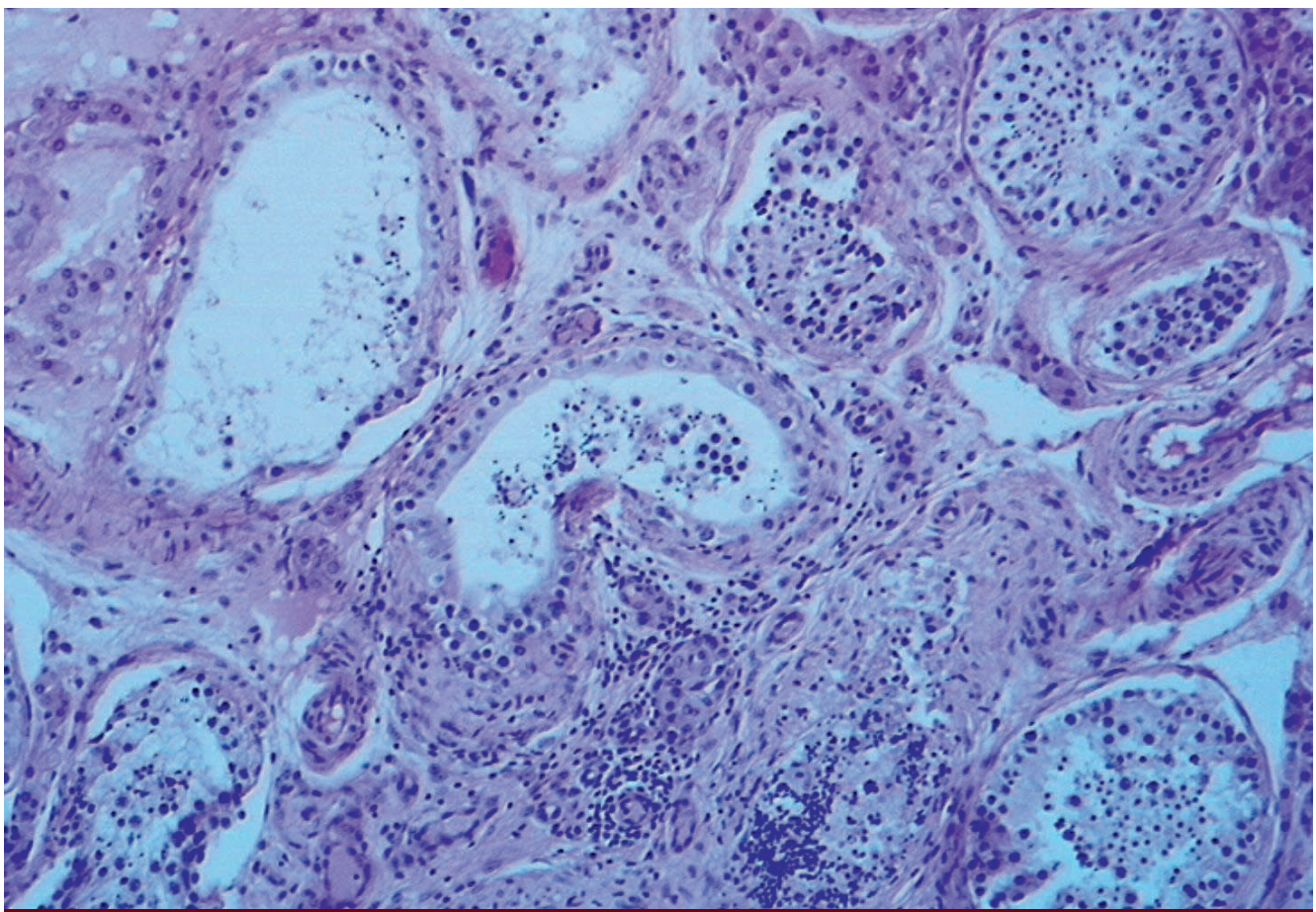
Although the female partner has historically borne much of the responsibility for a couple's inability to conceive, research shows that male infertility plays a significant part in many cases. Further research in this area could lead to improved assisted reproductive techniques, says **Professor Klaus Steger**

Research into underlying reasons for infertility in men



Photograph courtesy of Professor Martin Bergmann (Gießen Project)

A testicular biopsy of an OAT syndrome sufferer: seminiferous tubules with normal spermatogensis (upper right) can be seen in direct vicinity to tubules with spermatogenic arrest (upper left). The dark dots in the middle represent nuclei of lymphocytes – a characteristic of inflammation

Infertility affects one in six couples worldwide according to World Health Organisation (WHO) estimates, and while the female partner has historically borne much of the responsibility, it is now known that the male is involved in up to 50 per cent of cases. Around a third of these men display idiopathic infertility, in that the cause of their infertility remains unknown, an issue which lies at the core of the male infertility project's research agenda. "One of the short-term aims of our project is to improve the diagnosis of idiopathic infertility. As part of this it will also be important to improve our knowledge of the molecular control mechanisms involved in germ cell differentiation and fertilisation," says Professor Klaus Steger, the head of the Gießen project. Molecular biology techniques are being applied by both basic and clinical scientists within the project to various animal models and human biopsy material, work central to understanding the causes of infertility. "Treatment of any disease is doomed to be ineffective if you don't first know its exact cause," stresses Professor Steger. "At present, infertility is treated by applying an assisted reproductive technology (ART) technique, such as *in-vitro* fertilisation (IVF) or intracytoplasmic

sperm injection (ICSI). ICSI opens newzons in the treatment of male infertility, as it allows even men with severe spermatogenic impairment to father a child; however, pregnancy rates are still fairly constant at approximately 25 per cent live births per cycle. This outcome is put into perspective when we consider the cost of a 75 per cent failure rate in both psychological and financial terms to the couples undergoing the treatment."

Testosterone levels

Research into the underlying causes of male infertility holds the promise of greatly improving the success rate of ART treatment. The age of the couple is of course an important factor; however, while testosterone levels decrease in older men there are significant variations between individuals, and any reduction affects primarily sexual libido rather than sperm production. "Most of the couples attending our infertility clinic are aged between 20 and 30. Male infertility can be caused by diseases of the testis, the epididymis or the accessory sex glands, failure of sperm production or sperm transport, hormonal disturbances, infection and inflammation, varicocele and sexual dysfunction, the latter of which represents a particular problem in patients with type-2 diabetes," he says. There is also an ever-growing list of so-called lifestyle factors, including the over-use of nicotine, alcohol, anabolic steroids and recreational drugs; however, the focus of both the Gießen and the Münster projects is more on the genetic mechanisms involved in infertility. While the Gießen project focuses on the development and interaction of the different cell types within the testes, the Münster project concentrates on the differentiation of spermatogonial stem cells and oocytes. "It is well known that azoospermia in 20 per cent of cases is caused by genetic disorders including chromosomal aberrations, such as XXY, and microdeletions on the Y-chromosome," he outlines. "Both the Gießen and Münster projects are concentrating on genetic aspects of germ cell differentiation, eg. gene expression in normal development compared with aberrant gene expression in impaired development. As the lack of expression of a specific gene in impaired development suggests that it plays an important role in normal development, this gene may in future prove to be a key molecule for gene therapy."

This work in genetics is complemented by the project's research into several aspects of epigenetics, including the methylation of desoxyribonucleic acid (DNA) – also known as genetic imprinting – and modifications of the DNA-binding histones. Both processes are inherited and involved in the regulation of gene expression. "Evidence suggests that epigenetics plays an important role in early embryo development. Impaired spermatogenesis is often associated with aberrant DNA methylation, so it may be that the sperm cell is responsible for the higher incidence of the so-called imprinting diseases Angelmann, Prader-Willi and Beckwith-Wiedemann syndrome in children conceived with ART," explains Professor Steger. Increased knowledge of male germ cell differentiation, meaning a different gene expression pattern between the fertile and infertile situation, will improve the diagnosis of idiopathic male infertility; a goal which Professor Steger says is moving ever closer. "This will be possible in the near future. The cost of it will depend on whether we analyse only a few candidate genes or a complete dataset. Although such investigations could eventually lead to the development of measures to prevent male infertility, this will take some time," he acknowledges. "Infertility is broadly defined as one year of unprotected sexual intercourse without pregnancy. In Germany, this is a prerequisite for health insurers to pay a share of the overall cost of ICSI treatment for infertile couples. Insurance companies will pay for three cycles if the female partner is below 40, as it is known that the effectiveness of ART decreases in older women, while the number of children displaying genetic disorders increases."

Long-term objective

By contrast no significant statistical correlation has yet been identified between the age of the male partner and the outcome of ART. While Professor Steger believes that the long-term objective of infertility treatment must be to try and improve sperm production within infertile men, ART techniques

Research into the underlying causes of male infertility holds the promise of greatly improving the success rate of ART treatment

are still likely to involve treating both the male and female partner for the foreseeable future, even if the female suffers from no fertility problems. "Pregnancy requires not only the fertilisation of an oocyte by a sperm cell, but also the development of an embryo. As the latter takes place within the female partner the microenvironment of the embryo – namely hormone levels and female cycle – has to be optimised to ensure the optimal development of the embryo," he points out. However, the project's work is centred primarily on the causes of male infertility; both the quality and number of the male's sperm are important factors in this regard. "Some infertile men are azoosperm. This may be due to either an obstruction of the efferent genital tract or a failure of sperm production, eg. Sertoli-cell-only (SCO) syndrome. Even in the latter case, men may father a child, as testes exhibiting SCO syndrome in most cases contain some small foci with normal spermatogenesis that allow testicular sperm extraction which can be used for ICSI," continues Professor Steger. "However, the majority of infertile men exhibit the so-called oligoasthenoteratozoopermia (OAT) syndrome that is characterised by a decreased number of sperm cells (oligozoospermia), a reduced motility of sperm cells (asthenozoospermia) and an increased number of morphologically abnormal sperm cells (teratozoospermia)."

Male fertility is an enormously complex area. The testis itself includes a variety of (among others) dividing and differentiating germ cell populations and highly differentiated somatic Sertoli cells within the seminiferous epithelium; Professor Steger says research into each of these cell types is a crucial part of his project's work. "We cannot understand the collective behaviour of various cell types within a tissue without first understanding the behaviour of the individual cell types. Various cell types within the testis behave differently. Even the germ cell population itself is inhomogeneous, ranging from mitotically active spermatogonia – which represent the stem cells of spermatogenesis – to spermatocytes undergoing meiosis, right through to spermatids and spermatozoa representing haploid cells that merge with the oocyte to form an embryo," he outlines. Work in this area is ongoing, and some ambitious future objectives have already been identified. "Both the Gießen and Münster projects are funded by the German Research Foundation, (DFG) who have provided a three year grant that may be extended for another three years. In April 2010 – approximately the middle of the first funding period – we will hold a German DFG Reproductive Science Network Meeting in Gießen to promote scientific exchange between both projects," continues Professor Steger. "The long-term objective is to establish a reproductive science network in Germany involving basic and clinical scientists from andrology, biology, gynaecology and veterinary medicine working on stem cell differentiation, male and female germ cell development, as well as fertilisation and early embryo development." ★

At a glance

Full Project Title
Male factor infertility due to impaired spermatogenesis

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Germ Cell Potential

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