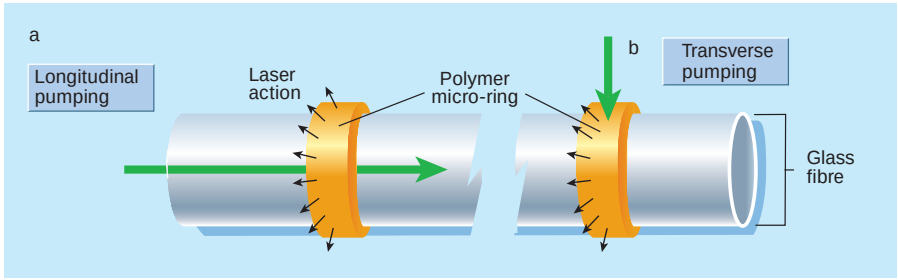

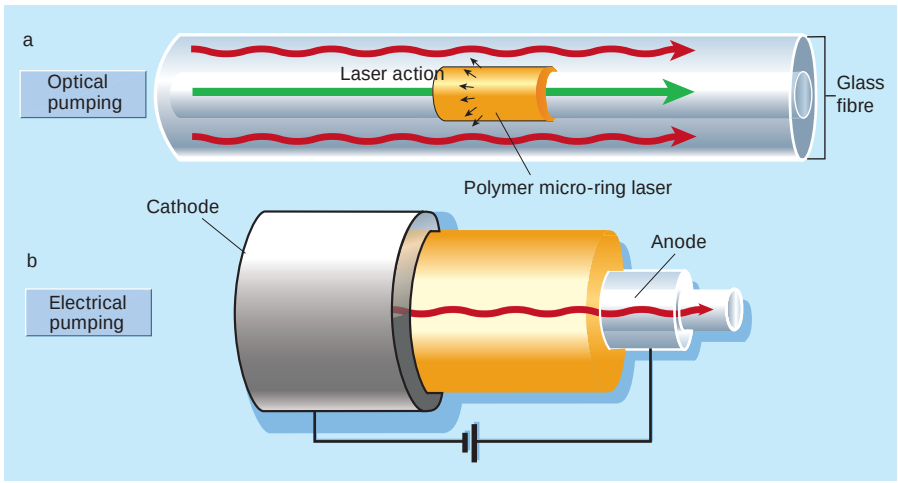

Figure 1 (top) **Pumping polymer micro-ring lasers. Pumping is necessary for laser action and ensuing amplification of the modulated (information-carrying) light beam in fibre-optic communications using light at visible wavelengths between 0.4 and 0.7 μm. The modulated beam is not shown here.** a, **Longitudinal pumping, which is generated by a beam (green) travelling along the optical fibre.** b, **Transverse pumping, which is produced with an external light source. Dou *et al.*[5] show that longitudinal pumping has considerable advantages.**

Figure 2 (bottom) **Speculative schemes for longitudinal pumping of polymer micro-ring lasers.** a, **Optical pumping. Here the excitation beam (green) is confined in an inner, single-mode fibre that is surrounded by the polymer micro-ring amplifier. The information-carrying beam requiring amplification (red) travels along the multimode cladding layer.** b, **Electrical pumping. The information-carrying beam (red) is amplified by a surrounding polymer medium, which is pumped by electrical flow between two electrodes: a semi-transparent anode (made of 'ITO') and an aluminium cathode.**

optical and electrical pumping. In Fig. 2a (optical pumping), two light beams are transmitted. The inner, excitation beam optically stimulates a surrounding polymer micro-ring laser, which then amplifies the modulated information-bearing beam. As depicted here, the optical-fibre system might consist of a single-mode fibre for the excitation beam, surrounded by a multimode cladding layer for the modulated beam. Or the system could instead use the central hole in a newly invented type of photonic crystal fibre[3,4], in which the polymer layer would be deposited on the inside surface of the hole.

The alternative — electrical stimulation of the optical-gain medium — is depicted in Fig. 2b. In this pumping scheme, the polymer is sandwiched between two cylindrical electrodes, and positive and negative charges are injected into the polymer active layer. In practice, electrically stimulated amplification rings would have to be stationed at intervals along the fibre. Other studies[9] with an organic diode, using PPV as the active layer, have already shown that light emission with cylindrical geometry is possible, and laser action in the form of stimulated emission should also be feasible. Alternatively, other organic compounds with emission in the infrared could be used in cylindrical configurations to boost light at 1.3–1.5-μm wavelengths, both optically[10] and electrically[11], in present fibre-optic systems.

For the moment, these amplification schemes remain pie in the sky. Nonetheless, the principles explored by Dou *et al.*[5] are promising — and one way or the other we will have to find ways to expand the capacities of fibre-optic systems. ■

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Genetics

Immaculate misconception

M. A. Surani

In mammals, mother and father make an equal genetic, but an unequal 'epigenetic', contribution to offspring. Studies of humans and mice with no maternal epigenetic contribution reveal more about this asymmetry.

William Harvey, an anatomist and personal physician to two kings of England, was taking a gamble when he proposed in 1651 that '*Ex ovo omnia*' — 'everything comes from an egg'. It wasn't until much later that the mammalian egg, or oocyte, was first detected and Harvey was proved right: a whole organism can develop from this remarkable cell. But what he did not know is that an input from sperm is also essential for mammalian oocytes to fulfil this potential. This is, of course, why sex is necessary and 'virgin' births are impossible in humans. The need for sperm lies in the fact that all genes are not equal. A fertilized egg contains two copies of every gene, one from sperm and one from oocyte. Usually, both copies are expressed in relevant cells in the embryo. But some genes are specifically labelled ('imprinted') so that only the maternal or paternal copy is active. So an embryo receives an equal genetic contribution from its parents, but the parental genomes are not functionally equivalent, explaining why both are needed. Indeed, embryos with two male or two female genomes cannot develop normally.

Three new papers[1–3] provide another graphic demonstration of the importance of these unequal 'epigenetic' contributions from sperm and oocyte. On page 539 of this issue[1], Judson and colleagues describe a unique case in which a mutation seems to prevent human oocytes from acquiring any

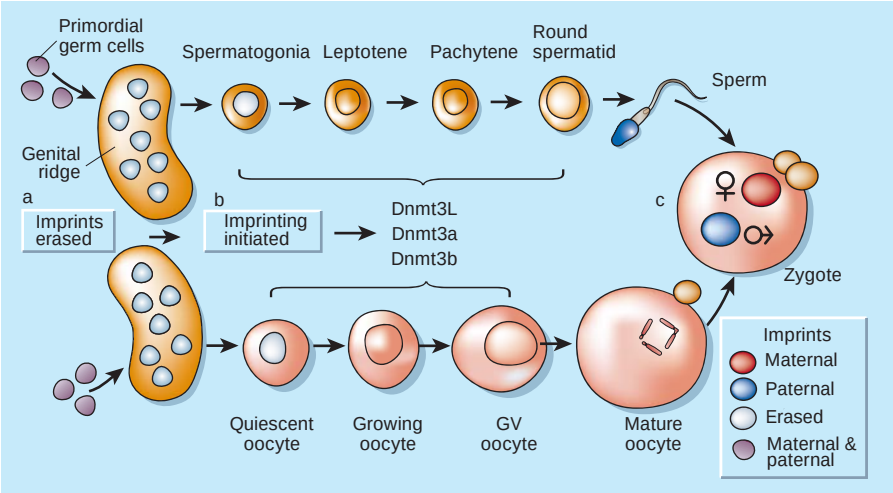

Figure 1 **Developing imprinting. Imprinted genes are those that are 'marked' in a parental-specific way.** a, **As primordial germ cells enter the genital ridge of developing female and male embryos, all imprinting marks are erased[10].** b, **Bottom, as female germ cells grow and develop into oocytes, the *Dnmt3L* gene, possibly with *Dnmt3a* and/or *Dnmt3b*, is involved in reintroducing maternal-specific imprints[2,3]. Top, these genes are also expressed during sperm development but how they function in paternal imprinting is unknown.** c, **After fertilization, a zygote is formed with both genetic and epigenetic (imprinting) contributions from the parental genomes. GV oocyte, germinal-vesicle oocyte.**

maternal-specific imprints at all. The mutant eggs fail to develop even after fertilization. Meanwhile, Bourc'his *et al.*[2] (writing late last year in *Science*) and Hata *et al.*[3] (in a report in *Development*) have described a remarkably similar outcome in mice with a mutation in the *Dnmt3L* gene, which is required for imprinting in mouse oocytes.

Nearly 50 mammalian imprinted genes have been identified so far, and their significance for human development is clear from Judson *et al.*'s study[1] of a woman in whom conceptuses (very early embryos) developing from normally fertilized eggs invariably died soon after they implanted into the wall of the uterus. Judson *et al.* analysed one such conceptus, and found that it had a normal genetic contribution from sperm and oocyte. The problem, it turns out, was with the epigenetic status of the oocyte: all the maternally inherited epigenetic marks (recognized as methyl groups on cytosine–guanine base pairs in particular DNA sequences associated with imprinted genes) were missing from the conceptus. Paternally inherited epigenetic marks were normal.

The physical characteristics of the conceptus were also revealing — they were similar to those that occasionally arise spontaneously after the embryonic loss of the maternal genome, leaving only the paternal genome. Why should a conceptus that lacks maternal imprints develop as if it lacks a maternal genome entirely? The reason is that, during the development of primordial germ cells, from which oocytes and sperm will form, all imprints are first erased (Fig. 1). New parental-specific imprints are introduced subsequently when sperm and oocytes begin to mature[4], with oocytes receiving most known imprints[5]. So a maternal genome that lacks maternal imprints functions more like a paternal genome in the fertilized egg — although not entirely[4,6]. Although relatively sparse, the epigenetic marks in sperm are essential, as a conceptus with two maternal genomes also fails to develop.

How, then, are imprints laid down in developing oocytes? Here the studies by Bourc'his *et al.*[2] and Hata *et al.*[3] are important, as they show that the *Dnmt3L* gene is crucial to this process in mice. Bourc'his *et al.*[2] engineered animals with a targeted mutation in both copies of *Dnmt3L*. The mutation had no immediate effect on development: the original, 'founder' males and females matured to adulthood, although the males did not produce sperm and were sterile.

The females lacking functional Dnmt3L protein did produce oocytes. But, after fertilization of these oocytes by normal sperm, conceptuses failed to develop after implantation, and showed several embryonic and placental abnormalities. These defects were clearly of maternal origin, as the embryos lacked all maternally inherited epigenetic modifications but, of course, not those from sperm[2]. Some of the abnormalities, for example in the placenta, were similar to those seen in conceptuses with paternal genomes only, or with genomes that lack all parental imprints[4,6]. Furthermore, because of the lack of maternal imprints, several imprinted genes were regulated abnormally, with some being repressed; this probably contributed to the observed abnormalities[2].

So it seems that *Dnmt3L* is crucial in laying down imprints in the female germ line, at least in mice. But in the human conceptus studied by Judson *et al.*[1], there was no identifiable mutation in the human *DNMT3L* gene (D. Bonthron, personal communication). Mutations in another gene must account for their observations.

Two possibilities are the *DNMT3A* and *DNMT3B* genes, which share similarities with *DNMT3L*. The encoded proteins are two DNA methyltransferase enzymes, which can initiate *de novo* DNA methylation[2,7,8]. Indeed, they might be required for *DNMT3L* to work, as *DNMT3L* does not encode the catalytic domain required for DNA methylation. Consistent with this idea, Hata *et al.*[3] show that the mouse Dnmt3L protein can interact with these enzymes, and that the absence of Dnmt3a, like the lack of Dnmt3L, results in the loss of maternal imprints in mice. But the methyltransferases cannot themselves detect specific DNA sequences that require *de novo* methylation, so some other modification might be needed first. This might involve the methylation of histone proteins — part of the packaging that enables DNA to be squeezed into the nucleus. For example, an interaction between methylated histone H3 protein and another packaging protein, HP1β, can lead to *de novo* DNA methylation[9].

Whatever the answers, the new papers[1–3] stress the importance of the epigenetic asymmetry between parental genomes for normal mammalian development[10] (Fig. 2). Even a slight deviation in the epigenetic marks on some chromosomal regions, such as on chromosomes 11 or 15, can result in devastating human diseases such as Beckwith–Wiedemann and Prader–Willi/Angelman syndromes[11]. Moreover, the cloning of mice and other mammals is possible because the donor nuclei, derived from adult tissues, possess the appropriate parental imprints[10].

Why imprinting exists at all remains

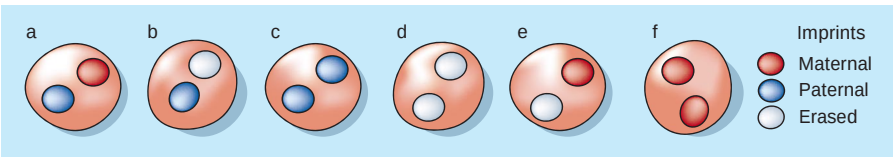

Figure 2 **The importance of imprinting.** a, **Epigenetic asymmetry between paternally and maternally derived genomes, as shown here, is essential for normal development.** b, **The absence of the *Dnmt3L* and probably *Dnmt3a* genes in developing mouse oocytes prevents maternal-specific imprinting[2,3]. After fertilization, the zygote contains a maternal genome with no imprints and a normal paternal genome; it cannot develop normally. Judson *et al.*[1] have described a similar outcome in a human patient, although the genetic basis is unclear.** c–f, **These combinations of genomes in different epigenetic states are also incompatible with full development[4].**

enigmatic. There are signs that, during evolution, a war broke out between the sexes that left the maternal genome with most of the DNA-methylation marks associated with imprinted genes[5]. Even now we observe the preferential demethylation of the paternal genome after fertilization; the maternal genome remains largely unaffected[12]. This suggests that maternally inherited proteins in the oocyte are used to demethylate, and so regulate the function of, the paternal genome after fertilization. Nevertheless, even the relatively few epigenetic marks that have survived in the paternal genome are crucial for development and hence a significant barrier to virgin birth. So for the time being men are indispensable. But with the increasing pace of research, even this barrier might be breached in the future. I for one will be following the unfolding story with fascination — and apprehension. ■

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Developmental biology

The plastic face

Massimo Pasqualetti and Filippo M. Rijli

In vertebrates, the face is formed in part by neural crest cells. It has been assumed that the developmental fate of these cells is inbuilt. New work, however, reveals a role for instructive signals from nearby cells.

Like many developmental processes, the formation of the face in vertebrates depends on the migration of cells from one part of the embryo to another. The main source of cells that contribute to the facial structures is the neural crest[1] — a ridge of embryonic tissue generated by the developing brain. Different bones in the head are formed from different populations of neural crest cells, according to the cells' position along the head-to-tail (anterior–posterior) axis of the embryo. So, for example, anterior neural crest cells migrate to form the brain-case and the nose and jaw bones. Neural crest cells from the posterior part of the brain help to make the neck bones. But beyond these general details, little is known about how facial structures are induced to develop at the right place and in the appropriate, species-specific, shape. Such developmental instructions might be intrinsic to the neural crest and fixed before migration. Alternatively, neural crest cells might be instructed by surrounding tissues during or after migration.

An early, landmark study of chick embryos[2] favoured the first of these models. But two new papers, published by Trainor *et al.*[3] and Couly *et al.*[4] in *Science* and *Development*, respectively, come down firmly in favour of the second. The two groups find that the neural crest cells that contribute to the face are developmentally 'plastic' — they do not themselves carry any information about their fate, but must be instructed by signals from other tissues to generate skeletal elements of appropriate shape and polarity. The authors also identify two sources of these signals.

During early vertebrate development, the neural crest forms from the neural tube — a long structure that will generate the brain and spinal cord, and which runs along the back of the embryo (Fig. 1a, overleaf). The part of the neural tube that gives rise to the brain is divided into segments — the forebrain, midbrain and hindbrain; the hindbrain is in turn subdivided into smaller segments called rhombomeres. Neural crest cells generated from the forebrain, midbrain and the first two rhombomeres migrate to cover the brain, as well as into the forehead region and first pharyngeal arch, and contribute to the brain-case, nose and jaws. By contrast, cells from the remaining rhombomeres fill the second, third and fourth arches, which form the neck. (Pharyngeal arches are the embryonic structures from which most cranial features develop.)

Nearly two decades ago, Noden[2] made a seminal discovery while investigating facial development. Using chick embryos, he replaced neural crest cells that were destined for the second pharyngeal arch with quail cells destined for the first arch. This resulted in the formation of extraneous jaw- and beak-like structures in the neck region — in other words, the grafted cells migrated to the nearest (second) arch, from which the neck forms, but gave rise to the morphology characteristic of the first arch. At face value, this implies that the fate of neural crest cells is set while they are still in the neural tube, determining which structures they help to form. But Noden pinpointed two potential contradictions. First, the grafted neural crest cells also contributed to normal second-arch-derived structures; and second, the extra skeletal elements invariably included jaw features but never forehead bones.

How can these results be reconciled? Trainor *et al.*[3] provide a solution. These authors carried out similar grafting experiments, and found that extraneous jaw structures were produced only when the isthmus (the boundary between the midbrain and hindbrain) was included with the grafted cells. The isthmus is a source of signalling molecules, particularly fibroblast growth factor-8 (FGF8), and normally represses the *Hoxa2* gene — the main determinant of the fate of second-arch cells[5–8] — in the first rhombomere[9]. Trainor *et al.* found that when the isthmus was transplanted posteriorly into subsequent rhombomeres, it inhibited *Hoxa2* in adjacent second-arch cells, which normally contribute to the neck but now develop as extra jaw bones. Adding FGF8 alone also inhibited *Hoxa2* in neural crest cells. But when Trainor *et al.* moved just the neural crest cells that were destined for the first arch, without the FGF8-secreting isthmus, the cells took on a second-arch fate. In other words, they were not irreversibly committed to their fate before migrating to the arches.

So it seems that signals from the neural tube inform neural crest cells about their original position. But where does information about the shape and polarity of facial bones come from? Couly *et al.*[4] provide evidence in favour of a tissue — the endoderm — that lies beneath the neural crest and lines the pharyngeal arches.

Using chick embryos again, these authors first excised all the neural crest cells that contribute to the face. They then showed that any short fragment of the region of the neural crest that does not express *Hox* genes can generate the entire facial skeleton. The findings again show that these cells are not endowed with intrinsic developmental information before migration. Couly *et al.* further discovered that distinct regions of the endoderm (regions I–IV; Fig. 1a) instruct *Hox*-negative neural crest cells to produce specific face and jaw bones. The removal of single regions of the endoderm prevented the formation of distinct subsets of facial neural-crest-derived elements. However, this might simply reflect the removal of a general signal needed for skeleton formation. More compellingly, individual stripes of endoderm grafted near their normal counterparts led to spectacular duplications of facial cartilage and adjacent bones (Fig. 1b), with orientations that depended on the orientation of the graft.

These results[3,4] suggest that distinct populations of neural crest cells respond to