The Disappearing Y Chromosome—
"I Told You So!"

To the Editor:

A recent article by Silber et al. (1) reported on testicular sperm extraction and intracytoplasmic sperm injection (ICSI) for azoospermia due to maturation arrest. The authors make two statements regarding the genetics of azoospermia: [1] “. . . it now seems likely that Sertoli cell only and maturation arrest both are mediated genetically, possibly by a common deletion in the same region of the Y chromosome.” and [2] “. . . the growing assumption that spermatogenesis is affected by defects in the Y chromosome would have us speculate that most likely the male offspring will grow up to have the same spermatogenic defect . . . when this possibility was presented to these patients, they accepted it.” (Vereb M, Lipshultz LI, Lamb DJ, Bishop C, abstract). We would like to make the following comments.

In addition to the cases of azoospermia and severe oligozoospermia caused by a deletion in the DAZ (deleted in azoospermia) gene on the Y chromosome (Vereb M, Lipshultz LI, Lamb DJ, Bishop C, abstract), there are a host of genetic disorders that are not found on the Y chromosome and that can affect male infertility (reviewed in Jaffee and Oates (2)). For example, there are the X chromosomal defects, such as the androgen receptor mutations, that affect male infertility (2). Kennedy’s disease, otherwise known as spinal and bulbar muscular atrophy, results from a mutation in exon 1 of the androgen receptor gene (2). These patients may present with testicular atrophy and oligozoospermia, as well as azoospermia. Chromosomal translocations, which can affect chromosomal pairing during spermatogenesis, have also been implicated in male infertility (2).

As well, there are a number of gene defects found in animal models that result in male infertility (3). One such transgenic model consists of male mice with the null mutation of the DNA mismatch repair gene PMS2 (4). The adult male mice were found to be sterile with maturation arrest at the primary spermatocyte level. Of significance, these mice were prone to sarcomas and lymphomas. Other autosomal chromosome mutations in humans leading to male infertility include cystic fibrosis transmembrane conductance regulator gene mutations and Kartagener’s syndrome (2).

In summary, it is likely that there are many specific gene defects that can cause idiopathic infertility. It would be naive of us to assume that genetic defects in spermatogenesis, which potentially can be passed on to future progeny via assisted reproductive technology, are specific only to the Y chromosome. Furthermore, the consequences of the inherited genetic defect may include other non-spermatogenic abnormalities in the offspring. We urge using greater caution with ICSI, careful monitoring of offspring of ICSI, and performing further research on spermatogenesis.

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August 16, 1996

REFERENCES

Reply of the Authors:

We, of course, agree with the above letter in reference to Silber et al. (1). We have always urged, and indeed have performed and reported, detailed genetic monitoring of intracytoplasmic sperm injection (ICSI) parents and offspring (2).

We have urged and reported chromosomal analysis and genetic mapping on all prospective ICSI candidates, as well as prenatal chromosomal screening and pediatric follow-up on all pregnancies. We insist
on extensive cystic fibrosis (CF) testing on all patients with congenital absence of the vas deferens, including studies of the entire CF coding sequence (particularly revealing in 90% of cases congenital absence of the vas deferens where CF mutations are not found on both alleles). In fact, we are part of the group in Europe that elucidated the T5 allele intron defect involved in the etiology of congenital absence of the vas deferens.

We propose (and have reported) preimplantation genetic diagnosis wherever indicated and technically feasible to patients who have potentially dangerous transmissible genetic defects detected on routine screening (3). Prenatal amniocentesis or chorionic villus sampling is urged for all patients as well, and long-term pediatric follow-up is funded extensively and reported continually.

Thus far, autosomal structural chromosomal aberrations are found in less than 2% of prospective ICSI patients with impaired sperm quality, and the details have been reported by us at the European Society for Human Reproductive Endocrinology the American Society for Reproductive Medicine postgraduate courses and workshops and are in press in Human Reproduction. These findings are consistent with other studies dating back to 1979 as mentioned in Bonduelle et al. (2). Deletions in the DAZ (deleted in azoospermia) genes, which we have also reported, occur in 13% of prospective testicular sperm extraction-ICSI patients, and thus far are the most common genetic correlate of male infertility (4). That is why we emphasized them. Patients with structural aberrations are counseled as usual and offered prenatal diagnosis to avoid the birth of chromosomally unbalanced offspring. Transmission of these paternal autosomal (1.2%) and Y chromosomal aberrations (13%) to ICSI children thus far has not resulted in any congenital abnormalities other than the likelihood of similar infertility in the offspring. The incidence of major congenital anomalies in our series of the first 877 ICSI babies has been 2.6%, which is not different from that reported in many large normal population studies.

We have also noted and reported a 1% incidence of sex chromosomal abnormalities such as XXX and XXY in ICSI offspring, which the authors of the letter failed to mention. There is certainly much more to learn, but we do have many joyous parents and children. We should all exercise great concern for our patients’ welfare. As our paper concluded, “future study will be necessary on a larger cohort of children and caution must be exercised.”

*Editorial Comment*

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This letter from Dr. Lamb points out the multiple candidate genes that may be involved in spermatogenesis and spermiogenesis. Dr. Lamb has written an excellent review on this topic for the Urologic Clinics of North America (1). The authors of the paper at which her correspondence is directed have made many significant contributions to our understanding of male infertility. The Center for Reproductive Medicine in Brussels, under the leadership of Andre Van Steirteghem, has led the way in many of the significant breakthroughs related to the pathogenesis and treatment of male infertility.

Apart from these advances in our knowledge, investigators still continue to trawl, dredge, or scavenge for genes and mutations in genomic DNA that are spermatogenesis specific. The majority of mutations or gene “knock outs” in mouse affect many other systems and result in complex phenotypes (2). Normal phenotypes with singular alterations in spermatogenesis are seen primarily in insertional mutants (i.e., thymidine kinase) that are the unanticipated product of transgenic technology. The lack of specificity seen with many of these mutations has encour-