

endpoints, a greater reduction in heart rate and respiratory rate and a greater increase in oxygen saturation with isosorbide dinitrate than with furosemide. The fall in heart rate is of interest, because it suggests reduced sympathetic drive; in other studies heart rate did not change significantly with infusion of isosorbide dinitrate or nitroprusside,^{1,2} but it did fall with isosorbide mononitrate given as bolus⁹ (table). However, the mean initial heart rate was only 91 (SD 5) beats per minute in the study by Nelson and colleagues and 94 (14) in that by Chatterjee and colleagues; these heart rates suggest that the pulmonary oedema in these two studies was not too severe, although nine out of 36 patients had clinical features of cardiogenic shock at presentation and there was significant mortality among Chatterjee's patients.^{1,2} Another interpretation of the lack of effect on heart rate of isosorbide dinitrate infusion is that it was not very effective at reducing sympathetic drive, perhaps because of prolonged vasodilatation and hence relative hypotension.

As with many other studies, all patients in the Cotter study received 40 mg furosemide (along with oxygen and morphine) intravenously before randomisation; local ethical considerations also dictated the use of low-dose infusion of isosorbide dinitrate as adjunctive therapy in the furosemide group. In effect, therefore, this study compares low-dose furosemide plus bolus isosorbide dinitrate against high-dose furosemide plus low-dose isosorbide dinitrate infusion. Unlike most other studies, data were acquired non-invasively, with the result that haemodynamic and oxygen-consumption benefits are inferred rather than demonstrated. In addition, the conclusions are further limited by the need to exclude certain categories of patients—those on chronic nitrate or diuretic therapy or with blood pressure lower than 110/70 mm Hg on admission. This latter exclusion may not (in retrospect) have been necessary since mean arterial pressure fell by similar amounts in both groups (132 [SD 14] to 107 [15] mm Hg with isosorbide dinitrate and 124 [24] to 103 [19] mm Hg with furosemide).

Intravenous isosorbide dinitrate has a rapid onset of action, with peak vasodilatation at 5 min,¹⁰⁻¹² but the short elimination half-life (0.6 h) requires frequent repeat dosing when given by bolus. Isosorbide-5-mononitrate shares the pharmacological actions of the dinitrate and is the main active metabolite formed after administration of isosorbide dinitrate,¹³ but it has a much longer half-life (5.1 h). The mononitrate therefore seems to represent a better long-acting nitrate for intravenous bolus use in acute pulmonary oedema. It produced appropriate symptomatic and haemodynamic benefits in an open study of acute pulmonary oedema,⁸ but no randomised, prospective comparison has been made with furosemide, and no intravenous preparation is yet available.

For intravenous nitrate therapy to displace furosemide for the management of acute pulmonary oedema, it needs to be effective in a single bolus injection in most cases, must be safe to use in the presence of moderate hypotension, and must be effective in patients on chronic long-acting nitrate or diuretic therapy. Bolus isosorbide dinitrate has not yet been shown to fulfil these criteria; bolus isosorbide mononitrate might, but a large, randomised prospective comparison with furosemide or a furosemide/isosorbide dinitrate combination is required. The evidence so far suggests that intravenous nitrates should have the potential to displace furosemide as first-line therapy for acute, cardiogenic pulmonary oedema in

the near future. To be accepted, however, the nitrate formulation may need further refinement.

Michael Gammage

Department of Cardiovascular Medicine, University of Birmingham and University Hospital Birmingham NHS Trust, Edgbaston, Birmingham B15 2TH, UK

- 1 Chatterjee K, Parmley WW, Ganz W, et al. Haemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. *Circulation* 1973; **48**: 1183-93.
- 2 Nelson GIC, Silke B, Ahuja RC, Hussain M, Taylor SH. Haemodynamic advantages of isosorbide dinitrate over frusemide in acute heart failure following myocardial infarction. *Lancet* 1983; **i**: 730-32.
- 3 Biddle TL, Yu PN. Effect of furosemide on haemodynamics and lung water in acute pulmonary edema secondary to myocardial infarction. *Am J Cardiol* 1979; **43**: 86-90.
- 4 Mukherjee SK, Katz MA, Michael UF, Ogden DA. Mechanisms of hemodynamic actions of furosemide: differentiation of vascular and renal effects on blood pressure in functionally anephric hypertensive patients. *Am Heart J* 1981; **101**: 313-18.
- 5 Pickkers P, Dormans T, Smits P. Direct vasoactivity of frusemide. *Lancet* 1996; **347**: 1338-39.
- 6 Northridge D. Frusemide or nitrates for acute heart failure? *Lancet* 1996; **347**: 667-68.
- 7 Lal S, Murtagh JG, Pollock AM, Fletcher E, Binnion PF. Acute haemodynamic effects of frusemide in patients with normal and raised left atrial pressures. *Br Heart J* 1969; **31**: 711-17.
- 8 Gammage MD, Murray RG, Littler WA. Isosorbide-5-mononitrate in the treatment of acute left ventricular failure following acute myocardial infarction. *Eur J Clin Pharmacol* 1986; **29**: 639-43.
- 9 Bosc E, Bertinchant JP, Hertault J. Utilisation de la trinitrine injectable (bolus de 3 mg) dans le traitement de l'edeme pulmonaire cardiogénique. *Ann Cardiol Angiol* 1982; **31**: 477-80.
- 10 Morrison RA, Weigand UW, Jahnchem E, et al. Isosorbide dinitrate kinetics and dynamics after intravenous, sublingual and percutaneous dosing in angina. *Clin Pharmacol Ther* 1983; **33**: 747-56.
- 11 Sporn-Radun S, Betzein G, Kaufmann B, Liede V, Abshagen U. Effect and pharmacokinetics of isosorbide dinitrate in normal man. *Eur Clin J Pharmacol* 1980; **18**: 237-44.
- 12 Taylor T, Chasseaud LF, Doyle E. Pharmacokinetics of isosorbide dinitrate after intravenous infusion in human subjects. *Biopharm Drugs Dispos* 1980; **1**: 149-56.
- 13 Down WH, Chasseaud LF, Grundy RK. Biotransformation of isosorbide dinitrate in humans. *J Pharm Sci* 1974; **63**: 1147-49.

Connexin 26 gene mutation and autosomal recessive deafness

See pages 394, 415

Genetic deafness is common, with an estimated prevalence of 1 per 2000 births. Writing in 1853, before the laws of mendelian inheritance had even been promulgated, Sir William Wilde recognised that the pattern of transmission of deafness varied from family to family, and he clearly identified autosomal dominant, autosomal recessive, and X-linked forms.¹ Latterly, attempts by researchers to identify homogeneous families on the basis of associated clinical features have led to the recognition of the clinically distinct syndromic forms of deafness, which have formed the basis of much recent progress.²⁻⁵ These advances represent a triumph for the rigorous clinical discipline of syndrome delineation, and the molecular diagnostic applications accruing will be widely valued by geneticists and their patients. However, these new investigations are likely to be limited in their application by the relative rarity of the individual syndromes to which they appertain. Most deaf patients, even with a family history suggesting a genetic cause, have no associated clinical features and are said to have non-syndromic hearing loss.

1997 will be seen as a watershed for genetic advances in non-syndromic deafness because of three separate developments. First was the report from Kelsell and colleagues⁶ that mutations in the connexin 26 (Cx 26) gene

caused deafness in families with both autosomal dominant and recessive patterns of transmission. Second, a mutation in the human homologue of the *Drosophila* gene, *diaphanous*, was identified in a large Costa Rican family with autosomal dominant deafness.⁷ Finally, the myosin VIIA gene, already known to be mutated in a subgroup of patients with Usher's syndrome, was additionally found to cause both autosomal recessive and autosomal dominant forms of non-syndromic deafness.⁸⁻¹⁰ Although the epidemiological significance of mutations in human *diaphanous* and myosin VIIA remains unclear in terms of their overall contribution to deafness in the general population, several reports have combined to underline the importance of the *Cx 26* gene with respect to the aetiology of autosomal recessive forms of deafness.¹¹⁻¹³ Initial data suggest that 50–80% of autosomal recessive congenital deafness may be due to the *Cx 26* mutation and that up to 70% of such mutations are due to deletion of a single nucleotide—loss of a guanine (G), leading, through a frameshift mechanism, to premature termination of the protein.

Inherited forms are thought to be responsible for approximately half of all cases of congenital deafness. The commonest inheritance pattern among non-syndromic deaf families is autosomal recessive, estimated to account for up to 75% of all such cases. However, in clinical practice, autosomal recessive non-syndromic deafness can be recognised only after the birth of a second affected child, because of the clinical non-specificity of congenital deafness as a presenting feature. Consequently, genetic counselling of families with a single deaf child has always had to be along unsatisfactory empirical lines, which would take account of the known chance of recessivity in the context of clinically indistinguishable deafness of environmental aetiology, new dominant mutations, and so on. In practical terms, couples with one congenitally deaf child are counselled a 10% recurrence risk, in the full knowledge that, were it possible to identify those families in which the deafness is autosomal recessive, the appropriate risk would be 25%.

The two related reports in today's *Lancet* addressing the value of *Cx 26* mutation analysis in investigating sporadically occurring deafness are therefore important. Not only do these reports prompt a timely re-evaluation of the appropriate investigation of the congenitally deaf child but they also serve to alter clinical practice in genetic counselling for deafness.

Xavier Estivill and colleagues show that about 50% of autosomal recessive non-syndromic deafness is due to *Cx 26* mutation, consistent with their previously published data.¹¹ More importantly, these investigators identified mutations at this locus in 37% of individuals with sporadically occurring deafness; almost a third of the mutations were due to homozygosity for the G deletion. Less striking, but highly significant nonetheless, are the data from Nicholas Lench and colleagues suggesting that approximately 10% of patients with sporadically occurring deafness have *Cx 26* mutations, and that three of the six mutations are homozygous for the G deletion. (It should be noted that the various contributors to this rapidly emerging area of research have yet to agree on the terminology for the G deletion, some referring to 30delG and others preferring 35delG.) It remains to be established, over much larger studies of sporadically occurring, congenital deafness whether the figure of 37% or 10% applies to individual populations. The prevalence

of the G deletion in *Cx 26* may also vary in different populations, as has previously been observed for the $\Delta F508$ mutation in the cystic fibrosis gene. Of more immediate relevance is the challenge that the possibility of testing for this mutation in deaf individuals and their families poses to clinicians investigating such cases.

The investigation of the congenitally deaf patient varies widely among paediatricians, otolaryngologists, audiological physicians, and clinical geneticists. This absence of agreed guidelines probably reflects the different backgrounds of clinicians investigating deafness. However, there has also been a reluctance to investigate, on the grounds that a cause that might alter management was unlikely to be identified. The data reported today render this view obsolete and should prompt a re-evaluation of practice by all concerned, especially since identification of *Cx 26* mutation will preclude the need for other aetiological investigations, often of a more invasive nature.

To date, the mutations found have all been identified under the aegis of research. As with so many other developments in molecular genetics, health services must identify avenues by which research discoveries can be rapidly incorporated into clinical service. For the UK, what better test of the flexibility of the National Health Service in this much heralded anniversary year can there be than to see the development of pertinent research, such as *Cx 26* mutation and non-syndromic deafness, for clinical services, where it clearly has a large part to play in moulding modern clinical practice?

William Reardon

Department of Clinical Genetics and Fetal Medicine, Institute of Child Health, London WC1N 1EH, UK

- 1 Wilde WR. Practical observations on aural surgery and the nature and diagnosis of diseases of the ear. London: Churchill, 1853.
- 2 Abdelkac S, Kalatzis V, Heilig R, et al. A human homologue of the *Drosophila eyes absent* gene underlies branchio-oto-renal (BOR) syndrome and identifies a novel gene family. *Nat Genet* 1997; **15**: 157–64.
- 3 Neyroud N, Tesson F, Denjoy I, et al. A novel mutation in the potassium channel gene *KVLQT1* causes the Jervell and Lange-Nielsen cardioauditory syndrome. *Nat Genet* 1997; **15**: 186–89.
- 4 Tyson J, Tranebjaerg L, Bellman S, et al. IsK and KvLQT1: mutation in either of the two subunits of the slow component of the delayed rectifier potassium channel can cause Jervell and Lange-Nielsen syndrome. *Hum Mol Genet* 1997; **6**: 2179–85.
- 5 Everett LA, Glaser B, Beck JC, et al. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). *Nat Genet* 1997; **17**: 411–22.
- 6 Kelsell DP, Dunlop J, Stevens HP, et al. Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997; **387**: 80–83.
- 7 Lynch ED, Lee MK, Morrow JE, Welch PL, Leon PE, King M-C. Nonsyndromic deafness DFNA1 associated with a mutation of a human homolog of the *Drosophila* gene *diaphanous*. *Science* 1997; **278**: 1315–18.
- 8 Liu X-Z, Walsh J, Mburu P, et al. Mutations in the myosin VIIA gene cause non-syndromic deafness. *Nat Genet* 1997; **16**: 188–90.
- 9 Weil D, Kussel P, Blanchard S, et al. The autosomal recessive isolated deafness, DFNB2, and the Usher 1B syndrome and allelic defects of the myosin VIIA gene. *Nat Genet* 1997; **16**: 191–93.
- 10 Liu X-Z, Walsh J, Tamagawa Y, et al. Autosomal dominant non-syndromic deafness caused by a mutation in the myosin VIIA gene. *Nat Genet* 1997; **17**: 268–69.
- 11 Zelante L, Gasparini P, Estivill X, et al. Connexin 26 mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans. *Hum Mol Genet* 1997; **6**: 1605–09.
- 12 Carrasquillo MM, Zlotogora J, Barges S, Chakravarti A. Two different connexin 26 mutations in an inbred kindred segregating non-syndromic recessive deafness: implications for genetic studies in isolated populations. *Hum Mol Genet* 1997; **6**: 2163–72.
- 13 Denoyelle F, Weil D, Maw MA, et al. Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene. *Hum Mol Genet* 1997; **6**: 2173–77.