Editor’s choice

The British Medical Bulletin, for its third print edition of 2011, has another set of fascinating reviews on a wide range of topics at the cutting edge of medical practice. Once again the second half of the edition has a series of reviews on the potential use of stem cells. These reviews are intended to be accessible to non-specialists, in order to bring this subject to a wide audience.

The first review is entitled Food additives: an ethical evaluation (page 7) by Mepham from the University of Nottingham, UK.

Food additives are an integral part of the modern food system, but opinion polls show that most Europeans have worries about them, implying a need for ethical analysis of their use. Food additives provide certain advantages in terms of many people’s lifestyles but there are disagreements about the appropriate application of the precautionary principle and of the value and ethical validity of animal tests in assessing human safety. Most consumers have a poor understanding of the relative benefits and risks of additives. It is concluded that a more informed debate is needed on the impact of food additives on consumer sovereignty, consumer health and on animals used in safety testing.

The second review is on Maternal mortality and millennium development goal 5 (page 25) by Van den Broek and Falconer from Liverpool School of Tropical Medicine, UK and the Royal College of Obstetricians and Gynaecologists, UK.

The maternal mortality ratio is a key indicator for measurement of progress against millennium development goal 5. For many countries, especially those with a high number of maternal deaths, only estimates are available. There is international consensus that efforts to reduce maternal mortality globally need to be intensified. Many countries lack accurate data on number of deaths in women of reproductive age and number of births, therefore statistical modelling has been used to calculate estimates. These have wide confidence intervals and may be disputed by individual countries. There is a need to adapt and implement methods for measuring maternal mortality to generate more accurate estimates. More data on the cause of death are needed.

The third review is on The epidemiology of thyroid disease (page 39) by Vanderpump from the Royal Free Hampstead NHS Trust, London, UK.

Thyroid disorders are prevalent. The most common cause of thyroid disorders worldwide is iodine deficiency, leading to goitre formation and hypothyroidism. In iodine-replete areas, most persons with thyroid disorders have autoimmune disease. The definition of thyroid
disorders, selection criteria used, influence of age and sex, environmental factors and the different techniques used for assessment of thyroid function are all under discussion. Environmental iodine influencing the epidemiology of non-malignant thyroid disease needs to be explored. Iodine supplementation of populations with mild-to-moderate iodine deficiency and an evidence-based strategy for the risk stratification, treatment and follow-up of benign nodular thyroid disease are timely research issues as is the question of any benefit in screening adults for thyroid dysfunction?

The fourth review is on Next generation sequencing—implications for clinical practice (page 53) by Raffan and Semple from the University of Cambridge, UK.

Genetic testing in inherited disease has traditionally relied upon recognition of the presenting clinical syndrome and targeted analysis of genes known to be linked to that syndrome. Consequently many patients with genetic syndromes remain without a specific diagnosis. New next-generation sequencing (NGS) techniques permit simultaneous sequencing of enormous amounts of DNA. These approaches are likely to be increasingly employed in routine diagnostic practice, but the scale of the genetic information yielded about individuals means that caution must be exercised to avoid net harm in this setting. The use of NGS in a research setting will increasingly have a major beneficial impact on clinical practice. However, important technical, ethical and social challenges need to be addressed through informed professional and public dialogue.

The fifth review is on the Prevention of type 1 diabetes (page 73) by Thrower and Bingley from Southmead Hospital, Bristol, UK.

Type 1 diabetes is a chronic autoimmune condition characterized by destruction of insulin-producing β-cells within the pancreatic islets. It is associated with considerable morbidity and mortality. Incidence levels are rising worldwide. The causes of the disease are multifactorial. There is a long pre-clinical period before the onset of overt symptoms, which may be amenable to intervention to prevent the disease. The exact nature of causative environmental factors is unknown and much debated. Immunotherapeutic intervention may represent the best option for disease prevention. Enhancement of ‘regulatory’ immune mechanisms currently shows the most promise as an approach to disease prevention and controlled clinical trials of early immunotherapeutic intervention are needed.

The sixth review is on Meniscectomy as a risk factor for osteoarthritis (page 89) by Papalia, Del Buono, Osti, Denaro and Maffulli from
Campus Biomedico University of Rome, and the Hesperia Hospital, Modena, Italy and the Barts and The London School of Medicine and Dentistry, London.

This review defines the risk factors responsible for development of knee osteoarthritis after surgical management of meniscal tears. The amount of meniscus removed, duration of preoperative symptoms and lateral meniscectomy show strong statistical association with onset of knee osteoarthritis. However, there are no unequivocal findings defining the risk factors responsible for the development of postoperative knee osteoarthritis. Comparing imaging findings of patients undergoing arthroscopic partial and open menisectomy, a lower incidence of knee osteoarthritic evolution was detected after arthroscopy. The amount of removed meniscus is the most important predictor factor for development of osteoarthritis. Minimally invasive procedures seem to reduce the incidence of long-term osteoarthritic changes of the knee compared with more invasive open or arthroscopic procedures.

The seventh review is on Colorectal liver metastases (page 107) by Sutcliffe and Bhattacharya from Queen Elizabeth Hospital, Birmingham and Barts and the London Hospital, UK.

Despite major advances in therapies for liver metastases, colorectal cancer remains one of the commonest causes of cancer-related deaths in the UK. Due to a combination of highly active systemic agents and low peri-operative mortality achieved by high-volume centres, a growing number of patients are being offered liver resection with curative intent. Patients with bilobar and/or extrahepatic disease, who would previously have received palliative treatment only, are undergoing major surgery with good results. It is not known if ablative therapies match the outcomes of surgical resection or how more patients can be rendered respectable. The use of other therapies, such as radiofrequency ablation and selective internal radiation therapy may help. New chemotherapy regimens for neo-adjuvant therapy and the development of new modalities of liver tumour ablation may also be useful.

The eighth review is on Melioidosis (page 125) by Limmathurotsakul and Peacock from Mahidol University, Bangkok, Thailand and the University of Cambridge, UK.

Melioidosis is an infection caused by the environmental Gram-negative bacillus Burkholderia pseudomallei, and has emerged as an important cause of morbidity and mortality in southeast Asia and northern Australia. The approaches to diagnosis and antimicrobial therapy are generally agreed. However, there is controversy over whether seroconversion signals the presence of a quiescent bacterial
focus and an increase in long-term risk of melioidosis. Melioidosis is potentially preventable, but there is a striking lack of evidence on which to base an effective prevention programme. An accurate map defining the global distribution of *B. pseudomallei* is needed, together with studies on the relative importance of different routes of infection. There is a marked difference in mortality from melioidosis in high-income versus lower income countries, and affordable strategies that reduce death from severe sepsis (from any cause) in resource-restricted settings are needed.

The ninth review is on Surgical management of symptomatic shoulders with partial thickness tears of the rotator cuff (page 141) by Papalia, Franceschi, Del Buono, Maffulli and Denaro from the University of Rome, Italy and The London School of Medicine and Dentistry, London.

The optimal management of partial thickness tears of the rotator cuff (PTRCT) is still controversial. The Coleman Methodology Score used to assess the quality of the studies showed great heterogeneity in study design, the sample, pre- and post-operative diagnostic assessments, and the score used to evaluate outcomes. The heterogeneity of the treatment options and of the outcome assessment methods makes it difficult to compare the results of the different studies. To improve the diagnosis and to choose the best treatment, it may be useful to measure the thickness of the rotator cuff to ascertain whether the size correlates with outcome. There is a need for adequately powered randomized clinical trials, using standard diagnostic assessment, common and validated scoring system comparing reported outcomes and duration of follow-up >2 years.

The following reviews are part of a subsection on stem cells. The tenth review, therefore, is on Human stem cell research and regenerative medicine (page 155) by Volarevic, Ljubic, Stojkovic, Lukic, Arsenijevic and Stojkovic from University of Kragujevac and the University of Belgrade, Serbia.

Stem cells are cells with the ability to grow and differentiate into more than 200 cell types. They review the characteristics and potential of human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs) and adult stem cells (ASCs). The differentiation ability of all stem cell types could be stimulated to obtain specialized cells that represent renewable sources of cells useful for cell-based therapy. The proof of functional differentiated cells needs to be investigated in more details using both *in vitro* and *in vivo* assays including animal disease models and clinical studies. Much progress has been made in the ASCs-based therapies. Meanwhile hESCs and iPSCs have emerged as novel approaches to understanding the pathogenesis of different
diseases. They discuss the limitations of stem cells and latest development in the reprogramming research.

The eleventh review is Stem cell-based therapy and regenerative approaches to diseases of the respiratory system (page 169) by Jungebluth and Macchiarini from the Karolinska Institutet, Stockholm, Sweden.

Despite treatment advances in many diseases of the respiratory system, outcomes remain poor. Current preclinical research and ongoing clinical trials are presented and their potential clinical impact and routine application discussed. Stem cell-based therapy may represent a promising alternative approach for otherwise irreversible respiratory diseases. Evaluating gene, epigenetic and protein regulation and the interaction with the environment under diseased and healthy conditions are being approached. It is necessary to detect approaches with significant scientific and clinical impact.

The twelfth review is on The use of stem cells to repair the injured lung (page 189) by Polak from Imperial College, London.

The structure of the lung is complex as it contains at least 40 different cell types. It interacts with the outside environment and the circulatory system, which make it susceptible to injury and disease. Stem cells with reparative properties can be found within the lung but outside sources of stem cells can also contribute to the repair of the injured lung. These include multi-potent stem cells from the bone marrow and pluripotent stem cells derived from the early embryo or from adult cells, which are made to reverse to a pluripotent state by the addition of viral vectors or non-viral agents. Much research is currently undertaken to define the mechanisms by which stem cells repair the injured tissue. These include the possibility of engraftment of exogenous cells or the release of growth factors from the cells to aid repair. Interest is now focussed on developing appropriate animal models to test the safety and efficacy of stem cell therapies and to understand the mechanisms by which stem cells undertake this task.

The thirteenth review is on Stem cells in bone diseases (page 199) by Beyth, Schroeder and Liebergall from Hebrew University Medical Center, Jerusalem, Israel.

Bone is an obvious candidate tissue for stem cell therapy. Their review provides an update on existing stem cell-based clinical treatments for bone pathologies. Stem cell therapy offers new options for bone conditions, both acquired and inherited. There is still no agreement on the exact definition of ‘mesenchymal stem cells’. Consequently, it is difficult to appreciate the effect of culture expansion
and the feasibility of allogeneic transplantation. Based on the sound foundations of pre-clinical research, stem cell-based treatments and protocols have recently emerged. Well-designed prospective clinical trials are needed in order to establish and develop stem cell therapy for bone diseases.

The fourteenth review is on **Stem cells in tendon disease** (page 211) by Sakabe and Sakai from Lerner Research Institute and Cleveland Clinic, Cleveland, OH, USA.

Tendon physiology and pathology are heavily dependent on mechanical stimuli. Tendon injuries clinically represent a serious and still unresolved problem since damaged tendon tissues heal very slowly and no surgical treatment can restore a damaged tendon to its normal structural integrity and mechanical strength. Identification of tendon cell markers has enabled us to study tendon healing and homeostasis. Clinically, tissue engineering for tendon injuries is an emerging technology comprising elements from the fields of cellular source, scaffold materials, growth factors/cytokines and gene delivering systems. The clinical settings to establish appropriate microenvironment for injured tendons with the combination of these novel cellular- and molecular-based scaffolds will be critical for treatment.

The fifteenth review is on **Stem cell therapy for articular cartilage defects** (page 227) by Årøen from Lørenskog, Norway.

Stem cells are easily accessible and have great potential for healing articular cartilage defects. These features make stem cell therapy an appealing approach for treating severely impaired joint function. Malalignment and instability corrections and proper rehabilitation are crucial prerequisites for surgical procedures involving stem cell therapy. Ethical concerns remain unresolved. No standards are established for inducing stem cell potential, optimizing culturing media or harvesting. Surgical scaffolds can improve results. Care givers should focus on re-educating patients. Improved funding is needed for developing the therapy and defining guidelines for stem cell therapy and demonstrating its effectiveness needs to be researched further.

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**Norman Vetter**

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