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Mechanisms and implications of testicular dysgenesis

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Testicular cancer is associated with dysgenesis of the testis. The first evidence that testicular germ cell cancer is of fetal origin came from studies in the 1970s of carcinoma in situ testis (CIS), the forerunner of seminomas as well as non-seminomas. These studies showed that the CIS cell had characteristics of primordial germ cells of the fetal testis. Later studies, including most recent molecular investigations have demonstrated that the phenotype of the CIS cell is gonocyte-like with stem cell characteristics like primordial germ cells. The available evidence seems to support our hypothesis from 1987 that dysgenesis of the fetal testis leads to Sertoli and Leydig cell insufficiency resulting in failure of differentiation of gonocytes into spermatogonia. The persistence of such stem cell-like germ cells in the testis during childhood and puberty may eventually cause germ cell cancer in young adulthood after the pituitary-gonadal axis has been activated. Sertoli and Leydig cell insufficiency may also lead to other male reproductive health problems, including poor spermatogenesis, cryptorchidism and some disorders of sex development. Robust epidemiological data have shown associations between all these symptoms and testis cancer. We have proposed that testicular cancer and some cases of male infertility, cryptorchidism and hypospadias may have the same origin in fetal life due to genetic factors and/or environmental exposures resulting in a testicular dysgenesis syndrome (TDS). A patient with mild form of TDS may have one these symptoms, while the more severe cases may harbour two or more, e.g. cryptorchidism, testis cancer and poor semen quality. Furthermore, an animal model for TDS has been reported.