Dear Sir,

We thank Egozcue and co-workers for giving us the opportunity to comment further on our recent findings on the meiotic potential of 46-XY and 47-XXY spermatogonia of men with non-mosaic Klinefelter’s syndrome (Yamamoto et al., 2002). Unfortunately, Egozcue and co-workers misunderstood the conclusions that were drawn.

It is true that a previous study by Mroz and co-workers suggested that mouse XXY-spermatogonia may not undergo meiosis (Mroz et al., 1998). However, we cannot rule out the possibility that a few 47-XXY spermatogonia in men with non-mosaic Klinefelter’s syndrome undergo meiotic divisions for the following reasons: First, conclusions from studies in rodents cannot be unequivocally transferred to the human. It is not uncommon for the biological rules characterizing/defining a given pathophysiology in rodents and the human to be opposite. For example, the reproducing element of the centrosome is maternally inherited in the mouse and paternally inherited in the human (Schatten et al., 1994; Sofikitis et al., 1996). Another example is that varicocele in the human means retrograde blood flow, whereas in rats with varicoceles there is no retrograde blood flow through the left testicular vein (Sofikitis and Miyagawa, 1993; Sofikitis et al., 1996). Thus we consider that the unequivocal transfer of the conclusions of Mroz and co-workers to the human may not be appropriate. Second, our recent study has provided clear and strong evidence that non-disjunctions of sex chromosomes during meiosis I and II of normal testicular 46-XY spermatogonia/primary spermatocytes do not occur in men with non-mosaic
Klinefelter’s syndrome (Yamamoto et al., 2002). The lack of findings in the latter study supportive of sex chromosomal nondisjunctions during meiosis I or II of 46-XY spermatogonia/primary spermatocytes allows us to suggest that the hyperhaploid 24-XY round spermatids and 24-XX round spermatids are produced by regular meiosis of few/some of the 47-XXY primary spermatocytes that are present in the seminiferous tubuli of men with non-mosaic Klinefelter’s syndrome.

Egozcue and co-workers did not interpret correctly another part of our study: we did not suggest that all the 47-XXY spermatogonia/primary spermatocytes undergo meiosis; probably a subpopulation of them does. We do not consider as a surprising finding the lack of testicular spermatozoa in the 12 patients with only 47-XXY spermatogonia/spermatocytes within their tubuli because (i) the number of 47-XXY spermatogonia/primary spermatocytes per tubule was small in the latter men (the majority of the tubuli were empty of cells or they had the appearance of Sertoli cell-only tubuli); (ii) only a few of the 47-XXY spermatogonia/primary spermatocytes may undergo meiosis; (iii) only a limited number of tubuli from each testicular sample were processed for mincing procedures and fluorescent in-situ hybridization techniques and subsequently some sperm existing within the testicular tissue may have not been identified; and (iv) 47-XXY spermatogonia/primary spermatocytes may undergo meiosis in some men, but not in others. Thus, the absence of haploid cells in the 12 men with only 47-XXY spermatogonia/primary spermatocytes in their tubuli may probably be due to inadequate support of the 47-XXY germ cells by the Sertoli cells in the latter men. This hypothesis is strongly supported by the significantly smaller testicular androgen binding protein profiles (a marker of Sertoli cell secretory function) demonstrated in our study for the men with Klinefelter’s syndrome who were negative for testicular haploid cells. In contrast, in other men with non-mosaic Klinefelter’s syndrome, some 47-XXY germ cells may undergo meiosis I and II due to adequate Sertoli cell secretory function.

We have not suggested that only spermatocytes with an XX bivalent and a Y univalent are capable of entering meiosis. This is not written anywhere in the paper. In contrast, we have clearly mentioned (i) the probability that (within the population of 47-XXY primary spermatocytes that undergo meiosis) a small subpopulation exposes an XY sex vesicle and a free extra X chromosome cannot be ruled out; and (ii) a novel suggestion that is supported by our findings is that an XX pairing and an univalent Y chromosome type of pairing occurs in the great majority of 47-XXY spermatogonia/primary spermatocytes that undergo meiosis, whereas an XY pairing and an univalent X chromosome type of pairing occurs in the minority of 47-XXY spermatogonia/primary spermatocytes that undergo meiosis. This suggestion can explain: (i) the increased proportions of XY and XX round spermatids in men with Klinefelter’s syndrome compared with obstructed azoospermic men, (ii) the increased proportion of XY round spermatids compared with XX round spermatids in men with Klinefelter’s syndrome, and (iii) the larger proportion of X round spermatids compared with Y round spermatids in men with Klinefelter’s syndrome. Thus the above novel suggestion can explain all the cytogenetic dynamics in our recent study (Yamamoto et al., 2002).

We have clearly mentioned in our study that there is a great degree of controversy in the international literature on the meiotic competence of 47-XXY spermatogonia/primary spermatocytes (Yamamoto et al., 2002). Several studies supporting the most popular theses (meiotic competence or meiotic incompetence of 47-XXY spermatogonia/primary spermatocytes) have been mentioned in the reference list of the latter study. The additional studies mentioned by Egozcue and co-workers in their letter do not add anything to the studies published previously and therefore have not been discussed.

References
N. Sofikitis1,4, D. Yiannakis1, A. Chatzikyriakidou1, D. Baltoyanni1, S. Tsambulas1, A. Tasos1, J. Georgiou1, M. Schrader2, Y. Yamamoto2, I. Miyagawa,3 X. Giannakopoulos3
1Department of Urology, Ioannina University School of Medicine, Ioannina, Greece
2Department of Urology, Freie Universit"at Berlin, Berlin, Germany, and 3Department of Urology, Tottori, University School of Medicine, Yonago, Japan

4To whom correspondence should be addressed.
E-mail: akrosmin@hotmail. com