EDITORIAL: THE CURE AND PROLIFERATION OF MALE INFERTILITY

In this issue of the Journal 2 important scientific articles are featured, which describe aspects of the new infertility technology that promises on the one hand to allow hopelessly sterile men to father their own genetic children, and on the other hand to proliferate even further the incidence and severity of male infertility in our population. Gil-Salom et al (page 2063) describe results in 154 couples with nonobstructive azoospermia undergoing testicular sperm extraction and intracytoplasmic sperm injection. Although they were not the first to develop such a technique for treating couples with otherwise hopeless male infertility, this is a reliable description of the technique in a large series and will become an important standard of reference. 1-3

Approximately 50% of azoospermic men with germinal failure actually have minute foci of spermatogenesis in the testes which can be extracted and used for intracytoplasmic sperm injection following testicle biopsy. 4 There is a minimum threshold of quantitative spermatogenesis which must be exceeded for sperm to "spill over" into the ejaculate. Therefore, in many azoospermic men who appear to be making no sperm there is actually a minute amount of spermatogenesis that simply does not exceed the threshold necessary for appearance in the ejaculate. Thus, what appears to be zero sperm production usually is not. This fact has been known since the late 1960s but its importance was not realized until the era of intracytoplasmic sperm injection. 1-4 Before 1994 irreparable obstructive azoospermia due to congenital absence of the vas or failed vasopididymostomy was considered untreatable. Now the retrieval of sperm for obstructive azoospermia has become a relatively simple and trivial issue. 5 However, the report of Gil-Salom et al takes us to another level and represents a massive experience with a huge number of azoospermic men undergoing testicle biopsy to retrieve sperm for intracytoplasmic sperm injection from those thought to have no sperm.

There has been a movement, mostly among gynecologists, to use percutaneous needle aspiration for these cases but controlled studies have demonstrated that open testicular biopsy is necessary to obtain the best results. Approximately 10% of men with nonobstructive azoospermia will have successful sperm retrieval with percutaneous needle biopsy but more than 50% will have successful retrieval with open biopsy. 6 Furthermore, Gil-Salom et al have demonstrated that open biopsy can be performed with local anesthesia as an outpatient procedure with as easy a recovery for the patient as needle biopsy. The only reason to prefer needle biopsy over open biopsy for nonobstructive azoospermia would be the unavailability of a urologist or the desire of a gynecologist to perform the procedure.

The major difficulty in these cases is the inability to predict which patients will and will not have successful sperm retrieval based on classical parameters, such as testicular size, follicle-stimulating hormone (FSH) level, clinical history, ultrason sound or karyotyping. The dilemma of the patient planning to undergo testicular sperm retrieval after his wife has been stimulated to retrieve numerous ova, only to find after all this preparation and effort that he may be one of the 50% with no sperm, is a daunting challenge to the urologist. A normal FSH level may merely mean that the nonobstructive azoospermia is caused by maturation arrest rather than the Sertoli-cell-only syndrome, because FSH is inhibited by the total number of spermatogenic cells and not specifically by the number of mature sperm or spermatids. 7 Thus, an elevated FSH signifies the likelihood of the Sertoli-cell-only syndrome and normal FSH signifies the likelihood of maturation arrest. However, the level of FSH in no way tells whether any normal sperm are present in the testis. We have been able to find enough sperm in men with a testicle volume of only 2 mL. and FSH greater than 25 IU/ml. for successful intracytoplasmic sperm injection and delivery of healthy newborns.

The authors incisively discuss the question of whether a prior testicle biopsy can be predictive of success or failure. Relevant to this issue our studies of the quantitation of spermatogenesis in these patients have demonstrated that spermatogenesis is multifocal and evenly distributed throughout the testicle, which is why in 80 to 90% of prior testicle biopsies can predict the success or failure of testicular sperm extraction. However, when spermatogenesis is extremely deficient, a small prior biopsy will not detect a tubule with spermatogenesis even though there may be the most minute amount present beyond the range of that small diagnostic biopsy. The only solution to this dilemma is whether to remove larger pieces of testicular tissue during testicular sperm extraction or to perform the procedure with a microsurgical approach that allows intraoperative determination of which tubules actually contain the few sperm.

This microsurgical approach to testicular sperm extraction is particularly useful in cryptorchid azoospermia or Klinefelter's syndrome, when fibrosis is interspersed with tubules having normal spermatogenesis. In these cases it is relatively easy with the microsurgical approach to remove the tubules that have spermatogenesis and thereby conserve testicular tissue. It will be much more difficult to accomplish this selection with maturation arrest when all tubules have spermatogenesis and in only an occasional tubule does the spermatogenesis go to completion. However, even in those cases the microsurgical approach to testicular sperm extraction will allow the removal of larger amounts of testicular tissue if necessary with a minimum amount of damage and secondary testicular atrophy. With these microsurgical improvements in testicular sperm extraction, a much greater success rate will be achieved for nonobstructive azoospermia than with blind needle aspiration.

The genetic implication of this dramatic improvement in the fertility potential of severely infertile men is studied in another excellent report by Ruckster et al (page 2068). It was more than a decade ago when we first suggested that most cases of nonobstructive azoospermia and severe oligospermia were of genetic origin. 8,9 Subsequent studies of the Y chromosome by our collaborative group, including Oates, Page and associates at the Massachusetts Institute of Technology, beginning with the detailed STRS map that was made available in 1992, led to the discovery that about 13% of azoospermic men and about 7% of severely oligospermic men have deletions of the Y chromosome which are not detectable on routine karyotyping. 10,11 This work is confirmed by Ruckster et al.12

Recently it has been clarified that large deletions of the Y chromosome encompassing several different spermatogenesis genes result in complete azoospermia and a failure to retrieve sperm successfully at testicular sperm extraction, whereas small deletions encompassing only 1 spermatogenesis gene are more likely to result in severe oligospermia or azoospermia in which sperm are retrievable from the testes. 13 It is because of the likelihood of transmission of these mutations of the Y chromosome to male offspring that the current report addresses the whole issue of preoperative screening and genetic counseling for men who are about to
undergo testicular sperm extraction with intracytoplasmic sperm injection. In a sense we are creating a growth industry for this technology because we can be relatively certain that the infertility of the father will be transmitted to the male offspring, as has never been observed. In previous eras severe male infertility or sterility resulting from genetic mutations would end with the sterile father. The techniques that we have developed, that is testicular sperm extraction and intracytoplasmic sperm injection, have allowed these sterile men to have progeny who will likely be sterile also.

However, as Rucker et al have shown testing of the Y chromosome is not the only aspect of genetic counseling that these patients must consider. Many such azoospermic men will be discovered to have a sex chromosomal abnormality, such as Klinefelter's syndrome (XXX). More importantly by a small percentage (approximately 1.5%) of azoospermic or severely oligospermic men will be discovered on chromosomal analysis to have "balanced translocations", an incidence approximately 7 to 10 times what is found in a fertile male population. However, this finding should not be the cause of profound alarm. Rucker et al and others have clearly shown that Klinefelter's XXX anomaly does not appear to lead to children with Klinefelter's syndrome. Furthermore, in almost 2,000 intracytoplasmic sperm injection offspring studied only 1 was discovered (at amniocentesis) to have an unbalanced translocation. Of the almost 2,000 infants 9 of 10 with translocations simply had a transmission of the balanced translocation of the father without any genetic consequences. Nonetheless, an awareness of the karyotype will be an important part of counseling these patients about the advisability of amniocentesis or chorionic villus sampling if they are concerned about the low risk of chromosomal error in the offspring.

Actually, the evidence is more reassuring than alarming in that the incidence of congenital abnormality in intracytoplasmic sperm injection children was no greater than in every normal population that has been studied (2.3%), and the chromosomal abnormalities in the offspring appeared not to occur with any greater frequency than in the normal population, except for a slightly higher incidence of Klinefelter's syndrome and other sex chromosomal abnormalities (0.8%). Even so, chromosomal testing of the parents would not have predicted which of these children would have Klinefelter's syndrome. Thus, careful genetic counseling for men with severe infertility is properly brought to our attention in this issue. However, there should be no cause for alarm because for the most part, with the exception of the transmission of infertility to the offspring, the newborns are otherwise as likely to be normal as those in a fertile population.

Sherman J. Silber
Infertility Center of St. Louis
St. Louis, Missouri

REFERENCES