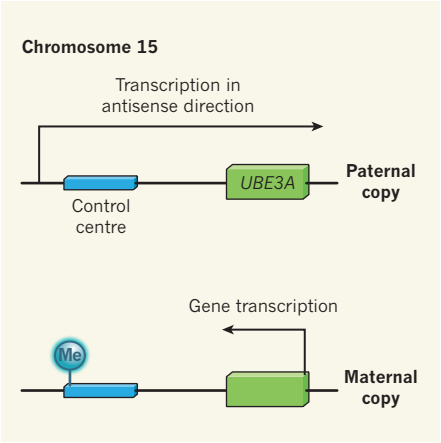

Figure 1 | Differential regulation of maternal and paternal *UBE3A*. Of the two copies of the *UBE3A* gene, only the maternal copy is expressed in neurons, with the paternal copy being silenced by genomic imprinting. Specifically, expression of paternal *UBE3A* is inhibited by transcription in the antisense direction of a long sequence that includes not only this gene but also the control centre that regulates its expression. In the equivalent maternal chromosome, the sequence encoding the control centre is methylated (Me) and so is not expressed. This inhibits transcription in the antisense direction and allows expression of *UBE3A*. Huang *et al.*[1] identify drugs that can activate expression of paternal *UBE3A*. Such drugs could be useful for treating Angelman syndrome, a disorder in which maternal *UBE3A* expression is absent or very low.

To search for compounds that could activate the silent paternal copy of *UBE3A*, Huang *et al.*[1] used a mouse model that had an altered copy of *UBE3A*, isolating cortical neurons from the brains of the animals shortly before birth. The mice were engineered so that their neurons expressed a fluorescently tagged version of UBE3A in response to drugs that activated the paternal copy of its gene. The screen focused on drugs already approved for human use — so that a future clinical trial might be undertaken more readily — and it identified 16 inhibitors of topoisomerase enzymes that were positive in the assay.

The authors focused on topotecan, the most active of the compounds. When they infused the drug into the lateral-ventricle region of the brains of living mice for two weeks, they found that the paternal copy of *UBE3A* was activated throughout the brain. Remarkably, a brief exposure to the drug also gave persistent *UBE3A* activation in spinal-cord neurons for at least 12 weeks after the termination of treatment.

Silencing of the paternal copy of *UBE3A* is probably mediated by an 'antisense' RNA transcript encompassing *UBE3A* on the paternal chromosome (but transcribed in the opposite direction to the gene sequence). Expression of this transcript is regulated by an imprinting control centre on the maternal chromosome (Fig. 1). The sequence functioning as the control centre, together with its promoter region, is methylated on the maternal chromosome, suppressing transcription in the antisense direction, which would silence the maternal *UBE3A*. The equivalent control centre on the paternal chromosome is unmethylated, allowing transcription of the antisense sequence and so silencing the paternal *UBE3A*. Huang *et al.* demonstrate that topotecan causes minimal change in methylation of the imprinting control centre on the paternal chromosome, but somehow still reduces expression of the antisense transcript for *UBE3A*, as well as for other paternally expressed genes that are part of the same transcript.

Reduced expression of paternally expressed genes is a potential drawback. If the 5–6-megabase deletion of chromosome 15 is inherited from the father, the child will develop Prader–Willi syndrome, because the deletion includes the genes involved in this disorder. Therefore, treatment with drugs such as topotecan could convert cells that have a molecular status characteristic of Angelman syndrome into cells with a Prader–Willi molecular status. Clearly, it would be preferable to reduce expression of the *UBE3A* antisense transcript while leaving expression of the other paternally expressed genes intact. But it is reasonable to hope that, after treatment with a topoisomerase inhibitor, cells would express a mixture of maternal and paternal transcripts — a situation that might greatly improve the symptoms of Angelman syndrome without causing notable symptoms of Prader–Willi syndrome. Of course, such treatment could also alter the expression of other genes across the genome, with unknown consequences. On all counts, a sequence-specific knock-down of the antisense transcript seems preferable.

An obvious question is how quickly a topoisomerase inhibitor could be prescribed for patients with Angelman syndrome. It is noteworthy that Huang and colleagues did not demonstrate any reversal of the symptoms in their mouse model, and so this is the next step before proceeding further in this direction.

Other issues concern risk–benefit assessments and regulatory processes. In the United States, topotecan has been injected into the cerebrospinal fluid of adults with neoplastic meningitis[4]. So at least in that country, a physician could theoretically inject topotecan into the cerebrospinal fluid of a patient with Angelman syndrome as a compassionate, off-label use of the drug. However, this seems quite risky in the absence of additional safety and dosage information in children. Presumably, the youngest infants would benefit most from the treatment, because normal brain development could then start as early as possible rather than being delayed by some years.

Systematic trials would require a regulatory process for investigating new drugs, and that would take at least a few months. Because the symptoms of Angelman syndrome are quite severe, and as there are no effective treatments

50 Years Ago

On December 19 Lord Mills announced in the House of Lords that the Government, after considering the question of decimal coinage … thought real advantage would follow from adopting a decimal currency. In view of the widespread use of accounting and other monetary machinery, the transitional cost would be substantial, but could be limited by choice of the size of the new units and careful timing of the change-over.
From *Nature* 13 January 1962

100 Years Ago

Mr. E. C. Snow, in his paper entitled "The Intensity of Natural Selection in Man" … has set himself to answer the following question: Has heavy infantile mortality any selective value or tendency to eliminate the more sickly and to spare the hardier children? Of the data available for the investigation of this problem, the most satisfactory are derived from the annual volumes of Prussian statistics … Thirty rural districts in Prussia were taken, and all the children in them born in the year 1881 were considered. It was ascertained for each district how many of these children died in the first two years of life and how many in the next eight … If the infantile mortality tends to weed out the weaker children, then in those districts in which the mortality among the children born in 1881 was highest in the years 1881 and 1882 it should tend to be lowest in the years 1883–90, since stronger children less likely to succumb to the ailments of childhood would have survived their first two years … We are of the opinion that, on the whole, the author is justified in saying: "Natural selection in the form of a selective death-rate is strongly operative in man in the earlier years of life."
From *Nature* 11 January 1912