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The Future of ORL-HNS and Associated Specialities Series

The future of neuro-otology

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What does the start of the new millennium hold for neuro-otology? There will certainly be changes in the way the sub-speciality is practised. Many of these changes relate to the way in which medical practice in general is changing and are largely driven by political, financial, educational and governance issues. To confine one's attention to areas of clinical and technological change, however, there are a number of specific areas in which we may expect to see exciting new developments. Some of these predictions are realistic, others more fanciful, but all are likely to come to pass in the foreseeable future.

Molecular biology

Tremendous recent developments in molecular biology are having an impact on all spheres of medicine and the state of the art is constantly changing. Many exciting advances in neuro-otology stem from the staggering progress in these fields. Genes codes amino acids and proteins are the fundamental currency of cellular transactions. Characterisation of the genetic basis of a disease allows definition of the role that the biochemical insult plays in the development of the disorder and the potential for modification of such a series of events is an exciting possible area for future research. Genetic characterisation is already known to us in the field of neuro-otology. The application of Knutson's 'two hit' model to familial cancer syndromes such as Neurofibromatosis type 2 (NF2) has driven the search for refinement of the diverse mutations of the NF2 gene on chromosome 22 that characterise this disorder. Clinical geneticists can already ascribe with considerable accuracy the risk to progeny of NF2 sufferers and completion of the mutation panel will, in the near future, allow definitive prediction in all families. Preclinical diagnosis will be the norm. Pre-implantation diagnosis will be a greater ethical problem for clinicians and affected families to face. This research is also carried over into the field of the sporadic unilateral vestibular Schwannoma. Tumour growth characteristics may be identifiable early in the evolution of the tumour and as will be discussed later, this information may dictate treatment. The idea of genetic manipulation of the disordered DNA of the affected gene is the philosophers stone to which molecular geneticists aspire. There are still formidable hurdles to overcome in the realms of tissue targeting and the mode of delivery, but it is not too fanciful to speculate that the future management of vestibular Schwannoma and indeed meningioma and glomus tumours will lie in the province of the molecular biologist.

The second area in which developments in molecular biology will continue to make a major impact is in deafness genetics. Any type of familial deafness whether syndromic or non-syndromic will come under scrutiny. Investigation of the genetic basis of named disorders such as otosclerosis or Menière's disease, in which familial cases lend themselves to study will become more prevalent. Both disorders currently evoke considerable debate in terms of pathogenesis and clarification will allow prevention or cure in the true sense. Our understanding of disorders associated with deafness such as Usher's syndrome, Pendred's syndrome and Waardenburg's syndrome has already been greatly enhanced by genetic insights but the most rapid future area promises to be in the field of non-syndromal hereditary hearing loss.[1] Over fifty genetic loci scattered throughout the genome have been identified using informative families and genetic tools such as linkage analysis. Several genes within these loci have been cloned for both autosomal and sex linked deafness. The products of these genes include the gap junction protein connexin 26, and structural proteins such as myosin 7. We thus have insight into the pathogenetic steps that lead to sensorineural deafness from failure of the hair cells of the inner ear. Some appetising possibilities are now apparent: mutation heterogenicity in the Pendred gene causing deafness without the thyroid dysfunction, genetic susceptibility to noise, a genetic predisposition to a stapes gusher or a large

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vestibular aqueduct, and perhaps most importantly a genetic predisposition to delayed progressive adult sensorineural deafness as a model for presbyacusis.

The human genome project should be finished by the year 2003. The genetic library will then be complete. All the books in it will have titles, and disorders will be confidently ascribed to one or more books. Disorders of spelling or pagination will be seen to give rise to certain disorders and the associated biochemical abnormalities will be readily recognised. It is highly likely that every individual will carry his or her genome smart card to be swiped routinely as a preliminary to consultation either at the general practitioner or at hospital. This simple screen, combined with a comprehensive yet rapid imaging protocol, would almost certainly provide the basis for diagnosis and treatment of most disorders in all fields not just in the special realm of neuro-otology and skull base surgery.

Advances in imaging

However impressed we may be by the current generation of magnetic resonance (MR) there can be no doubt that medical imaging is still in its infancy. We can confidently expect to be using MR to image down to and beyond the cellular level; indeed this technology is more or less available now. The notion of MR microscopy, a non-invasive method of acquiring a tissue diagnosis is not fanciful. Such technology would also yield an enormous amount of information about the pathology of inner ear disorders. Real time dynamic MR will eventually tell us what really does happen in the inner ear during an attack of Menière's disease and should also help us to decide once and for all what effect saccus surgery has on the process. Perfusion MR will tell us in real time what effects our surgery is having on the blood flow to the brain stem as we remove vestibular Schwannomas from the posterior fossa. Advances in 3 dimensional imaging, navigational surgery and remote surgery may allow us to operate without getting our hands dirty, and perhaps to direct surgery from our homes, hotel rooms or golf clubs. MR scanners will become as cheap and readily available as laptop computers, and whole body MR microscopy will complement the use of the genome swipe card at initial consultation.

Management of sensorineural deafness

Cochlear implantation

Changes will be seen in implant design, patient candidacy and in pharmacological manipulation of the auditory system.

The totally implantable cochlear implant. This is now in advanced stage of development and should be on the shelves in the next two or three years. Electric and piezo-electric microphones have been developed which can be implanted under the skin behind the ear or of the ear canal. They do have problems relating to frequency resolution and to possible extrusion. Other sensors have been developed which respond to movement in the tympanic membrane and ossicular chain including a piezo-electric bimorph cantilever, accelerometer and a fibre-optic lever system such as that developed at the University of Melbourne.[2] Whichever system is used it will require an implanted power source that can be recharged from outside the body.

Electrode design. Refinements of electrode design will lead to a more efficient use of power and a lower incidence of unwanted non-auditory effects. Increased electrode numbers may increase the efficiency of information transfer and the information from neural response telemetry should lead to more accurate fitting of speech processors.

Candidacy. The spectacular success of cochlear implantation in the habilitation of adults with an acquired profound hearing loss has lead to a revision of the audiological selection criteria. Individuals with less severe degrees of deafness are now regularly implanted. In most countries a best aided speech discrimination score of 20 per cent is now the threshold and in some a score as high as 40 per cent is accepted. The proposal by Gantz[3] to implant adults with a hearing loss confined to the high frequencies using a short electrode that just lies in the proximal end of the basal turn, indicates how the cochlear implant threatens to encroach on the traditional domain of the hearing aid. The degree to which this process of encroachment continues will depend amongst other things on the extent to which the purchasers of implants are prepared to finance this sort of expansion at present costs.

In the area of paediatric cochlear implantation we may expect to see changes. Vaccines against meningitis type C are currently being introduced into the UK. If effective vaccines are developed against type B, which is the commonest type to cause deafness, we could see a reduction in paediatric implant candidates by 25 per cent. Against that there will be an increase in numbers as less severely deaf children are implanted. Age at implantation will go down as patterns of screening and referral change and the ability to assess the hearing of very young children improves.

Nerve growth factors. The Melbourne group have already begun to study the possible use of neurotrophins such as NT3 and neuronal cytokine transforming growth factor NTG3 to prevent loss of neurons in the auditory nerve and thus optimise the effects of cochlear implantation.

Plasticity issues. One of the greatest challenges which is already being addressed is the identification of the factors which affect the changing plasticity in the auditory pathways as the child ages. Neurotrophins are assumed to be responsible for the establishment of neural networks in the primary auditory cortex and association areas during the first few years of life. They are also assumed gradually to be switched off as the child gets older with the result that older children and adolescents gain little speech recognition from implantation. Clark[2] has suggested

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that auditory plasticity might be restored by delivery of the critical neurotrophin to the auditory system by means of the implant device itself. This might in turn trigger the release of neurotrophin in the cochlear nucleus which might then reactivate the gene for the neurotrophin. It is envisaged that neurotrophin release might cause neural sprouting to occur at higher levels in the auditory system and encourage neural connections in the auditory pathways.

Hair cell regeneration. A potential threat to cochlear implant surgery is the recent interest in hair cell regeneration. As yet the evidence for this is not impressive and has come from experiments on the vestibular system of guinea pigs. Cochlear hair cell regeneration has not been demonstrated and little if anything is known about possible trophic factors that might stimulate regeneration. Recently a number of growth factors and neurotrophins have been identified that can increase immature-looking hair bundle production in damaged vestibular sensory epithelium in vitro and in vivo, but how these findings apply to the cochlea remains to be clarified. Nevertheless we cannot discount the possibility that work in this field might eventually bear fruit.[4]

Brave new world aspects of cochlear implantation. As Balkany[5] pointed out at the British Academic Conference in Cambridge in 1999, there is no technical reason why an individual with a cochlear implant with a radio antenna should not be able to receive messages, transmitted from a friendly or not so friendly remote source, perhaps beamed via a satellite link. Such an individual's location on the planet could in theory be plotted to within a few metres. Alternatively a cochlear implant system could relatively easily incorporate an interpreting facility capable of translating any received language into that of the listener. It does not require a great leap of the imagination to see that in the future individuals without cochlear implants could be at a decided disadvantage, a state of affairs that would doubtless appeal to the manufacturers.

Auditory brain stem implantation

This device grew out of cochlear implant technology and addresses the problem of the individual totally deaf because of a lesion at cochlear nerve level. These individuals are unsuitable for cochlear implantation. The coded electrical stimulus is therefore delivered to the cochlear nucleus. Nearly all the recipients have been adult NF2 sufferers. Evolution is still at an early stage and there is no doubt that there will be advances in electrode design as penetrating rather than surface electrodes are developed and appropriate stimulation strategies are applied. It is only a matter of time before other types of cases are implanted including congenitally deaf children with cochlear nerve agenesis. Extensive experience of the effectiveness and long term risks of the ABI in adults must however be gained before the technology is applied to children.

Implantable hearing aids

The question of implantable and semi-implantable hearing aids for the management of moderate degrees of sensorineural deafness is a difficult one. The concept of an aid that is totally implantable is appealing from an aesthetic point of view. Furthermore from a functional standpoint they are attractive, because they should overcome the problems of acoustic feedback as well as getting rid of the meatal occlusion effect. However they should ideally be simple to insert preferably as a day case procedure under local anaesthesia by generally trained otologists. They should function effectively and should cause no injury to the ossicular chain. They should be cheap. At the present time many of these conditions are unfulfilled. Huttenbrink[6] has stated that development in digital hearing aid technology will eventually outflank that of implanted hearing aids, and as long as conventional digital aids are a cheaper alternative, purchasers may be hesitant about funding implantable devices in the immediate future. In the long term however new concepts and cheaper technology seem likely and this remains an exciting field with great potential for the otologic surgeon.

Vestibular Schwannoma surgery

As indicated previously it seems likely that eventually treatment of vestibular Schwannoma will be in the hands of the molecular biologist, who will be able to manipulate the disordered gene by encouraging the production of the missing tumour inhibiting protein. In the meantime we have to consider the position of surgery and the role of stereotactic radiotherapy. The latter modality has an instant appeal in that it purports to avoid the need for surgery. It is now being widely recommended in some quarters as an alternative to surgery. The claims of its protagonists need to be subjected to rigorous scrutiny. Talk about tumour control rather than eradication, fears about the possible malignant change in benign tumours, doubts about its alleged freedom from side effects to adjacent and not so adjacent neural structures should all make neuro-otologists sceptical. We should welcome level 1 evidence of its efficacy but until it is available we should be cautious and would do well to bear in mind the *British Medical Journal* editorial headline which described it as 'Triumph of marketing over evidence based medicine.'[7]

One might imagine a change in the way in which decisions are made about conventional excisional surgery for vestibular Schwannomas. If it was possible to predict the rate at which an individual tumour might grow it would help surgeons to decide which tumours to remove. Such predictions might be possible from detailed imaging techniques or perhaps by identifying a reliable cellular marker in tissue obtained at endoscopic biopsy. Vascular Endothelial Growth Factor (VEGF) is one of a number of possible candidate markers currently under scrutiny.

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The future is not easy to predict. Janus, who looked in both directions at once would doubtless agree, although it is debatable whether the images that history has left us are in any way more reliable. It is probable that these speculations grossly underestimate the exciting developments that await us as neuro-otologists in the decades to come. It will be fun being proved wrong.

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