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► COVER: 'Illumination' by Patrick Morgan

Things are rarely black or white in biology. Inborn errors of metabolism are a prime example — initially considered strictly as classical Mendelian traits caused by single-gene lesions, they are now thought of as some of the best examples of gene–environment interactions that can lead to complex diseases. In their Review on page 449, Brendan Lee and colleagues argue that many complex diseases can be likened to specialized cases of inborn errors of metabolism, in which several biochemical pathways have been impaired. Our view of inborn errors of metabolism has evolved as our understanding of them has increased. According to Lee and colleagues, the concept of metabolic flux is crucial in understanding how genotype and environment interact to give rise to a disease phenotype. Moving away from the notion of static genetic and biochemical defects, ultimately we will need to contend with the dynamic metabolome.

These conceptual advances have been accompanied by advances in technology, thanks to which state-run public health programmes of newborn screening for metabolic disorders have become routine in many countries, especially with the introduction of tandem mass spectrometry-based screens. In the United Kingdom all babies are screened for phenylketonuria (PKU) and congenital hypothyroidism (CHT), and in some areas also for cystic fibrosis, sickle-cell disorders and other conditions. The list of metabolic conditions for which newborns are screened in the United States is impressive, and an estimated 4.1 million infants are tested annually for genetic and metabolic disorders.

High on the agenda of paediatricians and medical geneticists is the issue of standardization of such screens, while laboratory-based scientists are focusing on how to understand the metabolome using genomics, proteomics and physiology.



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