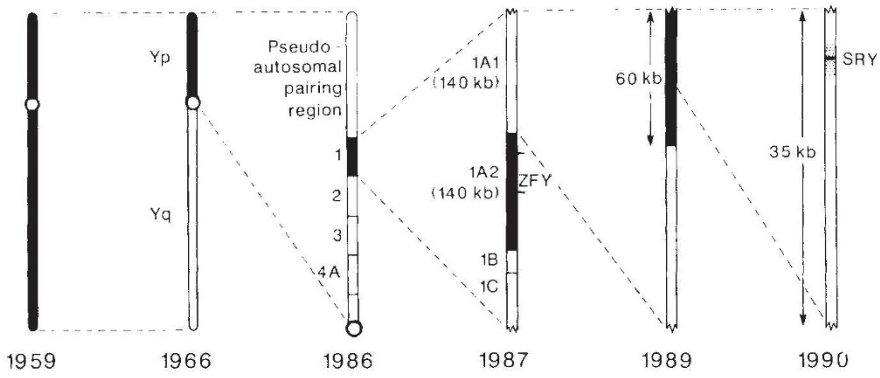
SEX DETERMINATION

The making of male mice

Anne McLaren

LAST year saw the discovery[1,2] of the best candidate yet for the long-sought-after testis-determining gene in mammals (see figure). Its claims rested initially on its localization: in both the human and the mouse, it was located within the region that constituted the smallest amount of Y chromosome DNA known to induce masculinization, and in the human it appeared to be the only gene within the relevant 35-kilobase region. It was therefore named *SRY* (human), *Sry* (mouse), for sex-determining region of the Y chromosome.



The hunt for the testis-determining factor from 1959, when the Y chromosome was shown to be male-determining in both mouse and man, to 1990 and the identification of the sex-determining region (*SRY* in humans, *Sry* in mice). For references see the previous News and Views article on the subject[9].

The candidacy of *Sry* was strengthened by the observation that it was expressed in the developing mouse gonad at the expected time for testis determination; and unlike the previous best bet, *ZFY*, it was not expressed in the developing ovary of mouse embryos in which the testis-determining gene on the Y chromosome (*Tdy*) was known to be defective. Within a few months, further support was forthcoming: *Sry* turned out to be expressed in the gonadal somatic cells previously shown to be responsible for testis determination[3], the gene was absent from the *Tdy*-defective mouse mutant[4], and two sex-reversed XY women were found to have mutations in *SRY* that were not present in their father's gene[5,6]. It seems that an intact copy of *SRY*/*Sry* is necessary for testis determination. But is it, in the absence of the rest of the Y chromosome, sufficient?

For mice, the answer is yes, at least sometimes. On page 117 of this issue[7], Koopman *et al.* describe 11 XX mice transgenic for *Sry* on a 14-kilobase DNA fragment. Three were sex-reversed males, eight were females.

The point is made. *Sry* alone can induce maleness; but certain unsatisfactory features remain. Why only three sex-reversed males? The transgene was inserted in multiple copies: was this a factor? Did the three males carry more copies of *Sry* than the eight females? We are not told. Was *Sry* expressed in all 11 transgenics, or did the eight females fail to express it because it was inserted in an inappropriate region of the genome? One of the transgenic females has transmitted the transgene to her progeny, which should allow expression to be examined in the embryonic gonad, but this crucial information is not yet available.

Koopman *et al.* have also produced mice transgenic for the human *SRY* gene. These raise yet more questions. Three integrations were achieved, giving rise to two transgenic lines, and transgene expression in the developing gonads was demonstrated, but no sex-reversal of XX embryos was seen. Would sex reversal have been achieved if more *SRY* transgenics had been made? Or is the human *SRY* product ineffective in the mouse? Or perhaps *Sry* is sufficient to determine maleness, but *SRY* alone is not? Of the four XX human individuals who showed masculinization with only 35 kilobases of *SRY*-containing Y chromosome DNA, all developed testicular tissue but none showed fully normal development of male genitalia[8].

Most of these questions will probably be answered in the next few months. If mammals turn out to resemble *Drosophila* and *Caenorhabditis* in having a complex cascade of sex-determining genes, the sequence will take longer to unravel. We know that *Sry* must be part of that cascade; what the transgenic results tell us is that the other genes in the cascade, whether they precede or follow *Sry* in the regulatory sequence, must be on the autosomes or on the X chromosome, not on the Y. It seems that *Sry* is indeed *Tdy*, the testis-determining gene on the Y. □

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COSMOLOGY

Dark dark matter

Craig J. Hogan

AMONG the suggestions that the Universe is made mainly of invisible material, one of the most predictive is a proposal put forward by Sciama[1,2]. In this scheme, this 'dark' matter includes neutrinos with a mass of 27.7 ± 0.5 electronvolts (about 0.005 per cent of the electron's mass). The particles are not however entirely dark: they decay occasionally (the lifetime being of the order of 10^{23} seconds) to produce ionizing photons with an energy of 13.8 ± 0.2 electronvolts sufficiently copiously to ionize gas in galaxies today and in the distant intergalactic medium. Until recently these hypothetical decays have eluded direct observational constraints. But the hypothesis has now been dealt a blow by two similar experiments[3,4], one reported on page 128 of this issue[3], which show that the mass of dark stuff in galaxy clusters does not have the ultraviolet glow which would have been expected if it included such decaying neutrinos.

Massive neutrinos have long been a favourite hypothetical candidate for the dark matter that pervades the Universe. The total number of neutrinos can be predicted from the way they would have interacted with the hot radiation early in the Universe. So we know that if the one dominant species had a mass of about $100h^2$ electronvolts, where h is the present rate of expansion of the Universe (Hubble's constant, in units of 100 km s^{-1} Mpc^{-1}), it would just suffice to give the Universe the magical critical density, long preferred on aesthetic grounds, which makes space 'flat' (devoid of gravitational curvature) and gives the Universe zero total energy.

A new twist was given to this idea by Sciama, who noticed that if such particles decayed slowly, it would help to solve several other cosmological puzzles by providing a diffuse source of ionizing photons to strip electrons off atoms in intergalactic and interstellar gas. In the interstellar medium, we have an accurate calibration of the electron density along several lines of sight to pulsars, and very simple models of ionization by stars fail to predict this sufficiently uniformly. The distant intergalactic medium is known to be highly ionized, from the absorption spectra of distant quasars, and the source of this ionization has not yet been identified. Sciama showed that both puzzles could be explained