of chaos into a system that should ideally perform in exactly the same way over many writing cycles.

The origin of the non-uniform initial state is still a mystery, although the authors might be on the right track when they suggest that the very strong magnetic fields generated by the electron pulse excite non-uniform precessional modes. Because such dangerous 'deformations' of the spin distribution must be avoided to achieve reliable recording, there is an intrinsic limit on the minimum switching time between magnetization states. No matter how short and strong the magnetic-field pulse, magnetic recording cannot be made ever faster. Tudosa and colleagues' finding and their interpretation of it are bound to trigger numerous follow-up experiments, such as measuring the switching trajectory on a microscopic scale. ■

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Genomic imprinting

Mice without a father

David A. F. Loebel and Patrick P. L. Tam

In mammals, genomes from both parents are generally needed to make viable offspring. But changing the expression of 'imprinted' genes can render the father's contribution dispensable.

Sexual reproduction in animals ensures that each individual normally inherits one set of genes from each parent. But viable offspring that have only maternal genes — none from the father — can be produced through parthenogenetic reproduction in plants and most groups of animals. A notable exception is mammals, in which fathers remain a necessity. But why is this so? On page 860 of this issue, Kono and colleagues[1] provide the most compelling evidence so far that a phenomenon called genomic imprinting is the stumbling block.

The importance to mammals of a proper combination of parental genes is highlighted by studies of mouse embryos that contain only maternally or paternally derived chromosomes. In embryos containing only female-derived chromosomes, the 'extra-embryonic' tissues that are required to support embryonic growth develop poorly, and the embryo dies soon after it has implanted into the womb[2,3]. By contrast, the development of embryos that contain only paternal chromosomes is retarded, but the extra-embryonic tissues develop comparatively well[2,3]. This seems to indicate that the paternal copies of some genes are more important for development of the extraembryonic tissues, and that maternal copies of the others are more essential for fetal development.

The most likely explanation for this is that the maternal and paternal genomes are not exactly equivalent, but are endowed with different 'imprints', which lead to differential gene expression in the embryo. Imprints, or 'epigenetic modifications', mark the two copies of each gene as being inherited either from the mother or from the father. They are chemical changes to DNA or to chromosomal proteins that are heritable through cell divisions, but do not involve changes to the DNA sequence.

Imprinted regions of the genome typically cover large chromosomal domains of 1 million base pairs or more, and may involve the coordinated regulation of several genes. *Igf2* and *H19*, for instance, are imprinted genes that are located on mouse chromosome 7,100 kilobases apart. These two genes are oppositely imprinted — expression is from the maternal copy of *H19* and the paternal copy of *Igf2* (Fig. 1, overleaf). The regulation of expression involves several nearby stretches of DNA, which act as enhancers, promoters and an insulator of gene expression.

The insulator (or boundary element) is upstream of *H19*, between this gene and *Igf2*, and is identified as a differentially methylated domain (DMD). According to a current model, this region cooperates with enhancer elements that are downstream of *H19*. On the maternal chromosome, an enhancer-blocking protein (CTCF, which recognizes the DNA sequence CCCTC) binds to the DMD, preventing the enhancers from interacting with the promoter of *Igf2*, and instead favouring *H19* expression[4,5]. But on the paternal chromosome, the DNA of the boundary element is methylated; the blocking protein cannot bind, and *Igf2* can be expressed while *H19* is not.

Epigenetic modifications of the maternal genome occur during oocyte (egg) maturation. In earlier work, Kono and colleagues[6]

100 YEARS AGO

A Study of British Genius. **Mr. Havelock Ellis recognises three great foci of intellectual ability in England:— (1) the East Anglian focus; (2) the south-western focus; and (3) the focus of the Welsh Border. The first of these is the most recent and the most mixed ethnologically, as East Anglia is very open to invasion, and all kinds of foreigners have settled there. The second is the largest and oldest, and the population has much darker hair; it may be called the Goidelic-Iberian district. The district is defended by Wansdyke and Bokerley Dyke. The third is termed the Anglo-Brythonic district. The Anglo-Danish part of England — Lincolnshire, Nottinghamshire, Derbyshire, Yorkshire, and thence into Scotland — has its own peculiar anthropological characters. Its children have usually been more remarkable for force of character than for force of intellect. East Anglia is productive of great statesmen, ecclesiastics and scholars, and of musical composers and painters. It has no aptitude for abstract thinking; its special characters seem to be humanity, patience, grasp of detail, and love of liberty. The people of the south-western focus are sailors rather than scholars, and courtiers rather than statesmen; they are innovators and pioneers in the physical and intellectual worlds, and, above all, are impressive, accomplished, and irresistible personalities. The genius of the Welsh Border is artistic in the widest sense, and notably poetic; there is a tendency to literary and oratorical eloquence, frequently tinged with religious or moral emotion, and there are no scientific men of the first order.**
From *Nature* 21 April 1904.

50 YEARS AGO

The announcement in *The Times* of April 12 of the production of element number 100 by Prof. G. T. Seaborg and his collaborators at the University of California follows closely on their discovery of element 99… Identification of the new isotope was presumably based on the α-decay systematics, built up by Prof. Seaborg and others, which have proved extremely reliable in this field. Element 100 is stated to behave chemically like erbium, its analogue in the rare-earth group. There is no reason for believing that this will be the last new element to be prepared, although the increasing probability of spontaneous fission as the atomic number advances would appear to limit the total number of elements to about 110.
From *Nature* 24 April 1954.

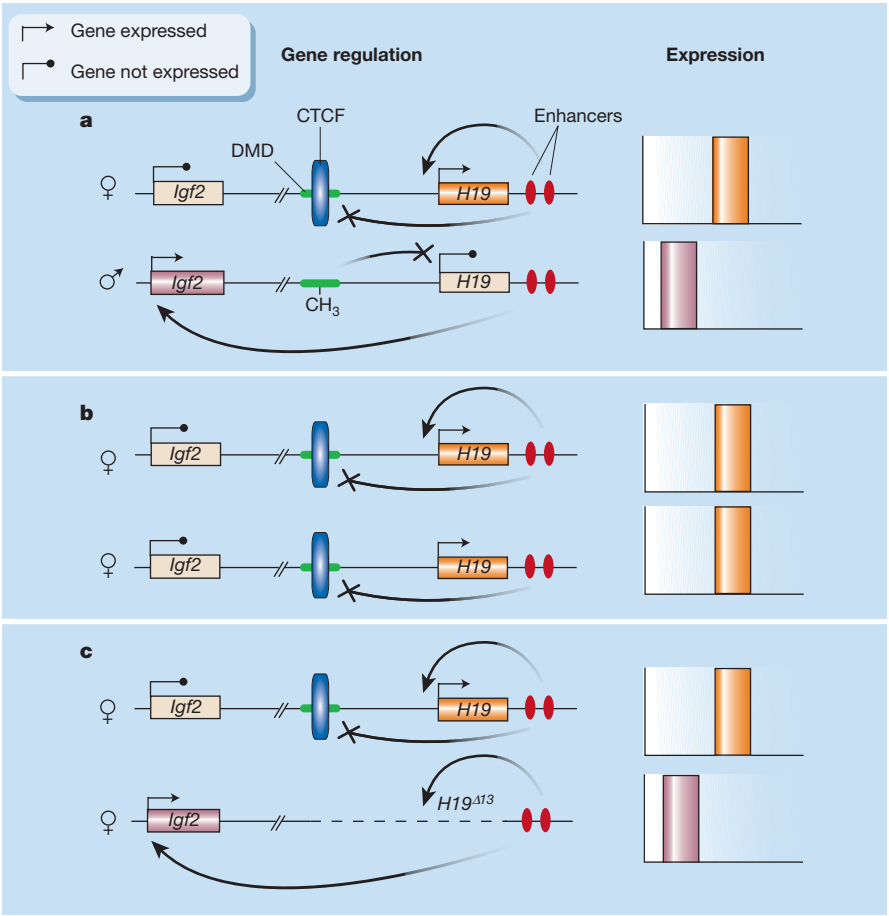

Figure 1 **No need for males?** a, **The *H19* and *Igf2* genes are found on the same mouse chromosome and are oppositely 'imprinted': in normal embryos, *H19* is expressed only from the maternal chromosome and *Igf2* only from the paternal chromosome. On the maternal chromosome, the protein CTCF binds to the differentially methylated domain (DMD), blocking the access of enhancers to *Igf2*. Thus, *H19* is expressed instead. On the paternal chromosome, the DMD is methylated (represented by CH_3), and so CTCF cannot bind; the enhancers therefore have access to *Igf2*, which is expressed, whereas *H19* is silenced. Modified from ref. 5.** b, **In conventional parthenotes, which have two maternal genomes, no *Igf2* is expressed and the embryos die.** c, **Kono *et al.*[1] combined the chromosomes from a fully grown egg (which has all maternal imprints) with the chromosomes from a non-growing egg from which the DMD and *H19* were deleted ($H19^{\Delta 13}$). These deletions mimicked the absence of paternal *H19* activity and enabled *Igf2* expression, leading to viable adults.**

found that by combining the chromosomal complements of a non-growing egg from a newborn mouse and a mature, fully grown egg, parthenogenetic embryos could survive for longer than normal. Because one set of chromosomes came from an earlier stage of egg development, it had not acquired the maternal imprints and so might have been able to express some genes that normally would be expressed only from the paternal chromosome.

To see whether further altering genomic imprinting might influence the developmental potential of parthenogenetic embryos, Kono and colleagues[7] used the same techniques to test whether the 'unimprinted' genome of a non-growing egg that lacked the *H19* gene region[8] had any impact on embryonic viability. Indeed, parthenogenetic embryos that lacked one copy of *H19* survived nearly to term, but died with a poorly formed placenta. These embryos evidently lacked *H19* expression from one set of chromosomes — as do normal embryos. But because the DMD remained present and unmethylated on the chromosome from the non-growing egg, it presumably prevented *Igf2* expression.

Kono and colleagues[1] have now carried out similar experiments with mice in which both *H19* and the DMD are deleted[9]; they refer to the animals as $H19^{\Delta 13}$ mice (Fig. 1). The authors combined chromosomes from non-growing oocytes from these mutants with chromosomes from mature oocytes of normal mice. In theory the deletion of *H19* from the non-growing oocyte's genome should mimic the lack of paternal *H19* activity, and, because the DMD is missing too, the blocking protein cannot bind to it; the upshot should be that *Igf2* can be expressed, as would be paternally derived *Igf2*. Even if we assume all this, however, the result is surprising: two apparently normal, live female pups were born. One of them reached adulthood, and even produced offspring.

A further surprise came from microarray analysis of the expression of over 11,000 genes. The expression levels of more than 1,000 genes in the surviving $H19^{\Delta 13}$-carrying parthenotes were more similar to those of normally fertilized embryos than to those of parthenotes with two intact copies of *H19*. This widespread effect on gene expression cannot be put down to a direct effect of the lack of one copy of *H19*. One possibility is that the changes in gene expression are indirect effects of the improved growth of the $H19^{\Delta 13}$ parthenotes. But it's amazing that altering the expression of just two imprinted genes can have a ripple effect on the rest of the genome.

Of particular interest is the effect on the expression of other imprinted genes. The expression of *H19* and *Igf2*, as well as of *Dlk1* and *Gtl2* — another pair of oppositely imprinted genes, which are located on a different chromosome to *H19* and *Igf2* — in normally developing $H19^{\Delta 13}$ parthenotes was comparable to that of normal mice. But in growth-retarded $H19^{\Delta 13}$ parthenotes, *Dlk1* and *Gtl2* were not expressed at normal levels. Taken as a whole, the work of Kono *et al.*[1,6,7] provides good evidence that incorrect expression of imprinted genes is one of the major reasons why natural parthenogenesis in mammals has not been possible. What is still not understood is why such a barrier to single-parent reproduction has evolved.

This work[1] also raises the question of why only a small proportion of the embryos survived, and why the effects on gene expression are so variable. Perhaps some of this can be explained by the outbred nature of the mouse strains used. It will be particularly pertinent to determine how altering the activity of the *H19* gene can change the expression of so many others, especially that of apparently unconnected imprinted genes. Until we fully understand the role and regulation of imprinted genes in development, it seems that the participation of the father in reproduction will remain necessary. ■

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