Genetic aspects of male infertility

Faulty Sperm

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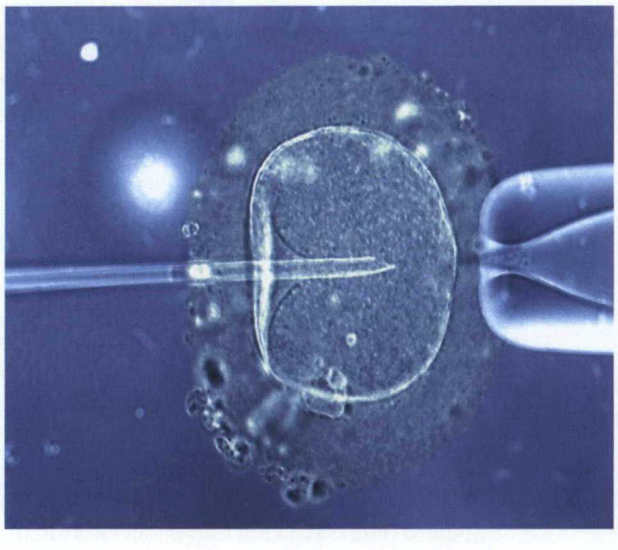
The latest findings indicate that the causes of infertility frequently lie on the part of the male. Fortunately, this is a condition that we know how to treat

World Infertility Day was marked for the seventh time this June, with educational efforts organized to raise public awareness about infertility and to encourage individuals affected to seek medical assistance as early as possible. This event was initiated back in 2001 by the American Infertility Association (AIA), in cooperation with the International Consumer Support for Infertility (ICSI). Throughout the world, infertile couples have to cope with not only financial barriers, but also the stress that comes from public enunciations of their condition. Major problems are posed by existing stereotypes (in Bangladesh, for instance, infertility is considered to be a curse that brings bad luck) as well as ignorance, prejudice, false humiliation, and a lack of social acceptance. Since Luisa Brown's birth in the UK back in 1978, more than two million children have now come into the world via *in vitro* fertilization. That offers some hope to the many couples faced with infertility who have not given up, demonstrating that this is a condition that can indeed be treated.

The latest research findings and information collected by the World Health Organization (WHO) identify infertility as a social disease which affects 10-18% of couples. The so-called male infertility factor is currently estimated to account for 40-60% of all cases. Apart from genetic factors, a very important role in causing infertility is played by lifestyle and circumstances stemming from modern civilization, such as the age of the parents, their history of diseases, conditions, or defects in their reproductive organs, improper function of the hormonal system, psychologically-related disturbances, consumption of various medicines, and the impact of the external environment, including stress and use of alcohol/cigarettes. Statistical data indicate drastically low sperm cell quality parameters in an ever-increasing group of men, which is in turn reflected in the rising infertility rate.

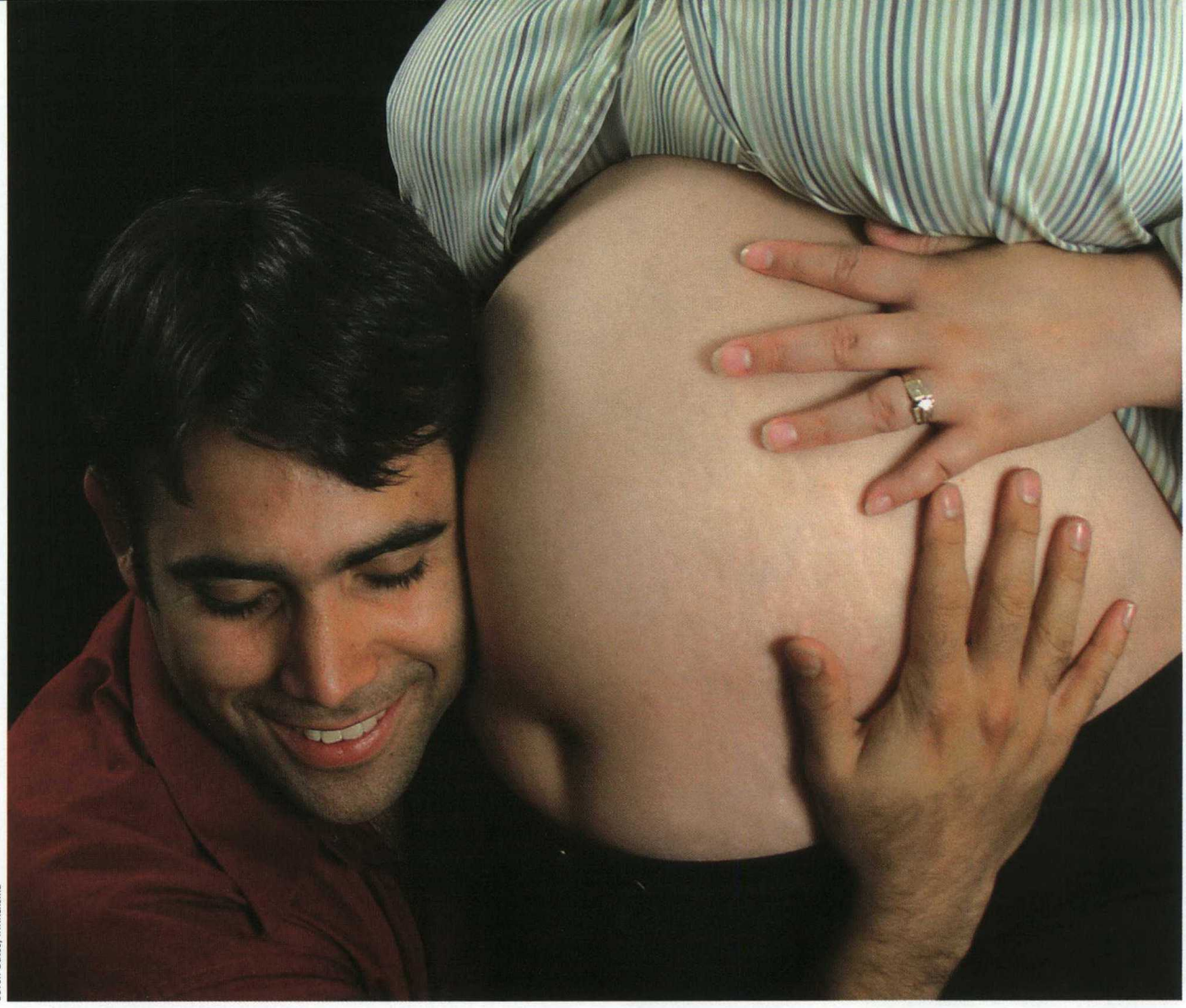
Problem in the genes

Genetic factors are one of the most important and very frequent causes underlying reproductive failure. The most common genetic factors involved in male infertility include chromosome aberrations (including Klinefelter's syndrome, chromosomal translocation), deletions in the Y chromosome (microdeletions mainly in specific regions), various genetic mutations (e.g. in the cystic fibrosis gene or the androgen receptor), and genetic polymorphism (i.e. differences between gene variations). Male genetic factors (including chromosomal aberrations) currently cause some 10-15% of cases of reduced fertility. The frequency of chromosomal aberrations is significantly higher in infertile men. In men with azoospermia (an absence of sperm cells in the semen), the frequency of chromosomal aberrations alone stands as high as 15%. The most frequent abnormalities are aneuploidy (an abnormal number of chromosomes) and structural aberrations, caused for example by DNA instability, causing in consequence the breaking of chromosomes. Aneuploidy conditions in humans are caused by errors in the segregation of maternal and paternal chromosomes and by erroneous gametogenesis. Normal ejaculate usually exhibits 10-14% of



East News

The ICSI procedure introduces a single sperm cell of normal appearance and behavior into the oocyte. Such a cell might, however, contain damaged DNA, and then *in vitro* fertilization will not succeed



Seven Bates, www.sxc.hu

Infertility is can be treatable: more than two million children have now been born into the world through the *in vitro* method

spermatozoa with chromosomal aberrations. Within the population of infertile patients, chromosomal aberrations occur significantly more frequently, both in sperm chromosomes and in the chromosomes of peripheral blood leukocytes. The highest percentage of aberrations is seen in the sex chromosomes.

Reciprocal chromosomal translocations

A frequent genetic factor leading to male infertility is called reciprocal chromosomal translocation (RCT). Such translocations occur with a frequency of 0.9 in 1000 cases. They involve the reciprocal exchange of part of the genetic material between two chromosomes, without a change in chromosome number. RCT carriers very frequently do not show any visible signs, and in fact it is not fully clear which of the translocations negatively affect the spermatozoa. It is estimated that the incidence of RCT is seven times higher in men with a reduced (oligozoospermia) or zero sperm count (azoospermia) than in the general population. Interestingly, the presence of translocated chromosomes may not in practice be accompanied by changes in spermatozoon morphology. This could pose a serious problem for *in vitro* fertilization. Standard sperm tests which solely evaluate cell morphology therefore may not detect translocation. During the procedure of ICSI (intra-cytoplasmic sperm in¬jection), an individual sperm cell which displays correct appearance and movement is injected into the oocyte. There

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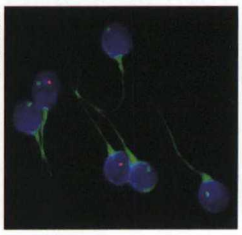


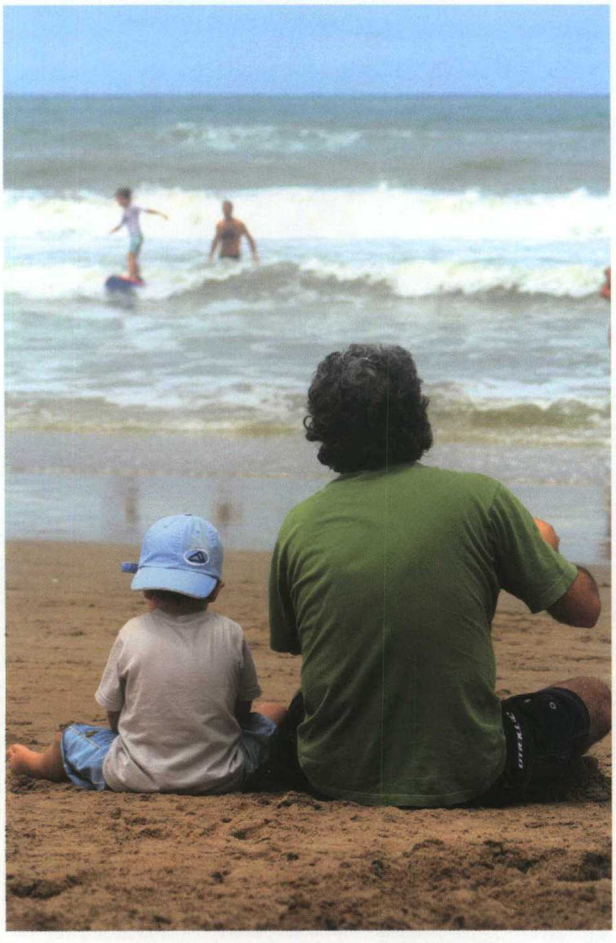
Sperm abnormalities, such as chromosomal translocations occurring during spermatogenesis, can be evaluated via the FISH (florescent in situ hybridization) technique, using centromere probes. Here the centromere of the X chromosome is shown in green, the Y chromosome in red

is therefore a high risk of applying a sperm cell with incorrect DNA. If it is damaged, the *in vitro* technique will not succeed. Embryos may die at an early stage of development or an embryo/fetus may show developmental disorders, leading to miscarriage. The FISH technique (florescent in situ hybridization) can be and is used to evaluate chromosomal translocations which occur during spermatogenesis. The percentage of genetically balanced and unbalanced gametes is identified in the meiotic segregation pattern (three-color FISH with molecular probes marked with fluorochromes).

In the right place

Research over the past 10 years has made significant progress in identifying the nuclear organization of the genome, in both the diploid somatic cell and the haploid gamete. Increasing attention is focusing on studies meant to confirm that each chromosome in fact occupies a strictly specified location within the cell nucleus, called a chromosome territory (CT). Such territories, together

Sebastian Danon, www.sxc.hu



An ever-increasing group of men show drastically low sperm cell quality parameters, which is in turn reflected by the rising rate of infertility

with the spaces between them (interchromosome compartments - IC) and elements of the nuclear matrix form the intranuclear architecture. The positioning of chromosomes is probably one of the important epigenetic factors regulating gene expression and correct genome function. It seems that in diploid cells in both plants and animals, territory size and location depends on the size of the chromosome, the number of genes, their transcription activity, the stage of the cell cycle, and the type of the cell. The male reproductive cell, in particular, exhibits the most interesting genome organization scheme.

A sperm cell is the end product of spermatogenesis. It is characterized by a special chromatin structure, closely linked to the irreversible condition of "putting the genome to sleep," a state in which it cannot be subjected to either transcription or replication. Because the chromatin adopts a transcriptionally inactive, maximally condensed conformation, the sperm cell nucleus constitutes only 5% the size of a diploid somatic cell. This conformation is the result of more than 80% of the histones being replaced by protamines, alkaline proteins of low molecular weight. In consequence, DNA is not in the superhelix shape but rather adopts a toroid one. Both the territories and the chromatin of individual chromosomes are condensed four to six times. Interestingly, the chromosomes in a sperm cell take on a "hairpin" configuration. The centromeres of sperm chromosomes, meaning the narrow structures to which chromosomes bind during division, form a cluster in the central region of the sperm cell nucleus, called a chromocenter. Teleomeres, the stability-providing entities at the ends of chromosomes, become situated alongside the sperm cell membrane, forming dimers and tetrameres. It is possible that teleomeres are the first element of the paternal genome which comes into direct contact with the egg cell cytoplasm. As a result, this chromosome configuration is crucial for the correct deconsensation of chromatin during fertilization, and that in turn is critical for correct zygote development. In this respect, the sperm nucleus offers a unique model for analyzing the topology of individual chromosomes, especially in men with reproductive problems, including RCT carriers. It turns out that chromosome location may differ in RCT carriers as compared to a control group of fertile males. Our research has shown that in a group of 6 RCT carriers the chromocenter region was shifted closer to the acrosome (the front part of the sperm cell head) and also to the periphery of the cell nucleus. These changes may certify a link between spermatogenesis disturbances in RCT carriers and changes in the intranuclear architecture of sperm cells.

Selection to the rescue?

Natural selection prevents most of the abnormalities which cause infertility, including translocations, from being passed on to progeny. However, natural selection sometimes breaks down, especially when assisted reproduction techniques are applied. This in fact increases the risk of a genetic defect being passed on to the next generation. In view of the huge number of factors that can lead to infertility in men, attention has to be paid also to chromosome typology. Changes in chromosome location may prove to be one of the most important epigenetic elements critical for sperm function and for early embryonic development, currently unrecognized and treated like other reproductive failures. ■

Further reading:

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