A clue to Kartagener's

John Aitken

THE prospect of using transgenic mice to probe the causes of human infertility is raised by Merlino *et al.*, writing in *Genes & Development*[1]. The authors have created a transgenic line exhibiting an immotile sperm syndrome that exactly duplicates a flagellar disorder observed in infertile men.

The mice were generated by inserting the complementary DNA for a human epidermal growth factor (EGF) receptor into the mouse genome, driven by the chicken β-actin promoter. One of the resulting transgenic lines (AE24) established a unique pattern of expression, in which extremely high levels of EGF receptor RNA were expressed in the testes but not any other tissue examined. *In situ* hybridization studies indicated that the transgene was transcribed during meiosis, as early as the primary spermatocyte state of spermatogenesis, whereas the appearance of human EGF receptors was delayed until the post-meiotic stages of sperm differentiation. The implication is that the transcription of the transgene was being influenced by a testes-specific enhancer and its expression was being regulated by a translational control mechanism.

The most intriguing aspect of the AE24 line is that about half of the males homozygous for the transgene were infertile. Moreover their infertility was associated with a lack of sperm motility, due to a disorganization of the axoneme (the flagellar central core), frequently involving the loss of microtubule pairs 4–7. This phenotype is identical to a pathology, described by Escalier and David[2] in cases of human infertility, which is characterized by the presence of spermatozoa in the ejaculate that are normal in every respect except for a loss of motility.

This condition is one of a fascinating number of flagellar mutants in human males that are responsible for infertility. The best characterized is a hereditary condition known as Kartagener's syndrome[3], which is associated with the complete absence of dynein arms (the site of ATPase activity) from the axonemes of all ciliary and flagellar structures in the body. As a result, affected patients suffer from chronic sinusitis and bronchiectasis and, more unexpectedly, situs inversus, involving a left–right inversion in the location of key organs such as the heart and liver. Women exhibiting this condition are fertile (so much for ciliary currents wafting eggs down the fallopian tube) but men are sterile, the absence of dynein arms in the sperm tail leading to a complete loss of sperm motility. Apart from the loss of motility, the spermatozoa from Kartagener's patients are perfectly normal, and if micromanipulated so that they come to lie adjacent to plasma membrane of the oocyte they will fuse with the membrane and fertilize the egg[4]. The possibility of using *in vitro* fertilization technology to treat such patients is therefore being pursued, although whether this is a laudable objective is another question.

Other mutants

In addition to Kartagener's syndrome, a number of other flagellar mutants are known in the infertile male population; they involve the absence of radial spokes, transposition of microtubule doublets from the periphery to the centre of the axoneme (8+2), loss of the central sheath and microtubule deletion. The results of Merlino *et al.* show that a rational approach to understanding the aetiology of these conditions might be to make use of transgenic animals. The important observation that axoneme assembly is normal in the testes is one early fruit of ultrastructural studies of the germ cells generated by the AE24 line; however, microtubule deletion is apparent in spermatozoa located in more distal regions of the reproductive tract, such as the epididymis and vas deferens. In other words, this particular flagellar defect involves a latent instability of the axoneme, rather than a failure to assemble this structure during spermiogenesis. Variations between cells in the rate of microtubule disassembly may explain why the clinical picture is often characterized by variation in the proportion of cells in a given ejaculate expressing a specific flagellar defect[5].

Transgenic animals may therefore provide an important source of clues about the circumstances responsible for creating the pathological flagellar mutants in man. Such clues are badly needed — the infertile male is the most common cause of intractable human infertility and yet there are few, if any, treatments to tackle this condition. □

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DAEDALUS

Skimmed water

THE hovercraft is a good idea poorly implemented. It floats elegantly on a cushion of compressed air; but it compresses that air, and propels and steers itself, with clumsy airscrews. Daedalus now proposes improvements.

Firstly, he says, the air cushion should be compressed not with a fan, but directly from the craft's forward motion. The envelope of his new 'ramcraft' skims the water all round it, except in front, where it rises into an air-intake. Air scooped in by forward motion is compressed and trapped by the ram effect, and supports the craft. With careful aerodynamic design, almost the full theoretical stagnation-pressure should be reached under the envelope (compared to some 20 per cent of it under a typical aircraft wing). Even so, at low speeds the resulting lift will only be a few kilogrammes per square metre. This modest 'wing-loading' enforces a very light style of construction, and Daedalus's design is a sort of cross between a tent and a hang-glider. Its big fabric wing gapes high in front to form the air-inlet, but curves down to the ground at the back and sides to trap the air. A few light guy-ropes and spars define its shape. Stationary, the ramcraft will be a sad and droopy sight; but when it starts to move, the ram-pressure of entering air will soon inflate it to shape, and lift it off. At a few metres a second, it should be fully inflated and airborne. Daringly, the passenger and control cabin hangs beneath the wing itself, in the pressurized region. Passengers will not even notice the small over-pressure.

The ramcraft will propel itself over water in flying-fish style. This creature often skims along with its tail still submerged, and wagging fast to maintain speed. So the ramcraft will simply extend a propeller into the water on a long angled shaft, and steer and propel itself from the thrust. No noisy, inefficient airscrews are needed.

To let the ramcraft ride safely up onto a beach or apron, Daedalus will fit the blade-tips of its propeller with small angled traction-rollers. They will then roll smoothly over solid ground, continuing to propel the craft by a form of linear worm-drive action.

Daedalus will initially launch the ramcraft as a small personal fun-vehicle, combining the scary delights of hang-gliding and water-skiing. But like balloons and other tension structures, and unlike conventional boats and aircraft, it should get better as it gets bigger. Huge bulk-carrier ramcraft, little more than acres of brightly-coloured, self-inflated fabric, may yet challenge the supertanker for dominion of the seas. DAVID JONES