30% of Down's syndrome births are in this category and the majority of Down's syndrome pregnancies remained undetected. The introduction in 1975 of screening maternal blood for analytes altered in Down's syndrome stems from an observation that levels of maternal serum alphafetoprotein (AFP) were significantly lower in affected pregnancies. Other biochemical analytes in maternal blood with much higher predictive values for Down's syndrome have since been found. Current screening protocols are now able to predict the syndrome in 90% of pregnancies, irrespective of maternal age, for a false positive rate of 2%. There is now no place for recommending amniocentesis in mothers over 35 years, as this leads to an unacceptable low detection rate and miscarriage in an estimated 1% of women tested.

One of the most promising protocols for Down's syndrome screening uses an ultrasound scan for nuchal translucency plus biochemical markers in the first trimester. Patients with a very low risk (75%) do not require further tests, while the remaining 25% undergo further biochemical screening at 16 weeks. Amniocentesis is required in only 2% of pregnancies, compared with the 30% where advanced maternal age alone is used as the indication. Thus screening leads to a welcome reduction in procedure-related miscarriage.

In a number of centres prenatal fetal chromosome analysis is being replaced by a molecular method (QF-PCR) that provides a diagnosis within 48 hours and is much less expensive. The disadvantage of QF-PCR is that while it can be used effectively for the autosomal trisomies and Turner syndrome, it is not designed to exclude the relatively small number of unbalanced structural chromosome abnormalities that can only be identified by fetal karyotype analysis. There is currently much controversy among health providers about whether the benefits of recognising all such chromosomal syndromes justify the substantial costs involved in karyotype analysis when the screening programme is specifically designed to detect Down's syndrome.

Knowledge that fetal cells are present in the mother's blood in very small numbers throughout pregnancy has prompted efforts over the past 20 years to exploit these cells for non-invasive prenatal diagnosis. Success has been achieved in only a few cases of Down's syndrome, as fetal cells have proved difficult to isolate. Hopes of achieving a practical method for fetal diagnosis using this strategy have largely been abandoned. Interest has turned instead to exploiting fetal DNA in the maternal plasma; this is derived from the breakdown of placental cells. Using molecular methods, DNA sequences from the Y chromosome can be recognised reliably in 100% of pregnancies from six-weeks gestation in women carrying a male fetus; the absence of Y DNA indicates a female fetus. Genes transmitted to the fetus from the father can also be identified, and this has practical use in the diagnosis of genetic diseases such as Huntington's disease. The most widely used indication, however, is the diagnosis of a Rhesus positive fetus in a Rhesus negative mother at risk for haemolytic disease of the newborn. The diagnosis of chromosome abnormalities from fetal DNA has recently been accomplished and should soon be available.

Advances in dysmorphology: from diagnosis to treatment

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As a trainee paediatrician in the late 1960s/early 1970s efforts to reduce neonatal mortality and morbidity were focused almost entirely on management of respiratory distress syndrome and other complications of prematurity. The contribution of birth defects to neonatal mortality was regarded as an insurmountable problem with no likely possibility of change. Maybe, perversely, this encouraged me to explore this area further via a roundabout career route. Genetic clinics had by then been set up in Great Ormond Street Hospital and Guy's Hospital in London, in Manchester and Edinburgh and in a number of other centres but clinical genetics was not recognised as a specialty and there were no formal training programmes. Post-MRCP and a registrar job in paediatrics, I entered the field as a clinical assistant and was lucky enough to be appointed in 1978 to one of the first three senior registrar posts in clinical genetics.

The main textbook for the branch of clinical genetics known as dysmorphology, *Recognisable patterns of human malformation* by David Smith,[1] contained details of around 150 syndromes. Smith had captured the term 'dysmorphology' to describe the study of abnormal development and birth defect syndromes. At that time we knew the underlying genetic causes of a number of syndromes, including Down's, Edwards and Patau syndrome, were due respectively to trisomy 21, 18 and 13 and a few of the more subtle chromosome deletions and duplications. A considerable number of malformation syndromes had also been described clinically, many published between 1965–80 in the Birth Defects Original Article series supported by the US March of Dimes Birth Defects Foundation; for some their inheritance pattern could be inferred from the family history but, of course, the underlying genes were not identifiable with techniques available at that time.

It was in the early 1980s that dysmorphology in the UK began to advance. Recognising that descriptions of syndromes were published in a large number of journals, many unavailable in university and hospital libraries, Robin Winter and Michael Baraitser decided to utilise the emerging information technology and develop a system for the computerised storage and retrieval of information on rare dysmorphic syndromes.[2] This system was enthusiastically adopted by all the emerging regional genetic centres in the UK and by many overseas and its sophisticated successor is still in everyday use and now contains details on 4,141 syndromes, 41,105 references and 15,000 photographs.[3] Baraitser, Winter and I also founded a journal, *Clinical Dysmorphology,* and the Dysmorphology Club which still meets three times a year and is attended by colleagues from the UK and Europe; it has been responsible for the initiation of numerous

research studies and delineation of newly recognised disorders. Of course diagnosis is only the first step in clinical management, but for parents of children with rare disorders it is seen as crucial to understand the outlook and needs of the child, the risks of recurrence and to access services and support.[4]

From the 1990s, and continuing to the present time, the genetic mechanisms underlying hundreds of malformation syndromes have been identified utilising a variety of techniques. Original studies relied on samples from large families and were very labour intensive. Identification of most of the first genes associated with syndromes was by positional cloning; for example using this approach *PAX3* was shown to be the gene mutated in Waardenburg syndrome type 1[5] and *Treacle* as the gene mutated in Treacher Collins syndrome.[6] Another successful approach relied on identification of key patients with small chromosomal deletions, and then using a candidate gene strategy to pinpoint the precise gene(s) involved in cohorts of patients. Examples include Rubinstein–Taybi syndrome[7] and holoprosencephaly.[8,9]

Many involved in studying common disorders in the population may question the value of these discoveries in such rare disorders; however this knowledge has provided many new insights into normal developmental pathways and disease mechanisms applicable to complex diseases. By clinical and molecular grouping of rare disorders and examining possible interactions of the encoded proteins, further disease genes have been identified.[10,11] Somatic mutations of the Ras signal transduction pathway, which regulates cell proliferation, differentiation and survival, have been well-known in oncogenesis but germ line mutations are now known in one of the more common genetic disorders (neurofibromatosis type 1) and in several more rare disorders (Noonan, Costello and cardiofaciocutaneous syndromes).[12] These discoveries also mean that targeted therapies are now beginning to be a real possibility and treatment trials are set to begin for several groups of genetic diseases including Marfan syndrome and other conditions where disordered transforming growth factor-β (TGFβ) signalling has been demonstrated and for Ras pathway-related disorders.[13]

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