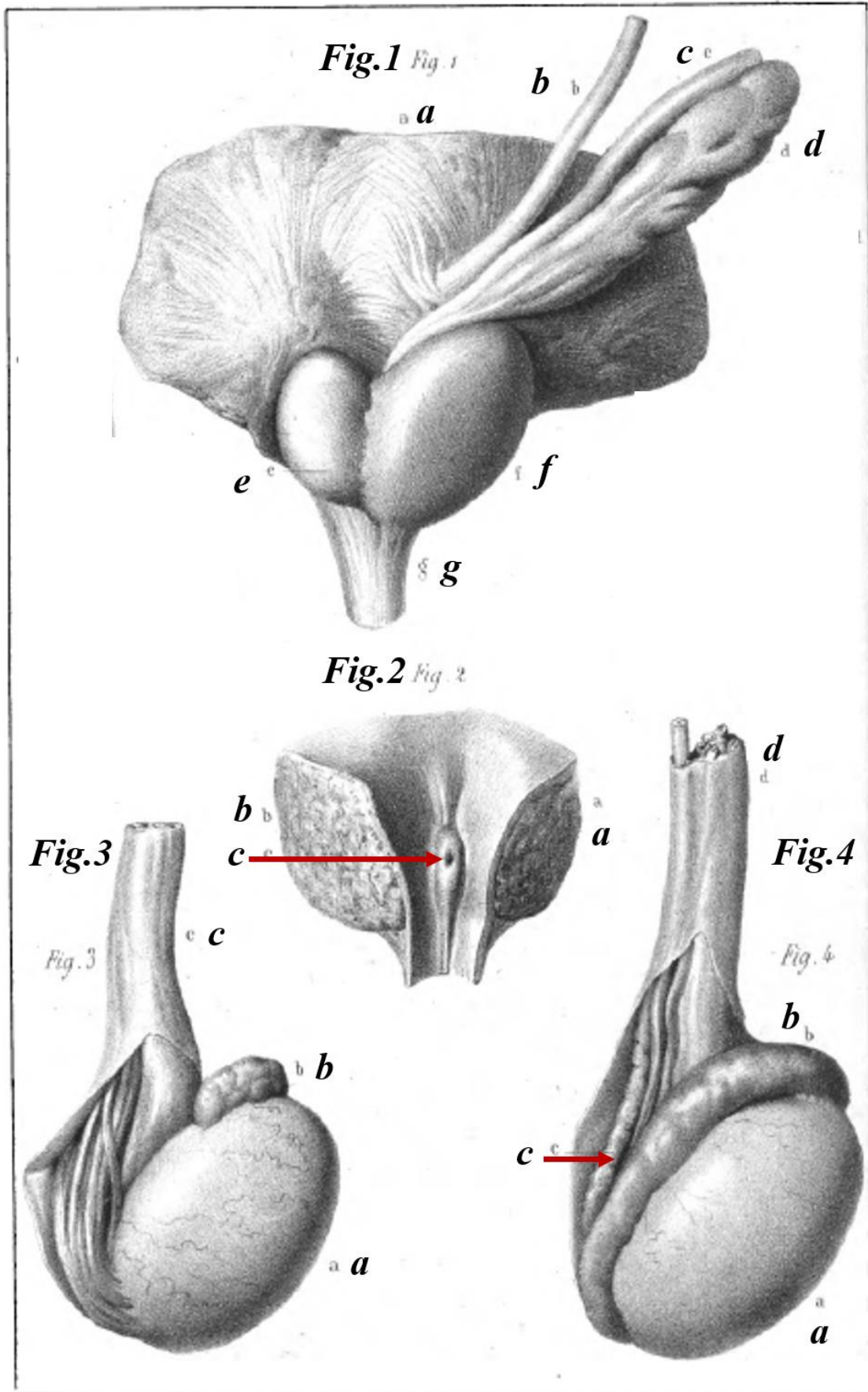


Figure 2



Levaille del et lith.

Imp. Le Normoir, Paris.

Figure 3

