Andrology in its widest sense is a fast growing medical discipline with special emphasis on the disturbances of male reproductive function including erectile dysfunction and problems of the ageing male. There is a great need to educate both the specialists who practise as andrologists, such as endocrinologists, urologists and dermatologists, as well as the general practitioner, who is often involved in the management of these patients. Three international scientists from different medical disciplines (dermatology, endocrinology and urology) have created an alternative to a classical textbook by providing a new format in this book to facilitate the review of information in the field provided by a large number of international experts.

This textbook is written in two parts. Part I provides easily accessible, brief, problem-oriented information about modern andrology including male factor infertility, male contraception, male genital tract infection and tumours. The book is intended to be of use to the busy clinician and to provide quick access to didactic information about current practice. Part II is subject-oriented and provides the background scientific information for the recommendations in Part I. The three editors are recognized experts in the field and have invited key international scientists to write various sections of this book but, by their extensive sub-editing, have created a homogeneous concept. The key features of this book are the clear recommendations about current practice and easy access to the underlying science. I have no doubt that this textbook will be an asset to the clinical andrologist by facilitating information on to the rapidly increasing scientific data in the fast growing field of andrology.

It is the aim of this textbook to reach doctors working in the field of andrology all over the world but should be of particular value in European countries. The book will be valuable for urologists, andrologists, dermatologists, endocrinologists, gynaecologists, reproductive biologists, general practitioners, gerontologists, psychologists, psychiatrists, paediatricians and paramedics including all professions allied to medicine as well as pharmaceutical companies working in the field of andrology. I am sure that the book will be a great success and will be of great value to its readers.

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Andrology is the medical practice of disorders that afflict men. These include congenital and acquired abnormalities of the male reproductive system as well as disorders of the male endocrine system. As these may be treated by different disciplines including endocrinology, dermatology, urological surgery, plastic surgery, oncology, venereology, and sexual medicine, it is difficult for doctors in these various specialties to have a holistic view of andrology. We hope that this book will be a source of reference to the broad spectrum of andrological conditions and that it will promote a holistic view of andrology and catalyse interdisciplinary co-operation in the management of andrological disorders.

The book is written in two parts: Part I presents current clinical practice, whereas Part II provides the reader with more detail on the theoretical background. The reader will find chapters on the diagnosis and treatment of disorders of male fertility, disorders of male sexual function, sexually transmitted infections, disorders of androgen status, including ageing changes, and chapters on benign and malignant growths of the male reproductive organs. In addition, we have included chapters on phytotherapeutics and aesthetic dermatology and medical cosmetics because in practice many men seek these treatments and the competent andrologist needs to understand alternative as well as traditional approaches.

Our contributors are from many different countries and each is an acknowledged expert. Wherever possible, reference has been made to the results of randomized clinical trials and it has been our intention that the information in this book should be evidence-based. All contributors were asked to present a comprehensive review of their field as well as their own work.

In previous years, andrological problems have been relatively ignored but this is changing because of the development of effective treatments such as phosphodiesterase inhibitors for erectile dysfunction and 5-α-reductase inhibitors for prostatic enlargement, and as a result, greater media coverage of andrological disorders. Therefore, more men seek treatment and increasingly men expect their clinician to be well informed about all aspects of andrology. We hope that this book will help advance towards that objective.

Wolf-Bernhard Schill, Frank Comhaire, Timothy Hargreave
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Andrology: Definition, Clinical Issues and Prevalence

W.-B. Schill, F. Comhaire, T.B. Hargreve

Andrology is a young interdisciplinary medical specialty derived linguistically from the Greek word “andros”, which deals with the male with special emphasis of the physiology and pathophysiology of male reproductive functions. Therefore, primarily, its clinical focus is the diagnosis and therapy of male fertility disturbances. Thus, andrology is the male equivalent of gynaecology and deals with the disorders of the male reproductive organs. In some parts of the world, andrology is closely connected or even an integral part of in vitro fertilization centres. According to the definition of the World Health Organization (WHO), andrology is engaged in all aspects of male reproductive health.

In addition, andrology is concerned with problems of erectile dysfunction. Approximately 10% to 15% of andrology patients consult for disturbed sexual dysfunctions. The diagnosis and management of penis problems includes lack of firmness of penis erection or bending and deformity of the erect penis (Peyronie’s disease). Recently, treating the ageing male has become another important issue. Because of dramatic changes in the demographic development of the age pyramid, there will be a tremendous change of the ratio old to young men within the next 20 years. Therefore, consultations on the part of older men will greatly increase, particularly in terms of health prevention and hormone dysfunction.

Further areas of andrological activities are the diagnosis and management of testicle problems and prostate disorders, for example prostate enlargement, inflammation or cancer (the latter being mostly a genuine problem of urology) prevention and rehabilitation, primary and secondary hypogonadism, delayed puberty, adverse drug side effects and environmental pollutants with regard to fertility, cryopreservation of semen and testicular tissue, forensic paternity problems, family planning, male contraception and basic andrological research. All these issues are of increasing importance for the further development of clinical andrology.

In summary, the following subjects are within the field of responsibility of andrology:

1. Male fertility and infertility
2. Erectile dysfunction and sexual disturbances
3. Ageing male and hormone replacement therapy
4. Male reproductive tract inflammation and infection
5. Testicle problems (testicular tumours)
6. Prostate disorders (BPH, carcinoma)
7. Primary and secondary hypogonadism
8. Delayed puberty
9. Prevention and rehabilitation
10. Adverse drug side effects
11. Environmental pollutants
12. Cryopreservation of semen and testicular tissue
13. Forensic paternity problems
14. Family planning
15. Male contraception
16. Basic andrological research

Historically, the term “andrology” was introduced in Germany in 1951 by the gynaecologist Harald Siebke from the university of Bonn, who considered andrology as a counterpart to gynaecology (Schirren 1985). Thereafter, andrology developed within the field of dermatovenereology (as in Egypt), where it was associated with names such as Döpfmer, Heinke, Adam, Meyhöfer, and Schirren (Adam 1986; Schirren 1989). The importance of andrology was acknowledged in 1958 when the newly established German Society for the Study of Fertility and Sterility considered andrology as a main part of its activities. In 1970, the Comité Internacional de Andrología (CIDA) was founded in Barcelona, followed in 1973 by the Nordic Association of Andrology, in 1974 by the American Association of Andrology, and in 1975 by the German Society of Andrology. In 1976, the American Society of Andrology was established, followed in 1981 by the formation of the International Society of Andrology (www.andrology.org), which in 2005 was made up of 41 national member societies with more than 10,000 members. In 1992, the European Academy of Andrology was found-
ed with the formation of andrology training centres on a European level (European Academy of Andrology, 2001). Today more than 16 training centres in Europe (Belgium, Denmark, Germany, Italy, the Netherlands, Poland, and Spain) have been appointed after a stringent international reviewing process by the European Academy of Andrology. Andrological activities have also been strengthened by ESHRE and other international societies involved in reproductive medicine. Dramatic changes have occurred after the availability of in vitro fertilization in the years after 1978, followed by intracytoplasmic sperm injection in the early 1990s. It is particularly remarkable that apart from infertility treatment, the spectrum of diseases treated is expanding via erection and ejaculation disorders to problems of the ageing male as well as to urological issues concerning inflammatory and neoplastic diseases of the testes, epididymides, and the prostate.

The international development of andrology shows that the field is mainly represented by clinicians from urology, endocrinology, dermatology, and gynaecology, depending on history and scientific activities. Thus the rapid development of andrology over the past 25 years (Prins and Bremner 2004) is reflected by the fact that in addition to several national andrological journals there are presently five international andrological periodicals available (Andrologia as the first international journal founded by Carl Schirren in 1969, Journal of Andrology, International Journal of Andrology, Asian Journal of Andrology, Archives of Andrology) and at least ten journals that are exclusively concerned with scientific questions of reproductive medicine and reproductive biology.

Curiously, the term “andrology” was first anecdotaly used as early as 1891, when JAMA published an editorial entitled “Andrology as a specialty” (Niemi 1987). This editorial was soon forgotten but contained passages that are still valid today, after more than 110 years, and can therefore be considered a milestone of reproductive medicine. Later, in 1902, the first surgeon to treat the problem of obstructive azoospermia successfully was Edward Martin (1859–1938), who as a clinician already pointed out the need for accurate diagnosis in the treatment of male infertility and thus was recently considered as the founding father of modern clinical andrology (Jequier 1991).

Remarkably, from the historical point of view, one of the first books on human semen came from Joel (1953), Thaddeus Mann (1964, 1981) and Rune Eliasson (1971), the two latter particularly on seminal plasma biochemistry. In 1960, two German books were published on the subject of andrology: Male Fertility Disturbances, with more than 880 pages edited by the dermatologists Schuermann and Döpfner, and The Male Gonad by the anatomist Tonutti in collaboration with colleagues from internal medicine and dermatology. Thus today most of the German university clinics of dermatology have training facilities and departments in andrology. In addition, during the last 50 years andrology was substantially influenced by urology (Macleod 1951; Macleod and Gold 1951a–c; Macleod et al. 1964; Tulloch 1953; Amelar et al. 1977; Kelami 1980; Whitfield et al. 1998) endocrinology (Hellinga 1950, 1957, 1976; Rosemberg and Paulsen 1970; Steinberger 1970, 1971; Comhaire 1996; Nieschlak and Behre 2000), immunology (Rümke and Hellinga 1959; Rümke 1965, 1970), and gynaecology (Schoysman 1961, 1964, 1968; Insler and Lunenfeld 1986). For example, andrology has been firmly integrated into the graduation rules for urologists, where important surgical procedures to overcome a severe male factor had been established. Historically, the term “andrology” as a medical subspecialty officially has been used in Italy since 1989, in France since 1993, in Poland since 1995, and in the Netherlands since 2003. Also, the European Dermatology Forum (EDF) is using the term “andrology”.

Therefore, the activities of the European Academy of Andrology (EAA) are of particular importance for the proclamation of andrology to receive more attention and awareness by the European health politicians. The most recent progress is the acceptance of andrology as a medical specialty by the medical associations of Indonesia (2002), and Germany (2003). In the latter, the acquisition of an additional skill in andrology may be acquired by dermatologists, endocrinologists, and urologists, but not by gynaecologists. A medical qualification officially certified by the medical association allows the identification of the specialist by the patient, guarantees quality control and efficiency assurance, and attracts more medical professionals to the field.

The diagnosis and treatment of childless couples require a particularly close cooperation between andrology and gynaecology, which has been conducted to the formation of centres of reproductive medicine in many places throughout the world. The causes of barren marriage stem equally from the female and the male, but in some cases may be compensated by the high fertility of the other partner. If there is coincidentally a sterility factor in both partners, a compensation is no longer possible, leading to a severe infertility problem. The definition of infertility commonly used is that more than 12 months are required to conceive. However, infertility shows considerable geographic variation. In general, the male factor contributes one-third to one-half of all factors that contribute to a couple’s problem with conception (Hull et al. 1985). The prevalence of primary and secondary infertility is estimated to be 15% or more of all couples in their reproductive age (Bruckert 1991). Thus, the percentage of couples seeking medical advice and treatment for infertility is in the range of 5% to 17%. Lastly, 3% to 4% of all couples remain involuntarily childless at the end of their reproductive life phase (Templeton 1992).
Concerning the prevalence of male factor infertility, it is estimated to be in the range of 7% of all men, under the assumption that a male factor is responsible in about half of the involuntarily childless couples. This incidence is above the prevalence of diabetes mellitus (Nieschlag and Behre 2000). In contrast to earlier reports that the male's age does not influence the couple's fertility, new data suggest that in addition to the female age factor, the age of the male should not be neglected (Dunson et al. 2004).

Besides a careful medical history, physical examination, and at least two spermograms, andrological diagnosis comprises the enlarged semen analysis, including biochemical parameters and sperm function tests, hormonal diagnosis, immunological and microbiological examinations, cytogenetic analysis and, if necessary, testicular biopsies. Further diagnostic and therapeutic procedures may be required in interdisciplinary cooperation with urology, gynaecology, endocrinology, radiotherapy, sexology, psychosomatic medicine, neurology, psychiatry, and cytogenetics.

Both history taking and clinical examination of the male patient are essential for the andrological workup and the diagnosis of a male factor in the case of infertility. Often only the clinical examination of the patient allows the correct interpretation of the semen parameters, leading to an aetiopathologically orientated therapy. Therefore, to improve the management of andrological problems, formal training and training courses in clinical andrology are urgently required (Jequier 2004). This is underscored by the fact that presently only a few textbooks and WHO guidelines on the subject of andrology are available (Rowe et al. 1993, 2000; WHO 1999; Nieschlag and Behre 2000), together with some international congress proceedings (Waites et al. 1997; 1999; Nieschlag and Behre 2000), together with some textbooks and WHO guidelines on the subject of andrology are urgently required (Jequier 2004).

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Andrology: Definition, Clinical Issues and Prevalence 3
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Layout and How to Use the Book

F. Comhaire

In everyday practice, the clinician is faced with patients consulting for different problems related to the broader field of andrology.

The first concern will be to rapidly gain information that is immediately applicable for the management of the patient.

The first part of the present book aims at providing this “express” information in a condensed manner and using a systematic sequence. Under the heading “Problem: . . . ,” the following items are addressed in sequence:

1. Definition of the disease
2. Etiology and pathogenesis
3. History taking, physical examination, technical and laboratory findings
4. Differential diagnosis (when applicable)
5. Treatment
6. Expected treatment results
7. Prognosis
8. Prevention (when applicable)
9. Complementary considerations

The second part of the book includes more extended and detailed information giving the rationale, scientific background, and literature references and is organized into four major sections:

1. Understanding normal anatomy and function
2. Mechanisms of dysfunction and pathogenesis
3. Diagnostic tools
4. Therapeutic options

Whenever required or desired, the clinician can cross-reference from Part I to Part II in order to discover or ascertain the consensus-based and current knowledge supporting the guidelines that are summarized in Part I.

Although this book can perfectly serve as a teaching instrument, this is not its primary purpose. The editors have instead aimed at creating a working instrument for the everyday practice of the busy clinician. Neither the choice of the topics nor the contents of the book focus on completeness or considerations which are mostly irrelevant for clinical practice.
In modern, rational and scientific medicine, the pressure of society on practitioners is continuously increasing. Good health is considered a right, rather than a privilege, and the population expects diseases to be overcome promptly and efficiently. This applies to all diseases, including infertility.

More than before, it is emphasized that diagnosis and treatment must be based on the current best evidence that is acquired by high-standard scientific research and is applied judiciously and conscientiously. Good clinicians have always relied on their personal experience and judgment to decide on the treatment strategy for individual patients, which may sometimes differ from current evidence (Kirk-Smith and Stretch 2001). The approach based on personal experience is sometimes questioned and even rejected as “authority-based” and, therefore, unscientific. The seeming difference between experience and evidence may result in conflicting views on, for example, the treatment of the infertile male with far-reaching ethical and economic consequences. The problem is complicated by the fact that different therapeutic strategies affect not only the consulting couple, but also the health and happiness of the future child.

First of all, there may be problems in defining the outcome of treatment, e.g. of infertility. In the heterosexual couple, it is not just the dichotomy between whether or not there is a successful delivery, but several nuances must be considered. The time needed to reach the desired pregnancy, the physical and emotional invasiveness of treatment and its economic impact on society and the couple, possible adverse effects of the treatment for the mother, and the health of the offspring must be included in the decision-making process.

Men can only prove their fertility through the intermediate of their female partner (Steinberger et al. 1981), and the potential fertility of the latter is suboptimal in approximately half of the couples consulting for male infertility (WHO 1987). Therefore, some trials rely on an intermediate end-point to estimate the effect of treatment, namely sperm quality. However, the relation between semen characteristics and men’s fertility is complicated, and techniques of sperm analysis are often poorly reproducible. So far, there is no single test on semen that can confidently predict the fertilizing potential. Treatment by means of in vitro fertilization (IVF) with or without ICSI hold an increased risk for congenital malformations (In’t Veld et al. 1995; Sutcliffe et al. 1999; Koudstaal et al. 2000; Wennerholm et al. 2000; Hansen et al. 2002) or impaired development of the offspring (Strömberg et al. 2002), and must be used with extreme restraint. Such techniques should be reserved as an ultimate option when other solutions are excluded or have turned out to be ineffective (Mitchell 2002). Otherwise “children may become the nameless, faceless, voiceless victims of reproductive technology, because they do not have standing to oppose the use of those new technologies” (Berry 2002).

In the second place, the quality of current best evidence must be questioned and put through serious scrutiny. Evidence-based medicine attaches the highest value to evidence gained from double-blind randomized prospective trials (Ellis and Adams 1997). The crossover method should, however, be avoided in trials of reproductive medicine (Khan et al. 1996). Meta-analysis of selected trials is also considered highly valuable; whereas prospective (open label) cohort trials score much lower as to their scientific reliability. The lowest level is awarded to retrospective cohort studies and case studies. The reliability of meta-analysis is, however, highly questionable (Editorial 1997). It has indeed been documented that the correspondence between the conclusions of meta-analysis as compared to those of (subsequent) large-scale randomized trials is only 67% (LeLorier et al. 1997), so hardly better than by chance (50%). Hence, selecting treatment based on the evi-
dence of meta-analyses may be incorrect in as many as one-third of patients! We should not bestow too much confidence to the conclusions of meta-analyses, particularly if these contradict medical experience or results of either prospective or retrospective cohort studies. This is particularly true if the trials on which the meta-analysis is based yield highly divergent outcomes (Comhaire and Mahmoud 2004; Evers and Collins 2004).

In addition, concern has risen about the reliability of the published randomized trials. Many of these are co-ordinated and financed (“sponsored”) by companies (Miller and Shorr 2002) that have direct interest in a favourable outcome of the trial (Smith 1998; Stelfox et al. 1998), whereas the results of trials not generating the expected positive outcome may never be published, disclosed or cited (Kjaergard and Gluud 2002). Similarly, centres that dispose of particular techniques have a commercial interest in claiming high success rates (Teris 1998; Van Steirteghem 1998; Wilson 2002), and it may take years or even decades before the statistical manipulations are unveiled. For example, recent publications report the “real” effective success rate of assisted reproductive techniques such as IVF and ICSI to be more than 40% lower than those claimed or extrapolated from theoretical models (Schroder et al. 2004).

There are many pitfalls that are inherent to the proper methodology of randomized trials (Cleophas 1996; Schulz and Grimes 2002). In correctly performed trials, the “blind” assignment to patients to groups is done by an external and independent body (Kiene 1996a, b; Ferguson et al. 2004), and not by the clinician or the centre directly involved in patient care. Furthermore, inevitably an unintentional bias in selecting cases will take place as soon as patients must consent to participate in a placebo-controlled trial, since a particular type of person may refuse to do so, or indeed accept recruitment because of perceived opportunistic self-interest.

It is usually accepted as self-evident that results obtained in randomized trials may confidently be extrapolated to the general population. However, participants of such trials are recruited on the basis of well-defined inclusion and exclusion criteria, and the selected “cases” may not be representative of the real-life patient population seen by clinicians. In the case of infertility treatment, many different factors can coincide in each particular couple and the implementation of recommendations gained from another (trial) population to individual couples may be unwarranted (Ellis and Adams 1997). Examples of confusing factors that are usually not considered are lifestyle (tobacco, alcohol, sedentary lifestyle, stress), educational and social status, exposure to environmental or professional agents, ethnic background, genetic constitution, etc.

Too often, no (statistical) evidence of effect is interpreted as evidence of no effect. Whereas the latter may be true, there are many reasons why it may in fact not be correct. Evidencing the effect of a particular treatment that results in relatively minor improvement (e.g. from 15% to 25% success) requires a large number of cases in the treated and the control groups in order to reach a reasonable power of confidence. Any trial not reaching this number of participants will suffer from a type 2 or beta error, and the conclusions are invalid. Large trials commonly require a multi-centre effort, which introduces additional confounders such as the diagnostic adequacy (Kassirer and Kopelman 1989) and the therapeutic (surgical) expertise of the clinicians (Nilsson et al. 1979; Olive 1996), the quality of the laboratory (Clements et al. 1995; Neuwinger et al. 1990), etc.

Finally, randomized trials are subjected to ethical concerns when the implementation of a reasonably validated treatment comes into conflict with the requirements of trial protocol (Hope 1995). From the philosophical point of view, evidence suggests that something is scientifically proven, and therefore the observations are in agreement with the “truth” (Kaptchuk 2001). Whether the truth always corresponds to the “good” is another question (Hope 1995).

Progress in medicine depends on high-quality scientific research and on the evidence gained from this. But the outcome of trials and meta-analyses must be confronted with the knowledge on, for example, pathogenesis and epidemiology, as well as the experience from individual and cohort observations, which may all contribute valuable indirect evidence. Furthermore, the quality of current practice must continuously be controlled by means of auditing. The judicious amalgamation of the so-called hard direct evidence with more soft indirect evidence, well-balanced and validated by a group of experts, will produce the best possible evidence by consensus. It is this consensus-based evidence that is implemented in the present book.

References

Economic Cost and Cost-Effectiveness

F. Comhaire, A. Mahmoud

Optimal health care is a universal human right. Alas, this right can be claimed only by a fraction of the world’s population, and many persons in large areas are deprived of this right. On the other hand, the financial cost to implement this right in both poor and wealthier parts of the world is enormous. In addition, providing adequate health care to the population seems to be a rather low priority in certain countries where greater financial means are being invested in other projects (e.g. waging wars). In so-called developed and wealthier countries, the care for an increasing proportion of ageing persons, the enhanced prevalence of certain diseases related to the modern lifestyle, unsuitable nutrition and environmental contamination, for example, and the availability of new but commonly expensive modalities of treatment make the cost of medical care for the entire population hardly bearable.

Therefore it is mandatory and, in fact, part of the deontological obligation of all clinicians to make the best possible use of financial means, both public and private money, by selecting the most cost-effective modalities for diagnosing and treating the patient. Also, the cost-effectiveness of methods for the prevention and/or early detection of diseases, or of impaired health and function must be assessed.

For the majority of problems in the field of clinical andrology, there are several possible options with regard to investigation and management. Aside from the fact that internal and external auditing is required to assess the good quality of the care delivered, medical strategies must continuously be evaluated as to their cost-effectiveness and the optimal approach.

In the field of surgery, the endoscopic approach may sometimes be as effective but less expensive compared...
to open surgery, by shortening the duration of hospital stay and the time needed to recover and to resume economically rewarding work, for example.

Also, in vasectomized patients surgical reversal is more cost-effective than IVF with ICSI (Pavlovich and Schlegel 1997).

Another example relates to the systematic and periodic measurement of prostate-specific antigen (PSA) in the blood of men over a certain age, in view of the early detection and more effective treatment of cancer of the prostate.

With respect to the management of reproductive disorders, the World Health Organization and the United Nations Population Fund have set the goal to universal access to reproductive health care no later than 2015, including the prevention and appropriate treatment of infertility (WHO 2003). Considering the enormity of this task and its massive financial consequences (Collins et al. 1997), methods for the diagnosis and management of the infertile male in particular should be scrupulously evaluated for their cost-effectiveness (Comhaire 1995).

Cost not only refers to expenses carried by the public healthcare systems and insurance, but also by the patients involved (Collins 2002; Pratt 2004). In doing so, it is the cost per delivery of a healthy singleton that must be the end-point, but the effective cumulative pregnancy rate and the time needed to attain the desired pregnancy are also important (Comhaire et al. 1996).

Calculation of the direct cost per delivery is rather simple and can be done by dividing the cost per treatment by the rate of success in terms of the probability of a healthy singleton will result from that particular treatment. A clear-cut example of this calculation is the cost per delivery after in vitro fertilization in case of couple infertility due to oligozoospermia (Neumann et al. 1994). The net cost per treatment cycle, including medication for ovarian hyperstimulation, cycle monitoring, pick-up and laboratory expenses amounts to a minimum of 2,500 €. The take-baby-home rate per treatment cycle is approximately 20%, so the direct cost per delivery is between at least 12,500 €. Other estimations result in a cost per successful outcome in the first treatment cycle of US $60,000 (Griffin and Panak 1998). This cost increases with the increasing number of treatment cycles (Trad et al. 1995), reaching approximately US $114,000 in the 6th cycle (Neumann et al. 1994). Estimations do not include indirect costs and economic factors, such as time away from work, cost for postnatal care of the newborn which is approximately five times higher than after natural conception (Callahan et al. 1994; Wolner-Hanssen and Rydhstroem 1998), and complementary expenses for the treatment of congenital defects or problems during development.

Using this approach, it is possible to estimate the cost per successful delivery for different modes of treatment of the infertile male (Fig. 1; Comhaire 1995). The best cost-effectiveness is, in order: tamoxifen treatment, one or two cycles of IUI (Goverde et al. 2000; Philips et al. 2000), and varicocele treatment (Schlegel 1997; Penson et al. 2002). Since the spontaneous pregnancy rate during counselling (also referred to as treatment-independent pregnancy rate or tender loving care) is relatively low, the cost-effectiveness of this approach is poor, particularly in couples with longer duration of infertility (Mol et al. 2000). Also, the cost per delivery of IUI is high in the 3rd and 4th cycles of IUI, because of the decreasing conception rates. There is preliminary evidence that complementing established treatment modalities by food supplementation may decrease the time to pregnancy, reducing the cost per delivery. The cost per delivery of IVF for male subfertility is highest, even more when used in older women (Legro et al. 1997), while ICSI may be slightly better from this point of view because of the higher immediate success rate. It is a matter of debate whether or not insemination with donor semen should also be included in the comparison of cost-effectiveness (Granberg et al. 1996).

Knowing the frequency of particular aetiological andrological diagnoses in the patient population visiting infertility clinics, the effective cumulative pregnancy rates and cost per successful outcome of various treatment modalities, it is estimated that no more than 80 deliveries can be obtained with an investment of 1 million € when IVF is used as primary treatment, as compared to approximately 300 deliveries when treating the subfertile men in agreement with the WHO guidelines (Comhaire 1995). Therefore, the latter ap-
Three ethical principles underpinning all medical ethics are respect for autonomy, beneficence and justice.

Consideration of these principles has to be balanced between the individual, the couple, the future child, the family and society as a whole.

In general, consideration of the interests of the future child takes precedence over consideration of other parties.

Consent is a process of giving the individual all the information necessary for that individual to make a free choice.

Consent is not just signing a piece of paper.

Reproductive advances such as intracytoplasmic sperm injection (ICSI), sex selection, cloning and germ-line genetic repair pose particular ethical problems.