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Microcephaly is a rare condition, but nevertheless has the potential to tell us a lot about how the human brain evolved and what controls neurogenesis. In their review article on this topic, Gemma Thornton and Geoff Woods lead us through the genetics of primary microcephaly highlighting the fact that 4 genes responsible for this condition are all critically associated with the centrosome and mitosis during neurogenesis in utero. Thus this group of rare conditions with an incidence of between 1:30,000 and 1:2,000,000 may be able to provide unique insights into the processes that explain what caused the human brain to evolve.

Jack Price in his review article rehearses the arguments for the utility of stem cells in the treatment of disorders of the CNS. He concentrates on four main types of stem cells for CNS repair; endogenous neural precursor cells and their recruitment; exogenously grown neural stem cells which are transplanted; ES cell culture and manipulation with subsequent engraftment and finally non neural stem cell transplants to replace damaged neuronal networks. This is a clearly written account by an acknowledged expert in the field and is a very useful summary of what can seem a rather baffling, complex and often hyped field.

What is the best way to count cells in histological sections of nervous tissue? This is the question that Stan Lazic addresses in his review on stereology which is the target of our "Techniques in Neuroscience" series in this issue of the ACNR. Stan takes us through the principles underlying the older and more modern approaches to stereology highlighting the limitation and advantages of the various different approaches. In so doing he provides us with a very useful summary of an often neglected area of neuroscience research but which is often critical in characterising anatomy and pathology in a range of neural structures both in health and disease.

Colour vision is a peculiar thing as we assume that what we see as a certain colour is just that. Whilst we can assume this, and live our lives according to this rule, it is of course an artificial situation as Petroc Sumner explains. In this beautiful account in the "Visual Neurioscience" series, he explains how the colour system operates in the human retina and its CNS projections, as well as how it varies in other species- such that you may be alarmed to know that your pet goldfish will be viewing you very differently to how you see yourself!! Finally he touches upon adaptation and colour constancy, in what is a very interesting and stimulating article.

The use of cervical collars is widely advocated in some circles whilst frowned upon by others primarily because there is often confusion as to what are the indication, uses and types of such devices. We are therefore fortunate to have Datta et al take us through this issue. They highlight the different types of orthosis for neck control including those used to treat traumatic injuries of the cervical spine as well as those considered in patients with neurological disorders such as motor neuron disease.

The recent ABN case report winner by Monaghen et al is written up in this issue of the ACNR and makes for sober reading. The patient had a Wernicke-Korsakoff syndrome with the 'pulvinar sign' and had treatment with TPN which did not contain thiamine. This nicely written up case thus highlights that making a diagnosis is one thing, but making sure it is probably treated is another.

The diagnosis of patients with idiopathic normal pressure hydrocephalus is often fraught with difficulty; do they truly have it or are the enlarged ventricles simply secondary to a neurodegenerative, atrophic or vascular small vessel process? In the article by Peter Whitfield and Maric Czosnyka we are treated to a superlative account of the best approach highlighting the positive predictive value of the various tests employed to help in the diagnosis and thus treatment of this condition including shunting. In addition a pragmatic account is given on the use and maintenance of shunts in this and other hydrocephalic conditions which overall produces a well-rounded and instructive account of a complex area of neurological practice.

Dr Felix Geser in the historical section of ACNR explores the roots of neuropathology and clinical neuroscience. He takes us through its origins in the pre 20th Century highlighting the main players and their contribution to the field and how this evolved out of a number of disparate, separate strands of scientific practice and discovery. The article is a fascinating personal perspective on a very exciting time of scientific and medical discovery.

Finally we have our usual book and journal reviews- the latter is dominated by Dr Coles an his passion for calculating numbers needed to treat!! So we hope you enjoy this latest issue and don't forget to visit the website and feedback suggestions for improvement.

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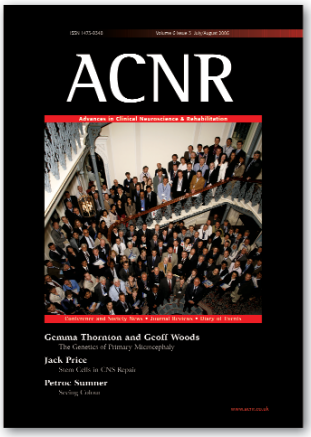

Cover picture shows delegates at the Association of British Neurologists Spring Scientific meeting in the foyer at the Grand hotel, Brighton, UK. For a report on this meeting see page 35.

The Genetics of Primary Microcephaly

Clinical definition

Autosomal recessive primary microcephaly (MCPH) is the term used to describe a genetically determined form of microcephaly previously referred to as *microcephaly vera* or *true microcephaly*.[1,2] It is clinically diagnosed using the following guidelines;

1. Microcephaly (> -3SD) is present at birth.
2. Degree of microcephaly does not progress throughout lifetime.
3. Mild to severe mental retardation without other neurological findings (fits are rare).
4. Height/weight/appearance are all normal (except with mutation in *MCPH1*, where some reduction in height may be observed).

MCPH affects neurogenesis *in utero*. The brains of affected individuals are characterised by a significant reduction in the size of the cerebral cortex (presumably the cause of the observed mental retardation). There is also a smaller general reduction in the rest of the central nervous system (CNS), although the architecture is preserved.[3,4]

Inheritance of MCPH

This disorder is rare in most populations, with incidences ranging from 1/30,000 to 1/ 2,000,000, but is more frequent in populations practicing consanguineous marriage.

Despite MCPH cases presenting with almost indistinguishable features, this disorder is genetically heterogeneous. Six autosomal recessive loci have been identified so far and named *MCPH1-6* (reviewed in reference 1). Each locus was mapped from a single large consanguineous family by autozygosity mapping using microsatellite markers or SNPs spaced throughout the human genome. Studies conducted to date suggest that *MCPH5* is the common locus in all populations.[5,6]

For these loci, four of the genes which are mutated in MCPH have been identified, *MCPH1 (Microcephalin), MCPH3 (CDK5RAP2), MCPH5 (ASPM)* and *MCPH6 (CENPJ)*. The current knowledge for each form of MCPH is summarised in Table 1.

The MCPH genes

A brief summary of current knowledge for each is given below, in chronological order of discovery.

MCPH1

MCPH1 encodes an 835aa protein which was named Microcephalin.[2] *MCPH1* mutations are a rare cause of primary microcephaly, and affected individuals display a broader phenotype than reported for other forms of MCPH.[2] It has been shown that *MCPH1* primary microcephaly is allelic to premature chromatin condensation syndrome (PCC),[7] which led to the identification of Microcephalin as a negative regulator of Condensin II, a protein complex involved in chromosome packaging.[8] Clinically, patients with mutations in *MCPH1* display an increased number of prophase-like cells on standard cytogenetic analysis – a clinically useful discrimination unique to *MCPH1* microcephaly.

Microcephalin contains three BRCA1 C-terminal (BRCT) domains, also found in DNA repair and cell cycle checkpoint proteins.[2] These domains seem to bind phosphoproteins to control DNA damage-induced cell cycle checkpoints.

Three functions have so far been reported for Microcephalin: small-interfering-RNA (siRNA)-mediated depletion of *MCPH1* identified a role in regulating chromosome condensation during the cell cycle (hence PCC); a role in DNA damage response through the regulation of BRCA1 and Chk1 ; and MCPH1 (as BRIT1) was identified as a negative regulator of the catalytic subunit of telomerase.[1,7,8]

MCPH5

MCPH5 mutation is the most common cause (~50% of cases) of the MCPH phenotype.[5] It is a large gene and encodes the human orthologue of the *Drosophila* gene *abnormal spindle* (asp), called "abnormal spindle mutated in microcephaly" (ASPM). The reported mutations are spread throughout the *ASPM* gene and result in truncated ASPM protein products ranging in size from 116 – 3357aas.[1,6]

ASPM is predicted to contain an *N*-terminal microtubule binding domain, two calponin homology domains (common to actin binding proteins), 81 isoleucine-glutamine (IQ) repeat motifs (predicted to change conformation when bound to calmodulin), and a *C*-terminal region of unknown function.[4]

Structural projections and comparison with myosin suggest that when ASPM is present at the centrosome, it assumes a semi-rigid-rod-conformation, with microtubules bound by the N-terminus and centrosomal components interacting at the C-terminus.

ASPM is found near the centrosome and is thought to play an essential role during neurogenic mitosis. Studies have shown that *Drosophila asp* recessive mutants are larval lethal or infertile with dividing neuron progenitors unable to conclude asymmetric cell division.[9] The asp protein is required for microtubule organisation of the mitotic spindle poles and the central spindle in mitosis and meiosis.[9,10] In contrast, *ASPM* mutations in humans produce a mitotic defect restricted to the brain. This may be due to a functional overlap between ASPM and NuMA (Nuclear mitotic apparatus protein 1), another protein shown to regulate spindle dynamics.

MCPH3

MCPH3 encodes Cyclin dependent kinase 5 regulatory associated protein 2 (CDK5RAP2).[11] Little is yet known about the function of CDK5RAP2, however it was originally identified as a negative regulator of cyclin dependent kinase 5 (CDK5) through its inhibition of CDK5 regulatory protein 1 (CDK5R1). CDK5 is divergent from the rest of the CDK family, other members of which are ubiquitously expressed and regulate mitotic checkpoints. In contrast CDK5 expression is restricted to the brain, where it regulates the creation,

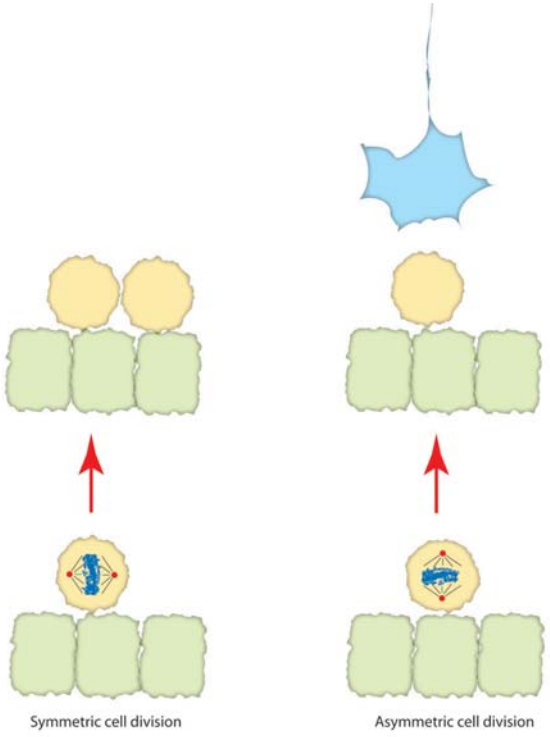

Figure 1: Cell divisions during neurogenesis
Neural progenitor cells (yellow) lie above the neuroepithelium (green cells) in the developing nervous system. During cell division, the centrosomes (red circles) produce a mitotic spindle (black lines) of microtubules attached to the condensed chromosomes (indicated in blue). The orientation of the spindle to the neuroepithelium is dependant on the positioning of the centrosomes. Alignment parallel to the neuroepithelium results in symmetric cell division, increasing the progenitor pool (left hand diagram).
In contrast, alignment of the spindle perpendicular to the neuroepithelium results in asymmetric cell division which maintains the progenitor pool cell numbers whilst producing neuronal committed precursors (right hand diagram).

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Table 1: The MCPH loci

MCPH	Locus	Gene	Known/predicted domains	Known/predicted functions	Localisation at mitosis
1	822-pter	Microcephalin	• 3 BRCT domains	• Regulation of chromosome condensation during cell division • DNA damage repair through BRCA1 regulation • Inhibitor of Topoisomerase catalytic subunit	Centrosome
2	19q13 1-13.2				
3	9q34	CDK5RAP2	• N-terminal α-tubulin association	• Negative regulation of CDK5 • Promotes production of microtubules at centrosomes	Centrosome
4	15q5-q21				
5	1q31	ASPM	• Microtubule association domain • Calponin homology • IQ motifs	• Direct interaction with cytoskeleton • Binds microtubules at N-terminus • May bind centrosomal components at C-terminus	Centrosome
6	13q12.2	CENPJ	• Tcp10 domain • Microtubule depolymerising domain • 4.1R-135 binding domain	• Depolymerises microtubules • Depletion causes multiple spindles • Interacts with 4.1R-135	Centrosome

migration and degeneration of neurons.[12] The Drosophila orthologue *centrosomin (cnn)* has been studied and *cnn* mutants display reduced cell numbers in both the central and peripheral nervous system.[13] CDK5RAP2 is located at the centrosome throughout the cell cycle and its N-terminus interacts with the γ-tubulin ring complex, which initiates microtubule nucleation,[11] required for spindle formation. The restriction of CDK5RAP2 mutations to MCPH and not a more widespread growth disorder is probably due to the complementary tissue expression pattern of a mammal specific homologue called Myomegalin.

MCPH6

The *MCPH6* gene encodes centromere-associated protein J (*CENPJ*, also known as *CPAP*, centrosomal protein 4.1- associated protein).[11,14] Despite its name, CENPJ is a centrosomal protein, and this localisation depends on non-erythroid protein 4.1 splice isoform 135 (4.1R-135).[14] Intriguingly, this protein is also responsible for recruiting NuMA to the centrosome. It has been demonstrated that CENPJ associates with the γ-tubulin ring complex, and *in vitro* evidence suggests that CENPJ may modulate microtubule nucleation and depolymerise microtubules.[15] This may suggest that an inverse relationship exists between CENPJ and CDK5RAP2 in regulating microtubule dynamics. RNAi depletion of CENPJ in HeLa cells resulted in a mitotic arrest with >40% of cells containing multipolar spindles, a finding similar to *asp* mutant neuroblasts in *Drosophila*.[9,16]

Both *Drosophila* and *C. elegans* contain a single orthologue to CENPJ. In worms, the orthologue SAS-4 is one of only five proteins essential for centriole duplication during mitosis in *C. elegans*.[17]

Are MCPH proteins key regulators of brain development?

All four MCPH genes identified are expressed in the ventricular zone (site of prenatal neuron production) during neurogenesis.[1] Furthermore, all of the genes encode proteins which are implicated in regulating mitosis, and the localisation data for these proteins suggests a key role for the centrosome or spindle pole body in the aetiology of this disorder.

This makes sense, as neurogenesis has been shown to rely on balancing symmetric versus asymmetric cell divisions in neural precursors. Symmetric divisions increase the progenitor pool, whilst asymmetric divisions result in the production of one progenitor and one neuron (Figure 1). This outcome is determined by the orientation of the mitotic spindle relative to the neuroepithelium, which in turn is determined by the positioning of the centrosomes upon mitotic commitment.[18] It is intriguing to speculate therefore that the reduced number of neurons leading to MCPH may be a result of a failure to regulate spindle assembly/orientation during the critical period of neurogenesis. If this is so, then the study of these proteins may provide valuable insight into the production of neurons by neural stem cells.

Conclusions

Studies to identify the proteins disrupted in the recessive disorder primary microcephaly have identified four centrosomal proteins that seem to be crucial for mitosis during neurogenesis. Currently it is unclear which specific function of each protein is critical to neuron production, although studies of orthologous proteins in model organisms have provided some clues. However, the MCPH proteins have all undergone Darwinian positive selection in the primate/human lineages, which may also have altered their functions.[1,19,20]

As the field evolves, studies of the effect of MCPH protein disruption in affected individuals may provide us with a clearer model of the factors regulating human neurogenesis. Furthermore, combining the study of MCPH protein function with the nascent field of neural stem cell based therapies may ultimately enable controlled production of specific neural lineages – a potential benefit to those suffering from a number of neurodegenerative disorders.

In the immediate future however, the identification of the causative genes for MCPH provides a number of benefits for affected populations. Prenatal diagnosis allows detection of the recurrence of the disorder in affected families, postnatal diagnosis allows us to distinguish the disorder from other possibilities, and most importantly, carrier testing can be offered to consanguineous families where the disorder is known to occur.

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Stem Cells in CNS Repair

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There is no question that stem cells are an enormously hot topic. You can be sure something is afoot when stem cell scientists become US Presidential Special Advisors, report to House of Lords Select Committees, are interviewed on Newsnight, and appear in Doonsbury cartoons. So, what are the prospects that stem cells will have any influence on clinical neuroscience? In this short review, I will identify what seem to me the four most immediate areas of impact.

Endogenous stem cells

Stem cells are usually defined as having two seminal properties: the capacity for extended self-replacement, and multipotentiality (defined in the nervous system as the potential to generate neurons, astrocytes, and oligodendrocytes). The mammalian nervous system is poor at cell regeneration, so the first question is do endogenous neural stem cells (NSCs) exist? If adult brain tissue is cultured under non-adherent conditions and high concentrations of growth factors, then stem cells indeed emerge to give rise to 'neurospheres'—aggregates of expanding brain tissue.[29] In vivo, this stem cell activity is concentrated in two specific regions: the granule layer of the hippocampus and the subependymal layer, areas rich in adult neurogenic activity.[19] Remarkably, at these in vivo sites the stem cells themselves turn out to be 'specialised' astrocytes.[8] So, if the brain does have stem cells, why does it not repair itself more successfully? Of course, 'lower' vertebrates do repair damaged neural tissue: it is just we mammals that do so poorly. Is that because of a dearth of resident stem cells, or have we lost the repair mechanisms?

Probably, it is the former. Nakitomi et al (2002) infused FGF2 and EGF (the growth factors that expand neurospheres) into mouse hippocampus following ischaemic brain injury and replaced a substantial proportion of lost CA1 pyramidal neurons, far more than seen in controls.[22] This implied that if stem cells can be expanded in vivo then they can indeed home to sites of cell loss and differentiate appropriately. One therapeutic avenue, therefore, would be to drive this process.

NSC Engraftment

If there are not enough endogenous cells, can we graft more? Cells from human 'neurospheres' have been grafted into animal models of disease. They differentiate to an extent,[9,11] but reports of functional effects have been few and inconsistent.[15,23] Another strategy is to use conditional-immortalisation to generate lines of NSCs in culture. NSCs from aborted fetal tissue can be engineered to express an immortalising oncogene (typically SV40 T or c-myc). Such cells expand almost infinitely in culture, without their multipotentially being compromised.[3,10] So when the oncogene is turned off (using an engineered molecular switch), the cells still differentiate as neurons, astrocytes, and oligodendrocytes. Much evidence suggests that immortalised NSC lines grafted into the damaged brain can replace lost neurons and glia, inhibit further neurodegeneration, and bring about a degree of functional improvement.[27] There are now reports of human lines, grown to clinical grade under GLP conditions that would be suitable for clinical studies.[26] Evidence suggests these lines are safe and have efficacy in animal models of stroke and are suitable for clinical trials. These may prove to be the earliest NSCs to provide proof-of-concept for this approach to neurodegeneration.[1]

ES Cells

Embryonic stem cells (ES cells) justifiably get the lion's share of stem cell publicity because they have the greatest clinical potential, but they also have the most profound ethical and technical concerns. Because they are derived from blastocytes (cells of the pre-implantation embryo) they are not just multipotential but pluripotential; that is, they can generate all the cell types in the body. Their potential in regenerative medicine is therefore enormous, but the problems are commensurately large.

- ES cells can be tumorogenic when undifferentiated.[5]
- Their wide potential requires precisely controlled differentiation, otherwise they could generate inappropriate cell types following engraftment.
- Human ES cells will be difficult to grow to GLP because they require 'feeder cells' and cannot be grown in defined conditions.[6]

There has been startling progress in generating neural cells from mouse ES (mES) cells. For example:

- Wichterle et al (2002) manipulated mES cells to generate progenitor cells, which generated motor neurons following engraftment into a chick embryo.[32]
- Kim et al (2002) and Björklund et al (2002) both engrafted mES cells into a rat model of Parkinson's Disease and generated graft-derived dopaminergic neurons and improvement of motor dysfunction.[4,12]

Nonetheless, human (hES) cells will be required for clinical studies, and progress here is more modest. Such cells have been shown to engraft neonatal or adult rodents,[21,28,31,33] but there are few reports yet of functional improvement following engraftment with hES cells.[25] Clinical trials with hES-derived NSCs are probably still a little way off.

Non-CNS stem cells

Several other stem cell types have been engrafted into the damaged CNS of experimental animals in order to evaluate their potential for repair. They include

- Olfactory ensheathing cells
- Haematological Stem Cells (HSC: Bone marrow- or Umbilical Cord Blood-Derived)
- Mesodermal Stem Cells (MSC).

The target indications have been equally diverse including:

- Stroke
- Spinal Cord injury
- Traumatic Brain injury
- Multiple Sclerosis
- Batten's Disease.

There are too many individual studies to discuss in this short article, but a common thread links many of the studies. The conventional view of adult (or fetal) stem cells was that they were tissue restricted: ie. NSCs give nervous tissue; HSCs give blood cells; etc. This view was challenged by studies indicating that tissue-specific stem cells could transdifferentiate into progeny from a different lineage. To cite just one pivotal study, Mezey et al (2000) presented *prime facia* evidence that bone marrow infused into mice differentiated into neurons and glia: the so called, 'Blood into Brain' discovery.[18] The number of 'transdifferentiating' cells are low, however, and might be better explained by fusion of host and grafted cells.[17] None the less, the findings have proven sufficiently robust to maintain interest, and both HSCs (from bone marrow and umbilical cord) and MSCs are actively being studied at this time for their potential to repair CNS damage.

Several reports suggest that infusion of these stem cell types brings about functional improvement in animal models of disease, for example in stroke.[13] The question

that arises, however, is whether efficacy is linked to transdifferentiation. The case against is that functional recovery can be observed where little neural differentiation can be seen, and is often quite fast in comparison to cell replacement. Optimal recovery is observed in most laboratories when the stem cells are administered within a few hours post-lesion, suggesting a neuroprotective effect. They appear to induce structural change in the host brain rather than replacing lost cells, the 'classic' stem cell mode of repair. So while this approach is clearly 'cellular therapy' it might not be 'stem cell therapy' in the pure sense. Then again, NSCs in the studies cited above might also be working through means other than cell replacement: studies with both conditionally-immortalised NSCs and neurospheres suggest that they too repair where they do not replace.[15,20] Again, the evidence is that they have a neurotrophic or 'plasticity-inducing' effect on the host tissue.[24]

Clinical Prospects

So, how far are we from the clinic?

- As we have seen, ES cells have fundamental problems to overcome before they are likely to reach trials.
- Enhanced endogenous neurogenesis seems an attractive therapeutic approach and a number of growth factors and other agents can mediate an effect.[14,16] Evidence suggests that drug companies are pursuing this possibility.[2]
- Clinical grade, conditionally-immortalised hNSCs have been generated,[26] and clinical trials are reported to be imminent.[1]

The most advanced, however, are clearly the various non-neural cell types that have already entered clinical trials. Several rigorous trials have been presented, supported by strong preclinical data and scientific rationale. Examples are the trials of HSCs in Multiple Sclerosis.[30] Others, however, have generated considerable concern because their trial methodologies have not met international standards and patients have not been sufficiently followed-up for an accurate evaluation of efficacy to be made (see for example, reference 7). Others go further: some researchers have insisted that stem cell trials should not go ahead in the nervous system until the mechanistic basis for their action has been thoroughly understood.[3] This goes well beyond what is usually required of novel medicines of course, and is unlikely to be heeded. So will a few reckless trials blight the field, or will stem cells emerge as a fundamental paradigm shift in the treatment of neurodegenerative disease? Fortunately, not being a US Presidential Special Advisor, I do not have to read the future. 'Our responsibility', said Richard Feynman in a different context, 'is to do what we can, learn what we can, improve the solutions, and pass them on.' Stem cell researchers might do worse that to heed that advice.

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The author is a consultant for ReNeuron Ltd, a UK company developing stem cell therapies.

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Seeing Colour

Colour is such an integral part of our visual experience that most people assume perceived colour comes directly from the physical properties of objects themselves – my shirt *looks* yellow because it *is* yellow. That this assumption is not continually proved wrong by everyday experience is a testament to the cleverness of our visual system. But the assumption is wrong because colour is invented within the brain, and the colours we perceive are determined by many factors that differ between species, between people, between different parts of the retina, between each environment an object may be seen in, and also between moments in time. Therefore there is no consistent one-to-one mapping of the light entering my eye into the colour I perceive.

Yet, whenever and wherever I look at my shirt, it (nearly) always looks yellow. This is no happy accident: achieving such consistency underpins the main advantages of having colour vision – detecting and recognising objects by their colour.[1] In fact, one could say that the aim of a clever visual system is to create the illusion of simple correspondence between an object and its perceived colour – to enable us to live by that wrong assumption.

The physics

Electromagnetic radiation in the visible range (wavelengths between about 350 and 700nm) is not categorically different from other wavelengths of electromagnetic radiation, but it happens to be very useful for perceiving the world: lots of it reaches the Earth's surface from the sun and most objects reflect some portion of it. Crucially, differences in chemical and physical properties cause most objects to differ in the proportion of each wavelength they reflect, and this spectral signature, the object's 'reflectance spectrum', can potentially be used to identify the object.

Our visual system attempts to represent these useful differences in reflectance as differences in colour, such that objects reflecting mostly longer wavelengths are perceived as reddish, while those reflecting shorter wavelengths are perceived as bluish. However, the light reflected from each object is a product of both the reflectance spectrum and the incident light that hits the object in the first place, and the incident light will change between sun and shade, blue sky and cloud, indoors and out, and also due to different objects reflecting light towards each other. Thus every time we see an object, the actual pattern of wavelengths reaching the eye from it may be markedly different.[2]

Sampling the received light

Humans sample daylight mainly using three types of cone photoreceptor, which have different spectral sensitivity: longwave (L), middlewave (M) and shortwave (S) cones with peak sensitivities at about 560 nm, 530 nm and 430 nm respectively.[3] The fundamental building blocks of colour perception are created from the ratio of responses in each cone class. Relatively high L cone activity leads to perceiving red, relatively more M cone activity produces perceived green, and more S cone activity produces a blue sensation.

The outputs of the cones are coded by other retinal cells into two channels: a comparison between L and M cone signals (often referred to as red-green) and a comparison of the S cone signal to the pooled signals of L and M cones (often referred to as blue-yellow, but more accurately, lilac-yellow).[1] 'Trichromatic" colour vision, based on three types of cone, is also present in some fish and probably many marsupials,[4] but it is not the norm amongst vertebrates, and even where it occurs it is not normally like human colour vision. For example, a maturing flower that changes from green to yellow in humans, due to increasing ratio of L to M cone response, changes colour in the opposite direction for honey possums: their L to M cone ratio decreases.[5] This happens because the spectral tuning of the honey possum's M cone, with peak sensitivity near 500 nm, is very different from ours.

Genetic mischief among the human L and M pigment genes causes around 2% of men to go without either L or M cones, and with such 'dichromatic' vision they cannot discriminate between spectra that to the rest of us appear highly distinct (eg. red vs green, or blue vs pink[6]). Similarly, most placental mammals have only two types of cone, but they certainly don't all perceive the world in the same way: the S cone in many rodents, for example, is maximally sensitive to wavelengths shorter than 400 nm, which humans cannot see and call 'ultra-violet'.[7] Some mammals have no colour vision at all (notably all whales and seals tested so far[8]), while most birds, on the other hand, have four types of cone pigment, and potentially have colour vision that can discriminate between many spectra that look the same to us.[9]

Thus the way we sample the received light is the first big influence on how we perceive colour, and the sampling is different for different animals. It differs even amongst human trichromats: around 6% of men have 'anomalous' sensitivity in their L or M cones, and even amongst 'normal' trichromats, only about 60% of L pigments have the longest known sensitivity.[10] Thus there is really no such thing as 'normal colour vision'.

Adaptation

The myriad of ways animals may sample light need not concern the individual human, for whom incoming spectra might still be consistently mapped to perceived colour according to the ratio of responses in his particular L, M and S cones. But the ratio produced by any given spectral input changes from moment to moment and across the retina, because each cone cell is continuously changing sensitivity due to adaptation (see Figure 1). A general rule of sensory cells is that when they are active they become less sensitive, and it is chiefly by this method that we cope with the large changes in light

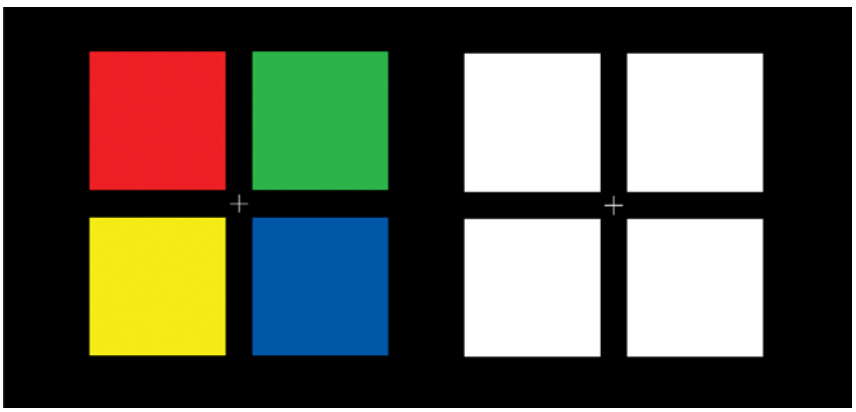

Figure 1. Adaptation to colour: Stare at the cross between the coloured squares on the left for 2 minutes. Then look at the cross between the white squares on the right. Where your L cones are most adapted from viewing red, the square now looks greenish. Similarly, adaptation to green, blue and yellow produce pink, yellow and lilac after-effects, respectively.

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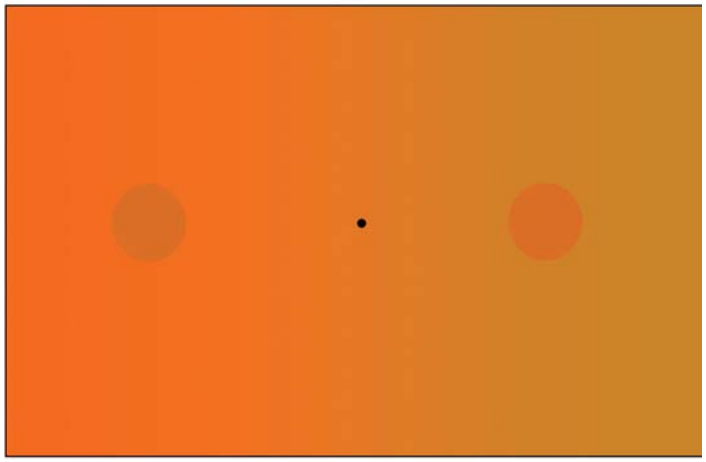

Figure 2: Simultaneous colour contrast: Look at the central dot and judge whether the two circles appear the same colour. They are identical, but the colour we perceive depends on the objects' environments.

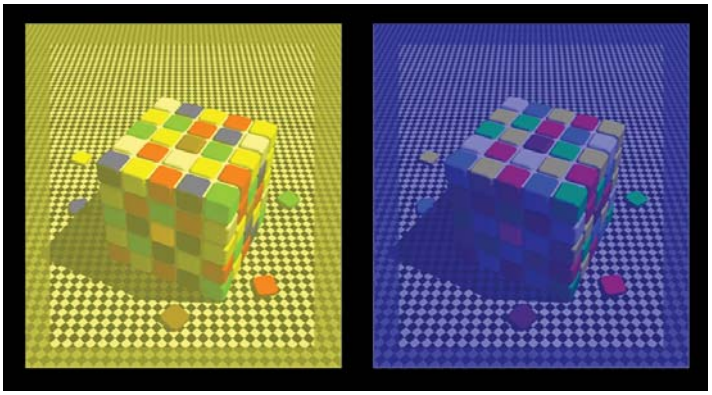

Figure 3: Colour constancy. The tiles that appear blue in the left image are physically very different from the tiles that appear blue in the right image. Likewise for all the other colours. In fact, the blue tiles on top of the left cube are identical to the yellow tiles on top of the right cube, which becomes apparent if you cover the rest of the images (with a paper cut-out for example, or see www.lottolab.org). This powerful 'illusion' is achieved because the brain interprets the images as two nearly identical cubes seen under very different illumination (yellow or blue), and the colours in each image were calculated to be consistent with this interpretation. In other words, our brain tries to 'see' objects rather than simply representing the actual light that reaches the eye. The images were created by Dr R Beau Lotto (www.lottolab.org).

intensity that occur when we step outdoors, for example, or when the sun appears from behind cloud. Adaptation means that from the earliest stage of processing, the ratio of cone responses represents changes in spectral input, rather than the absolute spectral input.[11] This serves three useful purposes for object identification:

1. Differences between objects are exaggerated.
2. The influence of the illumination colour (eg. yellow artificial light vs bluer natural light), is reduced.
3. Variations in spectral input across the retina, due to filtering by macular pigment for example, are largely not translated into differences in cone response ratio.

Contrast

The same three purposes are also served by mechanisms that compare inputs across space. Colour is perceived relative to neighbouring colours (see Figure 2), and this contrast process also begins at the earliest possible processing stage. Horizontal cells in the retina attenuate the output of cone cells if other cones nearby are active. Such 'lateral inhibition', like adaptation, is a general principle of our visual system and probably operates at every level, meaning that everything is processed relative to the environment in which it is viewed.

Colour constancy and visual knowledge

As discussed above, the spectrum of light we receive from any given object can vary greatly depending on the colour of the light source, shadows, and light reflected onto it from other objects. Despite this, we perceive a white shirt as white and a yellow shirt as yellow regardless of the environment it finds itself in.[2] This 'colour constancy' is achieved to a large degree by adaptation and contrast.[12] But on their own, these simple mechanisms are not enough, especially in the cases of shadows and local differences in light reflected from other objects.

To deal with this, our colour system has to take into account the shapes of objects, the layout of a scene and likely lighting source, before creating the colours we finally perceive (see Figure 3). It is not known exactly how this is achieved, but it must involve extensive communication between cells in different brain regions, especially those in cortical area V4 (if this region is damaged, colour perception is severely disrupted – a condition known as achromatopsia[13]). Importantly, all the calculations are achieved automatically and subconsciously.

For example, in a room in which the ceiling is white but one wall is red, a predominance of long wavelengths will be reflected from that wall onto the ceiling, making the light coming from the ceiling pink (ie containing more long wavelengths than short wavelengths). But we still perceive the ceiling as white because our visual brain takes account of the spatial arrangement of the ceiling and coloured wall, and automatically ascribes any pinkness coming from the ceiling to reflected light from the red wall, rather than to the properties of the ceiling itself.[14]

With clever tricks like this, our colour system continuously attempts to make colour represent the physical properties of an object itself, rather than the spectrum of light that happens to be reaching us from the object in any given circumstance. Thus what we see is actually our brain's interpretation of objects, rather than any simple representation of the light entering our eyes. It is this automatic interpretation that makes colour vision so useful for detecting and recognising objects despite changes in their environment.

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Hydrocephalus. A Practical Guide to CSF Dynamics and Ventriculoperitoneal Shunts

Hydrocephalus is defined and the mechanisms of CSF hydrodynamics discussed. Supplementary tests used in the investigation of idiopathic normal pressure hydrocephalus are reviewed with a detailed explanation of constant flow CSF infusion tests. The principles governing valve selection are illustrated.

Hydrocephalus is the abnormal accumulation of CSF within the cranium due to defective CSF production, flow or absorption. The CSF usually accumulates within the ventricular system, however 'external hydrocephalus' with widening of the subarachnoid spaces is described. Hydrocephalus can be due to **obstructive** causes preventing normal CSF flow through the CSF pathways, or due to abnormal absorption of CSF: **communicating** hydrocephalus. CSF flow studies frequently show a complex picture with contributions from both mechanisms. Overproduction of CSF that exceeds the absorption capacity of the arachnoid granulations is rare.

CSF physiology

CSF is mainly produced by passive ultrafiltration of plasma with some active electrolyte transport from the ventricular choroid plexus. The rate of CSF production is around 20ml/hour, although MRI evidence suggests that this may increase significantly during sleep. To maintain equilibrium, CSF is normally absorbed into the major venous sinuses by a passive mechanism through the one-way valves of the arachnoid villi. The normal CSF pressure at the reference level (the foramen of Monro) in the recumbent adult is 100-200mm H_2O (7-15mmHg) with mean pressures of 20mmHg regarded as elevated. Pressures from 0-7mmHg do not usually signify any pathology. The CSF pressure fluctuates with the arterial pulse wave and respiratory excursions.

Symptomatic patients with obstructive hydrocephalus continue producing CSF. CT and MRI scans identify the site of obstruction. The definitive treatment for most of these patients is removal of the obstructive cause. If CSF diversion is required and the outlet of the IIIrd or IVth ventricle obstructed, a IIIrd ventriculostomy is usually the first choice treatment, particularly in newly diagnosed patients with aqueduct stenosis.

Communicating hydrocephalus occurs when the lateral, IIIrd and IVth ventricles appear to communicate freely. The absorption capacity of the arachnoid villi is exceeded or obstruction of CSF flow occurs within the subarachnoid space. This condition is usually managed with a ventriculoperitoneal shunt system and provides the focus for this paper.

Normal pressure hydrocephalus

In the pre-CT scan era Adams et al. reported three cases of ventriculomegaly associated with gait disturbance, dementia and incontinence.[1] All three patients had normal CSF pressure (140-50, 160 and 175mmH_2O) on lumbar puncture but improved with either a ventriculo-atrial shunt (two cases) or a Torkildsen (lateral ventricle to cisterna magna) diversion (one case). Two cases were idiopathic and one due to a cyst in the IIIrd ventricle. The condition is now classified as (i) Primary or **Idiopathic Normal Pressure Hydrocephalus (INPH)** and (ii) **Secondary Normal Pressure Hydrocephalus**. In the latter group of patients a well-established cause is evident (eg. subarachnoid haemorrhage, traumatic brain injury, meningitis). Whilst the primary pathology may increase the certainty of diagnosing hydrocephalus, the results of treatment may be confounded by the original brain insult.

Even in the presence of a classic triad of symptoms the response to treatment is often disappointing. Indeed Black reported that 67.2% of patients with gait, cognitive and urinary symptoms and signs improved with a shunt.[2] The outcome was significantly worse in patients with only dementia and gait disturbance (31.6% improved). Overall, 35.4% of the 62 patients studied suffered complications, including subdural haematomas and fits. The challenge therefore lies in increasing diagnostic accuracy and timely management at a point when symptoms and signs are retrievable.

Clinical feature of INPH

The Symptomatic Triad

The **gait** disturbance in INPH includes at least two of the following features: wide based stance, out-turned feet, decreased step height, decreased step length, decreased speed, increased trunk sway, *en bloc* turning requiring three or more steps for 180°, and poor heel-toe walking. **Cognitive features** are wide-ranging and include attention deficits, psychomotor retardation, impaired recall and memory deficits, executive dysfunction, behavioural and personality changes. Such features can be quantified using a summative mental state examination. **Urinary dysfunction** is characterised by nocturia, urgency, frequency or incontinence reflecting a low capacity neurogenic bladder.

Evidence-based clinical diagnostic criteria for the diagnosis of INPH have only recently been developed. A consensus panel recommends that INPH candidates be categorised into 'probable' and 'possible' groups based upon history, examination, brain imaging and CSF opening pressure.[3]

Probable INPH

This requires a gait disturbance and either cognitive and/or urinary disturbances in a patient over 40 years old. In addition the history, imaging and lumbar puncture opening pressures must be consistent with the diagnosis. The imaging findings are characterised by ventriculomegaly not due to atrophy or obstructive hydrocephalus, associated with one or more of the following; temporal horn enlargement, a callosal angle of 40° or more (due to bowing of the corpus callosum), periventricular lucency not due to ischaemia and a flow void in the aqueduct or IVth ventricle. The accepted range of CSF opening pressure for probable INPH is 70-245mmH_2O (5-18mmHg).

Possible INPH

This group may have a more acute history in a younger patient with only one of the triad of symptoms and an opening CSF pressure outside the guidelines above. The imaging findings may appear to be consistent with atrophy.

Imaging

CT and MRI scans provide useful information that helps support a diagnosis of normal pressure hydrocephalus. Ventriculomegaly is an essential finding (Evans ratio >0.3; Widest inter-frontal horn distance / Internal skull distance at level of frontal horn). Other findings such as large temporal horns and sulcal obliteration are inconsistent. Although periventricular and deep white matter lesions

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are commonly observed in T2-weighted MRI they are also associated with hypertension and cerebrovascular disease and are therefore not pathognomic of hydrocephalus.[4] Post-shunting MRI scans do show an improvement in the frontal horn periventricular changes but such pre-operative features are not required to predict a good outcome.[5] Calculation of the 'stroke volume' of CSF moving in a craniocaudal direction during systole using phase contrast CSF velocity MR imaging has shown that a volume greater than 42µL correlated with a favourable response to shunting.[6] This is characterised by a signal flow void. PET cerebral blood flow (CBF) studies have shown that pre and post-shunt assessments of haemodynamic reserve using a carbonic anhydrase inhibitor to stimulate increased $PaCO_2$ indicate that shunt responders show an improvement in their cerebrovascular reserve compared with non-responders.[7] This suggests that altered CBF dynamics are important in the pathogenesis of INPH and in determining the success of treatment. Unfortunately specific thresholds for low CBF have not been identified as pre-operative predictors of treatment success.

Due to the diagnostic conundrum and the difficulties in determining shunt responsive cases several other tests have been developed to aid management. These include intracranial pressure monitoring, CSF infusion tests, the tap test and a period of CSF drainage. The main drawback of these tests is the low sensitivity and poor predictive value of some tests (see Table 1). The additional tests that are often used are detailed below.

Table 1: Predictive value of additional tests in the assessment of idiopathic normal pressure hydrocephalus (data derived from Marmarou et al[10]).

Test	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Positive likelihood ratio*
Tap	*26-62%*	*33-100%*	*73-100%*	*23-42%*	*0.93 - infinity*
CSF Drainage	*50-100%*	*60-100%*	*80-100%*	*36-100%*	*2.5 - infinity*
Calculation of Rcsf	*44-92%*	*46-100%*	*75-92%*	*27-92%*	*0.88 - 12.5*

ICP monitoring

Patients with INPH frequently have normal ICP. However, 24 hour monitoring may reveal several abnormalities that indicate poor cerebral compliance (Figure 1). An ICP recording shows systolic and diastolic pulsations. Plateau (A) waves with elevations exceeding 50mmHg for periods of 5-20 min are not normally seen in patients with idiopathic hydrocephalus. However, careful analysis of the ICP trace – using computer software with threshold filters – reveals low amplitude (commonly 1-5mmHg) superimposed B waves with a period of 30 seconds to 2 minutes.[8] The prevalence of B waves appears to increase during normal REM sleep and with rises in intracranial pressure. A recent detailed analysis in patients with communicating and non-communicating hydrocephalus indicates that B waves are commonly observed but have a poor correlation to clinical outcome.[9]

Tap test

Many authors have reported the withdrawal of 40-50ml of CSF as a useful test, with responders benefiting from shunt insertion. However the test has a low sensitivity (26-62%) and should not be used to rule out a diagnosis of idiopathic normal pressure hydrocephalus.[10]

External Lumbar CSF Drainage

This test developed from the concept that a trial of controlled CSF removal (10ml/hr) for 72 hours might predict shunt responders. The sensitivity of

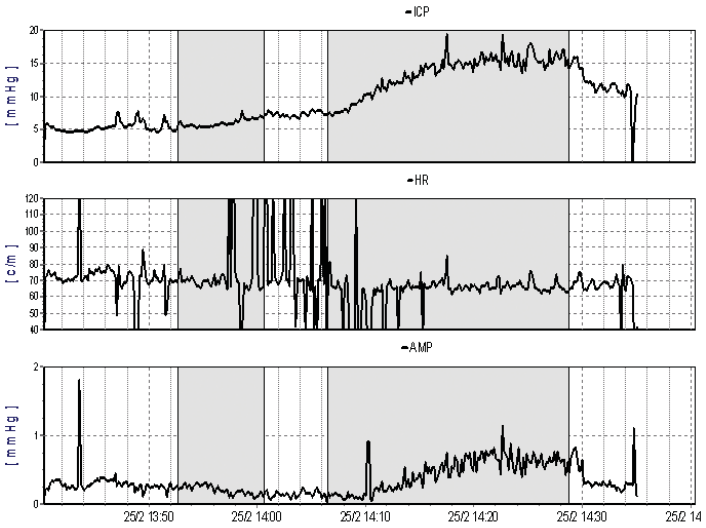

Figure 2A: CSF infusion study performed via a ventricular access device – normal result showing ICP, heart rate and ICP pulse amplitude; infusion rate 1.5ml/min. The opening pressure (5mmHg) and amplitude were normal. During infusion the ICP increased to a plateau of 15mmHg, enabling calculation of resistance to CSF outflow (7mmHg/ml/min). The low pulse amplitude and absence of vasogenic waves are characteristic of a normal study. Measurement of the heart rate from the pulse amplitude enables the technical quality of the recording to be assessed.

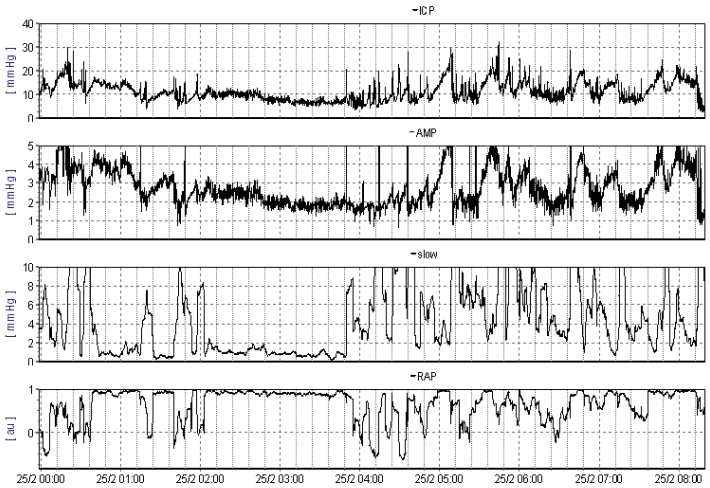

Figure 1: Overnight ICP monitoring in a normal pressure hydrocephalus patient who responded to subsequent VP shunt insertion. Graphs show ICP; Amplitude; Slow B waves and RAP coefficient. The baseline pressure was normal (8-10mmHg) with many vasogenic waves exceeding 20mmHg. The pulse amplitude of the ICP waveform was elevated, especially during the vasogenic waves. The averaged amplitude of the slow B waves was above 5mmHg and the derived RAP coefficient was above 0.7 most of the time, signifying poor compensatory reserve.

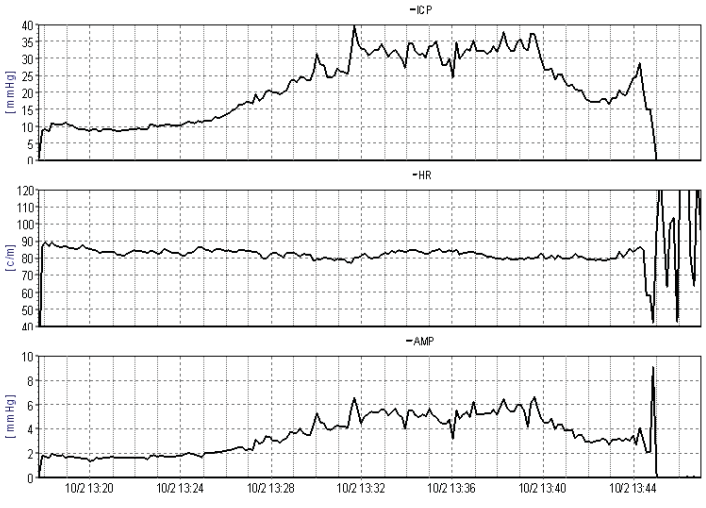

Figure 2B: CSF infusion study performed via a ventricular access device – patient with probable idiopathic normal pressure hydrocephalus, infusion rate 1.5ml/min. The opening pressure is normal (10mmHg) but CSF infusion produces a plateau around 34mmHg enabling the R_{csf} to be calculated (16mmHg/ml/min). This level is just below the 18mmHg/ml/min threshold described by Boon et al.[12] Strong vasogenic waves are also evident at pressures above 25mmHg with an increase in the pulse amplitude. The derived Pressure Volume Index (PVI) was elevated (9.1ml) reflecting poor compensatory reserve.

the test has been reported as 50-100% with a specificity of 60-80% and a positive predictive value of 80-100%.[10]

CSF infusion test

The resistance to CSF absorption by the arachnoid villi can be measured and helps predict shunt responsive patients.

The test is commonly performed in the left lateral position using a constant infusion technique. Lumbar puncture needles are inserted at 2 levels; the use of a solitary needle with a three-way tap is not as reliable. A pressure transducer is connected to one needle and the baseline opening pressure recorded. Normal saline is infused at 1.5ml/min through the second needle whilst the pressure is continuously measured. In most patients the pressure rises steadily and then reaches a plateau. The resistance (R_{csf}) to CSF absorption can be calculated using an Ohm's Law analogy:

$$R_{csf} = \frac{\text{Plateau pressure (mmHg)} - \text{Baseline pressure (mmHg)}}{\text{Infusion rate (ml/min)}}$$

The R_{csf} in normal subjects ranges from 6 to 10mmHg/ml/min. It increases in the elderly. In such cases the rate of CSF production probably decreases to prevent hydrocephalus ensuing.[11]

By using an infusion rate of 1.5ml/min a 30-mmHg increase in CSF pressure provides evidence of the R_{csf} exceeding 20mmHg/ml/min. The use of higher infusion rates (eg. 3ml/min) imposes limitations in that the pressure needs to rise by 60mmHg to confirm an R_{csf} of 20mmHg/ml/min. We recommend aborting the test if CSF pressure exceeds 50mmHg. In this case a minimum value for the R_{csf} can still be calculated using the (peak pressure – baseline pressure) as the numerator in the equation. Boon et al. have reported that in patients with probable NPH (mainly idiopathic but also including some secondary cases) a positive response to shunting was likely if R_{csf} exceeded 18mmHg/ml/min with a PPV of 92% and a likelihood ratio of 3.5 in their series of 95 patients. However, the sensitivity of the test at this threshold was only 46% although the specificity was high at 87%.[12]

Performing the infusion test via a frontal ventricular access device appears to minimise the effect of CSF leakage around lumbar needles and may increase the predictive value of the investigation (Figures 2A and 2B). With sophisticated computer analysis (see www.neurosurg.cam.ac.uk/icmplus) of the pressure waveform further information about the elastance and compliance of the craniospinal axis, including the Pressure Volume Index (PVI), can be derived both in lumbar and ventricular CSF infusion studies. This may assist the decision making process in borderline cases.

Choosing a CSF shunt

Most neurosurgeons advocate a ventriculo-peritoneal shunt (VP shunt) as the preferred system for implantation. In some circumstances (eg. inadequate absorption in a patient with multiple previous abdominal operations) alternative sites are required (eg. ventriculo-pleural, ventriculo-atrial). VP shunt insertion is associated with numerous potential complications. These include:

- Peri-operative intracranial bleeding
- Infection
- Shunt blockage
  - Proximal catheter
  - Valve
  - Distal
- Shunt component disconnection or migration
- CSF over-drainage
  - Low pressure headaches
  - Intracranial haematomas (usually subdural)
- CSF under-drainage

Attention to detail during the placement of a VP shunt is crucial to minimise the risks of shunt insertion. Meticulous sterility, accurate catheter placement and secure connections between shunt components are essential. Consideration needs to be applied to the choice of shunt hardware. The ventricular catheter most widely used is a straight non-flanged device with multiple apertures in proximity to the catheter tip. There is no consensus over the best anatomical site for catheter placement. The distal catheter provides a conduit to drain CSF to the peritoneal cavity. Distal slit valves are unnecessary and may increase the risk of distal obstruction provided a valve is utilised proximally. Antimicrobial impregnated ventricular and peritoneal catheters have been developed in an attempt to reduce shunt infection rates.

Valves

Valve systems with different hydrodynamic properties have been developed to try and minimise complications such as over-drainage with low-pressure postural headaches and subdural fluid collections. The properties of valves have been independently evaluated *in vivo*.[13] Valves are designed to be (1) flow regulated or (2) differential pressure regulated (Figure 3). The Orbis Sigma Valve is the archetypal flow controlled device. CSF flows though a diaphragmatic aperture whose diameter decreases as the flow rate rises above 20ml/hr. This **increases** the resistance of the valve, regulating flow. A safety mechanism leading to a reduction of resistance at differential pressures of 25-30mmHg is incorporated to avoid acute severe elevations in intracranial pressure.

Most valves are differential pressure regulated. These devices are

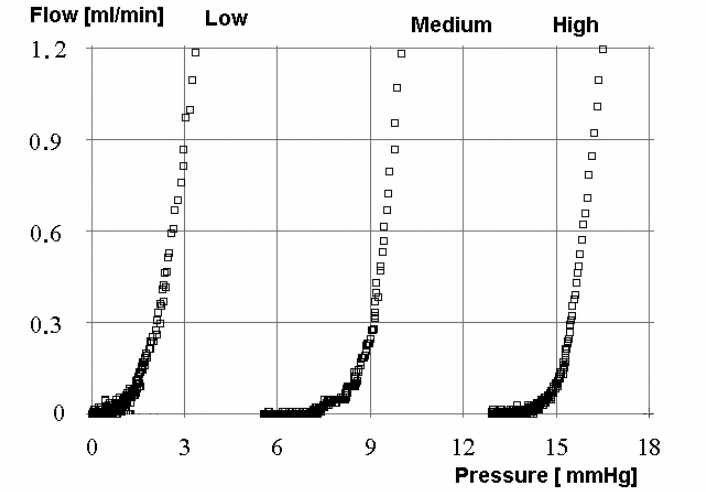

Figure 3A: Flow-pressure curves for a differential pressure-regulating valve. The pressure regulating mechanisms try to maintain the same differential pressure across the valve regardless of the flow rate. In practice most manufacturers market high, medium and low-pressure valves each with different pressure flow characteristics.

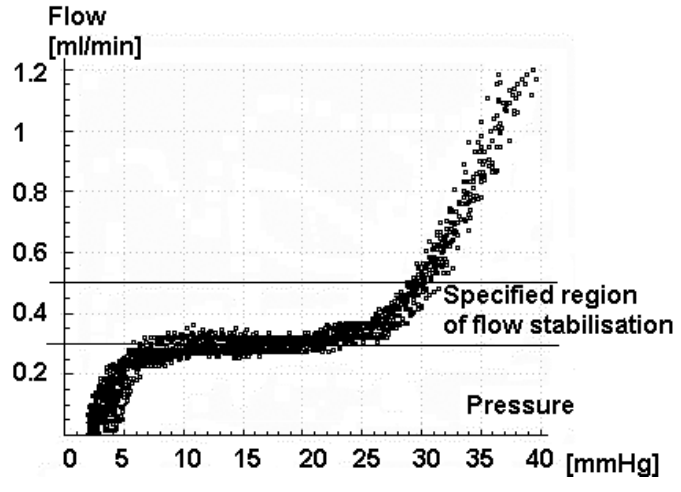

Figure 3B: Flow-pressure curve for a flow regulated valve. The flow regulator attempts to change its resistance in response to the differential pressure thereby maintaining flow at a constant level. The Orbis Sigma Valve has a variable resistance that increases in the mid-range acting as a flow control mechanism.

designed to open if the pressure differential across the valve exceeds a set value. However, as the pressure across the valve increases the resistance **decreases** allowing as much CSF to flow as is required to reduce the ICP near to the opening pressure. Postural over-drainage symptoms are common and may be averted to some extent using anti-siphon devices to minimise flow in the erect posture. Pressure-regulated valves that can be reset using transcutaneous programming devices to higher or lower pressure differentials according to clinical need are now implanted as a matter of routine.[14] Clinical studies, including data from the UK Shunt Registry, do not show significant differences in the shunt revision rate between different valve systems, although the management of complications such as subdural haematomas or hygromas is more readily managed using adjustable valves.

Outcome

The primary pathological process (eg. subarachnoid haemorrhage, head injury) is an important determinant of outcome for patients with secondary hydrocephalus. In patients with idiopathic NPH, comparisons between studies are confounded by the range of symptoms exhibited in this elderly group of patients with significant co-morbidity. Certainly a widely used validated outcome assessment tool would help compare outcomes between studies. In addition, the diagnostic difficulties and variable treatment thresholds between centres influence outcome. The duration of follow-up is also important, with a reported decrease in clinical improvement at 5 years compared with 1 year. Improvements in gait decreased from 76% to 47%, improvements in memory disturbances decreased from 48% to 38%, and improvements in urinary symptoms reduced from 58% to 29%.[15]

Summary

Simple hydrodynamic physics can be used to help the clinician understand CSF physiology and valve mechanics. Despite advances in neurodiagnostic techniques the diagnosis and management of patients with probable INPH requires sound clinical judgement. In clinical practice we use clinical, radiological, ICP and CSF infusion tests to help select patients for shunt insertion. A standardised easily applied mini-battery assessment tool would be useful to provide an objective measure of treatment effect.

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Box 1
Diagnostic testing

The data of Boon et al[12] are used to demonstrate the concepts around the efficacy of a diagnostic test. For any test a simple table can be constructed.

Rcsf >18mmHg/ml/min	*Shunt responsive (SR) hydrocephalus*		*Non-shunt responsive hydrocephalus*		*Totals*
Test Positive	*33*	*a*	*3*	*b*	*36*
Test Negative	*39*	*c*	*20*	*d*	*59*
Totals	*72*		*23*		*95*

From this data several parameters can be calculated:

Sensitivity = a/(a+c) = 33/ 72 = 46%

Specificity = d/(b+d) = 20/23 = 87%

Likelihood ratio for positive result = sensitivity/ (1-specificity) = 46/(1-0.87) = 3.5

Positive predictive value = a/(a+b) = 33/36 = 92%

Negative predictive value = d/(c+d) = 20/59 = 34%

Prevalence of SR hydrocephalus = (a+c)/(a+b+c+d) = 72/95 = 76%

Pre-test odds of having SR hydrocephalus = Prevalence/(1-prevalence) = 0.76/(1 - 0.76) = 3.2

Post test odds of having SR hydrocephalus = Pre-test odds x Likelihood ratio = 3.2 x 3.5 = 11.2

Post-test probability of having SR hydrocephalus = Post test odds/ (Post test odds + 1) = 11.2/12.2 = 92%

If the R_{csf} test had a very high sensitivity a negative result effectively rules out the diagnosis of shunt responsive (SR) hydrocephalus. This is not the case. The R_{csf} test does have a high specificity. A positive result therefore makes the diagnosis of SR hydrocephalus very likely. Tests that produce big changes from the pre-test to post-test probabilities are likely to be clinically useful. The likelihood ratio of 3.5 is in the mid-range, but given that most patients investigated turned out to have SR hydrocephalus (high prevalence) the probability of having the target disorder was high if the Rcsf exceeded 18mmHg/ml/min. If a second independent test is performed with a different likelihood ratio, eg. B wave analysis of ICP recordings at 1mmHg threshold[9] (Likelihood ratio = Sens/(1-Spec) = 0.78/(1 - 0.6) = 1.95), this can be used to adjust the post-test probability of having SR hydrocephalus:

Post test odds of having SR hydrocephalus = 3.2 x 3.5 x 1.95 = 21.8

Post test probability of having SR hydrocephalus = 21.8/22.8 = 96%

Therefore a combination of investigations can prove useful at helping to determine whether or not shunt insertion likely to be beneficial. Using Boon's data at the 12mmHg/ml/min threshold, the likelihood ratio reduced to 1.4 and the post-test probability to 82%. Whilst this seems quite high it is only just better than clinical acumen alone (76% of patients with clinical features had SR hydrocephalus in this series).

Orthoses for Neck Control

Introduction

Cervical collars are used widely to immobilise the neck following injury in the prehospital stabilization of trauma patients and as part of definitive treatment of vertebral column injuries either on its own or for post operative immobilisation. Cervical collars are also useful in certain neurological conditions such as motor neuron disease where by providing support to easily fatigued neck muscles they enhance the person's functional capacity in areas such as eating and reading. A large number of different designs are available and they all help by reducing motion variably at the joints in the cervical spine and at the occipitocervical junction and in so stabilising the spine, reduces pain and discomfort and protects the spine from secondary injury.

Classification and biomechanics

Different and rather nondescriptive eponyms are frequently employed for orthotic devices. Confusion can be avoided by using a descriptive nomenclature for orthosis based on the body segments they immobilise. Thus spinal orthoses can be broadly divided into cervical orthoses (CO), head cervical orthoses (HCO), cervico thoracic orthoses (CTO), thoraco lumbosacral orthoses (TLSO), lumbosacral orthoses (LSO) and cervicothoracolumbosacral orthoses (CTLSO). The remainder of this article looks at the former three in some detail.

The capacity of an orthosis to immobilise the spine is a primary measure of its effectiveness. A clear recognition and understanding of the differences in function between the various orthoses available is required of the clinician so that informed decisions can be made regarding the choice of orthosis and appropriateness of the orthosis for a particular clinical condition. Orthoses vary in how much they can restrict movement in the neck and stability they can provide. The movements possible in the neck are forward flexion, extension, rotation and lateral flexion. For an orthoses to be effective, it must be able to prevent or limit all these movements. The presence of a myriad of designs is a reflection of the attempts that have been made to reach this ideal and also a testament to the limitations of the existing designs. A number of studies have attempted to compare the effectiveness of the more popular designs available using radiographic techniques. The limitation of many of these is that effectiveness has been addressed in terms of the total range of motion allowed in the cervical spine. This approach is unsatisfactory because it disregards the fact that the cervical spine is segmental and that it is segmental motion that needs to be controlled rather than that of the cervical spine as a whole. Some devices are better at controlling movements at particular segmental levels and efficacy of motion restriction by level is the key characteristic to address. The concept of total range of motion also ignores the possibility of paradoxical movement between motion segments, a phenomenon known as snaking which has been reported by several authors and can be troublesome even in constructs like the halo jacket.[1]

All orthoses work by a combination of sensory feedback and physical restriction. It is likely that in addition to the physical restriction, an orthosis works by reminding the user to not turn his / her head too far or too quickly, by a decrease in the load on injured muscles and ligaments caused by the added support that the collar provides to the head, and psychological support among others. Many of these factors rely on compliance and an understanding on the part of the user. Where such compliance is not forthcoming as in patients who are unconscious or psychologically disturbed, the clinician should consider carefully the use of additional measures to provide stability to the neck.

Cervical orthoses

Cervical orthoses such as soft collars which are used following mild injuries to the neck such as whiplash injuries use only sensory feedback and have no ability to restrict movement. They remind the user to limit movement, which in turn provides good pain relief. They are made of dense foam with a stockinette cover and fasten at the back with a Velcro strip. The drawbacks in using them for long periods are that patients can become dependent on them and they can lead to wasting of the neck muscles from lack of use.

Head cervical orthoses

Head cervical orthoses are generally more rigid collars made of various plastic materials in different designs to provide greater support and restriction. Most of the commonly used ones such as the Aspen collar (Figure 1), Philadelphia collar (Figure 2) and the Miami collar are prefabricated.

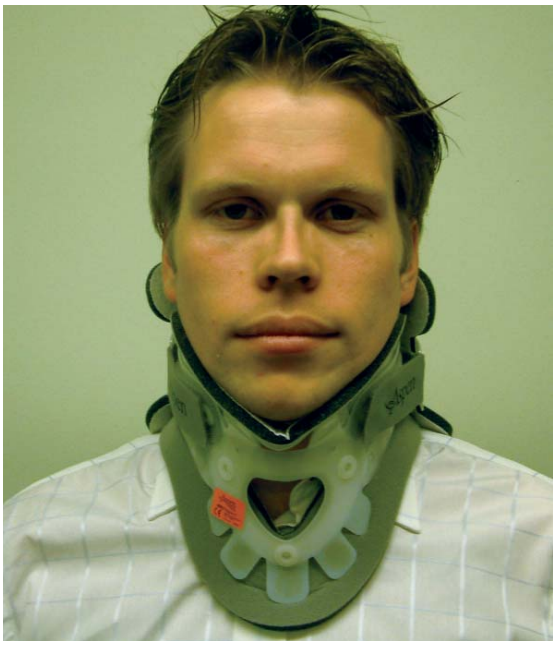

Figure 1: Aspen Collar – Note the central opening for a tracheostomy tube.

Figure 2: Philadelphia Collar, which is one of the most widely used head cervical orthoses.

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Askins and Eismont analysed the collars that accounted for 80% of the cervical orthosis market in the United States in 1995 and found that Philadelphia and Aspen collars when properly applied still allowed for 53% and 62% of normal neck rotatory motion respectively. 66% and 69% of normal lateral flexion was allowed by Philadelphia and Aspen collars respectively.[2] They found that NecLoc orthosis provided greater restriction of neck motion in all planes and was more effective than the Philadelphia and Aspen collars in reducing intervertebral motion. It is important to bear in mind that despite the use of collars, considerable movement is still possible in the cervical spine and additional measures should be taken to protect the spine where required. Both the Philadelphia and the Aspen are two piece collars with lateral fastenings. The Philadelphia collar is made of Plastizote and can accommodate a tracheostomy opening where as the Aspen collar is a polythene shell with cotton lined foam padding. Both of these are available off the shelf in various sizes, ensuring easy availability. The sizing and fitting of an orthosis is important to get the most benefit from any orthosis and should be carried out by a person accustomed to the use of the particular orthotic design. A poorly fitting device adversely affects the biomechanical properties of the device and its ability to immobilise and support the neck. The relatively minor advantages demonstrated or claimed by some devices need to be balanced against cost and patient comfort, the data on which unfortunately is not available for most if not all devices. Head cervical orthoses are useful for immobilization, but do not stabilise the spine. They are usually used for stable mid cervical injuries or post operatively when rigid control is no longer required.

Cervico thoracic orthoses

Cervico thoracic orthoses provide greater restriction of neck motion than the above mentioned collars. They are best exemplified by posterior cervical appliances with chin and occipital pieces which are connected to sternal and back plates with four metal uprights. The common ones in use include the Sternal Occipital Mandibular Immobiliser (SOMI), Philadelphia collar with extension, Aspen 2 post and Aspen 4 post cervical collars.[3] The SOMI is a light weight appliance which can be easily fitted and provides considerable restriction of movement in the mid to lower cervical region. SOMI has no posterior rods making it easier to use in those who are on bed rest. Sandler et al analysed the efficacy of different collars varying in restrictive range from a soft collar to a SOMI and found that although there was a decrease in the motion permitted by the more restrictive devices, the differences were not large.[4]

Head cervico thoracic orthoses

An HCTO provides maximum immobilisation of the cervical spine. Examples of this include the Minerva orthosis and the rigid halo. The former is a total contact appliance made of plastic materials over a positive body cast.[5] It encloses the upper trunk, neck and back of the head and has a band around the forehead. It is very effective in preventing lateral and rotational neck motions, being as effective as the halo in controlling injuries below C2. The halo is superior in restricting motion at the occiput, C1 and C2 levels.

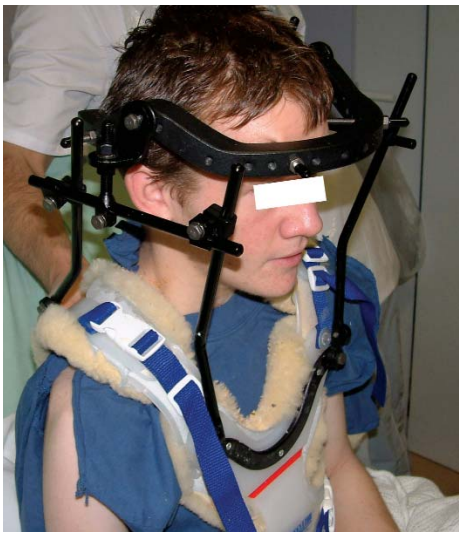

Figure 3: A halo jacket being used as the definitive treatment for a C2 fracture. A good fit is necessary for maintenance of reduction and for the avoidance of complications.

A halo orthosis (Figure 3) provides the maximum restriction of flexion and extension of the potentially unstable cervical spine and is frequently used for immobilisation of the neck after a period of cervical traction or spinal fusion. The halo consists of a halo ring, a vest and upright posts. Most modern halo rings are made of lightweight MRI compatible materials and accepts 4 pins. The ring used should be large enough to allow for a 1 cm clearance around the head the pins attach the ring to the forehead, two anterolaterally and two posteriorly. The pin sites are cleaned routinely with normal saline to prevent infection. The tension in the pins should be monitored regularly and if there is evidence of loosening, they should either be tightened or replaced. The halo vest which the ring connects to through 4 upright posts is made of prefabricated plastic material lined with sheepskin or a soft fabric. The vest should fit snugly to prevent pressure sores and loss of reduction. Once securely applied, patients can be mobilised in a halo and can participate in physical activities. Complications of the halo are numerous and include pin loosening, infection, ring migration, pressure sores, nerve injury, dysphagia, skull perforation and brain abscess. Other problems that the halo has also been associated with include an increased incidence of non union of some fractures and inability of the patients to tolerate the device.

Figure 4: A prefabricated MND collar. The padded spring supports the head while allowing forward flexion of the neck.

Complications with collars and bracing in general include pressure sores, muscle atrophy, allergic reactions and skin maceration. Monitoring the condition of the skin under the brace and skin hygiene is paramount when it comes to reducing complications. Further, brace treatment should be closely followed with regular clinical examinations and radiographs as appropriate.

Cervical orthoses in neurological conditions

In non traumatic conditions such as weakness in neck muscles due to a neurological condition, the expectations of an orthosis are very different to that of an orthosis used in an unstable spine. They may be required only at certain times in the day, should not compromise residual function and should be able to restrict only certain movements while providing support to the neck. The MND collar (Figure 4) is a good example of a collar designed to help improve the quality of life of patients suffering from motor neuron disease. It is made from padded spring steel; the design ensuring that only flexion of the neck is restricted while supporting the head on the shoulders. It is meant to be used when the patient is tired for activities that require an extended position of the neck such as watching television.

When muscle weakness is severe, the use of collars in isolation may not be appropriate as it can lead to the head falling forwards onto the collar resulting in excessive pressures on the chin and jaw leading to skin necrosis. In such situations the use of a collar should be resorted to only after correction of the sitting position to ensure the patient does not assume a slumped position. Many patients find it either difficult to tolerate the device or conversely find that it provides inadequate support. Where a prefabricated orthosis is not adequate, consideration should be given to the use of a custom made orthosis, which is the preferred choice of many departments in the country.

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Modern Stereology: A Method for Quantifying the Number of Cells in Histological Sections

Dr Stanley E Lazic has recently completed his PhD with Dr Roger Barker at the Centre for Brain Repair, University of Cambridge, where he examined neurogenesis in transgenic mouse models of Huntington's disease. Presently, he is further characterising neurogenesis/plasticity in these mice at Cambridge.

Quantifying the number of cells in particular regions of the brain poses certain challenges because cells are numerous, microscopic, and exist in 3-D space. This means that not all cells can be counted, special equipment is required, and cells can only be examined in 2-D planar sections. What is the best way then to determine the total number of cells (or nuclei, synapses, etc.) in a given structure or region of the brain? The field of stereology has developed to address this and similar questions.

Historical background to stereology

The term stereology is derived from the Greek word stereos, meaning solid, and consists of a set of techniques for quantifying the properties (eg. number, length, volume, etc.) of 3-D objects based on their appearance on 2-D sections.[1] Stereology became a formal discipline (complete with its own society—the International Society of Stereology) in the 1960s, and has progressed alongside advances in microscopy and computing. There is a distinction between older stereological methods, which are based on classical geometry, make assumptions about specimens (eg. cells are spherical), and often employ correction factors (eg. the Abercrombie correction[2]), and more modern stereological methods which do not make such assumptions or use correction factors. Since properties of biological tissue rarely conform to perfect geometric shapes, the assumptions of older methods can be unwarranted and can lead to inaccurate estimates (see [1,3-5] for reviews). These older methods have therefore come to be known as biased stereology, while the newer methods are referred to by a variety of names, including unbiased, assumption-free, model-free, design-based, or simply, the new stereology.

Modern stereology

Modern stereological methods typically use a light microscope attached to a motorised stage, a microcator to determine distances in the z-axis, and a digital camera, which are all connected to a computer running commercially available stereological software. The general approach is to sample regions in 3-D space, determine the number of cells in these samples, and then scale this up to estimate the total number of cells in the structure of interest. Estimating population parameters from samples is at the heart of statistical inference and underlies much of the theory of modern stereology. There are three main strengths of this approach. The first is that no assumptions are made regarding the geometry (eg. size, shape, and orientation) of cells, thus eliminating potential biases if these assumptions do not hold. The second advantage is the use of systematic random sampling, which ensures that each cell has an equal probability of being sampled, and thus the sampling procedure is unbiased, in the statistical sense. The third advantage is the use of a 3-D optical probe which ensures that each object is counted once and only once, and that larger cells have the same chance of being counted as smaller cells.

The two-stage method for determining cell number

There are two different methods of determining total cell number, and the most common is the *Nv* x *Vref* or two-stage method first used by Pakkenberg and Gundersen.[6] The logic behind this method is to (1) count the number of cells in a known volume of tissue, then (2) determine the total volume of the structure or region of interest, and (3) multiply these values together to determine the total number of cells in the structure (see equations below). Note that this number is the *total number of cells* in the structure, and is not a density measure (ie. number per unit of volume).

First, brains are sectioned in the standard way (Figure 1A) and equally spaced sections are selected, for example every 6th section or 12th section, with the first section being chosen randomly. After standard histological staining, for example with Cresyl violet (CV), the structure of interest—the striatum in this case (Figure 1B)—is outlined under low power on all the sections on which it appears, and the area of the outlined region is calculated by the software. The software then selects locations within the highlighted region in a systematic random manner (indicated by the black dots). Switching to a higher power objective lens, the software automatically moves the stage to the first location and the user counts the number of cells falling completely within the box (Figure 1C), or cells touching one of the two green lines. Cells falling partially in the box but touching the red lines are not counted, which ensures that the number of cells is not overestimated. The user needs to scan through the depth of the section at each location to ensure that all cells enclosed by the box in x-y-z planes are counted. The stage then moves to the next location (black dot) and another cell count is made. This continues until all areas have been counted, and this procedure is then repeated on the other side of the brain and on all the sections on which the striatum appears. To calculate the total number of CV stained cells (*N*) in the mouse striatum, the number of cells that were counted across all sections is divided by the number of boxes times the area and height of the boxes, and this is referred to as the numerical density (*Nv*; Equation 1). The area and height are constants; the area is determined by the user at the beginning of the experiment while the height is equivalent to the thickness at which the sections were cut. The volume (*Vref*) of the striatum can be calculated by summing the areas of the outlined structures, multiplying by the reciprocal of the sampling fraction (ie. if every 12th section was used, then multiply by 12), and the thickness at which the sections were cut (Equation 2). The final step is to multiply *Nv* by *Vref* to give the total number of cells in the striatum (Equation 3).

$$N_v = \frac{\sum (Number\ of\ cells\ counted)}{Number\ of\ boxes \times Area\ of\ box \times Height\ of\ box} \qquad (Eq.\ 1)$$

$$V_{ref} = \sum Structure\ areas \times \frac{1}{Freq} \times Section\ thickness \qquad (Eq.\ 2)$$

$$N = N_v \times V_{ref} \qquad (Eq.\ 3)$$

Drawbacks and controversies

Despite the advantages of modern stereological methods they have some disadvantages. They can still lead to biased estimates,[7] and vastly different estimates of neuron numbers have been obtained for the same structure in the same species, using the same ostensibly unbiased method (eg. 80,000 vs. 205,000 hippocampal CA1 neurons per half mouse brain).[8,9] In addition, modern methods have some assumptions as well which are occasionally not met in practice, such as 100% of the tissue being available for analysis (occasionally sections are torn or lost during pro-

cessing). Furthermore, these methods can be time consuming and require special equipment and a knowledge of stereological theory. Finally, Schmitz and Korr suggest that modern methods may have reduced power to detect significant differences and thus researchers may be disinclined to trade increased accuracy for decreased power.[10]

Summary

Modern stereological methods offer a theoretically unbiased way of determining the total number of objects in a given structure or region of interest. They are not without their limitations however, and researchers will continue to use both older and new methods depending on their appropriateness for addressing the objectives of the experiment.

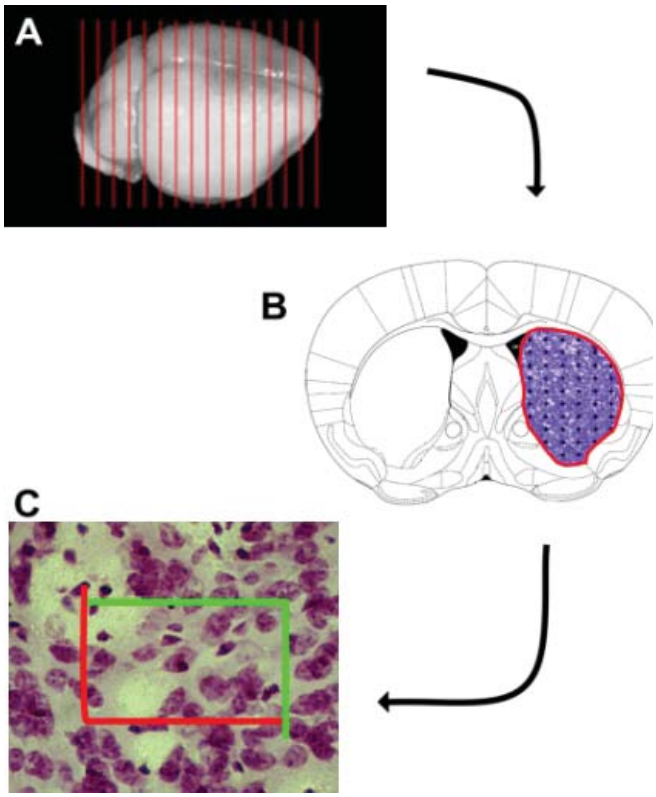

Figure 1: Sampling procedure for stereology. Sections through the brain are sampled at a certain frequency (eg. every 12th section; A). The structure or region of interest is outlined and locations (black dots) selected by the software in a systematic random manner (B). Under high magnification the number of cells that fall within the box or partially within but touching a green line are counted, while cells touching a red line are excluded. Schematic diagram adapted from Paxinos & Franklin.[11]

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The Roots of Neuropathology in Clinical Neuroscience: A Historical Perspective

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Historically and at present, neuropathology has strong ties with basic neuroscience, pathology and clinical disciplines such as neurology or neurosurgery. Although the history of neuropathology of the last hundred years is well documented, less is known about earlier days of medical research of the nervous system. This article focuses on selected major events and personalities from the beginnings of the 'neuropathological' research until the turn of the 19th to 20th and the early 20th century. This account will therefore provide physicians with a review of what has gone before in the 'discovery' of the disordered nervous system. Furthermore, knowledge about the roots of neuropathology may serve as a foundation for their current studies and future careers and may help to increase their understanding of neurology.

Introduction

Neuropathology consists of different threads woven tightly together. These threads are basic neuroscience, general and specific pathological processes, as well as clinical diseases and syndromes. It is interesting that in the past some of these elements have been the domain of specialists who actually were not neuropathologists. Thus, the neurofibrillary tangles found in Alzheimer's disease were described by Alois Alzheimer (1864-1915), a psychiatrist/neurologist. The lesions of multiple sclerosis were described by the neurologist Jean-Martin Charcot (1825-1893). Fundamental principles of neuropathology, such as those dealing with growth, degeneration and regeneration, were enunciated by the basic neuroscientist Santiago Ramon y Cajal (1852-1934) at the same time. Actually, the use to which Camillo Golgi`s (a histologist/pathologist; 1843-1926) silver stain was put by Cajal culminated in definitive studies of the cellular architecture of the central nervous system.

Figure 1: Engraving of Thomas Willis (1621-1675) by D Loggan, published in 1667.

Reproduced with permission from: Hughes JT, Thomas Willis 1621-1675: His Life and Works, RSM Press, 1991.

What history is and who actually 'makes' historical events or facts out of the innumerable events that happened, represents a fascinating question and may be, sometimes, debatable. At least history is something that happened some time ago - in the past and is usually written down later by someone else for whatever reason. In the case of the origins of research of the human nervous diseases in the 18th and 19th century, much of it was conducted experimentally on animals. Therefore, it had only an oblique relation to the human disease. For example, around 1730, Stephen Hales (1677-1761) decapitated frogs and found that reflex movements in the legs could still be produced by pricking the skin. However, if the spinal cord was destroyed, these reflex movements ceased. Similarly, the French anatomist Marie Jean-Pierre Flourens (1794-1867) observed the progressive deterioration of function by cutting connecting tracts and fibres in the brains of pigeons in a series of experiments. A pigeon with both its cerebral hemispheres removed became blind, whilst when only one hemisphere was removed, the bird lost sight in the eye on the opposite side. A pigeon from which he had removed the cerebellum could see and hear well but its balance was destroyed.[1]

At the same time as this experimental work on animals, anatomical methods and clinical descriptions of human disorders were combined in the emerging discipline of pathological anatomy, and with this the first atlas of brain diseases appeared providing detailed information about the neuropathological conditions of diseases affecting the nervous system.

In the following I try to recapitulate chronologically - albeit incompletely - the main milestones in the early history of neuropathology and its links to neurology and psychiatry. Although reports on the history of the last 100 years already exist,[2,3] coherent accounts on the earlier days of research of the nervous system with a specific focus on neuropathology are scarce, and this is what I shall focus on in this review.

Pioneer workers and milestones in the history of neuropathology

The pioneering pathologist Johann Jakob Wepfer (1620-1695) of Basel demonstrated that apoplexy or stroke was due to haemorrhage from the cerebral vessels in 1658. Distinguished investigations were also pursued by Thomas Willis (1621-1675) (Figure 1) (Willis, 1681),[4] using a combination of painstaking anatomical investigations, animal experiments as well as clinical experience (he coined the term: "We shall institute the whole neurology or the doctrine of nerves"). This lead to the publication of his *Cerebri anatome, nervorumque descriptio et usus (1664, translated 1681)* (Anatomy of the Brain), a highly influential early text. In this book, Willis for example, described a patient (dying from carcinoma of the stomach) in whom the left carotid artery was occluded yet the brain had not suffered since the right carotid was increased to three times its normal size. He concluded that a connection must exist between the circulations on the two sides, leading to the description of the Circle of Willis. A companion study, the *Pathologiae cerebri et nervosi generis specimen (1667)* (Pathology of the Brain, and Specimen of the Nature of the Nerves),[5] developed ideas about the nervous origins of various disorders such as epilepsy, narcolepsy and apoplexy. In this, Willis proposed that seizures are not an affection of the part that moves but a remote consequence of activity in the brain, albeit in response to a peripheral stimulus, or of the blood entering the brain. William Croone (1633-1684) postulated an interaction of spirituous juice from the nerves and blood agitating the space between muscle fibres and transmitting to them a force which expands their width and shortened their length. Extending or elaborating these ideas of Croone, Willis linked muscle contraction to an explosion of gunpowder, with new spirits being supplied to muscle by the blood (1670, translated 1681), "the first designation of motion is in the brain or Cerebel: its transmission ... is performed by the spirits within the nerves ... implant(ing) a contracture or elastic force".[6]

In 1686, Thomas Sydenham (1624-1689) described chorea, separating it from the old descriptions of dancing mania or St. Vitus's Dance and Giovanni Morgagni (1682-1771) in 1761 first suggested a classification of pathological anatomy (Morgagni, 1761).[7] However, it was not until the early 19th century that anatomical and clinical descriptions of neurological disease were correlated and illustrated systematically. In the first half of the 19th

century, Philippe Pinel (1745-1826) and Xavier Bichat (1771-1802) consolidated the discipline of pathological anatomy in the Parisian clinical demonstrations and dissections (see also Cruveilhier [1791-1874]).[8]

During the first few decades of the nineteenth century, pathological anatomy flourished in the British Isles, too. Indeed, it was Matthew Baillie (1761-1823) who established organ-based pathology as a separate science in the United Kingdom (1793, 1798-1803) such that by the nineteenth century, particular clinical conditions were beginning to be traced to specific nerves. Exquisitely artistic images of the normal structure of the cranial and peripheral nerves were produced by Charles Bell (1774-1842). He was important for the development of the concept of innervation and in fact described the functions of sensory and motor nerves. Strikingly, the propensity of the brain to manifest striking disturbances of function on the basis of apparently trivial disorders of structure was acknowledged by Bell and he showed that lesions of the seventh cranial nerve produced the facial paralysis later known as Bell's palsy. A classification based on inflammation, pressure, irritation, and inanition (1827-1831)[9] was introduced by Richard Bright (1789-1858). Robert Carswell (1793-1857) showed consummate artistry in the use of colour illustrations to picture and describe organs affected by various pathological conditions (1838)[10] but the first separate work on neuropathology, by Robert Hooper (1773-1835) published in 1826,[11] anticipated Carswell in attempting a classification (inflammation, tumour, diseased structure and unnatural appearance without tumefaction, and fluid collected around the hemispheres or extravasated), with descriptions of diseases affecting the meninges, brain, nerves, blood vessels, and sinuses.

Moritz Romberg (1795-1873) represents one of the most dedicated early explorers of neuropathology in the first half of the 19th century. In fact, he devoted his career to sorting out the jungle of clinical and pathological facts associated with neurological disorders. Romberg studied mainly diseases of the peripheral nerves, together with apoplexy, epilepsy and chorea, and gave attention also to tabes dorsalis establishing 'Romberg's sign'. Its syphilitic aetiology was established only later; however, as Romberg already recognised, its main lesion was wasting of the spinal cord. Romberg's *Lehrbuch der Nervenkrankheiten des Menschen* (Textbook of Human Nervous Diseases) (1840-1846)[12] was a pioneering attempt to produce a nosology of disorders of the nervous system. He divided neurological disorders into two groups, ie. those due to motor and those due to sensory dysfunction. Romberg`s symptom-based nosology would soon be discarded as old-fashioned and replaced by distinct neurological disease entities, each with its specific morbid anatomical changes. However, he was attempting to bring order to a tangled aspect of clinical medicine, herewith setting the agenda for his successors.[1]

Tabes dorsalis became a focus of clinical and pathological research, especially with the growing awareness of its syphilitic source, and it was discussed by Romberg (see above), Jean Cruveilhier (1791-1874) and others. Actually, it was the subject of a masterly account by Guillaume Duchenne (1806-1875). He was the first to describe many conditions including progressive muscular atrophy, locomotor ataxia and bulbar paralysis. As his description of tabes was so complete, it was named 'Duchenne's disease'. Its lesion-site was located in the posterior columns of the spinal cord, and its syphilitic origin was established by Duchenne.[1] He noted Bell`s work on facial muscle anatomy (ie. the dissection of the muscles of facial expression) and was the first to record facial expressions as they related to systematic faradic stimulation of facial muscles.

Figure 2: Clinical Lesson at the Salpêtrière, painting by A Brouillet (1887). Surrounding Dr Charcot (1825-1893), one may recognise, standing to his left, J Babinski, helping the patient. On the left side of the photograph, sitting in the first row, is Gilles de la Tourette. Pierre Marie is the third from left, sitting along the wall, and standing behind him is JB Charcot. Parinaud is second in the second row.
Reproduced with permission from: Philippon JH, Leroux-Hugon VM, Ricou PL, Poirier JG. The Charcot library. Neurosurgery. 2003;52(2):414-8.

Jean-Martin Charcot, a contemporary to Duchenne and professor at the Salpetrière in Paris, ranks as one of the most famous teachers of the time (Figure 2). He turned his active medical service at the Salpetrière Hospital into an international centre for the investigations of neurological diseases. Charcot gave the first comprehensive description of multiple sclerosis and the peroneal type of muscular atrophy. His *Leçons Sur les maladies du système nerveux faites a la Salpêtrière* (Lectures on Nervous Diseases Delivered at the Salpetrière) brought order to the classification (Charcot, 1872-1887)[13] of diseases of the nervous system. There is the common misconception that Charcot was exclusively preoccupied with hysteria. Notwithstanding this, as an ardent neurologist, he was committed to deploying patho-anatomical techniques to reduce the chaos of the highly complex neurological symptom-clusters or syndromes. In his *Leçons* he granted: Conditions like "epilepsy, hysteria, even the most inveterate cases, chorea, and many other morbid states come to us like so many sphinxes," defying "the most penetrating anatomical investigations". Charcot aimed to trace nervous phenomena to organic lesions, and with massive clinical or neuropathological scrutiny he undertook the examination of motor and sensory symptoms, bizarre visual abnormalities, tics, migraine, epileptiform seizures, aphasia, somnambulism, hallucinations, alexia, mutism, contractures, hyperaesthesias and numerous other deficits. It is also worth mentioning that he followed up James Parkinson's work on the 'shaking palsy' (Parkinson, 1817)[14] delineating what he termed the 'pathognomonic symptoms' (tremor and hastening gait). Indeed, it was Charcot who coined the term Parkinson's disease - a condition considered to be a syndrome of the motor cortex by William Gowers (1845-1915) and his predecessors, as the function and pathophysiology of the basal ganglia were at that time obscure.[15]

Jules Dejerine (1849-1917) was a younger contemporary to Charcot. He went to Paris in 1871 and worked on diseases of the peripheral nervous system for many years. In 1883, he described peripheral neuritis and, in 1886, muscular dystrophy, a slowly progressive disease producing wasting of the facial and shoulder-girdle muscles, later spreading to the pelvic girdle. In 1900, together with André Thomas (1867-1963), he introduced the term 'olivopontocerebellar atrophy' reporting two sporadic cases of late-onset ataxia.[16] Olivopontocerebellar atrophy is nowadays referred to as the cerebellar variant of multiple system atrophy. In these patients, the motor disorder is predominated by cerebellar over parkinsonian features, and dysautonomia and/or pyramidal signs also occur.

Multiple sclerosis also attracted attention with its lesions being illustrated by the first professor of pathological anatomy in Paris, Jean Cruveilhier, in the great *Anatomie pathologique du corps humain* (1835-1842) (Pathological Anatomy of the Human Body) (Cruveilhier, 1835-1842).[8] Volume I contains the livraisons numbers 1-20, and volume 2 numbers 21-40. Actually, Cruveilhier is credited by Charcot as having first illustrated the lesions of multiple sclerosis in the second tome of his pathological atlas bearing the title date 1835 (see above). However, the 40 livraisons of this work were published separately in parts and documentary evidence contained within volume 2 indicates that the putative case of multiple sclerosis cannot have appeared earlier than 1841.[17] Carswell's *Pathological Anatomy: Illustrations of the Elementary Forms of Disease* (1838)[18] represents the rival claim for priority. Cruveilhier related the clinical symptoms of numbness, falling or disordered voluntary movements of the limbs to 'grey degeneration' in the spinal cord, brain stem, cerebellum and even the cerebrum. In 1849, Friedrich Theodor von Frerichs (1819-1885) made an extended clinical study. Later on, Charcot gave the classical picture of incoordination, tremor and nystagmus and recognised that multiple sclerosis was a distinct entity and thus gave it its own nosological status with accurate clinico-pathological correlations along with comments on its frequency whilst speculating on the pathophysiology.[19] Carswell and Cruveilhier described the gross pathological

characteristics of multiple sclerosis and documented sclerotic patches with graphic illustrations. The first histological suggestion that multiple sclerosis is a primarily demyelinating disease was proved shortly thereafter by Charcot, who also is given credit for describing gliosis and fat-laden cells in its lesions. In 1863, Georg Eduard Rindfleisch (1836-1908), a German pathologist, first noted the perivascular inflammatory nature of multiple sclerosis plaques.[20]

At around this time, another neurological condition was studied - namely aphasia. Strikingly, losing the capacity to speak was associated with damage to specific cortical areas, especially on the left side as demonstrated by post-mortem examination of aphasia cases. It was Paul Broca (1824-1880) who first began to map those areas of the brain in 1861.[21] In fact, his association between aphasia and damage to the frontal cortex in M Leborgne became the first cortical localisation that was widely accepted; Broca held that the third frontal convolution (Broca's convolution) of the left cerebral hemisphere is more developed than that on the right side and that this is the centre of articulate speech. John Hughlings Jackson (1834-1911) published the first of his aphasia papers soon afterwards. He discussed aphasia mainly in the context of hemiplegia or epileptic seizures. He was not a localisationist, but considered the organisation of speech in the brain in terms of an interplay between the two hemispheres and was opposed to Broca's well known views. Jackson is revered but largely unread. In 1869, Henry Charlton Bastian (1837-1915) described the speech impairment known as sensory aphasia. Bastian had few friends and no disciples. This was in marked contrast to Carl Wernicke (1848-1905), who managed to found an influential school. Wernicke re-described sensory aphasia five years later and now it is named after him (Wernicke's aphasia). Indeed, the idea that the left hemisphere is special received a boost in 1874 when Wernicke demonstrated that left hemispheric injuries were also associated with a more 'sensory' kind of aphasia.

Benefiting from these new insights in the 19th century (namely the clinical descriptions, pathological anatomy, and reflexes), the further development of neurology may be measured by its leading textbooks. Romberg placed the emphasis on individual sensory and motor characters providing detailed accounts of symptoms, but did not group these into specific disease entities; Apoplexy, paralysis, epilepsy, chorea and tabes dorsalis were, in fact, the only nervous diseases he mentioned. In contrast, Charcot's textbook (1872) contained descriptions of many more named diseases, and symptoms and signs were fully integrated in the classical patho-anatomical manner. Thus, clinicians were identifying nervous diseases as such. Byrom Bramwell's (1847-1931) work on diseases of the spinal cord (1882)[22] was arranged by lesion sites and not by symptoms at all, and in the next edition, which appeared thirteen years later, the text had almost doubled in size and was similar to the *Manual of Diseases of the Nervous System* (1886-1888) by William Gowers.[23]

Further late nineteenth-century investigations, such as those coming out from Kraepelin's group and other German centres, helped to reinforce the links between psychiatry and neurology. Emil Kraepelin (1856-1926), the 'Linnaeus of psychiatry', devoted most of this time to the classification of mental disorders. At that time, there was a major controversy over the relationship between depression, degeneration and senile dementia in which Kraepelin became involved. Actually, he did not dispute that depression could be an early symptom or stage of senile dementia; but it was not an invariable symptom. Kraepelin disputed the idea that depression inescapably leads or 'degenerates' into dementia. However, in an elderly patient with 'melancholy' and an inability to 'retain impressions' dementia should be suspected. Thus, he was open to the possibility that dementia was not a life stage but a definite disease. Alois Alzheimer, his younger colleague, advanced this idea.

Alzheimer (Figure 3) offered classical descriptions of various kinds of neuropathology, including Huntington's chorea and general paresis of the insane. Two main stages in Alzheimer`s work can be differentiated[24] (Spielmeyer, 1916). Before his habilitation thesis on histological studies in the differential diagnosis of general paresis,[25] Alzheimer worked on clearly organically induced psychiatric disorders (mainly with progressive paralysis and the so-called 'arteriosclerotic mental disorders'). In the second phase of his career (1904-1915), questions as to the occurrence and relevance of anatomical alterations in the brains of patients with endogenous psychoses were given more attention. However, Alzheimer's name has become famous through his studies on the occurrence of demential processes, especially in the 51-year-old patient, Frau Auguste D. This patient had become conspicuous because of a restriction in her power of comprehension and memory, aphasic symptoms, disorientation, odd behaviour, and paranoid thought contents.[26] After the death of this patient, Alzheimer reported on this particular case entitled "*Über einen eigenartigen, schweren Erkrankungsprozess der Hirnrinde*" (on a peculiar, serious disease process of the cerebral cortex)[27,28] and delineated the clinical and neuropathological evidence for the origins of a particular form of the 'presenile dementia'. Indeed, Alzheimer described the neurofibrillary tangles in this disease that was named after him by Kraepelin. Alzheimer believed that he had described a little-known disease process, one that should not be forced into an existing group of disease patterns. He was convinced that this new early form of dementia had unique clinical and morphological characteristics. His views challenged the degenerationist ideas of senility that were popular among the French and contended that the dementia common among the old was not intrinsic to ageing; ie. it was not growing old per se that produced the organic alterations which constituted the pathological state of senescence.[1] He also dismissed the idea that dementia was a general condition - but, in fact, a specific or distinct disease entity.

Figure 3: Alois Alzheimer (1864-1915). Reproduced with permission from: Henry JM. Neurons and Nobel Prizes: a centennial history of neuropathology. Neurosurgery. 1998;42(1):143-55.

Conclusion

Medicine's response to the various above discussed contributions raises a question of fundamental interest: when and how and why does a new intellectual construct become normative, thereafter influencing the professional behaviour of the majority of workers in the field it attempts to explain? And, why does it take a long time for the various explanations (for example in the case of Alzheimer's disease seven decades) to become normative, and what finally causes their widespread acceptance? At least the time - and its 'time' including improved knowledge in the same or related research areas confirming (or not confirming) earlier results, special scientific interests, special medical needs, and specific societal, cultural and economic circumstances - may be regarded as a main discriminator between normative or not normative research. However, when using the term 'normative research', it should be made mention of the fact that high reproducibility along with a perceived significance of scientific findings is of greatest importance for the quick adoption of observations by the scientific community and their transformation into widely accepted knowledge.

Bibliography

The roots of the nowadays separate discipline 'neuropathology' evolved over several centuries, during which knowledge accumulated in structure and function, localisation in health and disease along with the reliability of physical signs and nosology of disease. This brief account is a personal communication of what the author thinks to be some of the main roots of neuropathology and he acknowledges that it is not complete. Several distinguished names such as Korbinian Brodmann, Constantin v Economo, Ludwig Edinger, Sigmund Freud, Sergej Sergejewitsch Korsakow, Theodor Meynert, Constantin v Monakow, Franz Nissl, Hermann Oppenheim, Jan Evangelista Purkinje, Adolf v Strümpell, Rudolf Virchow, Bernhard v Gudden, Adolf Wallenberg - among many others - do not appear because of the necessary brevity of this article. Furthermore, the references are highly selective as just the citied works are listed.

Finally, this brief essay can neither replace nor do justice to the scholarly writings devoted to the history of medical research of the diseased nervous system leading to the discipline neuropathology and for these accounts the reader is referred to the 'Further reading' section.

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Further reading

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This is the ABN Case Report Winner and we congratulate the authors on this achievement. This case report by Monaghen et al makes for sobering reading and highlights the point that making a diagnosis is one thing, but making sure it is properly treated is another.

If you would like to report similar interesting case reports then do contact us at: patriciamcdonnell@btinternet.com

The Woman who Mistook the Past for the Present

A 'variant' presentation of an old disease: a further differential for the 'pulvinar sign'.

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DT Murphy,
N Tubridy,
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The case is presented of a 41-year-old female surgical patient who was transferred to our care with an amnestic syndrome associated with ataxia and ophthalmoplegia. This followed a complicated surgical course associated with abdominal pain, vomiting, adhesions, ileus and parenteral nutrition. Wernicke-Korsakoff syndrome was suspected. Certainty regarding the diagnosis was complicated by lack of information regarding the thiamine content of Total Parenteral Nutrition (TPN) administered to the patient. An alternative diagnosis of Creutzfeldt-Jakob Disease with important quarantine implications had to be considered due to neuro-radiological abnormalities demonstrated on magnetic resonance imaging affecting the medial pulvinar, as well as prominent neuro-psychiatric features common to both disorders. Creutzfeldt-Jakob Disease has previously been misdiagnosed as Wernicke-Korsakoff syndrome. Wernicke-Korsakoff syndrome is an important under-reported differential diagnosis for the 'pulvinar sign'. Total Parenteral Nutrition is a dangerous misnomer as not all preparations contain total requirements of vitamin supplementation.

Case history

The case is presented of a 41-year-old woman who was well until her wedding day three months earlier. She was transferred to our hospital for investigation and management of grandiose delusions, gaze palsy, nystagmus, ataxia and memory impairment. Subsequently she developed seizures.

She had been investigated for epigastric abdominal pain that developed during her honeymoon in Central America. While abroad she had been vomiting and had reduced oral intake throughout that time. This occurred soon after the onset of bilateral leg oedema following multiple insect bites.

On her return to Ireland, she underwent an OGD

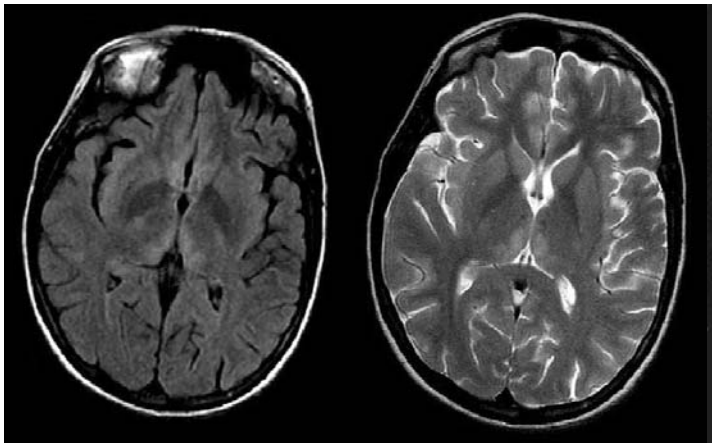

Figure 1a (left) and Figure1b (right): The inversion recovery image on the left and the T2 image on the right demonstrate the pulvinar sign with increased signal in the medial thalamus.

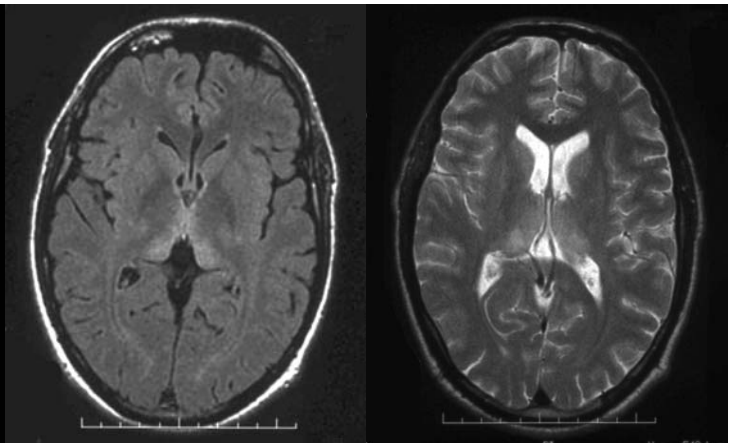

Figure 2a (left) and Figure 2b (right): Inversion recovery (left) and T2 (right) imaging provided for comparison from a 20-year-old male with variant Creutzfeldt-Jakob disease imaged on the same machine also illustrating the pulvinar sign.

and colonoscopy which were normal.

A laparoscopy was performed because of ongoing vomiting with abdominal pain and multiple abdominal adhesions were surgically lysed at laparotomy. She remained unwell after the procedure with episodes of constipation and vomiting and had poor oral intake. Recovery was delayed over 10 days before the passage of flatus.

The patient was readmitted after recurrence of severe vomiting and constipation. A second laparotomy was performed with resection of 32cms of ischaemic small bowel and further adhesion lysis one month before transfer. Recovery was once again complicated by paralytic ileus and she received TPN for twenty-five days.

Three months into her illness, she then began to demonstrate social withdrawal and became somewhat apathetic. She was referred to a psychiatrist and depression was diagnosed initially. Then confusion and agitation developed. It became apparent that her memory had deteriorated. She was seen by a neurologist.

Clinically she had the following findings: Her affect was flat with features of 'la belle indifference'. She had bilateral ptosis, square wave jerks and ophthalmoplegia to approximately 50% of the normal range. There was nystagmus in the horizontal and vertical planes. There were florid confabulations and she was unable to remember her recent marriage. There was no memory of her new husband as being more than a good friend. She was unable to retain any new information presented. The gait was broad-based and ataxic but there were no signs of peripheral neuropathy.

Investigations

Standard haematological investigations were all normal. Computed tomography of the brain and an electroencephalogram were normal aside from bilateral slow waves ascribed to phenothiazines newly administered for the control of anxiety. A lumbar puncture was performed and all indices were within the normal range.

Magnetic resonance imaging of the brain revealed high signal intensity lesions in the pulvinar bilaterally (Figure 1a and 1b). This is a well-described sign in variant Creutzfeldt-Jakob disease (vCJD) which has received considerable media and medical attention with the diagnosis of the first two indigenous cases in the Republic of Ireland. Our patient had worked regularly in the United Kingdom during the 1990s and had undergone surgery there.

Management

Clinically Wernicke-Korsakoff syndrome was suspected and therapy with intravenous thiamine was commenced immediately. However on the basis of the imaging and clinical presentation, it was deemed a necessary precaution to quarantine temporarily the surgical instruments used in the four procedures detailed above. This quarantine was removed after re-analysis of the lymphoid tissue of her resected small bowel failed to demonstrate prion protein. An absence of 14-3-3 prion protein in the cerebrospinal fluid, along with clinical improvement in the ophthalmological signs after intravenous thiamine, were supportive of the diagnosis of Wernicke-Korsakoff syndrome. Careful examination of the TPN regimen that was used revealed that it did not contain thiamine.

Discussion

Magnetic resonance imaging with high signal uptake in the pulvinar has been described in vCJD[1]. This sign has been demonstrated to have a high sensitivity for vCJD in the appropriate clinical context[2]. It is also reported in sporadic CJD[3]. Bilateral thalamic infarcts, perinatal ischaemia, iron deposition, copper deposition and neoplastic infiltration have all been associated with the pulvinar sign[4]. These changes are also reported in Fabry disease[5]. More recently this sign has also been described in paraneoplastic limbic encephalitis[6]. Wernicke-Korsakoff syndrome has been reported as part of the clinical differential diagnosis of CJD in one report[7]. Magnetic Resonance pulvinar abnormalities have been described rarely in Wernicke-Korsakoff syndrome[8,9,10].

'Total Parenteral Nutrition' regimens which do not contain supplemental vitamins may be more commonly available in pharmacy stocks because these products have a longer shelf life than compounds containing Recommended Daily Amount (RDA) requirements. We propose that TPN regimes which do not contain supplemental vitamins be termed 'Limited Parenteral Nutrition' (LPN) as an alert to avoid the risks of Wernicke-Korsakoff syndrome in nutritionally compromised patients who may receive parenteral nutrition for prolonged periods.

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Epilepsy in Children 2nd Edition

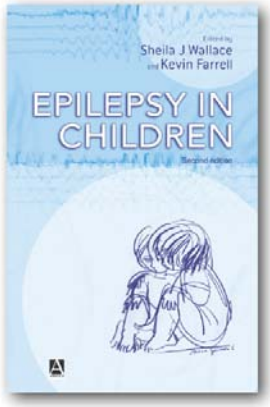
I've read this book in the last six months of my training as a specialist registrar in paediatric neurology – and I wish I'd read it in the first six months! The investigation and management of epilepsy in children is interesting, often complex and very different to the management of adults. This book is up-to-date and gives an in-depth overview of all aspects of looking after children with epilepsy. It is aimed at paediatric neurologists, paediatric epilepsy nurse specialists, and paediatricians with an interest in epilepsy, but would also be invaluable to an adult epileptologist, especially if they are involved in the transitional care of young people with epilepsy.

It is divided up into sections which are broadly divided into aetiology, pathology, pathophysiology, epilepsy syndromes by age, investigations, imaging, pharmacology, treatment and the cognitive, psychiatric and social aspects of epilepsy in children. Although there are contributions from many international authors, the layout of chapters is systematic and similar and includes 'key points' summary tables which are bordered and printed in a grey colour. These are very useful if just dipping in and out of the book, although it is annoying that sometimes they start on one page and end on the next. My only small disappointments were the lack of inclusion of some of the less well used antiepileptic drugs such as stiripentol, bromides and acetazolamide in the 'Review of individual drugs' chapter. Also it would have been helpful to have a review of the modified ketogenic diet which is used by most centres in the UK as opposed or in addition to the chapter on the classical ketogenic diet. I didn't find any errors in any section of the book.

Very poignantly, the book's main editor developed a brain tumour and died during the publishing of the book. Having never met or worked with Dr Wallace, I read the section movingly titled 'Sheila Wallace - an appreciation' with interest. She sounded like a truly inspirational hands-on paediatric neurologist and I'm sure she would have been delighted with her new book.

In summary, this book will be an invaluable addition to any department looking after children or young adults with epilepsy. With the new NICE guidelines there is an expectation that children with epilepsy will be managed by a paediatrician with a special interest in epilepsy or a paediatric neurologist, giving a book like this an increased audience for the future.

Dr Rachel Kneen, Royal Liverpool Children's NHS Trust, Alder Hey, Liverpool, UK.



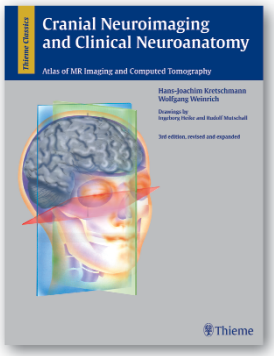
Editors: Sheila Wallace and Kevin Farrell
Published by: Arnold
ISBN: 0340808144
Price: £125

Cranial Neuroimaging and Clinical Neuroanatomy 3rd Edition

Now that neuroanatomy is barely taught in medical school, post mortems have become a rarity, and brain cutting sections are almost a historical relic, where do junior doctors learn their neuroanatomy? Increasingly the answer is in the radiology department. However, neuroradiology meetings tend to be hurried affairs. There are many scans to get through; and what is crystal clear to the seniors sitting at the front, may be rather obtuse to those at the back. But it takes a brave junior to keep interrupting: Where exactly is the semioval centre? Could you point out again the infundibulum? Show me again the supramarginal gyrus? This is where Cranial Neuroimaging and Clinical Neuroanatomy comes in. It's a very useful atlas comparing CT and MRI images with carefully constructed line drawings. The first edition appeared in 1984 followed the introduction of CT imaging, and the second edition, in 1992, incorporated magnetic resonance imaging. In this third edition all the CT and MRI images have been replaced with large sized illustrations, and there are double the number of images; in addition, the arterial territories of the infratentorial space have been introduced.

After introductory chapters, which include guidance on the choice of neuroimaging techniques now available, the book systematically goes through the skeletal structures, intracranial and vascular structures, neurofunctional systems, and neurotransmitters and modulators. There is clever use of colour and shading in the illustrations. The book will be helpful for students and experienced physicians alike, from a range of specialties linked with the neurosciences. I think readers will dip into it, rather than read it cover to cover. Thus it would have been helpful to have a simple "how to use this book" guide in a single page at the beginning, because many readers won't want to plough through the introductory pages. Also it might have been sensible to use the same numbers on the scans and graphic illustrations that accompany them. In general though, an excellent book that will be a useful addition to many collections.

Dr Tom Solomon, WCNN, Liverpool, UK.



Kretschmann and Weinrich
Published by: Thieme Classics
ISBN: 1588901459
Price: 199.00

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o rachael@acnr.co.uk

Cerebral Vasospasm: Advances in Research and Treatment

That hectoring criticism of the book review editor was necessary before I could muster the enthusiasm to review a book which had glowered from my shelf for six months, should tell you all that you need to know about this niche text, which is destined for institutional purgatory. Yet the importance of vasospasm to the morbidity of subarachnoid haemorrhages certainly justifies the editorial ambition to present an update on aetiology, pathogenesis, investigation and treatment of vasospasm. Although the title refers to advances in research and treatment it is in reality a compilation of research papers presented at the Eighth International Conference on Cerebral Vasospasm in Chicago, July 2003, rather than a considered critical review.

Compilations of proceedings from small international meeting are seldom cohesive or readable and are unlikely to be purchased by the generalist looking for a concise treatise on the state of art management. The editors have succeeded in producing a surprisingly readable text with high quality image reproduction, but it still feels more like an expanded meeting abstract compilation, than a definitive text.

Inevitably the focus of the text is neurosurgical and neuroradiological but despite its intention to consider research advances it revisits ad nauseam established tenets of neurovascular medicine, with an early emphasis on vasospasm as a function of endothelium and myocyte alone and a curious indifference to neurogenic mechanisms. A notable omission is reference to inflammatory mediators such as matrix-metalloproteinase in vasospasm given only one short review chapter. Those interested in genetic influences will struggle to find a précis that distils the interactions of endothelial factors and myocyte cellular signalling pathways involved.

I find it difficult to see who would purchase this book. Researchers active in the field will not find anything new within it. There are sections devoted to clinical medical, surgical and radiological management, and interesting series (some randomised) are presented, which explore intrathecal fibrinolysis, CSF drainage, protein kinase inhibitors, and transdermal nitroglycerin but they are insufficient to elevate this book to key text. A shame as there would be an eager readership for a definitive review of this important topic.

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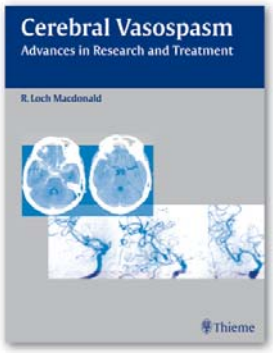
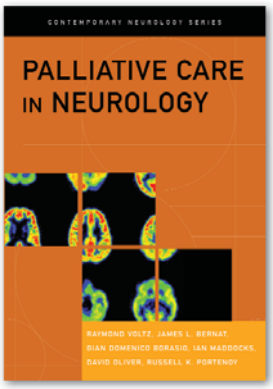
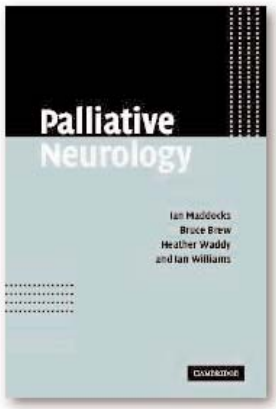


R Loch Macdonald
Published by: Thieme
ISBN-10: 1588902838 / 3131400617
Price: 139.95

Palliative Care in Neurology

There is a small but growing interest in the principles of palliative care and neurology. Recently 2 books have been published with deal with this area, Palliative Neurology (Maddocks et al, 2006) and Palliative Care in Neurology (Voltz et al 2004). Both are interesting, well written books by contributors in the forefront of their fields. Both begin by defining and discussing the principles of palliative care throughout the patients illness to the terminal phase, both cover specific points of palliative care that arise within specific neurological conditions and also the treatment of common symptoms that occur in many patients with a range of chronic progressive neurological conditions. The Maddocks et al book is perhaps more aimed at neurologists who wish to learn more about the basics of palliative care, and want a quick referral guide to symptom control. It does not address the role of specialist palliative care, versus general supportive and palliative care (as should be provided by the neurological multi-disciplinary team), and it is brief in the background pathophysiology and simplistic in some treatment recommendations. The Voltz et al book is a more weighty volume, densely written, without the quick reference boxes and summary diagrams of the Maddocks publication. However the book would have appeal to both specialists in palliative care who are being asked to expand service provision into neurology and to neurologists who need to know in more depth symptom control, communication skills and terminal care provision. It has the space to provide case histories to hang the more in-depth discussion of pathology, possible treatment options and other team referrals. It does not offer a quick reference guide to treatment, more the principles surrounding treatment options, such as class of drug rather than specific doses. It offers a more comprehensive guide on a range of issues such as: communication skills and has a fuller discussion around problems such as collusion, denial, anger etc. It is perhaps harder to find specific answers to questions such as 'what will help noisy terminal secretions?', and fails entirely to help with urinary spasms, both of which are easy to find in Palliative Neurology (Maddocks).





If you can only afford one - which one to buy? A difficult question and in true Palliative Care style one I will reflect back to you, 'what do you want'? If you need a quick and easy introduction to palliative care and answers to symptom control questions then Palliative Neurology (Maddocks et al, 2006, CUP) is for you, if you want a better understanding of the interface, application and pathophysiology behind aspects of palliative care and neurology and/or wish to develop the service, then Palliative Care in Neurology (Voltz et al 2004, OUP) is better.

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Palliative Care in Neurology
Editors: R Voltz, JL Bernat, GD Borasio, I Maddocks, D Oliver, K Portenoy
Published by: Oxford University Press 2004
ISBN: 0-19-850843-3
Extent: 448 pages
Price: £79.50

and

Palliative Neurology
J Maddocks, B Brew, H Waddy, I Williams
Published by: Cambridge University Press 2006
ISBN: 0-521-67249-X
Extent: p260
Price: £29.99

EDITOR'S CHOICE

The dangers of complex partial status epilepticus

This study identified 96 patients with their first status epilepticus episode by retrospective search of records. Fifteen patients died. Only five patients had non-convulsive status with coma but three of these died. For the purposes of this study 11 patients whose non-convulsive status was due to global anoxia were excluded but they all died as well. There were six deaths out of 42 patients with complex partial status and six out of 45 with convulsive status suggesting a similar mortality of 14%. All of the four patients with simple partial status survived. Of the 15 patients who died, 14 had what the authors call a potentially fatal aetiology, although the definition of this is not clear. Looking at it the other way around, of 56 with a potentially fatal aetiology, 75% survived. So, as in previous studies, the cause of the seizures was a key factor in predicting mortality, but even in the worst aetiological group there were many survivors. In this study additional variables were identified which carry a poor prognosis, including older age and severity of coma. Interestingly, duration of status over one hour was not an independent adverse predictor. Previous studies have suggested that Caucasians carry a higher risk but this was not borne out once the confounding influence of age was removed.

Probably the single most striking result of this study was the severity of the outcome for patients with complex partial status. What I could not glean from the data was whether this group were more likely to have a potentially fatal aetiology. Intuitively this is likely to be the case since most complex partial status is due to structural brain disease, whereas tonic clonic status may be due to treatable factors such as alcohol withdrawal, drug overdoses and metabolic derangements. This piece of information is important in deciding if patients with complex partial status need to be treated as aggressively as those with convulsive status. ***-MRAM***

Rosetti AO, Hurwitz S, Logroscino G, Bromfield E.
Prognosis of status epilepticus: role of aetiology, age and consciousness impairment at presentation.
JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY
2006;77:611-15.

ALZHEIMER'S: Don't forget the olive oil

Sloshing around the epidemiological literature for some time has been the suggestion that the Mediterranean diet is good for you. Fish, olive oil and wine in good measure, a fair amount of dairy products and low meat intake, keep the doctor away. And also Alzheimer's, if this New York group are to be believed. 4166 individuals started in the Washington-Heights-Inwood Columbia Aging Project and this particular study focused on the prospective follow-up of the 3436 that were not demented at the outset. Unfortunately, useful information on diet could only be gleaned from 2258 subjects, of mean age 77 years, who were followed-up every 1.5 years. 11% (n=262) developed Alzheimer's during the mean four years of follow-up. However, those who stuck to the diet were 40% less likely to develop the disease than the less compliant; this finding stood a rigorous testing for confounds. Not given in the text is the number needed to treat, which my trusty calculator tells me is around eight. Happily for this reviewer, those components of the Mediterranean diet which seemed especially helpful were alcohol and vegetables! But the combo seemed to the best of all. Of critical importance to any reader, ignored by the authors, is how long people need to have been on the Mediterranean diet to gain its protective effect? Can I stick with my "modified Atkin's diet" until 70 years old and then switch? Or do I need to stock pile the extra virgin olive oil now? ***-AJC***

Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA.
Mediterranean diet and risk for Alzheimer's disease.
ANNALS OF NEUROLOGY
2006;59(6):912-21.

PRION DISEASE: learning from cannibalism

★★★ RECOMMENDED

There is something gothic about the history of the prion hypothesis: the triumph of one sole thinker against establishment (as Pruisner would have it) on the sinister backdrop of the threat of a pandemic of dementia. This research in the Lancet, amazingly simple at heart, follows the tradition. A six-man team with "heavy-vehicle rescue equipment" patrolled the Papua New Guinea highlands for cases of kuru, the cerebellar prion disease transmitted by ritual cannibalism. Since this practice was outlawed in the mid 1950s, the incubation period could be defined by the most recent incident cases. Since 1996, eleven kuru patients have been found. The minimum incubation period for these people could be calculated at between 34 and 41 years. This is considerably greater than previous estimates of the mean incubation period of 12 years. Most of the affected patients were heterozygous for methionine and valine at position 129 in the PrP gene. The implication is that variant CJD, caused by eating prion-infected beef, may have a similarly extended incubation period. The authors remind us that the cow-to-man species barrier tends to prolong incubation periods. And one interpretation of the dominance of methionine homozygosity at PrP129 in the 160 cases of vCJD to date is that heterozygotes have a greater incubation period…. and so will make up a "second epidemic". Since rendering and butchering techniques were modified to reduce or abolish the risk of prion protein infectivity by 1990, new cases of vCJD may still be appearing in 2030 or so…. Or not. We'll have to wait and see. ***-AJC***

Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas D, Alpers M.
Kuru in the 21st century—an acquired human prion disease with very long incubation periods.
THE LANCET
2006;367:2068-74.

HUNTINGTON'S DISEASE (HD): supporting the striatum in HD with GDNF

GDNF has a long history with Parkinson's disease but in a recent issue of PNAS it has been shown to be useful in Huntington's disease. In this study GDNF was delivered via a recombinant associated adenoviral vector to the striatum of pre symptomatic H171-82Q transgenic HD mice. This led to a rescue of behavioural performance, reduced pathology both intracellularly and in terms of cell death and atrophy. This occurred 11 weeks after bilateral striatal injection of the trophic factor when the GDNF was widely distributed across the striatal complex as well as in afferent structures to it, showing robust expression several weeks after delivery. In addition the ability to prevent pathology was striking in contrast to some other studies using different transgenic mouse models of HD. However, whilst the mechanism by which GDNF achieves this effect is still unresolved, it adds to the emerging role of neurotrophic factors in HD including recent studies on the effect of huntington on BDNF and the value of encapsulated cells releasing CTNF as a potential treatment. ***-RAB***

McBride JL, Ramaswamy S, Gasmi M, Bartus RT, Herzog CD, Brandon EP, Zhou L, Pitzer MR, Berry-Kravis EM, Kordower JH.
Viral delivery of glial cell line-derived neurotrophic factor improves behaviour and protects striatal neurons in a mouse model of Huntington's disease.
PROC NATL ACAD SCI USA
2006:103;9345-50.

STROKE: Upright or left?

★★★ RECOMMENDED

There are a number of reasons why balance may be affected after stroke and if asked therapists may cite both sensory and motor contributing factors. However balance is often treated without consideration to perception, just by practicing staying upright or responding to perturbations. This may not be the most intelligent approach – if the underlying problems are not fixed then maybe balance will not improve. An interesting investigation by Bonan et al has revealed that subjective visual vertical (SVV) perception is often abnormal after stroke. SVV perception is measured by sitting subjects in a darkened room and asking them to adjust a luminous line to vertical. It was found to be abnormally tilted in 12 out of 30 stroke patients. In addition 12 patients showed more uncertainty than normal (i.e. greater standard deviation) in the judgement over eight trials. There were significant but unimpressive correlations with balance performance. SVV was more uncertain in patients with right hemisphere lesions and interestingly the amount of tilt was greater in patients with partial proprioceptive loss in the lower limb than in those with absent proprioception. These results suggest that assessment of sensory and perceptual factors may be useful for planning treatment for stroke patients with impaired balance and that maybe new treatments for neglect that work to recalibrate and integrate sensory inputs might contribute to restoring balance. ***-AJT***

Bonan IV, Guettard E, Leman MC, Colle FM, Yelnik AP
Subjective visual vertical perception relates to balance in acute stroke

ARCHIVES PHYSICAL MEDICINE REHABILITATION
2006;87:642-6.

PARKINSON'S DISEASE (PD): switching off pathology

Novel strategies for treating Parkinson's disease have been something of a theme in the journal review section of the ACNR and one exciting new initiative involves the silencing of pathogenic genes/proteins in PD using small interfering RNAs. This has been tried before in diseases of clear genetic origin such as Huntington's disease and spinocerebellar ataxias but in a new paper in Experimental Neurology, Martha Bohn and colleagues have applied this new approach to alpha synuclein - the protein that characterises Lewy bodies in Parkinson's disease and mutations of which, along with duplication and triplications, cause familial PD. In this study synthetic siRNAs were manufactured to human synuclein and linked to a lentiviral vector. They initially showed that the interfering RNA could successfully silence human alpha synuclein protein expression, in various cell lines, including the catecholaminergic SHSY51 cell line. Finally they virally overexpressed human alpha synuclein in the striatum of the adult rats and showed that their interfering RNA could switch production of the protein off two weeks later.
This is an important study because it highlights the possible efficacy of this approach in PD and other synucleinopathies. However many problems still exist with this approach including switching off the gene in idiopathic Parkinson's disease where it is not mutated or over expressed, not switching off the normal form of alpha synuclein given its presumably vital role in normal synaptic homeostasis and thirdly managing to give long-term delivery of such factors to multiple brain regions achieving silencing to a significant extent over years. Thus whilst this study shows the value of this approach in neurodegenerative disorders it raises more questions than it answers. ***-RAB***

Sapru MK, Yates JW, Hogan S, Jiang L, Halter J, Bohn MC.
Silencing of human alpha synuclein in vitro and in rat brain using lentiviral-mediated RNAi
EXPERIMENTAL NEUROLOGY
2006:198;382-90.

EPILEPSY: Not all spikes mean fits – take a family history

★★★ RECOMMENDED

We are all familiar with the patient who presents with a blackout and a strong family history of idiopathic epilepsy. On one level this increases the chance of the patient also suffering epilepsy. On another level it increases the chance of asymptomatic EEG changes, which need to be interpreted with caution. The extent of this potential problem is illustrated by the current study, which also highlights the significant number of symptomatic patients with presumed IGE whose EEG may be normal. In this study there were 31 probands with a secure electroclinical diagnosis of JME and 149 first-degree relatives, of whom 132 had a sleep-deprived EEG. Two of 52 parents (4%) were symptomatic and 13 of 68 siblings (20%), a total risk of 13% for first degree relatives. The clinical syndromes were JME (44%), epilepsy with grand mal on waking but no history of myoclonus (19%), childhood absence epilepsy in one patient and one with GTCS with no particular pattern. Of the symptomatic relatives, only 6 (37.5%) had a definitely abnormal EEG, with a further 12.5% with borderline changes and 12.5% with some focal abnormalities. Of the 106 asymptomatic relatives, seven (6%) had spike and wave on their EEG and a further 6% had borderline changes. This study supports previous studies in showing a major genetic component to this common syndrome. The high incidence of asymptomatic EEG changes in first degree relatives reminds one of the importance of a family history. It also begs the question: if these patients were followed up for long enough, would they have seizures? The study does not answer the question of the risk of epilepsy in the offspring of those with JME which has been addressed previously. ***-MRAM***

Jayalakshmi S, Mohandeas S, Sailaja S, Borgohain R.
Clinical and electroencephalographic study of first-degree relatives and probands with juvenile myoclonic epilepsy.
SEIZURE
2006;15:177-83.

STROKE: Good old rat poison for atrial fibrillation

★★★ RECOMMENDED

In the "ATIVE W" trial, co-ordinated in Canada and executed all over the world, people with atrial fibrillation and one other risk factor (previous stroke or TIA, hypertension and poor ejection fraction for instance) were randomised to receive old fashioned warfarin (target INR 2.0-3.0) or newfangled aspirin and clopidogrel together. The study was started in June 2003 and was stopped early in August 2005 by the data and safety monitoring board because of clear superiority of warfarin. Within the 6706 randomised patients, there were 165 primary outcome events (stroke, arterial embolus, MI or vascular death) in the warfarin group compared to 234 in the aspirin/clopidogrel arm: an annual risk of 3.9% versus 5.6% and a number-needed-to-treat of 48 (my calculation). Rates of major haemorrhage were identical in each group; interestingly, total bleeds were more frequent in the aspirin/clopidogrel cohort. The accountants will be delighted: a year of warfarin costs roughly £20 whereas clopidogrel with aspirin sets you back £1,600. The ATIVE W study is one third of a complicated triptych of clinical trials. ACTIVE A examines the effect of adding clopidogrel to people already receiving aspirin and ACTIVE I adds irbesartan to cohorts from the W and A trials….they are still being processed. These studies are funded by the manufacturers of clopidogrel and irbesartan: the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. ***-AJC***

The Active Group.
Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial.
THE LANCET
2006;367:1903-12.

EPILEPSY: Life through blue tinted spectacles

Case History: The patient comes through the door with a history of blackouts and is wearing blue tinted spectacles. And the diagnosis is…….. if you say non-epileptic seizures then this paper may change your mind. Photosensitivity triggers seizures and anxiety in high risk situations for susceptible individuals. The authors took 610 patients, median age 11.9 and two thirds female with proven type IV photoparoxysmal response on EEG and repeated their test whilst wearing Z1 lenses. These lenses are commercially available in Italy and attenuate light by over 90% in the range 480-600nm wavelength. The abnormal response to photic stimulation was abolished in three quarters of patients and significantly attenuated in a further 18%. The authors argue that patients who only have seizures in response to photic stimuli may prefer treatment with spectacles to medication, whereas those who also have seizures at other times will require additional medication. Not all photosensitivity is reproducible with photic stimulation but this paper suggests that a significant number of patients may be helped in this way. ***–MRAM***

Suppressive efficacy by a commercially available blue lens on PPR in 610 photosensitive epilepsy patients.
Capovilla G, Gambardella A, Rubboli G, Beccaria F, Montagnini A, Aguglia U, Canevini MP, Casellato S, Granata T, Paladin F, Romeo A, Stranci G, Tinuper P, Veggiotti P, Avanzini G, Tassinari CA.
EPILEPSIA
2006;47:529-33.

STROKE: Aspirin and dipyridamole…. The business?

I must admit to a heart-sink feeling when faced with trials like this in my favourite magazine. I know I ought to be interested… and they are all terribly worthy… but somehow they fail to excite the imagination. Ah well, at least this one is an academic study; you can tell because it has a long follow-up, poor patient retention and no drug company sponsorship…. The question being considered is whether your patient benefits if you prescribe dipyridamole (200mg bd, mainly slow-release preparation) in addition to aspirin for the secondary prevention of stroke or TIA. 2739 patients were randomised, mainly in the Netherlands and the UK. During the 3.5 years of follow-up, primary outcome events (fatal and non-fatal ischaemic stroke and all cardiac events) occurred in 173 (13%) patients on aspirin and dipyridamole and in 216 (16%) on aspirin alone. Although fantastically significant statistically, this gives a number of 104 (95% CI 55–1006) patients per year needed to treat with the combination regimen to prevent a death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication. This amounts to about £10,000 per event prevented: a local NHS hospital has already declared that this is "uneconomic". Now that really is a scandal. ***-AJC***

The Esprit Study Group.
Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial.
THE LANCET
2006; 367:1665-73.

Association of British Neurologists Spring Scientific Meeting

Brighton, UK, 19-21 April, 2006.

Renowned for its busy beach-front with nostalgic Victorian piers, brazen fairgrounds and rides, a feverish night-life with a diverse gay scene and termed by many as a 'pleasure dome', Brighton was none other than host to the ABNs spring scientific meeting.

With a backdrop of fairy lights and to the faint bark of sea-gulls, opening its doors to delegates was the luxury five star promenade hotel, The Grand. Some may have been reminded of the hotels turbulent past, involving eminent female politicians, party political conferences and terrorist acts.

Delegates at the meeting in the foyer at the Grand hotel.

Delegates gathered and eagerly awaited the opening platform presentations of the top scoring papers from Hirst, Fulton and Anderson, while trainers and educationalists met for an interactive and multi-media session with Professor CM Wiles and Dr GN Fuller. Focusing on development of teaching, appraisal and assessment, highlighting the use of multi-source feedback and MiniCEX, providing insight into nurturing high quality training schemes, and ultimately shaping the future of neurology and those who will delivery it.

The scientific programme unfolded, with epilepsy topics concentrating on surgical techniques and Foltynie presented interesting work with regard to drug reduction in pre-surgical evaluation. But the epilepsy highlight was surely Baxendale on 'Epilepsy at the movies', in the satellite symposium where we were amused by the complex partial seizure in 'Snow White and the seven dwarfs', intrigued by the pseudo-seizure at the presidential assassination in JFK and hooked by the time the post-watershed European films appeared.

Stroke papers outlined ethnic differences in stroke risk factors and stroke subtype, and Fulton demonstrated pathophysiological differences in small and large vessel stroke.

As enthusiastic investigators took the platform in turn, conquered nerves and answered tough questions a few other eager members took their turn at the tee after polishing rusty clubs and practising their swing, they then battled it out on the fairways and greens, hoping to achieve a semi-respectable score not too far off par, in the ABN golf outing.

'When in Rome, do as the Romans do', was not strictly true of the ABN in Brighton, although Manji, Nisbet and Churchill gave historical accounts of the gay scene, gay pride and the pink pound era, encouraging us to remove the taboo of HIV testing and outlined the therapeutic relevance of CD4 counts and viral loads in determining the aetiology of opportunistic infections in HIV infected individuals.

In multiple sclerosis the grey/white matter debate rages on, and was expanded further by exciting work from Gilmore using myelin protein immunohistochemistry to demonstrate the grey matter demyelination is more extensive than white matter demyelination throughout the spinal cord. Other MS research took the form of the initial clinical presentation findings (Hirst), MRI and post-mortem correlates (Schmierer), and an initial study on treating relapses at home (Chataway).

Up-to-date clinical series of CSF opening pressures and BMIs (Whiteley), and on neuroborreliosis (Lovett) added to daily neurological practice while Pearson expounded on the developing clinico-radiological entity of posterior reversible encephalopathy syndrome that is clearly a 'PRESing situation'.

As at previous ABNs and probably not the last either, neurology at the coalface, in the form of acute liaison neurology was described, as 'enjoyable, rewarding and resulting in a reduction of in-patient stay', by none other but by an acute neurologist (Dunn).

Dynamic, entertaining and revolutionary could only describe the guest lecture on 'Motion and emotion: the role of the basal ganglia' by Professor Yves Agid from Hopital Pitie-Salpetriere who thrilled and amazed us with the effect of brain stimulation on his patients and on monkeys affect. The science was great but the accent alone would have been enough to keep us in our seats, and certainly provided the essential je ne sias quoi!

Following an excellent ABN dinner and late-night disco the closing morning session certainly carried a more relaxed air, as the workplace suit turned into casual trousers with open necked shirts, the agenda too, a new venture for the ABN was informal though a fantastic case fest won by Monaghan with his tragic case of 'The woman who mistook the past for the present', a case of Wernicke-Korsakoff syndrome after total parenteral nutrition that in essence completely lacked thiamine.

Having almost forgotten to mention the ABN fun-run, it certainly can be said that the ABN in Brighton offered something for all tastes and persuasions. It was an exciting and diverse venue that boasted a packed scientific programme of 24 platforms, eight cases and 58 posters with closing scientific research platforms from Rosser, Spillantini and Collinge. It waits to be seen, how London and Cambridge will measure up in size and performance.

Ann Johnston
Specialist Registrar, Cardiff, Wales.

CONFERENCE PREVIEW: 6th Annual Brain Injury Legal Seminar

London, UK, 21 September, 2006.

The Brain Injury Social Work Group, in partnership with Stewarts Solicitors, are organising the programme for the 6th Annual Brain Injury Legal Seminar with presentations aimed at a wide range of professionals working within the field of brain injury and other related areas. The seminar will address topical issues of law, ethics and practice that will be of relevance to those working in the public, private and voluntary sectors.

The keynote speaker Professor Keith Andrews is the Director of the Institute of Complex Neuro-Disability, Professor, Centre for Leadership and Practice Innovation, Southbank University London and is highly regarded as an expert in profound brain injury and neuro-disability. He will deliver an address entitled 'Practical Decision Making in Withholding and Withdrawing Treatment' which will offer invaluable information including that of his own clinical experience and that of research.

Nathan Tavares, Counsel, Outer Temple Chambers, London will talk on 'The impact of Freeman-v-Lockett on state funding of care' which will shed light on the contentious issues of compensation monies and the responsibility for the funding of care by local authorities.

For further information contact:
BISWG Administrator Ms Lynn G Bellgard Tel/Fax: 0208 780 4530
Email: lbellgard@rhn.org.uk

To list your event in this diary, email brief details to Patricia McDonnell at events@acnr.co.uk by July 28th, 2006

2006

July

7th European Congress on Epileptology
2-6 July, 2006, Helsinki, Finland
W. www.epilepsyhelsinki2006.org/

International Congress on Neuromuscular Disorders 2006 (ICNMD)
2-8 July, 2006; Istanbul, Turkey
W. www.icnmd2006istanbul.org
E. pirayes@hotmail.com

Talk: Pain, drugs and plants
4 July, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

Towards an understanding of Parkinson's disease
4 July, 2006; Devon, UK
T. 01392 405171

NEW
BISWG North West & North Wales Regional Meeting
5 July, 2006; Birkenhead, UK
Info. Guy Soulsby
T. 0151 250 6247
E. guy.soulsby@merseycare.nhs.uk

11th Wye College Advanced Neurosciences Symposium
5-7 July 2006, Wye, Kent, UK
Web. www.bns.org.uk

BSRM/SRR Summer Meeting
5-7 July, 2006; London, UK
Info. BSRM
T. 01992 638865
E. admin@bsrm.co.uk
W. www.bsrm.co.uk

5th Forum of European Neuroscience
8-12 July, 2006; Vienna, Austria
W. http://forum.fens.org/2006

MS Trust Advanced Study Day
10 July, 2006; Liverpool, UK
T. 01462 476704
W. www.mstrust.org.uk/education.jsp

Multidisciplinary care in Parkinson's disease and parkinsonism from science to practice - the 11th National Conference
11 July, 2006; London, UK
W. http://www.mepltd.co.uk/conference_pd_2006.html
E. alockyer@mepltd.co.uk

13th International Meeting on Advanced Spine Techniques (IMAST)
12-16 July, 2006; Athens, Greece
W. www.imastonline.org/

10th International Conference on Alzheimer's Disease and Related Disorders
15-20 July, 2006; Madrid, Spain
Info. Kerri Leo,
T. 001 312 335 5813
E. internationalconference@alz.org

26th International congress of Applied Psychology
16-21 July, 2006; Athens, Greece
W. www.icap2006.com

4th International Conference on Memory (ICOM-4)
16-21 July, 2006; Sydney, Australia
W. www.psy.unsw.edu.au/Groups/ICOM4/

Techniques and Applications of Molecular Biology: A Course for Medical Practitioners
17-20 July, 2006; Warwick, UK
Info. Dr Charlotte Moonan
T. 024 7652 3540
E. Charlotte.Moonan@warwick.ac.uk
W. www.warwick.ac.uk/go/biosciencesshortcourses

International Neuropsychological Society (INS) Mid Year Meeting
26-29 July, 2006; Zurich, Switzerland
W. www.the-ins.org/meetings

COGSCI2006: 28th Annual Meeting of the Cognitive Science Society
26-29 July, 2006; Vancouver, BC, Canada
W. www.cogsci.rpi.edu/~rsun/cogsci2006/

August

10th European Conference on Epilepsy and Society
2-5 August, 2006; Copenhagen, Denmark
Info. International Bureau for Epilepsy
E. info@epilepsyandsociety.org
W. www.epilepsyandsociety.org

11th International Congress of Human Genetics
6-10 August, 2006; Brisbane, Australia
W. www.ichg2006.com
E. genetics@icms.com.au

9th World Down Syndrome Congress
22-26 August, 2006; Vancouver, BC, Canada
W. www.wdsc2006.com/

Teaching Course: Modern Trends in Epileptology as part of the 38th International Danube Symposium for Neurological Sciences and Continuing Education
28-29 August, 2006; Brno, Czech Republic
Info. Prof. MUDr. Ivan Rektor
E. irektor@med.muni.cz

September

10th European Federation of Neurological Societies Congress
2-6 September, 2006; Glasgow, UK
F. 00 43 1 88 92 581
E. headoffice@efns.org
W. www.kenes.com/efns2006/

1st Joint Meeting of European National Societies of Immunology Under the auspices of EFIS 16th European Congress of Immunology
6-9 September, 2006 - Paris, France
Info. ECI Paris 2006
T. +33 1 44 64 15 15
F. +33 1 44 64 15 16
E. eci2006@colloquium.fr
W. www.eci-paris2006.com

8th Eilat Conference On New Antiepileptic Drugs
10-14 September, 2006, Sitges, Spain
E. eilatviii@targetconf.com
W. www.eilat-aeds.com
T. +972 3 5175150, F: +972 3 5175155.

6th International Congress of Neuropsychiatry
10-14 September, 2006; Sydney, Australia
T. +61 2 9241 1478
E. info@inacongress2006.com

XXVIIIth International Congress of Clinical Neurophysiology
10-14 September, 2006; Edinburgh, UK
E. info@iccn2006.com
T.+44 (0)141 331 0123
W. www.iccn2006.com

MS Trust General Study Days
12 September, 2006; Hereford/Worcester, UK
T. 01462 476704
W. www.mstrust.org.uk/education.jsp

18th Congress of the European Sleep Research Society
12-16 September, 2006; Innsbruck, Austria
W. www.esrs2006.at/

XXXI Congress of the European Society of Neuroradiology
13-16 September, 2006; Geneva, Switzerland
W. www.esnr.org/02.asp

"Pain in Europe V", Triennial meeting of EFIC (European federation of IASP chapters)
13-16 September, 2006; Istanbul, Turkey
Info. Ms. S.Wheeler
E. efic@internet.gr
F. 30-210-992-6382
W. www.efic.org

ECNS 2006
13-17 September, 2006; Boston, MA, USA
W. www.ecnsweb.com/cn_2006.htm

Talk: Cannabis and the brain
14 September, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

NEW
Sally Letson Symposium - Neuro-Ophthalmology Update
14-16 September, 2006; Ottawa, Canada
T. +613 232 4414
F.+613 232 0120
W. www.eyeinstitute.net
E. info@confersense.ca

EANO VII : European Association for NeuroOncology Congress
14-17 September, 2006; Vienna, Austria
W. www.eano.de

Understanding and dealing with behavioural problems following brain injury
15-16 September, 2006; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

3rd Congress of the Euro Huntington Disease Network (followed by the meeting of the European Huntington Association)
15-17 September, 2006; Blankenberge, Belgium
W. www.huntington-disease.org

19th ECNP Congress
16-20 September, 2006; Paris, France
W. www.ecnp.nl/Congresses/frames/Congrframe.html

NEW
Multiple Sclerosis Care in the Community (distance learning)
18 September, 2006; Leeds, UK
T. 0113 2835918
E. CCNSenquiries@leedsmet.ac.uk/
W. www.leedsmet.ac.uk/health/cns/courses/mscep/index.htm

16th Migraine Trust International Symposium
18-20 September 2006; London, UK
Info. Hampton Medical Conferences Ltd
T: +44 (0) 20 8979 8300
E: mtis@hamptonmedical.com
W: www.migrainetrust.org

The International League Against Epilepsy (UK Chapter) Annual Scientific Meeting
20-22 September, 2006; Newcastle, UK
Info. Denise Hickman
T. 01323 740612, F. 01691 670302
E. denise@conference2k.com
W. www.conference2k.com

Eurospine2006
20-23 September, 2006; Istanbul, Turkey
W. www.eurospine2006.org

10 Years of Making a Difference - MS Trust Annual Conference 2006

CONFERENCE PREVIEW

Bournemouth, UK, 2- 4 November, 2006.

This year's Annual Conference will celebrate the progress made in delivering effective MS care and management during the past 10 years. It will also explore the challenges faced in continuing to develop and improve MS services for the future, alongside a wide range of practical clinical topics.

We are delighted that Dr Fred Foley, Director of Neuro-psychology and Psycho-social Research at the MS Center in New Jersey will be joining us to share his knowledge on improving coping skills, sexual function and mood in MS.

The programme will contain a number of plenary sessions, which will explore topics such as: 'Demographics – the facts and the challenges they present for the future', 'A decade of progress for MS: what next…?' and 'The case for specialist practice: MS specialist nurse and specialist therapist perspectives'. In the closing plenary session Dr Eli Silber (Consultant Neurologist, Kings College Hospital) will discuss both clinical and service development innovations for the future.

A choice of seminar sessions are available on the programme, to allow delegates to tailor the programme to their individual learning needs, topics include;

- Visual problems in MS
- Effective use of outcome measures in MS
- Sex: how far should we go…?
- 'The dog ate my trainers!' – motivating reluctant exercisers
- Managing bowel dysfunction in MS
- Ethical issues surrounding vulnerable adults
- Vocational rehabilitation in MS
- Impact of fatigue on dysarthria in MS

We have also introduced a new sharing best practice and innovation forum this year, where six speakers will share their experiences from different aspects of MS care and service delivery, topics will include Developing a care pathway for pregnancy in MS and Experiences and benefits of a new self referral system.

For further information contact:
Conference Secretariat, Medivents
Tel: 01462 744045
Email: mstrust@medivents.co.uk
or visit www.mstrust.org.uk/conference

The Electrode Company adds an IrDA wireless serial data link for users of the Lightman® microspectrometer

The Electrode Company Ltd specialises in non-invasive monitoring, optical sensors and high performance pulse oximetry. The Lightman® portable microspectrometer is now available with a dedicated IrDA infrared wireless serial data link. This will allow the user to download key data to any other IrDA device such as a PC, Laptop or PDA.

Downloaded data can be rapidly stored or re-transcribed into other formats, such as MSExcel, MSAccess and Lotus123. Individual sensor data can also be added, giving the user a valuable record and audit tool.

The Lightman is a unique, compact and hand-held device, which is easily operated by non-technicians and designed to be rapid and accurate in measuring SpO2 sensor performance. Its use will help reduce the number of patients put at risk daily from faulty SpO2 sensors.

For more information on the Electrode Company, visit www.electro.co.uk, or for details of the Lightman microspectrometer, telephone 01633 861772.

Three-laser Entry-level Confocal Microscope System meets the demand for affordable fluorescence imaging in diverse research applications

The Nikon e-C1plus

Having successfully filled the gap in the market for entry-level confocal imaging with its e-C1 microscope system, Nikon Instruments has announced the launch of its e-C1plus package. This has been specifically designed to meet the high demand for confocal imaging in increasingly diverse research applications. With the addition of a three laser-line option, the new e-C1plus can achieve increased flexibility, whilst remaining affordable and generating unsurpassed fluorescence images.

With three lasers, the e-C1plus can be used for almost any imaging technique required today, including simultaneous dual-channel fluorescence, DIC, time-lapse recording, and spatial analysis.

Live 3D images can be captured effortlessly as the settings and procedures required can be viewed in a single window, eliminating the need to switch between multiple windows. Furthermore, using the simple and intuitive Graphical User Interface (GUI), experimental set-up, image analysis and processing can all be carried out by the click of a mouse.

For more information please contact the Nikon Sales Office, Email: info@nikon-instruments.com or visit www.nikon-instruments.com

New hope for MS sufferers

Schering UK announced that Betaferon® (interferon beta-1b) has been granted marketing authorisation by the European Commission for an extension of its indication to include the treatment of the first clinical event suggestive of multiple sclerosis (MS).

This is a significant milestone in the treatment of MS. Traditionally, MS requires at least two clinical events for a definite diagnosis, but it is now known from MRI scanning that the disease is usually active and causing hidden damage long before the first symptoms declare themselves. The approval provides a very important treatment option for patients at risk for MS, as Betaferon® has been shown to delay the progression of the disease to clinically definite MS (CDMS). Left untreated, 85% of people who experienced a first clinical event (a first attack) have been diagnosed with MS within two years.

The label extension is based on results from the international BENEFIT* study which showed that Betaferon® 250mcg treatment in the early phase of the disease reduced the risk of developing CDMS by 50 percent compared with placebo. Furthermore, patients in the Betaferon® group were two times better protected against developing MS as defined by the McDonald diagnostic criteria. Betaferon® demonstrated clinical efficacy in all subgroups evaluated, and was very well tolerated, with 96% of patients electing to remain on long-term treatment after the placebo-controlled study had ended.

Betaferon® is now indicated for the treatment of patients with a first clinical event suggestive of MS, relapsing remitting MS with two or more relapses within the last two years, and the treatment of patients with actively relapsing secondary progressive MS.

"The MS Trust welcomes this development which is positive news for people with MS in the UK," said MS Trust Director of Services Nicola Russell. "People with MS should be given the option of drug therapy before nerve damage has occurred so the earlier that treatment can begin, the better."

For further information: Sophie Binks – sbinks@schering.co.uk / 01444 465613 or Nicole Lim – nlim@schering.co.uk / 01444 465617.

Nikon Instruments opens World-class Molecular Imaging Centre at University of Oxford

Researchers can now 'see' single molecules, measure their properties and track their movement

Thanks to a partnership with Nikon Instruments, the University of Oxford has created a world-class advanced imaging facility; the Nikon Oxford Molecular Imaging Centre (NOMIC), at the University's Chemical Research Laboratory (CRL).

Unlike conventional imaging systems, where researchers must mix and match their studies to achieve results, the new high-tech suite allows biomedical and nanotechnology scientists to view events at a sub-microscopic level in real-time in a single integrated network. Hagen Bayley, Professor of Chemical Biology, said, "The opening of the new suite is a notable event. It allows researchers to 'see' single molecules, measure their properties and track their movement".

NOMIC is Nikon's fourth global imaging. The three other Nikon centres of excellence are based at University of Heidelberg in Germany, Harvard Medical School in North America, and recently Hokkaido University in Japan. More details on the NOMIC partnership can be found at www.nikonomic.co.uk

For more information please contact the Nikon Sales Office Email: info@nikon-instruments.com Website: www.nikon-instruments.com

Professor Richards, Chairman of Chemistry, University or Oxford and Dr Hideaki Okamoto, General Manager, Design Department, Nikon Instruments opening NOMIC.