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Male fertility across history: where are we heading?

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Abstract

The evaluation of male infertility has followed the technical limits of each period. Early clinical descriptions recognized anatomical abnormalities, particularly scrotal venous disease and testicular atrophy. Microscopy later converted the ejaculate and the testis into measurable material: first through sperm counts, then through motility, morphology, sperm kinematics, quantitative histology, daily sperm production and standardized semen analysis. Subsequent work made clear that the conventional triad is clinically useful but weak as a direct measure of fertility, because fertile and infertile men overlap across these variables and because fertilization requires functions not covered by routine semen analysis. This narrative review follows selected landmarks in the history of male infertility, including Celsus, Curling, Macomber and Sanders, MacLeod, Amann, Mortimer, Yanagimachi, Kruger and Menkveld, Guzick, Setchell and the WHO manuals, and places them in a clinical framework. The later sections discuss contemporary and emerging evaluation, including sperm DNA fragmentation, acrosomal and zona-binding assays, mitochondrial function, epigenetic profiling, microRNA, proteomics, metabolomics, next-generation sequencing, exome sequencing and single-cell approaches. The premise is not that semen analysis should be replaced. It is that semen analysis should be interpreted within a layered andrological assessment, in which the patient, the ejaculate, the testis and the couple's reproductive endpoint are considered together.

Keywords*: andrology, molecular profiling, semen analysis, sperm function, varicocele.*

Introduction

Male infertility - or fertility - is a difficult concept to adequately define. While the World Health Organization will state that a one-year period of attempting to conceive without the use of contraceptive measures is a good definition (albeit statistical in nature) of conjugal infertility (World Health Organization, 2025a), a male factor is defined either by altered semen, altered advanced sperm characteristics, or by the presence of clinical conditions that negatively affect male fertile potential, such as varicoceles (American Urological Association, 2020; Minhas et al. 2025). In humans, there is no possible means of determining the actual fertility performance of an ejaculate or individual, as is done in production animals, where testing against a large cohort of females is routine (Amann, 1989). As we move through the history of andrological evaluation, we will, hopefully, demonstrate what were the tools available at the time to investigate male infertility, what advancements they brought, what were their limitations, and what the next steps brought. We will then move towards what future tests and techniques may bring so that determination of a term that resists even to philosophical definition - Thomas Kuhn would maybe diagnose the area of andrology as a whole as in a pre-paradigmatic state - is achievable (Kuhn, 1962).

With this frame, the historical sequence should not be presented as a list of discoveries. It is more useful to follow the tool that was available at each moment and to ask what that tool allowed the clinician or investigator to conclude. When the only available tool was inspection, the problem was anatomical. When microscopy became clinically organized, the problem became cellular and numerical. When sperm function was studied, the problem became one of interaction between a gamete and the reproductive tract or oocyte. When molecular profiling became possible, the problem no longer fitted comfortably inside the categories of count, motility and morphology. This is the reason Celsus, Curling, Macomber and Sanders, MacLeod, Amann and the later spermatology literature are still very relevant (Amann, 1989; Amann and Hammerstedt, 1993; Amman and Howards, 1980; Celsus, 1935; Curling, 1856; MacLeod and Gold, 1951a, 1951b, 1951c; Macomber and Sanders, 1929; Marte, 2018). They are not historical ornaments; they are steps in the construction of the language still used when an infertile man is evaluated.

The purpose of this review is therefore deliberately clinical. The question is how male infertility came to be investigated, what was gained by each method, and where each method failed. That framework also helps explain the present. A modern semen analysis is indispensable, but it is not a direct measurement

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of fertility. A molecular assay may be informative, but it is not a complete reproductive diagnosis. A varicocele may be visible, but visibility does not automatically establish reproductive causality. The history of the field is, in large part, the history of learning how to make these distinctions.

Anatomical and clinical description: Celsus and Curling

The earliest point at which male infertility can be discussed without imposing a modern vocabulary on the past is not the sperm cell, but the testis. In *De Medicina*, Celsus (1935) described enlarged and tortuous veins in the scrotal region associated with a smaller ipsilateral testis (Celsus, 1935; Marte, 2018). The retrospective interpretation is, of course, varicocele, but the important point is not whether Celsus understood varicocele as it is understood now. It is more relevant that he associated, at the time, a testis exposed to a recognizable scrotal abnormality to present some disfunction.

Curling's (1856) contribution in the nineteenth century was to move this same lesion from descriptive anatomy toward function. In his 1856 treatise on diseases of the testis, spermatic cord and scrotum, Curling coined the term “varicocele” as an abnormal dilation of the veins within the pampiniform plexus, and reported this lead to a decrease in “the secreting power of the gland” (Curling, 1856). This step was perhaps one of particular interest, because Curling moved form observation to determination of a clinical outcome that derived from these altered veins.

The persistence of varicocele in contemporary guidelines shows that this historical line was not abandoned; it was refined. Modern practice does not treat every ultrasound finding, and it does not treat subclinical varicocele as equivalent to clinically relevant disease. Intervention is restricted to clinical scenarios in which the lesion, the semen phenotype, the reproductive history and the couple's prognosis justify it (American Urological Association, 2020; Minhas et al. 2025). The underlying question remains close to the one inherited from Celsus (1935) and Curling (1856), but it is now asked with better tools: physical examination, standardized semen analysis, sperm DNA fragmentation in selected settings, and an understanding of chronic testicular stress.

Microscopy, counting and the measurable ejaculate

The discovery of spermatozoa and the later development of semen analysis are separated by more than a technical interval. Seeing sperm cells was not the same as having a clinical test. The clinical transformation required counting, reproducibility, comparison with reproductive outcome and a method that could be standardized and used by more than one laboratory. That is why the early twentieth century is so important. It converted microscopy from a descriptive instrument into a diagnostic language (Macomber and Sanders, 1929; Andrade-Rocha, 2017).

Macomber and Sanders (1929) are central to that transition. In 1929, they related spermatozoa counts to reproductive performance and to male aging, and placed concentration at the center of male-factor evaluation (Macomber and Sanders, 1929). The numerical values used at that time cannot be carried into current practice without adjustment. Collection methods, counting techniques, reference populations and statistical standards have all changed. The historical importance of the work is therefore not the specific threshold, but rather the decision to treat the ejaculate as a measurable cell population whose properties could be related to conception.

That decision gave andrology a powerful instrument and a lasting problem. The instrument was the count. The problem was the temptation to let the count stand in for fertility *per se*. A low sperm concentration clearly carries clinical meaning, especially when it is severe or combined with other abnormalities, but fertility is not the number of spermatozoa in one chamber. The man with a low count may still conceive; the man with an apparently acceptable count may still have spermatozoa unable to complete fertilization, or may carry a testicular, genetic or systemic condition that a basic count will not identify. Much of later andrology can be read as an attempt to preserve the value of quantification without letting it become reductionism.

MacLeod (1943) then gave semen analysis much of its modern structure. His 1943 work on oxygen, metabolism and motility of human spermatozoa already suggested that the sperm cell was metabolically fragile and that movement depended on the biochemical environment in which the cell was maintained (MacLeod, 1943). In the 1951 series with Gold, he organized comparisons between men of known fertility and men in infertile marriages, building the grammar that still anchors conventional semen analysis: concentration, motility and morphology (MacLeod and Gold, 1951a, 1951b, 1951c).

The important feature of that work is that it did not produce an absolute value that distinguished fertile and infertile men. Although these two groups were statistically different, it was noted that removal

of the lower 5% to 15% of patients from the altered group would render groups indistinguishable. At the time, MacLeod was demonstrating that semen analysis was not born as an ontological separator of fertile and infertile states; it was born as a probabilistic laboratory description. The more abnormal the semen phenotype, the greater the concern. But individual fertility, especially in humans, remained inferred rather than measured. This is exactly the problem raised in the opening paragraph: unlike production animals, human fertility cannot be tested by controlled mating against a large number of females.

Microscopy also expanded the question beyond the ejaculate. Once quantitative histology was applied to the testis, the field could estimate daily sperm production, germ-cell yield, epididymal reserves and the relationship between production and output. Amann and Howards' work on daily spermatozoal production and epididymal reserves in men is important in this respect (Amann and Howards, 1980). It showed that microscopy could be physiological, not merely descriptive. It allowed the investigator to ask not only how many spermatozoa were present in semen, but how much sperm the testis was producing and how the epididymis contributed to what appeared in the ejaculate.

The WHO manuals later standardized this laboratory inheritance. The sixth edition of the WHO laboratory manual is central to practice because it insists on procedure, quality control, comparability and careful interpretation (World Health Organization, 2021). Standardization is not a secondary technical matter in male infertility. This is particularly concerning in a test that requires technical intervention during the diagnostic phase, and in which computerized analyses are not completely able to deal with pre-analytical and analytical sources of variation. The WHO contribution is therefore best understood as a clinical safety mechanism: before a result can be interpreted, it must be produced correctly.

Morphology, kinematics and sperm function

After count and motility became routine, the field naturally turned to the form and behavior of the sperm cell. Strict morphology, associated historically with Kruger and later refined and debated through Menkveld and others, represented an attempt to make sperm shape clinically predictive rather than merely descriptive (Kruger et al., 1986; Menkveld, 2010). The question was reasonable: if a sperm cell must traverse the female reproductive tract, bind to the zona pellucida, undergo the acrosome reaction and fertilize the oocyte, then structural abnormalities of the head, midpiece or tail should not be dismissed as cosmetic. Morphology was a way of bringing cell biology into the routine report.

At the same time, motion was being treated with increasing precision. Mortimer's work on sperm kinematics and capacitating human spermatozoa helped move motility beyond the subjective categories of moving or not moving, progressive or not progressive (Mortimer and Mortimer, 1990). Computer-assisted sperm analysis and the study of sperm kinematics made it possible to describe velocity, linearity, amplitude and hyperactivation-related patterns. Clinically, this was important because it recognized that motility is not a single property. A spermatozoon may move and still not move in the way required for fertilization.

The same logic explains why the zona-free hamster egg penetration assay, associated with Yanagimachi's work, and later hemizona and sperm-zona binding assays became historically important (Yanagimachi et al., 1976; Oehninger et al., 1989). These assays tried to test events that routine semen analysis could only imply: capacitation, acrosome competence, zona binding, penetration and interaction with an oocyte model. They were imperfect and are not routine in most current clinical settings, particularly after ICSI changed the treatment landscape. Still, they changed the clinical question, because they moved andrology from 'how many sperm are present and how do they look?' to 'what can these spermatozoa actually do?'

This functional analysis expanded to a series of tests that measure the many specialized activities of sperm as they traverse the female reproductive tract and fertilize an oocyte. Acrosome integrity, induced acrosome reaction, sperm-zona interaction, zona-free penetration assays and mitochondrial activity assays should be placed in this same historical group. They are not all equally useful in routine practice, and some lost clinical space when ICSI made it possible to bypass several steps of gamete interaction. However, they do inform of testes that are or are not able to adequately produce sperm, and this has increasing clinical utility to understand conditions that are associated not only to fertility, but also to general male health. Moreover, they demonstrated an important concept: a spermatozoon may have acceptable concentration, motility and morphology and still fail because mitochondrial activity is poor, because the acrosome is functionally deficient, because zona binding is impaired or because capacitation is abnormal. Meta-analytic work on sperm function assays reinforced both sides of the issue: these tests can be biologically informative, but their clinical prediction is not absolute (Oehninger et al., 2000).

This is the point at which Guzick becomes essential. In the large multicenter comparison of fertile and infertile men, sperm concentration, motility and morphology could be arranged into fertile,

indeterminate and subfertile ranges, but the overlap between groups was substantial (Guzick et al., 2001). The conclusion is clinically uncomfortable and necessary: none of the conventional semen parameters (concentration, motility, and morphology), alone, is diagnostic of infertility. The conventional triad has value because it stratifies risk, not because it determines fertility. That observation should be kept close to every modern discussion of advanced testing. The limitations of semen analysis do not mean it is useless; they mean its result must be interpreted as one layer of evidence.

Amann brought this limitation to its conceptual form. His work asked whether fertility potential could be predicted accurately from a seminal sample, and his answer was cautious (Amann, 1989). Later, with Hammerstedt, he emphasized that *in vitro* evaluation of sperm quality is necessary but that no single test can contain fertility as a whole (Amann and Hammerstedt, 1993). That position remains clinically correct. The ejaculate has to deliver several necessary attributes, and failure of any of them may matter. The test that measures one attribute well may still fail to classify the reproductive capacity of the sample. This is not because tests are of low quality or predictability – it arises from the biological variability that gives cause to the infertile state.

Standardization and therapeutic inflection

Two developments changed modern male infertility in different ways: standardization of semen analysis and ICSI. Standardization made the diagnostic language more reliable. ICSI changed the treatment possibilities. The first was methodological; the second was therapeutic. They should be discussed together because the treatment revolution sometimes created the impression that diagnosis had become less important. But clinically, it is quite the opposite.

The WHO manuals gave laboratories a common framework for collection, ejaculatory abstinence interval, liquefaction times, volume, concentration, motility, vitality, morphology, leukocytes, processing, and quality control (World Health Organization, 2021). Their importance is particularly evident when one considers how easily semen results are affected by pre-analytical and analytical variation. Without standardization, the same man may appear to move between categories because the laboratory changed rather than because his biology changed. For a test that already has limited direct predictive power, poor method makes interpretation still weaker.

ICSI, introduced clinically by Palermo and colleagues in 1992, changed the reproductive options for men with severe male-factor infertility (Palermo et al., 1992). A single spermatozoon could be injected into an oocyte. Men with very low counts, surgically retrieved spermatozoa or defective sperm-oocyte interaction now had a route to biological paternity that did not exist before. Historically, this is one of the major turning points in the field of infertility. Male factor infertility then became a treatable (and potentially inheritable) disease.

Yet ICSI also created a diagnostic paradox. It can bypass several sperm functions, but it does not explain why those functions failed. It can use a spermatozoon from a severely impaired testis, but it does not make the testis normal. It can produce fertilization in cases in which sperm-zona interaction is defective, but it does not remove genetic, epigenetic or systemic risk from the clinical discussion. For that reason, ICSI should not be treated as the end of male infertility investigation. It is troublesome, though, that it has allowed for male fertility diagnosis to be bypassed, leading to missed opportunities in interventions in the male that could significantly improve outcomes, as well as diagnose diseases at an early stage.

The same point applies to non-obstructive azoospermia. Microdissection testicular sperm extraction, introduced by Schlegel, changed sperm retrieval by making the search for spermatozoa more selective and less random (Schlegel, 1999). It is now part of the modern management of severe spermatogenic failure. But micro-TESE also illustrates the clinical need for better classification. Two men with non-obstructive azoospermia may look similar in the ejaculate, because both are azoospermic, and still differ profoundly in histology, genetics, endocrine background, focality of spermatogenesis and retrieval prognosis. The operation can find sperm in some cases, but the field still needs better tools to know who these men are before the operating microscope is opened.

Thermal physiology and varicocele as a model

Thermal regulation deserves a separate place in this history because it connects ancient anatomy with modern sperm biology. Setchell's Parkes Lecture summarized a central physiological fact: the mammalian testis is temperature-sensitive, and the scrotum is part of the system that permits spermatogenesis to occur below core body temperature (Setchell, 1998). This is not a small anatomical detail. It explains cryptorchidism, fever, occupational heat exposure, lifestyle-associated heat burden and

varicocele. Current NIOSH (National Institute for Occupational Safety and Health) guidelines, for example, recognize that men who are exposed to high temperatures in their work environments, such as bakers and welders, may present significantly prolonged time-to-pregnancy, and recommend that healthcare providers question workers exposed to high heat loads about their reproductive histories (Jacklitsch et al., 2016; Thonneau et al., 1997).

Varicocele, however, is a more prevalent – and more challenging – condition. It is considered the main treatable cause of male infertility (Jensen et al., 2017), and it allows the clinician to follow a visible or palpable lesion into testicular physiology, semen quality, oxidative stress, DNA fragmentation, mitochondrial activity, acrosomal status and, eventually, molecular profiles. In adolescents with varicocele, sperm nuclear DNA fragmentation was already measurable before the adult infertility narrative was fully established (Bertolla et al., 2006). In adult men, varicocele has been associated with altered sperm functional integrity (Blumer et al., 2012). These findings make varicocele a good example of why conventional semen analysis is necessary but incomplete. The same lesion can affect several biological layers, and not all of them are visible in concentration, motility and morphology.

This is also where a clinical mindset is important. It is not enough to say that varicocele is associated with altered biomarkers. The useful question is whether those biomarkers identify a subgroup of men in whom the lesion is biologically active and clinically relevant. That is different from using advanced tests indiscriminately. A test becomes clinically mature when it changes risk assessment, counselling, timing of intervention or selection of treatment. In varicocele, the future is not the mere addition of more markers. It is the integration of physical examination, semen phenotype, oxidative and DNA injury, molecular profile and reproductive history in a way that avoids both undertreatment and overtreatment.

The present clinical model: layered assessment

The current evaluation of male infertility is best understood as layered assessment. The first layer remains the clinical history, physical examination and semen analysis. This is not old-fashioned. It is the only way to identify many treatable, heritable or clinically important conditions. The second layer includes endocrine, genetic and imaging evaluation when indicated. The third layer includes advanced sperm testing, molecular profiling and specialized assays in selected cases. Problems arise when these layers are confused: when semen analysis is treated as a direct fertility test, or when molecular assays are ordered as if they could replace the clinical examination.

This is the practical meaning of the current guideline position. Semen parameter values above or below lower reference limits do not, alone, predict fertility or infertility (American Urological Association, 2020). However, multiple abnormalities increase clinical concern, and some findings require directed investigation. Azoospermia, severe oligozoospermia, small testes, clinical varicocele, recurrent pregnancy loss, repeated ART failure, hypogonadism, ejaculatory dysfunction and suspicion of obstruction are not equivalent clinical situations. They should not receive the same laboratory algorithm.

Sperm DNA fragmentation illustrates how the layered model should work. It is useful when the clinical question fits the biology of the assay: recurrent pregnancy loss, unexplained infertility, repeated ART failure, varicocele with suspected sperm injury, or cases in which the conventional report appears insufficient to explain the reproductive history (American Urological Association, 2020; Minhas et al. 2025). Its value lies in adding a chromatin-integrity layer to the conventional semen phenotype. Its limitation is the same as for other tests: it cannot by itself define the fertility of the man.

The same reasoning applies to mitochondrial activity, acrosome integrity, induced acrosome reaction and sperm-zona assays. They should not be remembered only as historical tests that were displaced by ICSI. They represent a clinical principle: spermatozoa need to perform a sequence of tasks. A modern test should be judged by whether it illuminates one of these tasks in a way that is relevant to management. A mitochondrial assay may be most relevant when asthenozoospermia, oxidative stress or varicocele-associated dysfunction is being investigated. An acrosomal test may be more relevant when fertilization failure or suspected gamete interaction defects are present. The question is never whether the test is biologically interesting. The question is whether the biology is connected to the patient's reproductive problem.

The present has also incorporated the idea that the infertile man may be a patient at risk beyond reproduction. AUA/ASRM and EAU documents both emphasize the association between male infertility, abnormal semen parameters and broader health concerns (American Urological Association, 2020; Minhas et al. 2025). This point changes the status of the consultation. The man is not only the source of a gamete. He may have an endocrine disorder, genetic condition, testicular cancer risk, metabolic disease, prior gonadotoxic exposure, medication effect or lifestyle factor that matters independently of ART. This is one

reason the male partner should not be bypassed simply because IVF or ICSI is technically available.

Molecular profiling and reclassification

Molecular profiling is the natural continuation of the functional era, but it should be handled with caution. The promise of epigenetics, microRNA, proteomics and metabolomics is not that they will produce another single test to replace semen analysis. The more realistic promise is classification. Men who are currently placed in broad and often unsatisfactory categories - idiopathic infertility, unexplained infertility, normozoospermic infertility, varicocele-associated infertility, non-obstructive azoospermia - may be separable by mechanisms that routine semen analysis does not detect.

Proteomics has been particularly useful for making this point. Studies of seminal plasma in adolescents and adults with varicocele showed that protein profiles can differ according to disease and treatment state, and that molecular pathways may capture oxidative stress, inflammation, spermatogenesis, mitochondrial function and sperm-epididymal interaction in ways not visible in a routine report (Zylbersztejn et al., 2013; Camargo et al., 2016). The association between seminal plasma proteome and sperm functional traits strengthens the concept that the seminal plasma is not simply a vehicle for spermatozoa, but part of the reproductive phenotype (Intasqui et al., 2016).

Epigenetic profiling brings a different layer. DNA methylation and other epigenetic signatures may reflect spermatogenic disturbance, environmental exposure, altered testicular physiology or defects carried by spermatozoa despite apparently acceptable conventional parameters (Cheung et al., 2019; Lujan et al., 2019). The clinical use of these markers is not yet routine, and it should not be overstated. Yet, it is important to realize that sperm carry more than a haploid genome; they carry chromatin architecture and epigenetic information.

MicroRNA and metabolomics occupy a similar emerging position. MicroRNAs are involved in spermatogenesis and sperm function and have been explored in spermatozoa, seminal plasma and testicular tissue as candidate biomarkers (Barbu et al., 2021). Metabolomics may capture energy metabolism, oxidative pathways, accessory gland contribution and biochemical conditions of the ejaculate that are not summarized by count, motility or morphology (Blaurock et al., 2022). These approaches are still closer to research than to routine clinical decision-making in most settings, however, and it is important to avoid overstating their clinical importance at this stage.

Genomics is further along in selected phenotypes. Karyotype, Y-chromosome microdeletion testing and CFTR analysis remain part of classical evaluation when indicated. Next-generation sequencing and exome sequencing are now extending the diagnostic field, particularly in severe oligozoospermia, non-obstructive azoospermia, extreme sperm phenotypes and apparent idiopathic spermatogenic failure (Minhas et al., 2025; Stallmeyer et al., 2025). This trend is likely to reduce the space occupied by the term idiopathic. That will have practical consequences: counselling will become more specific, inheritance risk will be better addressed, and surgical or ART strategy may be adjusted according to the underlying diagnosis.

Single-cell work points to the next layer. Single-cell RNA sequencing of the human testis has begun to map germ-cell and somatic-cell populations with a resolution not available to histology alone (Shami et al., 2020). For clinical andrology, the immediate value is not that every patient will have single-cell testing. The value is that these atlases may redefine what a testicular biopsy means. A section called maturation arrest may contain several molecular states. Sertoli cell-only patterns may not all be equivalent. Focal spermatogenesis may become better understood as a cellular and transcriptional pattern rather than only as something found or missed surgically. The likely future is not routine single-cell testing in the clinic, but the translation of single-cell biology into better diagnostic categories, markers and therapeutic targets. And this, perhaps, is the best way to move andrology towards a paradigmatic state, if there is one to be had.

What this review did not cover in detail

A historical review centered on andrological evaluation cannot cover all of male infertility without becoming superficial. Several areas are therefore only acknowledged here. Endocrine infertility, including hypogonadotropic hypogonadism, testosterone exposure, anabolic steroid use, hyperprolactinemia and disorders of the hypothalamic-pituitary-testicular axis, deserves independent treatment because it is one of the few areas in which causal therapy may restore spermatogenesis. Obstructive azoospermia, ejaculatory dysfunction, sexual dysfunction, infection, leukocytospermia, immunological infertility, cryptorchidism, genetic syndromes, testicular cancer, oncofertility, lifestyle, obesity, environmental toxicology and fertility preservation also require dedicated discussion (Eisenberg et al., 2020).

The decision not to review these areas in detail should not be read as a statement that they are

secondary. It is the opposite. They are too clinically important to be inserted as short paragraphs into a historical account of semen evaluation. The endocrine chapter, for example, has its own internal history: gonadotropins, testosterone physiology, pituitary disease, exogenous androgen suppression and medical induction of spermatogenesis. Even genetics was brushed over somewhat superficially herein. Similarly, obstruction and microsurgical reconstruction belong to a surgical history different from the history of semen parameters. This manuscript focuses on the history of examinations of semen, and how the field came to evaluate the male gamete and the male reproductive phenotype, with emphasis on the tools that shaped clinical interpretation.

Future directions

The immediate future of male infertility is unlikely to be defined by one new test. More probably, it will be defined by better integration. Semen analysis will remain the entry point because it is accessible, inexpensive compared with molecular assays, standardized and clinically familiar. It will not, however, retain its diagnostic-intensive or treatment-defining force. Hopefully, it will not be the sole definition of reimbursement for medical costs. It may also potentially increase its value in preventative medicine of general male health.

One future direction is genetic. Exome and other NGS-based approaches are likely to become more common in severe male-factor phenotypes. Studies in this area may change counselling before micro-TESE, clarify recurrence or inheritance risk, avoid repeated empirical treatment, and define which men require additional systemic evaluation. As this happens, andrology will have to learn how to communicate uncertain variants, incomplete penetrance and findings that matter for the man but not only for the couple's immediate reproductive plan.

A second direction is molecular classification. Proteomics, metabolomics, microRNA and epigenetic profiling may help separate men who now look similar in the routine report. This is where a great deal of research effort should be placed. The most useful molecular tests will not be the ones that merely correlate with concentration or motility. The useful tests will be those that identify mechanisms, predict treatment response, define prognosis or reclassify idiopathic cases into clinically meaningful groups. We have previously used the term homeorhesis to explain the altered but stable proteomic profile of seminal plasma in adolescents with varicocele (Camargo et al., 2016). Semen is still semen, and it is still equilibrated. But it is different, inflammatory, with increased protein turnover. It is doing something other.

A third direction is prevention. The debate about secular trends in sperm counts, including the meta-regression by Levine and colleagues, has been interpreted in many ways (Levine et al., 2023). The safest clinical reading is not alarmism, but surveillance. Environmental exposures, heat, obesity, smoking, alcohol, medications, anabolic steroids, infections and delayed presentation all matter because they may be modifiable or preventable. The WHO 2025 guideline places infertility within a broader strategy of prevention, diagnosis, treatment, counselling and public-health access (World Health Organization, 2025). That is appropriate. Male infertility is not only an ART problem.

A fourth direction is restorative. In men with diffuse germ-cell loss, the field still lacks therapies that reliably rebuild spermatogenesis. Advances in testicular cell biology, organoid systems, stem-cell models and single-cell atlases may eventually help define interventions that are not simply sperm selection or sperm retrieval. That future remains experimental. It should not be sold clinically before evidence exists. But as a research direction, it is coherent with the historical arc reviewed here: from observing the testis, to counting its output, to understanding the cell, to classifying the molecular failure, and eventually to trying to modify it.

The clinical endpoint should remain modest and rigorous. We need tests that help decisions. We need classifications that change counselling. We need biomarkers that are robust across laboratories. We need to understand molecular profiles as they explain the patient. We need to keep the male partner in the center of infertility care, not as an accessory to ovarian stimulation or embryo culture, but as a patient with a reproductive and general health phenotype.

Conclusion

The history of male infertility is the history of imperfect tools used with increasing discipline. Celsus and Curling placed the testis and its scrotal environment in the clinical field. Macomber and Sanders made the ejaculate countable. MacLeod organized concentration, motility and morphology into a practical laboratory language. Quantitative microscopy extended the problem back to the testis and daily sperm production. Kruger, Menkveld, Mortimer, Yanagimachi and others made sperm form, movement and

function increasingly visible. Guzick showed the overlap that prevents conventional parameters from being treated as diagnostic absolutes. Amann formulated the essential limitation: no single seminal test can accurately define fertility potential.

The contemporary evaluation of male infertility should therefore be layered. Semen analysis remains indispensable, but it is not sufficient. Clinical examination remains indispensable, but it is not sufficient. Genetics, DNA fragmentation, sperm function tests and molecular profiling may all be useful, but only when attached to a clinical question. The future of andrology will be strongest if it resists the temptation to replace one reduction with another. A count alone was never enough; a molecular marker alone will not be enough either.

What is achievable is a better approximation of a difficult concept. Male fertility in humans cannot be measured directly in the way it can be measured in production animals. It must be inferred from the man, the testis, the semen, the sperm cell, the couple and the reproductive outcome. The history reviewed here shows that each new method improved that inference and exposed a new limitation. That is probably how progress will continue: not by finally reducing male fertility to a single number, but by learning which layer of information is needed for each patient.

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