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Autoreproduction by hermaphrodites

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Human spermatozoa from anatomical sites other than the testicles (i.e. other than in semen), including the caput epididymis, can fertilize oocytes using intracytoplasmic spermatozoa injection (ICSI) (Spermatozoa Micro-Aspiration Retrieval Techniques Study Group, 1994; Van Steirteghem *et al.*, 1993a,b; Vankelecom *et al.*, 1994). Viable embryos and gestations have recently been achieved by ICSI of testicular spermatozoa (Vankelecom *et al.*, 1994), by electrofusion of round spermatids with eggs in mice (Ogura *et al.*, 1994) and ICSI of round spermatid nuclei in human eggs (Sofikitis *et al.*, 1995). Therefore, in the post-ICSI world, all that appears necessary to achieve pregnancy is a spermatozoon or spermatid, an oocyte and a uterus, the endometrium of which can be controlled, if necessary, with exogenous hormones. An intriguing question, albeit theoretical at present, can now be asked: 'Is it possible that true hermaphrodites could autoreproduce with the aid of ICSI?'

True hermaphroditism is a relatively rare 'experiment of nature' in which, by definition, both ovarian and testicular tissue are present in the same individual, and sometimes in the same gonad. There have been several extensive surveys of the diverse experience with human true hermaphrodites, including a review of 283 cases published since 1980 by Krob *et al.* (1994). The surveys and individual case reports document wide variability in phenotypic expression and karyotype patterns. However, it is clear that many hermaphrodites have oocytes and relatively normal uterine anatomy, about half menstruate, and there have been at least 22 pregnancies reported in 11 such individuals (Verp *et al.*, 1992; Krob *et al.*, 1994). The external genital phenotype has been normal female in many of these cases, although some females display variable degrees of clitoral hypertrophy (Krob *et al.*, 1994).

Uncommonly, true hermaphrodites can present clinically as a phenotypic male with a competent phallus and normal scrotum (Rosenberg *et al.*, 1963; Winters *et al.*, 1979) when testicular elements of the gonad predominate and provide adequate masculinization of the embryonic genital apparatus. In such cases, a testis or ovotestis is usually discovered at scrotal or inguinal surgery and mature germinal elements have been present within well-formed seminiferous tubules in some cases (Rosenberg *et al.*, 1963; Winters *et al.*, 1979; Aaronson, 1985). Furthermore, at least two hermaphrodites have fathered children, one having both a male and a female child (Shannon and Nicolaides, 1973; Parvin, 1982). In each of these two cases, there was one scrotal testis and an inguinal ovotestis, and spermatozoa concentrations in ejaculates were ~15–20×10^6/ml, with relatively normal motility and morphology. While paternity testing was not performed, there is little reason to doubt that these two hermaphrodites were indeed the biological fathers of their children.

Genetically, there does not appear to be a compelling reason why autoreproduction by at least some hermaphrodites should be impossible. In reviewing the substantial literature on genetic aspects of hermaphroditism, it seems clear that a variety of biological mechanisms apply in different cases. Some 46XX hermaphrodites have Y chromosome DNA sequences including *SRY*, while many do not (McElreavey *et al.*, 1992; Kuhnle *et al.*, 1993); in another 46XX individual, Fechner *et al.* (1994) have postulated the translocation of Y chromosome sequences to an X chromosome, with some inactivation of the translocated X. Mosaicism and chimaerism have been proposed as possible mechanisms particularly in cases with 46XX/46XY chromosome complements,

Mosaicism could arise through a variety of potential cytogenetic aberrations. Possible aetiologies for chimaerism have been nicely discussed by Ford (1969) and include two broad classes: (i) Two separate acts of syngamy encompassing dispermy with suppression of second meiotic division, dispermy with participation of ovum nucleus and nucleus of first polar body, dispermy with participation of ovum nucleus and nucleus of second polar body, dispermy with participation of two haploid

nuclei (daughters of the ovum nucleus), and fusion of one daughter of zygote nucleus with nucleus of second polar body; (ii) contributions from two independent zygotes encompassing early fusion of two embryos, and cellular exchange between dizygotic twins.

Dewald *et al.* (1980) have utilized a variety of chromosomal markers to suggest the mechanism of two separate acts of syngamy encompassing dispermy with participation of the ovum nucleus and of the second polar body in their case, while De la Chapelle *et al.* (1974) employed both cytogenetic and protein polymorphisms to support the mechanism of early fusion of two independent embryos in their patient. Verp *et al.* (1992) proved chimaerism in one patient, and Uehara *et al.* (1995) did so in another patient, and excluded certain of the above mechanisms by demonstrating two different maternal and two different paternal genotypes in some tissues. Uehara *et al.* (1995) provocatively suggest that chimaerism might originate from two oocytes in a binovular follicle, both of which fertilize and then subsequently fuse.

Regardless of the genetic cause of a particular case of hermaphroditism, meiosis in such individuals would be expected to produce a wide variety of genetically different gametes; hence any offspring resulting from autoreplication either of a mosaic or a chimaera through gamete formation and gamete fusion would be a genetically distinct as well as potentially normal child.

Thus, it can be speculated that autoreplication by certain human hermaphrodites is not biologically impossible. In principle, ICSI could be applied to facilitate spermatozoa–egg fusion in those cases where only spermatids or small numbers of spermatozoa are available on gonadal biopsy; in the very rare hermaphrodites in which oocytes and spermatozoa production are abundant, standard IVF could be employed.

If it is indeed true that in some hermaphrodites autoreproduction could be possible with medical intervention, another question may be asked: 'Is it possible that such autoreproduction could, with the greatest rarity, occur without such an intervention?' Indications exist in the mythology of various cultures which mention hermaphroditic reproduction, and there are references to virgin births in the historical documents of several different societies.

It should be apparent to the reader that while we postulate that medical intervention could possibly facilitate hermaphrodite autoreplication, we do not propose the clinical use of such an intervention. The specific circumstances, if any, which would justify the application of this theoretical strategy to a patient are far from clear; obviously the ethical issues involved would be extraordinarily complex.

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