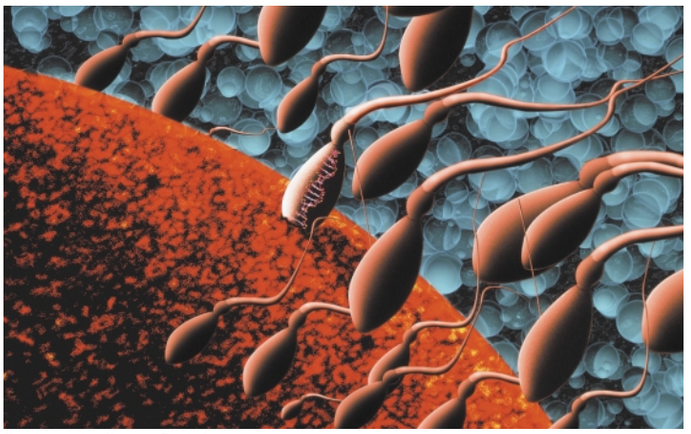

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POPULATION GENETICS

Reproductive technologies — a long-term cost

That human society is far from ideal should come as no surprise. Such a thought has rarely troubled population geneticists though, as their theoretical models are based on the behaviour of ideal populations. A report published in *Genetical Research* now brings reality to bear on these models by proposing that patterns of human reproductive behaviour cause a large and rapid increase in the frequency of genes responsible for genetic diseases — an effect that has become more pronounced as a result of advances in reproductive technology.

Over the past 40 years, humans have gradually acquired more control over the number, sex and health of their offspring. Widely available contraception has led to more effective family planning. In addition, embryo sexing and prenatal diagnosis allow parents to terminate a fetus at risk of developing a serious genetic disease. All three technologies have been mathematically scrutinized in this paper for their impact on the frequency of sex-linked mutations as a result of reproductive compensation, a reproductive strategy whereby the death of a fetus or infant is replaced by the birth of another. For example, imagine a family planned to have three children and one of them dies from a genetic disease. Full reproductive compensation will occur if a further child is produced to bring the family back up to three.

Using mathematical modelling, Ian Hastings has found that modern technologies substantially increase the frequency of deleterious sex-linked mutations over a short time span. These results are qualitatively obvious: by aborting a male fetus that tests positive for haemophilia A or Duchenne muscular dystrophy, for example, the mutation is removed from the population. However, that child has a 1 in 3 chance of being replaced by a carrier female. So, although the incidence of the disease decreases (as affected males are not born), the genetic frequency of the mutation rises.

The predicted effect of reproductive compensation on the equilibrium frequency of a sex-linked mutation (the frequency at which the rate of occurrence of a mutation balances its removal by selection) is striking — it rises 11% in the first generation, 7% in the second generation, then rises more gradually before stabilizing at a frequency 33% above its original value. These figures assume equal mutation rates in females and males; the effect is even greater when mutations occur only in males.

This study is one example of how human society might rapidly influence genetic structure, in a way that is tantamount to relaxing selective pressure on a mutation. The value of these models rests on whether their predictions can be verified. Has there recently been an increase in the incidence of sex-linked genetic disorders? It seems so, although it is possible that this increase is attributable to improved diagnostic methods. The impact on society of the results described in this paper is unclear, but they question the simple-minded view that the frequency of a deleterious mutation can be reduced by prenatal selection.

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References and links

ORIGINAL RESEARCH PAPER Hastings, I. M. Reproductive compensation and human genetic disease. *Genet. Res.* **77**, 277–283 (2001)

FURTHER READING Hastings, I. M. Models of human genetic disease: How biased are the standard formulae? *Genet. Res.* **75**, 107–114 (2000)

IN BRIEF

MOUSE MODELS

A transgenic model for listeriosis: role of internalin in crossing the intestinal barrier.

Lecuit, M. *et al. Science* **292**, 1722–1725 (2001)

Listeriosis is a rare food-borne infection that chiefly affects pregnant women and immuno-compromized individuals. The causative bacterium, *Listeria monocytogenes*, is believed to cross the intestinal barrier of the host through the interaction between internalin, a pathogen surface protein, and a host receptor, E-cadherin, which is expressed on enterocytes. This paper confirms this infection mechanism by studying oral infection in two animal models, guinea pigs and transgenic mice that express human E-cadherin. This paper establishes mice as instrumental in analysing human bacterial diseases.

GENE NETWORKS

Positive feedback in eukaryotic gene networks: cell differentiation by graded to binary response conversion.

Becskei, A. *et al. EMBO J.* **20**, 2528–2535 (2001)

Positive gene networks form the basis of various biological processes in eukaryotes, but the consequences of positive feedback have never been investigated empirically. By constructing a synthetic gene network in *Saccharomyces cerevisiae*, Becskei *et al.* show that the graded response of cells to constitutive expression of a transcriptional activator can be converted to a binary (on/off switch) response when the activator is subject to autoregulation. As autocatalytic expression underlies cell differentiation, this circuit model could be used to study how cells make developmental choices.

MOUSE MODELS

Mice containing a human chromosome 21 model behavioral impairment and cardiac anomalies of Down's syndrome.

Shinohara, T. *et al. Hum. Mol. Genet.* **10**, 1163–1175 (2001)

Trisomy 21 (Ts21) is the most common genetic cause of aneuploidy, mental retardation and congenital heart defects in live-born infants. To investigate how gene-dosage imbalances contribute to Ts21 clinical features, Shinohara *et al.* generated mice mosaic for human chromosome 21 using embryonic stem cells that retain the chromosome. During development, this freely segregating chromosome was lost from some tissues, but behavioural tests revealed a high correlation between its retention in the brain and behavioural abnormalities in the mice — abnormalities that parallel those seen in Ts21 humans. The mice also had cardiac defects and other Ts21 phenotypic characteristics, making them a good model for future studies into the disorder.