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References and Notes

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Intracytoplasmic Sperm Injection

The imaginative essay "Sex in an age of mechanical reproduction" by Carl Djerassi (Essays on Science and Society, *Science*'s Compass, 2 July, p. 53), which includes an excerpt from his stage play *An Immaculate Misconception*, identifies a number of important broad ethical and social issues relating to the use of intracytoplasmic sperm injection (ICSI) that need wider appreciation and discussion. One hopes that his play may help expedite this process.

One question of great practical importance to those considering an attempt to conceive using ICSI technology and to those who already have offspring conceived in this way is whether offspring conceived by ICSI have an increased risk of any serious adverse health outcome. There are at least three theoretical concerns relating to the health of ICSI offspring. First, what is the extent of heritable conditions among offspring that were inherited from an affected parent, but which may have rendered that parent infertile before the introduction of ICSI (*1, 2*)? Second, what are the possible consequences of ICSI itself, which is a relatively invasive and traumatic procedure involving potentially toxic chemical baths (*2, 3*)? Third, what are the possible adverse consequences of using sperm that in many cases would not have been fit or mature enough to achieve fertilization before the introduction of ICSI (*4*)?

The risk of a number of adverse outcomes, ranging from still births, birth defects, and cancer to pediatric developmental delay, might be increased among ICSI offspring. More ICSI offspring must be studied before we can satisfactorily address the question of a birth defect excess. Consider a condition that normally affects 2% of births. To detect a doubling in the level of risk (with the use of a 5% one-tailed test of significance) and to ensure an 80% chance of detecting this risk, one would need to study 1000 ICSI offspring and 1000 control offspring. For a condition that normally affects 1 in 1000 births, the corresponding number of offspring that would need to be studied would be 20,000 in each group.

One of the largest series studied to date included 423 ICSI offspring (*5*), and the data were the subject of a detailed independent review (*6*). As a result of different definitions and methods of ascertainment of birth defects (*4*), the original investigators interpreted the data as providing reassurance (*5*), whereas the independent review investigators identified grounds for concern (*6*). The original investigators expanded their series to 877 offspring (*7*), but because they used a study methodology similar to that used in their first study (*5*), the conclusions are subject to the same questions. Large numbers of offspring would also be necessary to detect an increased risk of cancer (*8*). Finally, two recent articles and an accompanying editorial (*9*) have assessed the possible consequences of ICSI on mental and psychomotor development in the initial years of life, and further large-scale follow-up of ICSI offspring has been strongly advocated.

With such uncertainty, it is important to establish epidemiological systems to monitor these offspring so that in the future, potential parents may make the decision to opt for ICSI in an informed way—with an understanding of the magnitude of any risks for potential offspring to balance against the obvious benefits for the parents. Toward this objective, we are establishing in the United Kingdom, with the support and guidance of an expert advisory group, a national register of offspring conceived with the use of ICSI. We recognize that this is an area in which international collaboration is likely to be necessary to satisfactorily investigate whether some rare adverse outcomes occur in excess among ICSI offspring.

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Response

My essay ended with the statement, "Neither science nor the humanities have so far adequately prepared us for...the fact that the effective treatment of genetic infertility has made the uninheritable heritable." The purpose of my play was precisely to raise in nontechnical dramatic discourse the type of heritability questions described by Hawkins and Barratt in scientific terms backed by literature citations. Their questions are valid ones, but as with any new reproductive technology (for example, the introduction of oral contraceptives nearly 40 years ago), they have a catch-22 component: Answers cannot be obtained until sufficient "human guinea pigs" are available to carry out statistically meaningful epidemiological studies. The number of offspring required for such studies is appropriately listed by Hawkins and Barratt. The only consolation is that the number of ICSI offspring is rising so rapidly that reasonable answers to several of the questions should be available within a decade. Let us hope that the United States, with the largest number of offspring and the least regulation, follows the British example of establishing a national register of ICSI offspring.

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Expected Relatedness: Correction

In our report "The selective advantage of low relatedness" (6 Aug., p. 891), reference 15 contained an error. The expected relatedness in a colony as a function of the effective number of matings should have read, $(0.25 + 0.5)/n_e$, where n_e is the effective number of matings. This relation leads to an estimate of the effective number of matings in *Pogonomyrmex occidentalis* of 6.76, rather than 3.75. The larger, correct number was used in the procedure of reference 22 to determine the effect of diploid males. The smaller number was used in the procedure of reference 15 to determine the correlation of actual and estimated relatedness. Underestimating the number of effective matings results in a conservative estimate of the true correlation of actual and estimated relatedness. Using the procedure outlined in the reference, we find the correlation between estimated and actual relatedness to be 0.15 (±0.031 = SD, 1000 replicates). We estimate that the correlation between growth and actual colony relatedness is at least eight times the measured value of –0.102, that is, –0.86, rather than the –0.54 that we reported.

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CORRECTIONS AND CLARIFICATIONS

In the Techview article "Sequence server samurai" by P. Simakov (*Science*'s Compass, 20 Aug., p. 1226), the price given for InforMax Software Solution for BioMedicine was incorrect. It should have been $250,000, not $250.

In the article "Kansas dumps Darwin, raises alarm across the United States" by Constance Holden (News of the Week, 20 Aug., p. 1186), Fred Spilhaus should have been referred to as executive director (not president) of the American Geophysical Union.