OrphaNews Europe first reported on the increased prevalence of rare genetic diseases in the northern England metropolitan area of Bradford in December 2005, following a news article that appeared in the BMJ describing a local Member of Parliament’s controversial call for legislation that would ban consanguineous marriages in the UK. Bradford, located in the county of West Yorkshire, has a significant Pakistani community that practices marriage between first cousins, leading to an increased number of rare autosomal recessive disorders in the local population. Indeed, Bradford medical professionals are contending with over 140 different autosomal recessive diseases, whereas other typical districts of similar size in the United Kingdom usually see between 30 and 40 such disorders. OrphaNews Europe presents an interview with a professional who works with this growing group of patients. Bradford-based paediatrician and neurodisability specialist Dr. Peter Corry has worked extensively with rare disease patients in the area and published several studies on the subject:

OrphaNews Europe: How does the increased number of autosomal recessive illnesses impact your community’s medical resources?

Dr. Peter Corry: It has an impact on all services from conception and pregnancy, through paediatrics and other child health services towards either transition to adult services or sometimes death during childhood. I am speaking as a paediatrician working in Bradford, West Yorkshire. We cover a population of about 360,000 of whom about 106,000 are under 18 years of age. There are about 6,000 births each year, and about half are now of Pakistani origin. This population has a preference for cousin marriages and also marriage within the clan.

My own speciality is Neurodisability and I work with colleagues in our Child Development Centre. Our patients have learning or physical disability, with conditions such as Down syndrome, autism, cerebral palsy and spina bifida. However we have had an increasing number of patients with rare, usually autosomal recessive genetic, conditions and this also applies to colleagues in other branches of paediatrics here. In the past decade we have identified at least 148 different autosomal recessive conditions in our children. My answers will concern children with all sorts of conditions although, of course, I know most about the ones with neurodisabilities.

Many of the conditions are complex, many will be unfamiliar to staff, many will require liaison between local staff and more specialist teams. With limited resources, priority has to be given to the children with the most need, so that other children may not receive the routine services they would expect elsewhere.

And many of the rare disorders can be complex, affecting several organs. For instance, our patients with Bardet-Biedl syndrome need attention from an ophthalmologist, nephrologist, plastic surgeon and neurologist as well as our team at the Child Development Centre and others. It isn’t really possible to cope with all this in a 20 minute clinic session two or three times a year.
Unfortunately, many of these genetic conditions that we see are life-limiting, so we have to consider the increased number of children who may die in childhood. I have looked at deaths in my own patients over a period of 12 years (1993-2004). During that time there were probably nearly twice as many caucasian as Pakistani children in Bradford. 43 Pakistani children died, of whom 23 had an autosomal recessive genetic condition. 30 white children died, and none of them was thought to have an autosomal recessive condition.

An example of the pressure on our clinical team is that we have not yet had agreement to hold joint feeding clinics for children with disabilities. These would be so important to enable colleagues to work together on these complex and often life-threatening problems. We have not yet been able to start either the joint clinics with paediatrician, orthopaedic surgeon and physiotherapist to assess children with cerebral palsy who may benefit from surgery or clinics to assess and treat children with injections of botulinum toxin. And this is in a district with an extremely high prevalence of cerebral palsy. In recent weeks, we have been unable to see new patients within the 11 weeks of referral from family doctors, one of the Government health targets.

OrphaNews Europe: What are some of the more rare disorders that you see?

Dr. Peter Corry: There are now more than 20 children with primary ciliary dyskinesia, about thrice the expected prevalence. These children often have their heart on the wrong side and usually develop a gradually worsening lung condition.

I myself have cared for four children with Aicardi-Goutières syndrome, from three different families. These children can have severe neurological and developmental problems associated with intracranial calcification. There is a child with aspartylglucosaminuria, which is a condition that usually affects Finnish people. There are three or four children with hyperekplexia (startle disease) and one was reported in the literature when autosomal recessive inheritance was identified. A colleague looks after three children with Cockayne syndrome.

My colleague in haematology has had patients with extremely rare conditions such as protein C deficiency, Bernard Soulier syndrome, factor XIII deficiency and Glanzmann thrombasthenia, as well as the rare but more widely known thalassaemia and sickle cell disease. With factor XIII deficiency it is estimated that there are about 15 children in the area around Bradford out of about 50 in the whole of the United Kingdom.

The local ophthalmologists see many children with unusual types of retinitis pigmentosa and have several patients with familial exudative vitreoretinopathy.

Support from colleagues in specialist centres in the UK, as well as in Europe and America, has been invaluable. The Internet and improving communications generally has been useful, and we are making increasing use of the clinical summaries on Orphanet.
Dr. Peter Corry: The range of rare conditions that we see is so broad that I can only mention some of the treatments:

Children with metabolic disorders will often require specialised diets. Some of these will be quite complex. Many will need medication, and some will receive new treatments such as substrate deprivation or enzyme replacement. A few may be considered for bone marrow transplants or other "cutting edge" approaches. Especially for those with disorders of intermediary metabolism, frequent admissions may be needed in order to stabilise their condition.

We have many children with neurological conditions. They may need anticonvulsants for seizures or treatments to reduce spasticity such as oral or intra-thecal baclofen or intra-muscular injections of botulinum toxin. Many need orthopaedic surgery because of complications, such as joint contractures or hip dislocation and a few will have surgery to correct spinal curvature.

Some of the weaker children with neuromuscular conditions may need respiratory support with a ventilator or positive airways pressure when asleep, or even at all times of the day and night.

Artificial feeding through a naso-gastric tube or gastrostomy is needed for many with feeding or swallowing difficulties. Our dieticians treat 182 children who are tube-fed, of whom 50% are disabled children attending the Child Development Centre.

Children with anaemias, coagulation or platelet disorders may need regular transfusions of blood or blood products and may also require drug treatments. Children who have frequent intravenous treatments may need indwelling IV catheters.

The list of options seems to be getting longer all the time as new treatments are developed.

Hospital admissions are required, both for acute illnesses and for planned treatments. Many disabled children will be prone to life-threatening chest infections or may need admission to hospital following severe seizures. Some children may need regular admissions for courses of intensive treatment. This will aim to slow down deterioration, such as for children with cystic fibrosis or primary ciliary dyskinesia.

We do not have an intensive-care facility for children in Bradford so our patients are obliged to go to the regional centre in Leeds (or elsewhere, when it is full). More than a third of the beds in the regional ICU are usually occupied by patients from Bradford, although we have only about 6,000 of the 36,000 births in our region each year.

Many of the children need speech and language therapy, physiotherapy or occupational therapy. Our dieticians are also important for children with nutritional problems. We also have a very good service from children’s nurses in the
community, or from our hospital outreach team. They may help in the care of children in their homes or schools.

**OrphaNews Europe**: How do the national and regional authorities support this increased health burden?

**Dr. Peter Corry**: For a handful of children with rare metabolic conditions there are national funding arrangements, such as for expensive enzyme replacement therapy. However, this is probably for less than 10 of our children.

We have an increased number of children requiring bone marrow or organ transplants, and this is usually carried out at national centres.

I only have limited knowledge of the complexities of NHS funding, but generally the funding for medicines, procedures, surgery, nursing and therapies comes out of the local health budget. For our children, either inpatients or outpatients, this usually seems to be through the national system of tariffs (Payment by Results).

For readers outside the United Kingdom, the government allocates money to health authorities (now called Primary Care Trusts, PCTs). Some extra payments are made to districts with significant socio-economic deprivation or increased numbers of elderly patients. These PCTs must then pay for the family doctor service, as well as purchase outpatient and inpatient care for their population in hospitals and clinics. However, I am not aware of extra funding to cope with the large numbers of children with rare disorders in districts like Bradford.

**OrphaNews Europe**: Does the Bradford area have increased educational and social resources to meet the needs of your rare disease patients?

**Dr. Peter Corry**: I don’t know how the budget for these is allocated. We certainly have retained several special schools and have many dedicated colleagues working in education and social services, but they must be very hard pressed. Our impression is that there are insufficient resources to provide for the children with rare and complex conditions, as well as the more routine children with special educational needs.

One of my disappointments is that, because of the heavy clinical load, the children’s doctors cannot support the schools as we should. I have rarely been able to attend multi-disciplinary meetings concerning my patients, so the school staff does not get all the opportunities for medical support and advice that they deserve.

Respite care may be provided through the local social services, and can be extremely valuable for hard-pressed families, but as usual, we could do with more.

**OrphaNews Europe**: Could you discuss how the more-than 140 autosomal diseases are distributed in terms of prevalence?
Dr. Peter Corry: Most of these conditions are still rare, even in Bradford, and may affect fewer than 5 children each. It is only when they are lumped together in clinical groups that the significant picture may emerge. For instance, we have identified more than 70 children with neurodegenerative conditions, about 8% of the UK total. But this represents about 27 different conditions. Nine of these children have juvenile Sandhoff disease. The other conditions have affected smaller numbers, sometimes only one child. The prevalence seems to be increasing all the time. In 1986 we had eight children living with these neurodegenerative conditions, while in 1999 we counted 45.

As another example, Duchenne muscular dystrophy is usually thought to be the commonest neuromuscular condition. However out of more than 50 Bradford children with neuromuscular problems, only eight have Duchenne muscular dystrophy. We have seen more than 10 with spinal muscular atrophy in recent years, and we have about 30 with a variety of rare neuromuscular disorders.

We have more than 40 children with microcephaly, and most of these are related to one of the genes for primary microcephaly (mostly identified by Dr Geoff Woods and his team in Yorkshire).

Deafness is relatively common and probably more than 100 cases of deaf children have been linked to autosomal recessive genes.

OrphaNews Europe: Are there any patterns within this group of diseases, in terms of systems or organs affected? For example, are there certain symptoms or clusters of symptoms that you treat more frequently?

Dr. Peter Corry: I don’t think there are any particular patterns as the autosomal recessive conditions are so variable.

OrphaNews Europe: How many conditions are seen for which there is no current diagnosis?

Dr. Peter Corry: We still have many children who have unidentified conditions. For instance, we have several siblings with conditions best described as “cerebral palsy” but which seem to be occurring in a genetic pattern.

Again one of the additional pressures here is that we might be searching for a diagnosis for many years. I was looking after a child who seemed to have cerebral palsy. When he was eight or nine years old, he developed unusual “chilblains” on his skin. The local dermatologists were baffled. We then became aware of Professor Stephenson’s work in Glasgow, and realised that he had Aicardi-Goutières syndrome.

Another of our problems here is the lack of a central database or register. Most of the data we have is from the records of individual doctors. The study into Progressive Intellectual and Neurological Deterioration by the British Paediatric Surveillance Unit has been so useful, as we now have accurate information about the prevalence of
these conditions, and can make a direct comparison between Bradford and the rest of the United Kingdom. We have been hoping to develop a register of autosomal recessive disorders but were very disappointed when a recent submission for funding was refused.

And while there are problems developing a register of identifiable conditions, it becomes even more difficult for the children who have a pattern of symptoms or signs but no name for their condition. It was only from memory that we realised that one patient with an unusual combination of paraplegia and dysarthria was similar to another child who came to us several years later. It eventually turned out that they were distantly related. That is sometimes how we make a difficult diagnosis. We will realise that a new patient is related to another child and so we can target investigations on the condition found in the original child.

**OrphaNews Europe:** For what percentage of these autosomal recessive diseases do prenatal diagnostics exist?

**Dr. Peter Corry:** Probably still a minority, although there has been a gradual increase in knowledge. For instance, work by my colleague Yanick Crow has identified several genes for Aicardi-Goutières syndrome and prenatal testing for this has been carried out in Yorkshire. But even when genes are identified the work is often only being done in specialist research labs. Development of assays by mainstream diagnostic labs may be slow.

There are some conditions for which other markers such as metabolic tests are available, but again this often requires liaison with research labs in the UK or overseas.

**OrphaNews Europe:** For what percentage of the rare conditions does pharmaceutical treatment exist?

**Dr. Peter Corry:** There is such a wide range of conditions that it is very difficult to answer this.

Children with many different types of rare genetic disease will receive pharmaceutical treatment, but this will often be supportive, rather than curative. However, with new approaches in treatment, we can see dramatic improvements in life expectancy, such as has occurred for children with cystic fibrosis during my medical career. The condition isn’t cured, but life for many has been made a lot better.

Treatment is available for many, but not all, of the children with inborn errors of metabolism. This will usually be by diet or by medication, or often a combination of these.

For most of my patients with disabilities, treatment is usually for complications. Many children with neurological conditions will require anticonvulsants to reduce the frequency of seizures. They may need antibiotics when they develop chest infections.
OrphaNews Europe: What is the NHS policy in terms of reimbursement for these types of disorders?

Dr. Peter Corry: There is some central funding, perhaps as a result of the Orphan Drugs initiative. However this is usually limited to a few specialist treatments that would otherwise be too expensive for a small district.

The problem is with the day-to-day routine health care for many children. And things have got worse with the recent “Payment by Results” system in the National Health Service. There is a national “tariff” for children attending clinics. The hospital receives a fixed sum for each attendance. The problem for us is that the funding seems to be the same, no matter if the child has a fairly simple routine disorder or a rare and complex condition. There doesn't seem to be recognition that these children need more time and will usually require more complex treatment.

For the families themselves there are government financial benefits, such as the Disability Living Allowance and Carers’ Allowance. These depend on the severity of the child’s condition and should be paid whether the child’s condition is rare or common.

OrphaNews Europe: Does the Bradford experience correspond to prevalence patterns typically found in Pakistan or Bangladesh or certain regions of these countries? Do you see a founding effect?

Dr. Peter Corry: It is very difficult to compare because of different availability of health care and opportunity for diagnostic investigations. I think, particularly in the rural areas, that there are difficulties with access to specialists and diagnostic tests. There will be other priorities in view of infectious diseases and nutritional problems. However I have been encouraged to read of developments in genetics in Pakistan.

Also, with higher infant mortality rates there, it is likely that some of the children with rare conditions will die before a concrete diagnosis is made.

There do seem to be a large number of deaf children in Pakistan, and that would seem to fit in with the high rates of deafness which have been found here, often due to genetic conditions. Another interesting example is microcephaly for which five different gene loci have been described within the Pakistani population, both in the United Kingdom and in Pakistan. Genetic heterogeneity seems to be a real issue in this population. Colleagues also see a similar situation in respect of retinitis pigmentosa.

One point to remember is that many of our marriages involve one partner from Bradford and the other from Pakistan, with the first child often conceived in Pakistan. It would therefore seem very unlikely that similar conditions are not occurring there.

OrphaNews Europe: Do you feel that there is adequate awareness for Bradford’s circumstances at the national and the European levels?
Dr. Peter Corry: No. Perhaps if we had a thousand children with one particular rare condition, there might be more awareness. However, we have lots of small clusters of conditions, and the children may be attending different departments. They will never be more than a minority of the patients for each clinical team. The situation does seem to some extent “invisible”. 

However when you group them together, such as with the 27 different neurodegenerative conditions, you find that we have notified about 8% of all the children in the United Kingdom with these conditions. And that is for a population of about half a million people, less than 1% of the UK population. I am sure that better documentation of these genetic conditions would be very helpful. 

It has been gratifying to hear about the European initiatives for rare disorders. Perhaps things will change. 

OrphaNews Europe: Have either government or religious officials from Pakistan responded to this medical issue? Is there any counsel provided to their expatriated communities in Great Britain and other countries? 

Dr. Peter Corry: Although I visited Pakistan in 1994 I haven’t had any direct contact recently. However, colleagues in genetics regularly visit Pakistan, and have been in touch with doctors and representatives of the government of the Punjab. 

There are many similarities with populations in Arab countries. Judging by the papers presented at the recent 2nd Pan Arab Genetics Conference (www.cags.org.ae/2ndpahgc.html) held in Dubai during November 2007 they seem to be making quite rapid progress. 

Generally, in UK districts such as Bradford, more forums are developing where these sensitive but important issues can be discussed. Remembering that many Pakistani families in England are now second or third generation, the influence of politicians and other officials from Pakistan is lessening. There seems to be increasing understanding of what genetics can offer. We have also had good support and advice from Muslim chaplains in our hospitals, and there is a local initiative based in a children’s centre where Asian parents are discussing genetic issues. The contact address for this parents’ group is: pauline.naylor@bradford.gov.uk. 

OrphaNews Europe: Do you know of other communities, either in the UK or other parts of Europe, with whom you might consider collaborating to share research projects, and perhaps seek a larger access to funding? 

Dr. Peter Corry: I myself am primarily a clinician, but I’m sure there are opportunities for collaboration in joint research. This will be partly clinical and genetic, but also looking at ways for better communication between the planners and professionals on one side and the communities on the other.
In Bradford we have concentrated on these issues in the Pakistani population, but we are aware of other groups in Europe, who may have similar problems. Clinical and genetic reports about children with rare conditions often say that they are members of a particular minority group. For example, at a recent paediatric neurology meeting we heard of initiatives with Roma communities in Bulgaria. And as more people move here from Eastern Europe, Bradford doctors have noticed increasing numbers of children with retinitis pigmentosa from our growing Slovak Roma population.

**OrphaNews Europe:** The “Born in Bradford” project was developed to study the increased incidence of infant mortality in the area. Where is this project today?

**Dr. Peter Corry:** There are actually 2 different projects.

The Bradford and District Infant Mortality Commission reported in late 2006 on the high infant mortality here. I wasn’t directly involved myself, but their findings are available on [www.bdimc.bradford.nhs.uk](http://www.bdimc.bradford.nhs.uk). They found that poverty and disadvantage was strongly associated with infant mortality in both white and Pakistani populations. Among other findings it was noted that congenital anomalies were more likely among Pakistani-origin infants. Recommendations were made for further action.

Born in Bradford is a longitudinal birth cohort study aiming to study 10,000 children born here. The first births occurred in 2007. By December 2007 2,700 mothers had been recruited with 1,700 babies born. Detailed health information is collected including about consanguinity and family structure. DNA samples are collected from babies and parents. Again information can be obtained through their web-site [www.borninbradford.nhs.uk](http://www.borninbradford.nhs.uk)

**OrphaNews Europe:** What about the future generations? If the offspring of consanguineous couples again marry within a family circle, what would be the impact upon these diseases?

**Dr. Peter Corry:** If there already is a child with an autosomal recessive condition, then brothers and sisters have a high chance of being a carrier. If they marry a close relative that person also has an increased risk of being a carrier. So this couple would have a significantly increased risk of having a child with the original genetic condition. At least now we can offer genetic counselling, and genetic advances mean that for some conditions it can be established whether a relative is a carrier or not.

We had our first transcultural genetic counsellor in Yorkshire in 1987 and there are now five. This means that counselling in community languages is available, and more families are taking advantage of this. (Details from gulshan.karbani@leedsth.nhs.uk)

An ongoing piece of research here is looking at how the family networks in communities practicing consanguineous marriage can be used as a resource for genetic testing and counselling. This study is funded by the Department of Health and is based at the School of Health, University of Bradford. (For details contact Dr Aamra Darr, email: a.r.darr@bradford.ac.uk)
OrphaNews Europe: With the very large numbers and the pressures on your services, do you think there are any positive aspects for parents of children with rare disorders in Bradford?

Dr. Peter Corry: Well, while we are not specialists, we have a much broader experience than most children’s doctors in a more typical district. For instance, our newborn department often has to diagnose and treat babies with rare metabolic disorders. Often they will quite suddenly become ill. At least our senior doctors may often have seen the condition before, and the junior doctors will have access to protocols developed in the light of local experience.

There is very close contact with our colleagues in the Genetics service, and much of the research they have done means that families can have the latest advice on carrier or antenatal testing. We are also in contact with national or international experts, so that it may be easier to access their help.

Our situation with neurodegenerative conditions is known through the British Paediatric Surveillance Unit work I mentioned earlier, so we were some of the first to hear when researchers in Cambridge were doing a trial of substrate deprivation therapy in children with lysosomal storage disorders.

Families are often helped by contact with others who have been in the same situation, and over the years we have had a lot of contact with support organisations like Climb (for metabolic conditions) www.climb.org.uk and Contact a Family www.cafamily.org.uk. This organisation has recently appointed a family support worker in Bradford, who can speak to Pakistani parents in Urdu or Punjabi.

OrphaNews Europe: Does the situation in Bradford provide any lessons for the rest of Europe?

Dr. Peter Corry: I think the main lesson is that rare disorders are not always evenly spread across countries. We already know that some conditions are more common in different regions: thalassaemia, for example, is a condition of Eastern Mediterranean peoples, and there is a distinct Finnish genetic heritage. However there is an additional factor due to marriage patterns which may affect some population subgroups and which may cause significant increases in prevalence. These may be concentrated in local “hotspots” and may not be picked up by nationally based surveys.

Increasing migration may change the type of rare conditions that we see, as well as the prevalence. Clinicians may be presented with rare conditions previously unknown in their localities. Genetics services may need to broaden their counselling from nuclear families to more complex family groupings.

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