

BEHIND THE HEADLINES

Behind the Headlines reproduces selected clinical articles which have been published online at www.behindthemedicalheadlines.com in the preceding quarter, in order to disseminate this topical clinical information to a wider audience (including those Fellows and Members without Internet access).

The reproduced articles aim to educate and inform the wider College membership about specialist items that have been reported in the international medical and mainstream media: to the non-specialist it may not always be clear how accurately such stories – whether reporting results of scientific studies or issues of concern to health professionals – have been reported. To clarify such situations, expert clinical comments are commissioned on matters that are recurring in the international media, or about which different reports have caused conflicting messages for those practising in other specialties.

It is hoped that this section will be an invaluable source of independent and authoritative advice for Fellows and Members interested in updating their knowledge of new developments in other specialties.

IN THIS ISSUE

- Keyhole surgery for hernia – the key is good training and the hole is where the surgeon, and possibly the patient, may find themselves when poorly trained;
- Improving drug therapy for rheumatoid arthritis; and
- Insights into early fetal development.

KEYHOLE SURGERY FOR HERNIA THE KEY IS GOOD TRAINING AND THE HOLE IS WHERE THE SURGEON, AND POSSIBLY THE PATIENT, MAY FIND THEMSELVES WHEN POORLY TRAINED

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By now you might believe that surgeons must have come close to the Halstead dream of 'a perfectly safe cure for rupture'. After all, inguinal hernia is the most common surgical condition to affect men with almost 1,000 operations performed annually per one million of the population in the UK. Surely, practice makes perfect. Over 100 years ago Bassini described his sutured repair which was a milestone in hernia surgery. More than 25 years now have passed since Lichtenstein developed the tension-free mesh repair using polypropylene claiming rapid recovery and a 99% chance of permanent cure. This

is today's gold standard operation in the Western world. As so often seen in surgery, the early promise of an operation promoted by the specialist centre fails to materialise when rolled out across the surgical community. A recent, large-scale audit across Scotland¹ gathered data on over 4,500 procedures performed during 1998–99 and found that open mesh repair is the most common operation by far. However, it also showed that 80% of patients had in-patient rather than day case surgery, 10% of patients required post operative nursing care to deal with complications and almost one in ten patients required re-do surgery where a previous operation had failed to produce permanent cure and the hernia had recurred. Put simply, in routine practice surgeons use too much resource, have too many complications and fail to cure the patient in over 10% of cases. The more intensive follow-up used in the Medical Research Council (MRC) hernia trial² showed a complication rate of 30% and 40% for laparoscopic and open surgery respectively. Increasing concern is also being expressed about the complication of long-term groin pain, sometimes extreme and often untreatable, associated with mesh repair in particular but common to all types of hernia surgery. Most reports suggest that groin pain is more common and more severe after open surgery when the mesh is placed in direct contact with the ilio-inguinal nerve. Softer and more pliable meshes may reduce this problem but are unlikely to solve it completely. It is not surprising that surgeons are still actively looking for alternative approaches to manage this common condition.

BACKGROUND

This article was commissioned following the publication of a follow-up study in the *New England Journal of Medicine* which compared laparoscopic and open mesh repair surgery for hernia. Based upon an analysis of the data, the study recommended open mesh surgery for first hernia operations, rather than laparoscopy, and resulted in a high level of negative publicity for laparoscopic procedures.

Over the past decade, attention had turned to the laparoscopic approach based on the concept that minimally invasive surgery will reduce complications and accelerate recovery. There are two standard laparoscopic approaches either through the peritoneal cavity (TAPP) or via the extraperitoneum (TEP). The modern approach to an inguinal hernia is directly through the skin and opening part of the abdominal wall musculature to enter the inguinal canal, in effect further damaging the muscular structures that are already weakened. The TEP laparoscopic approach is 'preperitoneal' whereby the surgeon makes an incision well away from the hernia and dissects through all layers of the abdominal wall to enter a space between the muscles and peritoneum. It is relatively simple to develop this space as no major vessels or any nerves pass across it. The hernia is then pulled back into the abdomen and the muscle weakness then strengthened from within. The concept of preperitoneal surgery is not new and the famous surgeon Lloyd Nyhus, a strong advocate of this approach, attributed its first description to Professor Sir Thomas Annandale of Edinburgh University reporting in the *Edinburgh Medical Journal* of 1876. This was more than a decade before Bassini reported what was to become the gold standard technique for almost 100 years. The modern day laparoscopic TEP operation merely uses minimal invasive surgical techniques to exploit the Annandale approach. If TEP surgery were to become the new gold standard then Annandale might replace Bassini as the father figure of hernia surgery.³

In truth there is a paucity of scientific data with which we can compare the TEP and TAPP operations but there is a general view that the TEP approach is to be preferred, as it is perceived to be associated with reduced risk of injury to bowel, bladder and iliac vessels. There has been a torrent of randomised controlled trials (RCTs) of variable quality and size followed by the inevitable meta-analyses. Perhaps the least biased of these was reported by the National Institute of Clinical Excellence (NICE) in 2001.⁴ The National Institute of Clinical Excellence examined over 40 RCTs and reported that laparoscopic surgery was indeed associated with less pain and faster recovery, but also with increased cost and longer operating times. They concluded that for first-time hernia surgery, the open mesh repair remained the operation of choice but the laparoscopic approach may be considered for recurrent and bilateral cases. The National Institute of Clinical Excellence is currently revisiting this area and will report again in September 2004, accepting that their initial study was based on data gathered during the learning curve of laparoscopic surgery and also that longer term follow-up data was required to complete the picture (see Appendix 1).

The recent media coverage which gave rise to this article presented a rather bold and bald analysis of a paper from Utah, US, which reported a randomised trial of open vs laparoscopic hernia trial with 834 and 862 patients in each arm of the study and two years' follow-up.⁵ The open group had a complication rate of 33% and recurrence of 5% (rather higher than most other reports), but the laparoscopic group had a complication rate of 39% and recurrence rate of 10% (very high compared with other reports). They concluded that 'men with a hernia that has never been repaired before should undergo an open repair' exactly the same conclusion made by NICE three years previously.

Buried deeply within the text is an analysis of recurrence rate by experience. Surgeons who have performed more than 250 operations had similar recurrence rates of 5.1% and 4.1% respectively for laparoscopic and open surgery but less experienced surgeons had differing recurrence rates of 12.3% and 2.5%. Indeed, the poor results for laparoscopic surgery are entirely derived from less experienced surgeons. In their discussion they comment, 'These results should be interpreted cautiously.' I fail to see any good reason why! The data is very clear. Put into context, a recent report of TAPP surgery⁶ in over 3,000 UK patients has reported a recurrence rate of 0.16%, 50 times better than the Utah study. Our own experience in Edinburgh has also confirmed that results from laparoscopic surgery in the learning phase are poorer whereas, the open mesh repair has good results even in the hands of early stage trainees. TEP surgery is demanding. The anatomy is not well understood by most surgeons and the operating space is much smaller than the peritoneal cavity in which most laparoscopic surgery is done. This requires a higher degree of hand-eye coordination. A small quantity of blood can dramatically reduce vision and accidental puncture of the peritoneum, easily performed, reduces vision further. Many authors have emphasised the technical demands of TEP surgery and the long learning curve.

Are keyhole operations worse for hernia? Yes, if your surgeon is inadequately trained; but, No, if well trained and experienced. Most general surgeons in the UK and abroad are not trained in this particular technique but almost all do hernia surgery. There is little doubt that specialist surgical centres gain the best results but the NHS has not been known for developing such centres except in highly specialised fields like transplant surgery. If inguinal hernia surgery was to be removed from general surgery and become a specialist operation, such a move would not be warmly received by many for a variety of reasons, not least the potential loss of income that would follow. Nonetheless, this would be the quick fix solution. An alternative approach would be an aggressive training programme targeting existing consultants, possibly supported, or indeed led by, the Royal Colleges. If we are to derive the undoubted benefits of laparoscopic hernia surgery without reliving the disaster years of the early 1990s then training is the key to successful keyhole surgery. Surgeons need to learn how to learn.⁷

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APPENDIX 1

The final NICE report *Laparoscopic surgery for inguinal hernia repair* Technology Appraisal 83 was published in September 2004 and can be obtained at <http://www.nice.org.uk/page.aspx?o=222131> a summary of the guidance is reproduced below:

I Guidance

- I.1** Laparoscopic surgery is recommended as one of the treatment options for the repair of inguinal hernia.
- I.2** To enable patients to choose between open and laparoscopic surgery (either by the transabdominal preperitoneal [TAPP] or by the totally extraperitoneal [TEP] procedure), they should be fully informed of all of the risks (for example, immediate serious complications, postoperative pain/numbness and long-term recurrence rates) and benefits associated with each of the three procedures. In particular, the following points should be considered in discussions between the patient and the surgeon:
- the individual's suitability for general anaesthesia
 - the nature of the presenting hernia (that is, primary repair, recurrent hernia or bilateral hernia)
 - the suitability of the particular hernia for a laparoscopic or an open approach
 - the experience of the surgeon in the three techniques.
- I.3** Laparoscopic surgery for inguinal hernia repair by TAPP or TEP should only be performed by appropriately trained surgeons who regularly carry out the procedure.

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IMPROVING DRUG THERAPY FOR RHEUMATOID ARTHRITIS

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Contrary to popular belief, rheumatoid arthritis (RA) does not generally follow a benign course and cases of 'mild' or 'self-limiting' disease are by far the exception rather than the rule. Rheumatoid arthritis usually leads to irreversible joint damage and disability, and is associated with substantial morbidity and increased mortality compared with the general population.¹ Patients with active RA suffer from significant decline in functional capacity and some studies report a 40% work disability rate within five years of the onset of disease.² A real breakthrough in the treatment of this devastating disease would therefore be very welcome news indeed. The recently published Trial of Etanercept and Methotrexate with Radiographic Patient Outcome (TEMPO) study has attracted much media attention and 'blockbuster' headlines, which have understandably raised patient demand and expectation for biological therapy.³ But how much of the hype is justified and when should we be diverting scarce healthcare resources to extend the availability of these therapies are key issues.

BACKGROUND

Following the publication of two studies that suggested different methods of alleviating pain in rheumatoid arthritis, through the use of targeting B-cells and statins, this commentary was commissioned to provide readers of *The Journal* with an update on developments in this area.

In this double-blind placebo-controlled study, the combination of the anti-Tumour Necrosis Factor (anti-TNF) drugs etanercept (ETN) and methotrexate (MTX) was compared against therapy with each drug alone in 682 patients with established RA. At 52 weeks, 35% of patients who received the combination of ETN and MTX achieved remission (absence of disease activity when measured by a standardised disease activity score), while the remission rates for patients who received MTX or ETN alone were 13% and 16% respectively. Radiographic progression (an indirect measure of structural joint damage) was retarded in 80% of patients who received the combination therapy compared

to 68% and 57% in the patients that received ETN and MTX alone, respectively. Improvement in functional disability was also better among patients who received the combination. Combination therapy was well tolerated and adverse events were no more common in the combination arm than in either of the monotherapy arms.

Remission, usually defined as <1.6 units of a composite index or Disease Activity Score (DAS), is a tough goal to achieve in RA and an even harder one to maintain. The rate of achieving remission in the combination arm of TEMPO is impressive and higher than some other studies of biological therapies.^{4,5} However, another recent pivotal study that has attracted much publicity has also demonstrated that it is possible to achieve similar remission rates without recourse to biological agents. The 'tight control for rheumatoid arthritis' (TICORA) study⁶ compared routine out-patient management with an intensive strategy comprising liberal use of intra-articular steroids and regular objective assessments of disease activity (based on DAS) for protocol-driven escalation of conventional therapy. The results for remission rates were impressive: 65% vs 16% for intensive vs standard care respectively, with similarly favourable outcomes for physical function (based on Health Assessment Questionnaire) and quality of life (based on Short Form 36). Thus, using conventional agents more effectively may achieve similar benefits to biological therapies.

Furthermore, it should be noted that only one-third of the patients who received the ETN and MTX in the TEMPO trial achieved remission, two-thirds had a suboptimal response. Although the numbers of patients receiving the combined therapy who achieved 20%, 50% and 70% improvement in their disease activity (assessed by the criteria devised by the American College of Rheumatology) was much higher at 85%, 69% and 43% respectively, these measures only imply partial response. In other words, these patients had persistently active disease and will probably suffer further functional decline and structural damage. This is a reminder that RA is a chronic disease with a course measured in decades, and that long-term success depends upon sustainable therapeutic benefit. All too often the benefits of treatment reported in clinical trials of RA are transient and their impact on long-term outcome minimal. However, two recent studies confirm the longer-term benefit of controlling active disease either with conventional (FIN-RACo)⁷ or biological therapy.⁸

Patients recruited to the TEMPO trial had long-standing disease with a mean disease duration of about six years. This raises the issue of the optimal timing for biological use and whether such drugs should be used much earlier in the course of inflammatory arthritis. There are two persuasive reasons why this may be the case. First, we now have convincing data that biological agents can halt radiographic progression in RA and therefore prevent structural damage and disability,⁹ so why wait for damage? Second, and perhaps more controversially, there is some evidence that a 'therapeutic window' exists before the disease becomes persistent and when its biology may be fundamentally altered. Indirect evidence to support this hypothesis comes from several studies that have demonstrated better medium and long-term clinical, radiological and functional outcome with early intervention. Similarly, studies in which disease-modifying therapy has been delayed for even as little as eight to nine months suggest that long-term outcome is compromised.¹⁰

We have alluded briefly to a few of the challenges to improving medical therapy for RA. This includes the use of biological therapies and of optimising combination regimes utilising our improved understanding of mechanisms of drug action and interactions. At approximately £8–10k/per annum/patient, funding for biological therapies is another major challenge but it is clear that a strong health economic argument may be proposed on the basis of their ability to reduce long-term disability. Our enthusiasm to heed the results of the TEMPO and similar trials and to increase the use of biological therapy for RA must, of course, be tempered with caution. These drugs are associated with an increased susceptibility to infection, particularly TB, and their effect upon the development of malignancy, particularly of the lymphoproliferative system, is not yet clear.

The last decade has witnessed biological therapies emerge from 'bench to bedside' and there can be no doubt that they represent the most important advance in therapeutics for RA since the pioneering work that led to the discovery of cortisone by Hench and Kendall in 1949. It is no coincidence that the two great British pioneers of anti-TNF therapy, Professors Maini and Feldman from the Kennedy Institute in London, were similarly honoured with the prestigious Lasker Award for Clinical Medical Research in 2003. Biological therapy represents a major breakthrough in therapy for RA, for the first time offering the chance of halting radiographic progression and structural damage. And that's big news.

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INSIGHTS INTO EARLY FETAL DEVELOPMENT

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The development of ultrasound has resulted in real-time three-dimensional (4D) images of the fetus, that are remarkable to the public and physicians alike. Not only do such images offer more accurate delineation of congenital anomalies such as facial clefts, central nervous system abnormalities and cardiac defects, but there are obvious benefits for intrauterine procedures such as fetal surgery. Obstetricians have also found parental reactions to the pictures of their unborn baby particularly rewarding.

BACKGROUND

This article was commissioned following media reports of a new type of ultrasound which produces vivid real-time three-dimensional (4D) images of fetal movements and demonstrates that fetal developments occur much earlier than previously thought.

MOTOR AND SENSORY DEVELOPMENT

Images of the fetus 'walking' and 'thumb-sucking' have come as a surprise to the public, but such movements have, for several years, been well described in the literature. For those working in obstetrics and ultrasonography, these pictures are therefore remarkable only in their definition and real-time technology. There is no doubt that the fetus has complex movements, but what does it all actually mean?

Images showing the fetus taking steps are not surprising to paediatricians. Newborn infants can be shown to 'walk' when held upright on a flat surface. Even preterm infants can do so a short time after birth. Many of the behaviours demonstrated by the newborn in the early postnatal period are a function of primitive reflex activity, dependent on the development of spinal reflex arcs which are not under the control of the brain, and are complete in the fetus as early as eight weeks' gestation. Reflexes are very different from purposeful voluntary movements which develop during the first year of life. Such movements are dependent on the maturation of the central nervous system, and in particular on myelination, which starts from around 18 weeks gestation. In fact, all primitive reflexes have to be lost before voluntary movement can be mastered. Reflex activity usually disappears in normal babies by about eight months of age but may persist in those with neurological damage.

Most of what is known about fetal behaviour has been learned since the introduction of ultrasonography in the 1950s. The fetus exhibits a wide range of behaviours starting with slow flexion and extension of the spine and limbs at around 7.5 weeks' gestation. The variety of movements increases rapidly over the next three to four weeks and many different movement patterns have been described including breathing, truncal rotation, limb flexion/extension, sucking and yawning.¹ As the fetus progresses towards term the movements become more regular and coordinated as a result of increased maturation of the nervous system.

Fetal thumb-sucking can be demonstrated as early as 12–14 weeks gestation. Preference for sucking a particular thumb *in utero* has been shown to predict head position preference in the newborn and subsequent right or left-

handedness. Handedness was thought to be dependent on cerebral lateralisation. However, fetuses prefer one thumb to another from as early as 12 weeks' gestation, well before the brain has any control over movement. This early sucking behaviour is likely to be under reflex control. Stimulation of the brain is known to influence brain organisation and it is argued that this reflex activity may eventually stimulate the brain to develop 'handedness' and subsequent lateralisation of function.²

Sensory development in the fetus has been studied mostly in response to sound, and hearing can be shown as early as 23 weeks' gestation. Fetuses respond with a slowing of the heart rate during maternal speech. There is evidence to suggest that fetuses can differentiate between different speech sounds and show preference for the maternal native language. It may be that experience of speech prenatally begins the process of acquiring language postnatally.

FETAL LEARNING AND MEMORY

Fetal learning can be observed in studies of 'habituation'. Habituation is the reduction in a particular behavioural response that occurs when a new stimulus is presented repeatedly. In an environment of constant sensory stimulation, the ability to ignore meaningless stimuli is essential for the efficient functioning and survival of the fetus. Although very simple, it is one of the most widespread methods of learning and there is good evidence that habituation reflects a healthy nervous system. Habituation of the human fetus has been studied mainly in response to sound and has been shown as early as 23 weeks' gestation.³ Stimulation using other sensory modalities such as taste and smell, which are functional at earlier ages, may reveal habituation occurring even earlier in pregnancy. Studies have shown fetal habituation to be predictive of cognitive function in early childhood.^{3,4}

Other aspects of fetal memory have been investigated. Babies whose mothers consistently rested in front of a popular television programme during pregnancy became alert, stopped moving and showed slowing of their heart rate a few days after birth when the theme tune of the programme was played. This behaviour was not shown by babies whose mothers had not watched this programme during pregnancy.⁵ This indicates that the fetus is able to learn and remember familiar auditory stimuli, and retain this information over the birth period.

CLINICAL IMPLICATIONS

The behaviour of the fetus can be argued to represent the functioning and integrity of its nervous system. By building up a picture of 'normal behaviour' of the fetus it is possible to determine the well-being of the fetus. Different fetal behaviour has been observed in pregnancies complicated by maternal smoking or recreational drug abuse, fetal abnormality (e.g. Down's Syndrome) and in pregnancies which later spontaneously aborted.

Interest in the causes of cerebral palsy has led many researchers to conclude that most brain damage happens before labour.⁶ A recent study from Edinburgh showed that most infants who had neurological symptoms and who died in the newborn period had evidence of brain damage occurring during pregnancy.⁷ No obvious cause could be found when the pregnancy was reviewed. Routine ultrasound imaging in pregnancy now occurs throughout the developed world. The development of 4-D ultrasound may eventually provide detailed information about the normality of fetal behaviour. Measurements of the quantity and quality of fetal movement may allow us to determine the severity and extent of any neurological damage if present. The more severely injured the nervous system, the greater the differences in behaviour from a fetus with an intact nervous system. The identification of fetuses exhibiting such behavioural patterns may offer insight into the causation of intrauterine brain injury and allow optimal management of these pregnancies.

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