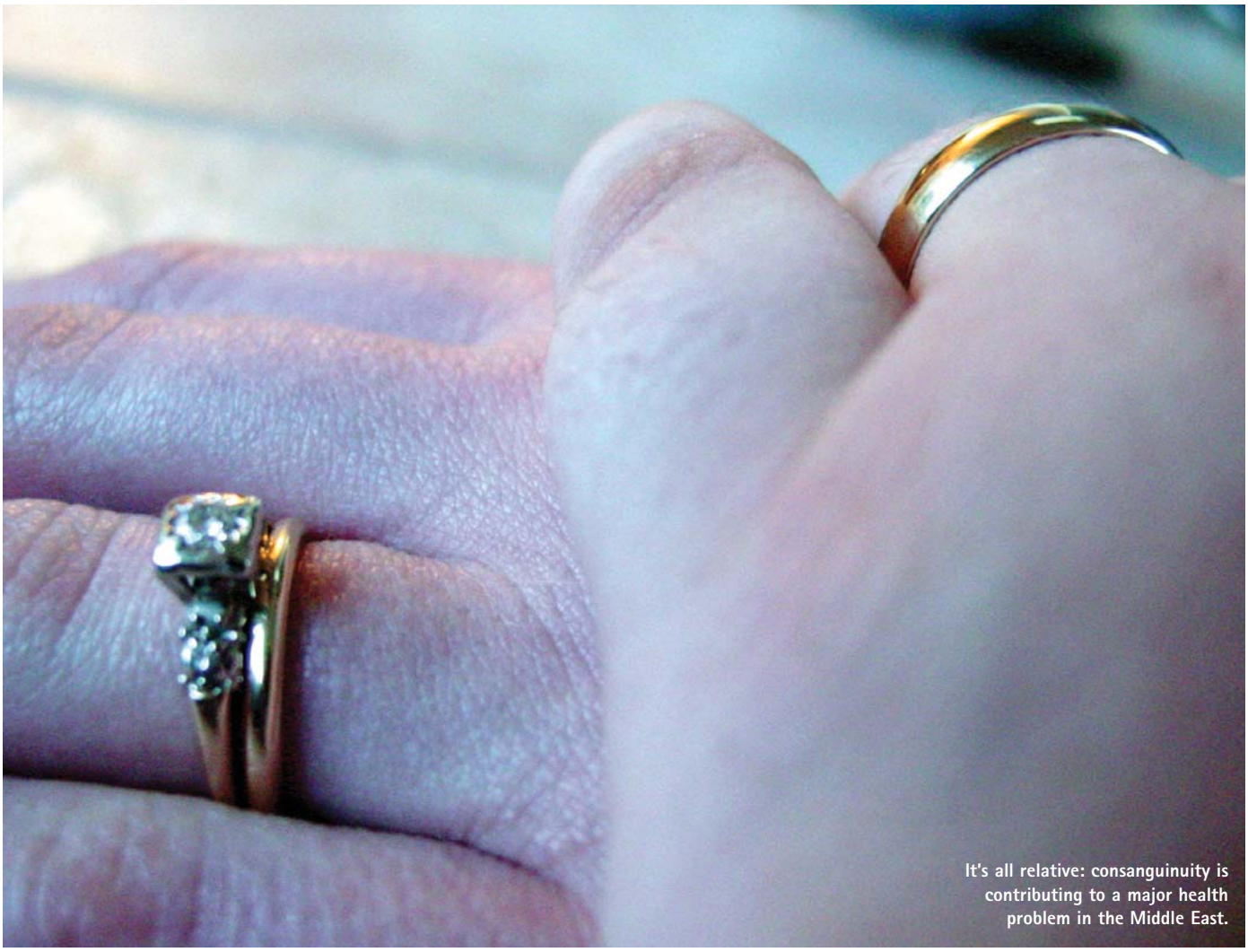

It's all relative: consanguinuity is contributing to a major health problem in the Middle East.

For better or for worse

The figures are disturbing – congenital conditions in the Middle East are the highest in the world. Experts point the finger of blame at the high rate of consanguinity. **Sarah Monaghan** reports.

In the Middle East, the phrase For better or for worse takes on extra poignancy.

According to World Health Organisation (WHO), a growing tide of hereditary disorders and congenital defects in the region is reaching such levels that it has become a 'major health concern'.

The reason? Experts point the finger of blame partly at high maternal and paternal age, but mainly at the high rate of consanguinity (marriage between people who are blood relatives).

Congenital conditions are now occurring, according to recent WHO figures, in 69 out of every 1,000 births. Hereditary disease and abnormalities are being found in two to five per cent of all live births and account for about 30 per cent of paediatric hospital admissions, often with tragic consequences: congenital malformations are currently recognised as the principal cause of infant mortality in the UAE, and the second leading cause in Bahrain, Kuwait, Oman and Qatar.

Most of the genetic fall-out of consanguinity is in the form of autosomal recessive disorders (disorders for which a person needs to inherit a copy of a defective gene from each parent). The more closely two people are related, the more genes they share - and the more likely that both will carry a copy for the same recessive mutation. If two individuals carrying the same recessive mutation mate, their child has a high probability of being affected by the disorder.

Genetic conditions that are widespread in the Middle East ➤

include mental retardation, blindness, hearing impairment, deaf-mutism and congenital heart disease, while the most frequently seen single gene diseases are thalassaemia, sickle cell anaemia and favism (glucose-6-phosphate dehydrogenase deficiency). The mild form of a-thalassaemia is now so common in the Arabian peninsula that a WHO report claims that up to 50 per cent of the population in Saudi Arabia is affected, 45 per cent in Oman and 24 per cent in Bahrain.

Most consanguineous unions are between first cousins (although marriage between persons otherwise biologically related such as second cousins are also categorised as consanguineous). In first-cousin marriages, the spouses share 1/8 of their genes inherited from common ancestors.

Close consanguinity has been practised in the Middle East for over 100 generations, even before the introduction of Islam in the 7th century. Today, the percentage of first-cousin marriages is reported by WHO to be 37 per cent in Pakistan; 32 per cent in Jordan; 30 per cent in Iran; 30 percent in Kuwait; 31 per cent in Saudi Arabia; 30 per cent in the UAE; 29 per cent in Iraq and 11.4 per cent in Egypt.

The tradition of consanguineous marriage is linked to the area's Bedouin tribal history and the fact that most marriages were between close relatives to guarantee the financial unity of the family. "The custom results from cultural and historical, rather than religious reasons," says Dr Youssef Abdulrazzaq of the department of paediatrics at UAE University. "Such marriages are considered to be more stable and economically beneficial through the maintenance of the family fortune, which is kept within the family structure."

Dr Abdulrazzaq recently carried out a study, *Consanguineous marriages in the UAE*, in Al Ain and Dubai, looking at a sample of 2,000 married women. He found that the rate of marriage between biological relatives was 54 per cent in Al Ain and 40 per cent in Dubai – staggeringly high figures. Dubai's particular high rate of consanguinity, suspects Dr Abdulrazzaq, is, paradoxically, due to the very economic success of the emirate. It has undergone such explosive expatriate population growth in the last three decades that less than 30 per cent of the UAE population is National. He explains: "Since UAE Nationals constitute a minority, this increases their feeling of isolation and promotes intermarriage." This trend, he adds, is also seen in migrant communities in Western countries where there is a limited availability of suitable partners, especially where they practise a religion not followed by the majority indigenous population. An example is the Pakistani community living in Britain.

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The keep-it-in-the-family approach in the UAE has to an extent been perpetuated by the creation of the UAE Marriage Fund, set up in 1994 by UAE President Sheikh Zayed to encourage Emirati men to take Emirati brides. The fund provides local couples with long-term loans of up to Dhs 70,000 to assist with wedding expenses and the purchase of a house. The loan is interest-free and reduces by 20 percent with the birth of each child.

A recent publication on genetic disorders among Arab populations claims over one hundred new genetic diseases that have come to light since the 1980s. In 2000, a typical example was discovered in four neighbouring villages in northern Jordan. Now known as Jerash Motor Neuronopathy after the affected region, it is a hereditary neurological disorder which causes paralysis in adolescents. Dr Abdelkarim Qudah, paediatric neurologist at the University of Jordan, studied 84 people in the four villages and found that 27 were suffering from the disease. All 27 came from nine highly consanguineous families located within the same cluster of villages.

WHO's Human Genetics Programme focusses on genetic counselling, premarital screening and health education, through which, it believes, it is possible to bring an understanding of genetic diseases to the community. Experts have observed that it is far less likely for marriages to be arranged between men and women who are both known to be carriers of a genetic disease, particularly in families which have already experienced the hardship of genetic disease.

A WHO report, based on a study carried out in Bahrain, has prioritised premarital counselling because it gives the couple the opportunity to recognise the risks they run in producing their offspring. WHO goes so far as to state that it should be "compulsory by law but the freedom of couples to act upon the advice should be ensured". In Bahrain the Ministry of Health has made premarital screening available in all primary health-care centres and many religious leaders are now also convinced of its benefits. Many are even advocating that it should become a legal requirement, with the proviso that couples are free to take medical advice and act according to their own decision.

But the solution is not so simple. The problem of intermarriage is often more a social one than a medical one and experts agree that certain attitudes remain to be overcome, especially in poor areas where illiteracy prevails.

"The woman often fears that if she conducts tests and they prove she is a carrier of a defected gene, she will end up being divorced," says Dr Qudah.

"It is can be seen as a shame for the woman to undergo testing before marriage," agrees Dr Essam Dohair, paediatrician and genetic blood diseases expert at Al Wasl Hospital, Dubai.

A recent report in *The Jordan Times* showed that many Jordanians viewed the results of their unions as fate. "All my ten children are disabled," said one ➤

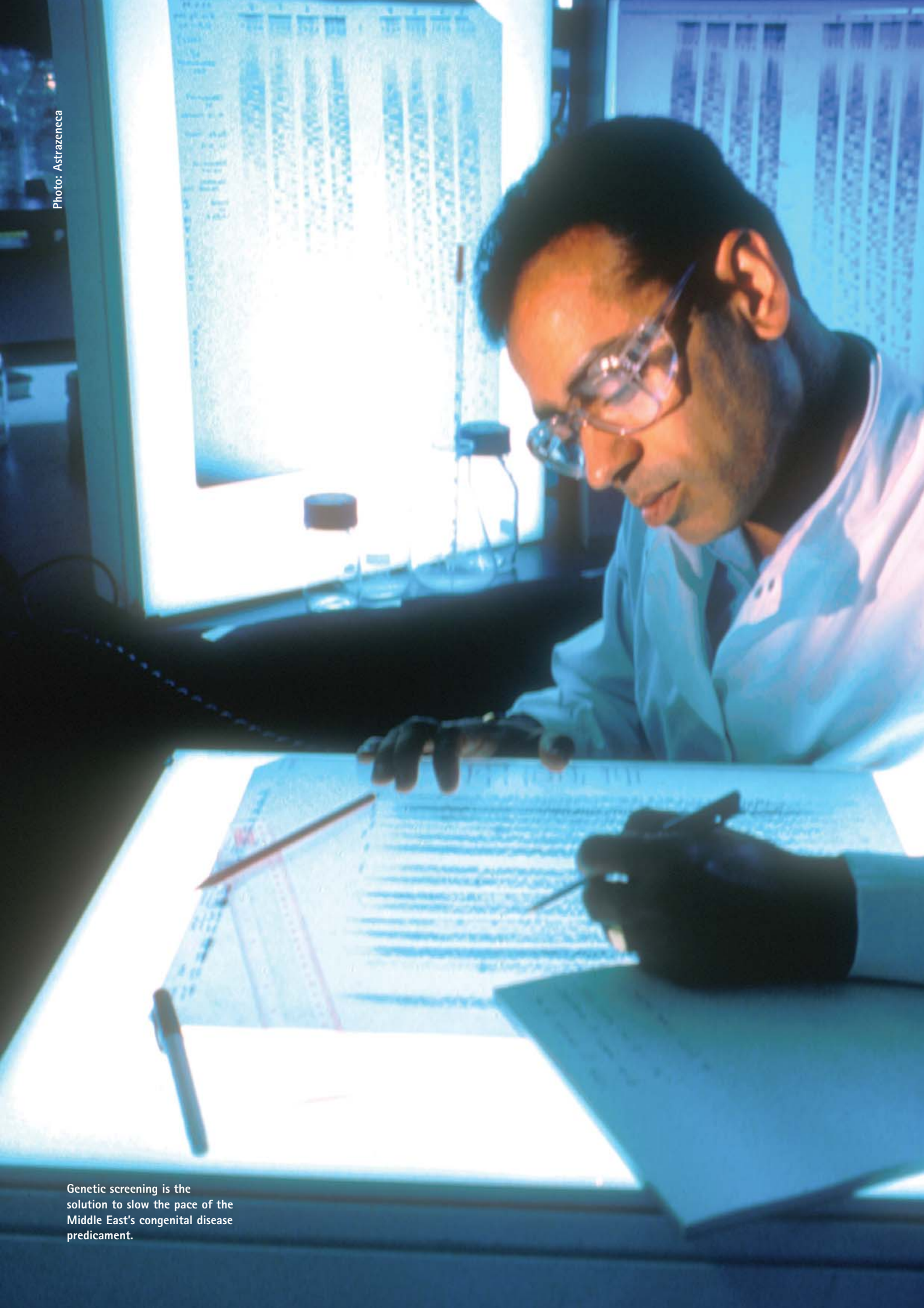


Photo: Astrazeneca

Genetic screening is the solution to slow the pace of the Middle East's congenital disease predicament.

Jerash, in northern Jordan, where a hereditary neurological disorder causing paralysis in adolescents has been identified in a cluster of four villages. All 27 sufferers come from nine highly consanguineous families.

father, who saw this as "God's will". He said he had believed it had been worth trying to father so many children in the hope that one would be free of disability.

Nonetheless, WHO has taken big steps forward with its community approaches for the prevention and control of hereditary diseases in developing countries.

Recommendations of experts' groups convened by WHO have been implemented successfully for the prevention and control of haemoglobinopathies, cystic fibrosis, haemophilia and birth defects in Cyprus, Italy, Thailand, Brazil, China, India, Mexico, Bahrain and Cuba. WHO has also helped introduce basic training and education of primary health-care workers in the field of genetic counselling.

But one of the limitations of present medical genetics practices is that couples may have to face the abortion of an affected foetus following prenatal diagnosis – a practice not acceptable to some cultures or religious groups.

Says Dr Dohair: "Some parents do not see termination as *halal* but as *haram* (not permitted). They know their child is diseased but they choose to keep it believing that God created them to take care of that child and that they will get their reward in heaven."

> Some parents do not see termination as *halal* but as *haram* (not permitted). God created them to have that child and they expect to get their rewards in heaven.

An alternative is pre-implantation genetic diagnosis (PGD). This allows the disease to be detected in eggs before fertilisation and in most Muslim countries, genetic diagnosis and discard of the affected pre-implantation embryos is allowed.

In the past the earliest diagnosis could only be made in the third month of pregnancy, usually through amniocentesis, forcing couples to take the traumatic decision of whether or not to have an abortion in the third or fourth month.

"PGD is the most recent and exciting progress in the control of congenital diseases because it allows us to screen for inherited disorders such as thalaessaemia, before pregnancy is established," says Dr Anver Kuliev of WHO.

In Cyprus, where one in seven Cypriots has the thalassaemia stigma and one in four couples face the possibility of conceiving a child with thalassaemia, the method has been used with great success at the Maroni Centre which is the only PGD centre in the Eastern Mediterranean.

Until recently almost one quarter of Cypriot couples at risk from having a thalassaemic child have had to experience two or more terminations of pregnancy before they could have a normal child. The centre is also open to couples carrying thalassaemia genes from outside Cyprus.

Genetic screening and controls have also been highly successful in other countries such as Sardinia and Greece but Cyprus is perhaps the world's greatest success story.

The population of Cyprus (both Greek and Turkish) has one of the highest rates of beta-thalassaemia carriers in the world, and in the past, one of every 158 infants was born with the condition. In the early 1970s Cypriot paediatricians began programmes for population screening. Combined with health awareness, prenatal diagnosis and abortion, these have resulted in almost complete prevention of new births of children with thalassaemia.

Cyprus is a shining example of the powerful effect of genetic counselling and health education. With greater awareness, its glow could spread across the Middle East. ■

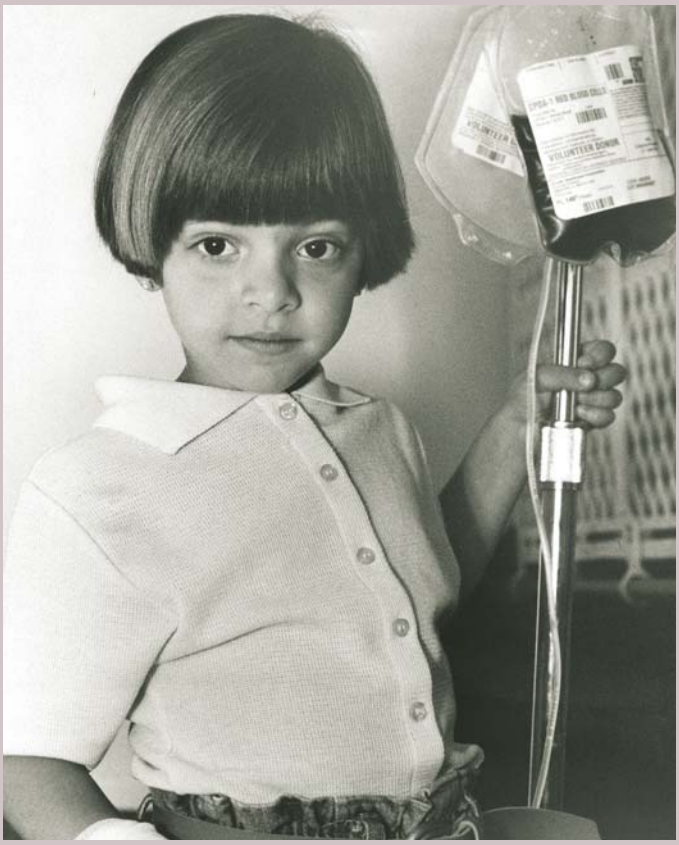
Screening out the genes

Consanguinity is part of a big problem in the UAE where one in 12 nationals is already a carrier of the beta-thalassaemia trait., says Sarah Monaghan.

Thalassaemia disease is seen in almost every country, every religion and every community but it is particularly prevalent in populations belonging to the Middle East and Gulf region, Mediterranean countries, northern parts of Africa, South East Asia and Indian Sub-continent. Spread of this genetic defect has been dramatically affected by the high incidence of consanguineous marriages in these populations and most patients' ancestors can be traced back to these areas. The origin of the defective gene is thought to be related to selective advantage against malaria.

Children affected by beta-thalassaemia major develop severe anaemia in early infancy and require monthly blood transfusions throughout their lives. These transfusions increase iron accumulation in the body and can lead to toxicity and damage to major organs. The iron deposits are therefore removed by regular administration of a medication called Desferal which is given with a syringe pump for eight to 12 hours each day for five to six days a week. Patients who receive only blood transfusions are unlikely to survive beyond their second decade as they invariably develop complications due to iron overload. Patients, who are well managed however, can grow into normal healthy adults, marry and have children.

In the UAE, as many as 8.5 per cent of the National population carries the thalassaemia gene. Today, around 700 thalassaemia patients, aged from three months to 36, are being treated at the Dubai Genetic and Thalassaemia Centre, which was established in 1995. Research by the Emirates Thalassaemia Society indicates that in 60 per cent of those families affected, there is consanguineous marriage. "We have families here with five or six siblings under treatment," says Dr Essam Dohair, paediatrician at the centre.



Children with thalassaemia require careful management, monthly blood transfusions and nightly administration of Desferal to remove excess iron deposits.

The centre comes under the Department of Health and Medical Services of the Government of Dubai. Seventy per cent of patients are below 13 years of age. Forty four per cent of the total patients are Nationals while the rest include patients from GCC countries, other Arabs, Iranians and Asians. A further 600 thalassaemia patients are also managed in other hospitals of the Ministry of Health, spread all over UAE.

The centre is involved in research that is directly concerned with patient care, and has seen around 40 patients successfully cured of the disease through new bone marrow transplantation techniques. It also provides patient care and counselling services for other inherited blood disorders in the UAE population such as sickle cell disease, alpha-thalassaemia and G-6-PD deficiency.

In collaboration with the Emirates Thalassaemia Society, the centre is working hard to educate the UAE population. Says Dr Abdulla Al-Khayat, director of Al Wasl Hospital: "We have to stop this disease in its tracks, and we can, as long as we take the right steps."

The right steps, he says, are: providing prenatal diagnosis, carrying out an accurate survey of beta-thalassaemia incidence in the UAE population and increasing public health measures about the importance of premarital screening.

"Education is vital," agrees Dr Dohair, who assists with health education programmes taking place in schools and colleges across the UAE. "Once couples have awareness, they can have a well-planned future and make the right decision for themselves at the right time."

Education, he stresses, is also needed among other health professionals in the UAE, particularly at private health-care institutions which employ a mix of nationalities unfamiliar with the specific genetic characteristics of the Middle East. "We do find a lot of ignorance," says Dr Essam. "We know that the private sector is missing simple problems. They are often completely unaware that the diseases they are diagnosing are genetic."

When two thalassaemia carriers have a child, there is a one-in-\four risk that the child will have thalassaemia (the severe form is called thalassaemia major). This risk is same in each and ➤

(Left) Dr Abdulla Al-Khayat, director of Al Wasl Hospital: "We built this centre so that we could one day close it."

(Centre) Khalida Ali Khammas, social specialist at Dubai Genetic and Thalassaemia Centre, was awarded the Dubai Government Excellence Award in 2000 in recognition of her efforts to raise awareness about thalassaemia to a national level.

(Right) Dr Essam Dohair, paediatrician and genetic blood diseases expert at Al Wasl Hospital, Dubai: "It is can be seen as a shame for the woman to undergo testing before marriage."

every pregnancy, irrespective of the order of birth and sex of the child. For parents, this is a nerve-wracking game of chance because it is impossible to know in which pregnancy or in which order an affected child will be conceived. However, it is possible to precisely diagnose before three months of pregnancy (between nine and 11 weeks), whether the foetus is normal or is a thalassaemia carrier or has thalassaemia disease. The parents can then have the option to continue or to terminate the pregnancy.

Pregnant women at the centre are presently being sent to the UK for prenatal diagnosis at a cost of around Dhs 50,000 per diagnosis although the centre is in the process of setting up its own prenatal diagnosis service. This will represent a big saving to the Dubai Government which currently funds all treatment. Says Dr M Naveed, the centre's clinical geneticist: "Once we have set up our own service, it will cost us around Dhs 5,000 per diagnosis, so for one case we are now sending abroad, we will be able to complete ten here."

Women who have a positive result and then opt to abort their pregnancies are now being sent to the UK for the termination. In the UAE, abortion is illegal but a special religious fatwa or dispensation has been granted in the case of foetuses affected by thalassaemia, providing termination is undertaken at under four months. The centre has applied to the Ministry of Health to make it legal to perform terminations in the UAE.

Khalida Ali Khammas is the centre's social specialist, charged with providing genetic counselling. She is well-placed to do this. Her eldest son, Mohammed, suffers from the disease and she and her husband are first cousins. "I believe that I would have made a different decision if we had known we were carriers and had been given genetic counselling prior to marriage," she says. In 2000, Sheikh Mohammed bin Rashid Al Maktoum, Crown Prince of Dubai and UAE Minister of Defence, awarded Khalida the Dubai Government Excellence Award in recognition of her efforts to raise awareness about thalassaemia to a national level. Her mission now, she says, is to make the UAE a thalassaemia-free society and she is pushing for a government decree to make it compulsory for all couples to have blood tests and genetic counselling prior to marriage.

> Pregnancy is a nerve-wracking game of chance because it is impossible to know in which order an affected child will be conceived.

Eradication of thalassaemia in the UAE is a real possibility now that it is beginning to receive the priority it deserves. Educational awareness is taking place at all levels, with the Department of Health underlining its serious intent with the recent introduction of genetics as a compulsory subject for all medical students at Dubai Medical College. Likewise, the UAE Marriage Fund, which, in cooperation with the Ministry of Health and the Ministry of Justice and Islamic Affairs, is proposing the introduction of compulsory medical tests for all couples who plan to get married.

And in July, a Centre for Arab Genomic Studies was officially inaugurated at Al Wasl Hospital by UAE Minister of Health Hamad Abdul Rahman Al Madfa. At present, the research budget is about Dhs 1 million but it will increase in the future. Mr Al Madfa said that conducting genetic studies of Arab populations was crucial: "In the Arab world, genetic diseases represent a major public health problem due to the high rate of consanguinity and lack of public awareness," he said. The centre was established to bring together expertise in human genetics. "It is incumbent upon us to work with the latest scientific developments and make our own contribution. Arab scientists must join hands and benefit from each other's experience as well as from advances made anywhere in this vital field," added Mr Al Madfa.

Dubai's Genetic and Thalassaemia Centre – unique in that it provides the full gamut of patient care as well as enables prenatal testing and offers genetic counselling – has been recognised as a centre of excellence by the WHO and has been described as the 'best centre of its type worldwide' by the Thalassaemia International Federation.

On its current course, and with the right will behind it, it looks likely that its very success will be its demise and that in the UAE, thalassaemia will eventually become a disease of the past. In the words of Dr Abdulla Al-Khayat, director of Al Wasl Hospital, "We built this centre so that we could one day close it."

That day may not be so far away. ■