A Modern Approach to Male Infertility

by Sherman J. Silber, MD, FACS

There are many varieties of male factor infertility, but in the modern era they all appear to be treatable with one, single approach, i.e., intracytoplasmic sperm injection (ICSI). This is disturbing to many people, i.e., that a non-specific treatment, directed mostly at the female, should be the end all to solving the problem of male infertility. In 1994, Professor Robert Edwards, Editor of *Human Reproduction,* asked me to write a response to the following question: "What forms of male infertility are there left to cure?"[29] This was an amazing question. Two years earlier, the major stumbling block to treatment of infertile couples was the infertile male. With the exception of obstructive azoospermia (which could be treated with microsurgery) there had been, until ICSI, no treatment for male infertility that was uncontroversially regarded as effective.[21] I wrote the following to Dr. Edwards: "...with the exception of Kallman's Syndrome, all efforts to stimulate greater spermatogenesis in such patients using hormones or other treatments, including surgery for varicocele, have failed to demonstrate any effectiveness. Deficient spermatogenesis cannot be stimulated by any of the conventional modes of therapy utilized over the past 40 years."[1, 2, 3, 5, 7, 9, 18, 22, 23, 34, 37]

With the development of ICSI, we have now completely reversed the way we look at male factor infertility. With a few exceptions (i.e., when no sperm whatsoever can be located in the azoospermic man's testicle), the only limitation to treatment of male infertility may, in truth, be the female, and most specifically, the age of the female.[23, 24] With ICSI, the presence of only a few very weak, barely twitching spermatozoa in the semen specimen (even if there is 100% abnormal morphology) is all that you need for normal fertilization and pregnancy.[9]

Furthermore, men with obstructive azoospermia can now simply have their sperm retrieved from the epididymis or the testicle, frozen and saved for future procedures, and those few immature sperm can provide the same pregnancy rates as IVF in men with normal sperm counts.[10, 28, 31] These are sperm that would never have had much success using conventional IVF.[28] Even more dramatic is the azoospermic patient who does not have obstruction as a cause, but rather has an apparent *absence* of spermatogenesis. Azoospermic men with no obstruction and small testicles, used to be put on the hopeless list. Yet, now we know that in men with such severe conditions as Sertoli cell only, maturation arrest, post-cryptorchidism tubular atrophy, mumps, postchemotherapy azoospermia, or even Klinefelter's Syndrome, there is often an extremely minute amount of sperm production somewhere in the testicle.[6, 24, 27, 32] Remarkably, in men such as these, who were thought to be making no sperm, a few sperm can thereby be retrieved from the testes surgically and utilized for ICSI, yielding fertilization and pregnancy rates once again no different than in men with normal sperm counts.

This enthusiasm for ICSI, however, has caused a great deal of concern to scientists like myself, that an anti-intellectual approach may be descending upon the infertility community, such that infertile men will no longer undergo testing and investigations which would help us to better understand their problem. Many couples who undergo ICSI will not get pregnant. Therefore, the fact that there are virtually no types of male infertility that lack the possibility of treatment with ICSI does not at all nullify the strong need for continued intensive research in male infertility. This research must be directed at the *molecular level* so that perhaps future generations of men and women will not require ICSI.

Once a laboratory is extremely proficient with micromanipulation, the results with ICSI are not different from that achieved with standard IVF in fertile men. Thus, my concern that andrology studies be continued does not arise from any concern that ICSI is a problematic procedure.[15] In fact, we now have follow-up studies on close to 2,000 babies who have undergone detailed pediatric examination, and genetic studies.[26] Amniocentesis, chronic villus biopsy, and karyotyping of close to 2,000 ICSI pregnancies has revealed no increased risk of de novo autosomal abnormalities, and only a very slightly increased risk of sex chromosomal abnormalities (0.8% as compared to 0.4%) in patients with the poorest sperm counts. The risk of congenital malformation in all these babies is only 2.6%, which is not increased or any different from the incidence of congenital malformation in a great variety of huge population studies performed in all parts of the world.[26] It is evident from these follow-up studies that the technique of ICSI itself does not in any way increase the risk of any kind of congenital or genetic abnormality in the child. Of course, if the father has a genetic abnormality related to his low sperm count, then it is obvious that this could possibly be transmitted to the offspring. That is why we do insist on detailed molecular genetic testing, not just karyotyping, of all men with azoospermia or severe oligospermia who are about to undergo ICSI. Notwithstanding, it is widely accepted that ICSI is a completely safe procedure, no longer considered experimental, and no less successful and no more of a risk to the couple than standard IVF in couples with normal sperm and no male infertility at all.

But the quest to solve the problem of male infertility has not ended, because it would be much better if infertile couples did not have to go through ICSI or IVF. The molecular biology era is allowing us finally to understand the cause of (and potentially in the future a realistic treatment for) male infertility. Going as far back as the early 1980's, we became painfully aware of how ineffective all of our treatment modalities were for male infertility (with the exception of obstruction which could be treated with microsurgery). Despite momentary bursts of enthusiasm for drug therapy for deficient spermatogenesis, control studies always demonstrated that these hormonal regimens were ineffective. [2, 3, 5, 7, 8, 18, 22, 23, 34, 37]

There still lingers an enthusiasm in some circles for varicocelectomy, but most infertility centers now accept what we have been saying for the last eleven years, i.e., that pregnancy rate and fertilization rate are no different in men with varicocele who have undergone varicocelectomy than in men who have not undergone variococelectomy. [4, 5, 11, 17, 35, 36] This led us to speculate that perhaps deficient spermatogenesis, despite a variety of so-called causes is in most cases genetically determined (excluding, of course, mumps, orchitis, post-cryptorchidism testicular atrophy, post-chemotherapy azoospermia, etc.).

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The first phase of this genetic control of male fertility came from Professor Roger Short's analysis of infertility in the three types of great apes, i.e., gorilla, orangutan and chimpanzee.[20] Chimpanzees travel together in troops of about 40 males and females, and whenever anyone of the females in the troop goes into heat, every single male in the troop has intercourse with her. Consequently, one would expect that the male with the highest sperm count and the best quality sperm is most likely to be the father of any child born to any female who has had sex with multiple partners. The extensive sperm competition among the sperm of all the chimpanzees who have mounted her results in male offspring that have inherited the best sperm count. Therefore, chimpanzees would be expected to have high sperm counts because of their promiscuous mating behavior if we assume that sperm production, both quantitative and qualitative, is genetically transmitted. In fact, this is the case. Chimpanzees, who are extremely promiscuous, have gigantic testicles and huge sperm counts, and gorillas who are faithful to their mates, and in whom there is no sperm competition because the female is only having sex with one given mate for her entire lifetime, have very small testicles and extremely low sperm counts. Professor Short concluded from this that male fertility was a genetically transmitted trait.

The next suggestion from studies of exotic species came with the cheetah. All cheetahs in the world are so genetically inbred and identical that even skin grafts from one cheetah to another never reject. This inbreeding has resulted in all male cheetahs having an extremely poor sperm count with 90% abnormal forms and very low numbers. The infertility of the inbred male cheetah clearly demonstrates a genetic cause of the very same types of semen abnormalities that we see in the infertile human.[12, 13, 14] Therefore, we had speculated for the last eleven years that there may be a genetic cause for the majority of cases of oligospermia and azoospermia.

Now, in a collaborative study with the human genome project and the Massachusetts Institute of Technology, we have indeed found that about 11% of men with either azoospermia or severe oligospermia consistently are found to have deletions in the Y chromosome in a specific region we have called the AZF loci (short for "azoospermia factor"), and the first specific gene candidate localized to this area has been called DAZ (deleted in azoospermia).[16, 25] Deletion I of this DAZ gene is always associated with azoospermia or severe oligospermia, and thus far no normal fertile men have been found to have a deletion of this gene candidate. Furthermore, there is a homolog copy of this DAZ gene not only on the Y chromosome in men, but on chromosome 3 in both men and women, indicating it may even tell us something about female infertility.[19] There are undoubtedly many other genes and loci that affect sperm production, and we have only just begun the search. Furthermore, we know that about 1.3% of azoospermic or severely oligospermic men have chromosomal abnormalities, usually balanced translocation, that can give us other clues and doorways to explore with our molecular tools many other possibilities for genetic causes of male infertility. [26, 38]

Thus, although we are in a very wonderful decade whereby most types of male infertility can be treated successfully with ICSI, it is cumbersome and expensive for the wife to go through an IVF cycle simply because her

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husband is infertile. Therefore, continued investigation of the male in an effort to arrive at a definitive cure for male infertility is an important direction in which to go for the next millennium.

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