can any mechanism determine the constant's value and adjust it to zero? The answer in Coleman's approach is that the Universe peeks through a wormhole into a large empty universe thus escaping the problem of the obscuring matter and radiation in our Universe (see figure).

On the negative side, the approach relies on a shaky formalism and on many untested assumptions. It nevertheless comes up with the desired result, a zero cosmological constant. Of course, much would be forgiven if the theory could provide a correct value for another fundamental parameter, especially one that is non-zero. In principle, because Coleman's scheme is a method for predicting the values of the α_is and as all the parameters of nature are functions of these, it is a theory of parameters. Unfortunately, early results have been disappointing so it remains to be seen whether the Coleman–Hawking approach, if it is indeed correct, will prove revolutionary or merely comforting. □

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Sex determination

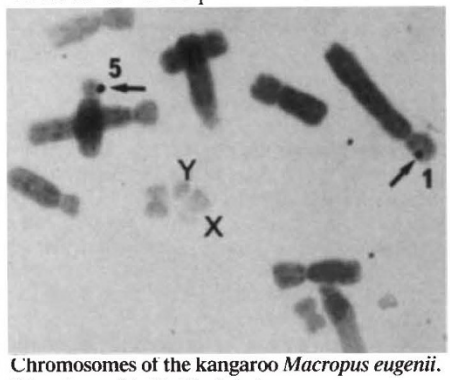
Right gene, wrong chromosome

Jonathan Hodgkin

In December last year, David Page and colleagues reported[1] on the human Y chromosome a 'zinc-finger' gene which is likely to be identical with TDF, the Y-linked testis-determining factor responsible for initiating male development. The identification of this gene, now called *ZFY*, touched off a predictable hunt for corresponding genes in other animals. In their original paper, Page *et al.* showed that *ZFY* is strongly conserved on the Y chromosome of various different placental mammals (eutherians), and also found that there is a closely related gene, *ZFX*, on the X chromosome of all these species. Now the hunt for *ZFY* cognates has extended to other vertebrate groups, with disquieting results. Exactly a year after identifying the zinc-finger gene, Sinclair, Page *et al.* report on page 780 of this issue[2] that the marsupial sequences most closely related to *ZFY* are on autosomes, not on the Y chromosome. This observation is based only on hybridization data, but it is unlikely to be wholly artefactual.

The result is disquieting because in marsupials, much as in eutherians, the Y chromosome is male-determining, and it is therefore expected to carry the equivalent of TDF. So if *ZFY* is autosomal in marsupials, it cannot be the primary Y-linked male determinant as it appears to be in other mammals. There are two possible conclusions: either *ZFY* is not TDF after all; or *ZFY* is testis-determining in eutherians, but something else plays the primary role in marsupials.

Several pieces of evidence favour the second possibility. The circumstantial evidence identifying *ZFY* as the human TDF is strong: for this not to be the case, it would be necessary to assume that the real TDF is an elusive, poorly conserved gene in the same small genetic interval (less than 300 kilobases) as *ZFY*. On the other hand, *ZFY* itself is strongly conserved (at least as measured by DNA hybridization) and it also has a primary structure consistent with a regulatory role. Second, it is misleading to regard the marsupial gene or genes as corresponding to *ZFY per se*; instead they could equally or better correspond to *ZFX*. The marsupial X chromosome (see figure) is smaller than the eutherian X, and does not carry an obvious *ZFX* sequence. Several of the genes conserved on the X chromosome in all eutherians are located on autosomes in marsupials, suggesting that a translocation has taken place. Consistent with this, Sinclair *et al.*[2] find that a probe for the Duchenne muscular dystrophy gene, which is near *ZFX* in humans, hybridizes to chromosome 5 in wallabies, in the same interval as the apparent *ZFY* cognate.



Chromosomes of the kangaroo *Macropus eugenii*. (Courtesy of A.H. Sinclair.)

In humans, both *ZFX* and *ZFY* could be required for testis formation. Some human XY female embryos have chromosomal defects in the Xp21 region where *ZFX* is located[3], and might have a non-functional *ZFX*. Therefore, one possible explanation of the results would be that in eutherians *ZFY* potentiates the expression or action of *ZFX*, which by itself (in XX or X0 individuals) cannot trigger testis formation; whereas in marsupials some other Y-linked gene would potentiate the autosomal gene, which can be called '*ZFA*'.

Genes hybridizing to a *ZFY* probe have also been detected in other vertebrate groups, but in these as well the most conserved sequences seem to be autosomal[4]. This is true of reptiles with a chromosomal sex-determination mechanism; reptiles with environmental (temperature-controlled) sex determination, such as turtles; and finally of birds, which have ZW female/ZZ male sex determination. So again, it could be that *ZFA* is consistently testis-determining, but under different primary regulation in each of these groups. Bull and co-workers have found that the turtle *ZFA* is transcribed during the critical temperature-dependent period for this species, which is consistent (but no more than that) with a role in sex determination.

Evolutionary differences in the primary sex determining signal should come as no surprise[5]. Even within a single taxonomic group such as Diptera there can be a bewildering variety of different sex-determination mechanisms, which may nevertheless turn out to have common underlying elements. Radical changes in mechanism can also be made artificially. For example, primary sex determination in the nematode *Caenorhabditis elegans* is normally achieved by the X chromosome-to-autosome ratio, as in the fruitfly *Drosophila*, yet it is possible to alter the system in various ways by mutating major autosomal sex-determining genes[6,7], so that the primary role is transferred to either autosome III (carrying the switch gene *tra-1*) or autosome II (carrying the switch gene *tra-2*). Many of the different vertebrate and dipteran schemes can be imitated by appropriate manipulation of nematode genes, although there seems to be little in common at the molecular level in the sex-determining genes of these three groups.

Seen from this perspective, the results obtained with *ZFY* probes are not discouraging, but they tend to focus more attention on *ZFX* as a possible major player in the process of sex determination. It remains essential to discover more about the functions of *ZFY* and *ZFX*, and what is involved in testis determination in biochemical terms: what do these zinc fingers regulate? □

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